A PHASE III OPEN-LABEL, CONTROLLED, RANDOMIZED, MULTICENTER STUDY EVALUATING THE EFFICACY AND SAFETY OF STRATAGRAFT® SKIN TISSUE IN PROMOTING AUTOLOGOUS SKIN TISSUE REGENERATION OF COMPLEX SKIN DEFECTS DUE TO THERMAL BURNS THAT CONTAIN INTACT DERMAL ELEMENTS AND FOR WHICH EXCISION AND AUTOGRAFTS ARE CLINICALLY INDICATED

NCT03005106

STRATA2016
PHASE III CLINICAL PROTOCOL

Original Protocol (V 1.0) Dated September 14, 2016

Amendment 1 (V2.0) Dated 30 May 2019

APPROVAL STATEMENT

The sponsor below has approved this protocol and pledges that this study will be conducted according to all stipulations of the protocol as specified in both the clinical and administrative sections, including all statements regarding confidentiality. By completing and signing the Clinical Protocol Approval letter and Form FDA-1572 "Statement of Investigator", the clinical investigator agrees to abide by United States federal regulations, applicable state regulations, and the study protocol during the course of the clinical trial conducted under an Investigational New Drug application.

SPONSOR: **STRATATECH, a Mallinckrodt Company**
510 Charmany Drive
Suite 150
Madison, WI 53719

[redacted]

Approved by: _____ **Date:**_____

[redacted] MD
Senior Director, Medical Affairs

SUMMARY OF STRATA2016 PROTOCOL

TITLE OF STUDY
A Phase III Open-Label, Controlled, Randomized, Multicenter Study Evaluating the Efficacy and Safety of StrataGraft Skin Tissue in Promoting Autologous Skin Tissue Regeneration of Complex Skin Defects Due To Thermal Burns That Contain Intact Dermal Elements and For Which Excision and Autografts Are Clinically Indicated

CLINICAL PHASE
Phase III.

STUDY OBJECTIVE
The objective of this study is to assess the efficacy and safety of a single application of StrataGraft tissue in the treatment of complex skin defects caused by thermal burns that contain dermal elements and for which surgical excision and autografts are clinically indicated.

STUDY RATIONALE AND DESIGN
The current standard of care (SOC) for severe burns and other complex skin defects is surgical excision of a sheet of healthy skin from an uninjured site on the patient and transplantation of this autologous skin graft to the primary injury after excision of nonviable tissue. While this process can be effective in providing closure to the original wound, it is associated with significant morbidity due to the iatrogenic donor site wound created from surgical excision of the autograft tissue that is then transplanted to the original wound. These donor site wounds are extremely painful, are prone to scarring, dyspigmentation and infection, are associated with a physiologic burden, and can convert to full-thickness wounds that must then be managed. In addition, the amount of healthy skin available for autograft transplantation is frequently limiting in patients with large burns, necessitating sequential reharvesting of available donor sites. As a result of these limitations, there is an urgent need for alternatives to the practice of donor site harvest and autograft treatment of severe burns and other complex skin defects.

The STRATA2016 phase III study is designed to evaluate whether treatment with StrataGraft skin tissue can promote the healing of complex skin defects due to thermal burns that contain intact dermal elements and for which surgical excision and autografts are indicated. StrataGraft skin tissue is an off-the-shelf, biologically active human skin substitute which is anticipated to provide immediate wound coverage, aid in wound bed conditioning, and promote autologous tissue regeneration and durable wound closure while reducing the amount of donor tissue harvested. It is anticipated that StrataGraft skin tissue will remain in the wound long enough to promote autologous tissue regeneration and be replaced over time by the subject's own cells rather than permanently engrafting.

Stratatech has completed STRATA2001, a first-in-human, dose escalation trial evaluating the safety of a single application of StrataGraft skin tissue in subjects with full-thickness complex skin defects of 5 to 73% total body surface area (TBSA) resulting from thermal injury, trauma, or necrotizing fasciitis. In STRATA2001, full-thickness wounds were temporized for 7 days with StrataGraft skin tissue or cadaver allograft prior to autografting. Autograft take was comparable in wounds temporized with StrataGraft tissue as compared to cadaver allograft. There were no changes in the types of adverse events (AEs) as the dosage of StrataGraft skin tissue was increased 5-fold across the cohorts from 44 cm^2 to 220 cm^2, and no AEs were product-related. StrataGraft tissue remained intact and viable throughout the 7-day placement period, suggesting the potential for continued biological activity during longer placement.

The STRATA2011 study, a follow-up to the STRATA2001 trial, was conducted as an open-label, dose-escalation, multicenter study evaluating the safety, tolerability, and efficacy of longer exposure to increasing amounts of StrataGraft skin tissue in promoting the healing of complex skin defects containing intact dermal elements. In STRATA2011, a single application of StrataGraft skin tissue was applied to deep partial-thickness burns and left in place to evaluate whether StrataGraft skin tissue promoted autologous tissue regeneration while reducing or eliminating the need for the surgical harvesting of donor sites for autografts.

The STRATA2011 study included subjects with thermal burns containing intact dermal elements and whose area of total injury ranged from 3 to 49% TBSA. Each subject had 2 comparable wound areas identified, excised to remove nonviable tissue, and randomized to receive StrataGraft skin tissue or an autograft. Thirty subjects were enrolled in this dose escalation study. Subjects in Cohort 1 received up to 220 cm^2 of StrataGraft skin tissue while those in Cohort 2 received up to 440 cm^2 of StrataGraft skin tissue. Cohort 3 was completed as a clinical comparability evaluation of StrataGraft skin tissue that had been cryopreserved and stored frozen. Subjects in Cohort 3 received up to 440 cm^2 of thawed StrataGraft skin tissue. None of the sites treated with StrataGraft skin tissue required autografting by Day 28. Additionally, 27 of the 28 per-protocol subjects had wound closure of treatment sites at the 3 month study session. No safety signal was seen following application of StrataGraft skin tissue. Molecular analysis of patient biopsy samples found no evidence of deoxyribonucleic acid (DNA) from cells of StrataGraft skin tissue after 3 months, indicating that StrataGraft skin tissue had not engrafted but was replaced by the patient's own skin.

The STRATA2001 and STRATA2011 studies provided several important clinical findings that informed the development of this Phase III STRATA2016 protocol:

- None of the complex skin defects containing intact dermal elements treated with StrataGraft skin tissue required autografting of these areas by Day 28. These results exceeded the metrics agreed to prior to the study that a 50% reduction in the StrataGraft-treated area requiring autografting is clinically meaningful.
- The absence of donor site harvest required for areas treated with StrataGraft skin tissue resulted in significantly less pain, fewer sequelae, and superior cosmesis relative to the autograft donor site.

- StrataGraft skin tissue did not permanently engraft and was replaced by the patient's own cells by 3 months.
- StrataGraft skin tissue remained intact, adherent, and viable in full-thickness skin defects for at least 7 days, during which time it likely acted as a continuous source of factors that are anticipated to promote autologous skin tissue regeneration.

The STRATA2016 Phase III study builds upon data generated by the STRATA2001 and STRATA2011 studies. This registration study is designed as an open-label, controlled, randomized, multicenter study evaluating the efficacy and safety of StrataGraft skin tissue in the treatment of complex skin defects due to thermal burns that contain intact dermal elements and for which surgical excision and autografting are clinically indicated. Targeted enrollment for the study is approximately 70 subjects who have thermal burns of 3 to 49% TBSA, including an area that contains intact dermal elements for which surgical excision and autografting are clinically indicated.

After surgical excision of nonviable tissue, 2 comparable areas of comparable depth on each subject will be identified and the areas will be randomized to receive StrataGraft skin tissue or a surgically harvested autograft. The intrapatient comparator allows for a matched control to eliminate significant underlying differences including immunologic, physiologic, and scarring variables inherent in this patient population that affect the healing trajectories of the burn. Two donor sites will be prospectively identified to provide sources of autografts for the control and StrataGraft treatment sites as needed. After surgical excision of nonviable tissue, the StrataGraft tissue and autograft will be placed on the treatment sites in accordance with the randomization.

Efficacy will be assessed by 1) evaluating the difference in the percent area of the StrataGraft-treated and autograft-treated sites that are autografted by 3 months and 2) evaluating the proportion of subjects achieving durable wound closure of the StrataGraft treatment site at 3 months without autograft placement. The pain of the donor sites will be assessed through Day 28, donor site sequelae will be assessed at each study session after treatment Day 0, and cosmesis of the treatment sites and donor sites will be evaluated at 3, 4, 6, and 12 months. Incidence of wound closure and percent wound closure will be assessed at Day 28, as well as 2, 3, 4, 6 and 12 months. Additional assessments include subject and physician satisfaction with the StrataGraft treatment site, duration of hospitalization due to donor site pain, presence of allogeneic DNA at 3 months, and need for scar manipulation therapy of the treatment sites for tissue normalization. Safety assessments include monitoring of treatment-emergent AEs, vital signs, safety laboratory parameters, incidence of wound infection, donor site complications, histologic wound bed analysis, immunologic responses to StrataGraft skin tissue, as well as concomitant medications and procedures.

[redacted]

[redacted]

Application of up to 440 cm^2 of StrataGraft skin tissue in the STRATA2011 trial was shown to be well tolerated with no evidence of safety concerns when applied to complex skin defects due to thermal burns that contained intact dermal elements. All subjects in the STRATA2016 study will receive a single application of up to 1,000 cm^2 StrataGraft skin tissue following surgical excision of nonviable tissue. The preidentified treatment sites must each be a single, contiguous wound area of comparable depth but the StrataGraft treatment site and control treatment sites may be non-contiguous to each other. The StrataGraft treatment site may be up to 2 times the area of the autografted comparator site. StrataGraft skin tissue will be left in place after topical application. Routine safety monitoring will be performed by the study's medical monitor (MM) and the Data and Safety Monitoring Board (DSMB).

Co-Primary Clinical Efficacy Endpoints

1. The difference in the percent area of the StrataGraft treatment site and control autograft treatment site that is autografted by 3 months.
2. The proportion of subjects achieving durable wound closure of the StrataGraft treatment site at 3 months without autograft placement.

Ranked Secondary Efficacy Endpoints

The difference between the StrataGraft and autograft donor sites in the average pain intensity through Day 14 based on the Wong-Baker FACES pain rating scale (FPRS).

The difference between the StrataGraft and autograft donor site cosmesis at 3 months based on observer Patient and Observer Scar Assessment Scale (POSAS) total score.

The difference between the StrataGraft and autograft treatment site cosmesis at 12 months based on observer POSAS total score.

Mechanism Endpoint

The proportion of the StrataGraft treatment sites that test positive for residual DNA from the cells of the StrataGraft skin tissue at 3 months.

Exploratory Efficacy Endpoints

[redacted]

[redacted]

Statistical Methods

The data will be summarized with descriptive statistics by treatment group, and the specific statistical tests comparing the treatments will be documented in the Statistical Analysis Plan. SAS version 9.4 or newer will be used.

Efficacy Assessments

Assessments	Methods	Schedule of Assessments
Percent area of the treatment sites autografted.	Clinician assessment supported by photodocumentation.	Days 3, 7, 14, 28 as well as 2, 3, 4, and 6 months.
[redacted]	[redacted]	[redacted]
Pain of donor sites.	FPRS.	Days 3, 7, 14 and 28.
Cosmesis of donor sites.	POSAS supported by photodocumentation.	3, 4, 6 and 12 months.
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Cosmesis of treatment sites.	POSAS supported by photodocumentation.	3, 4, 6 and 12 months.
Presence of allogeneic DNA.	PCR of short tandem repeats.	Baseline and 3 months.
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Safety Assessments

Assessments	Methods	Schedule of Assessments
Adverse events, including treatment-emergent adverse events.	Standard.	Throughout study duration.
Vital signs.	Blood pressure, temperature, and pulse.	Every study session.
Incidence of infection.	Clinical signs and symptoms; laboratory evidence as needed.	Every study session.
Concomitant medications.	Standard.	Every study session.
Concomitant procedures.	Standard.	Every study session.
Safety laboratory values.	Comprehensive metabolic panel (CMP) & complete blood count (CBC) with differential.	Baseline and Days 7 and 28.
Immunological evaluations.	Panel reactive antibodies (PRA).	Baseline, 28 days, and 3 months.
	Anti-bovine serum albumin (BSA) antibodies.	Baseline and 3 months.
Histologic wound bed analysis	For cellular integrity and tissue architecture.	Study Session #1.
Donor site complications.	Clinician assessment.	Days 3, 7, 14, 28 as well as 2, 3, 4, 6 and 12 months.
[redacted]	[redacted]	[redacted]

INCLUSION CRITERIA

Subject-specific criteria	Treatment site-specific criteria
• Men and women aged ≥ 18 years. • Written informed consent. • Sufficient healthy skin identified and designated as a donor site in the event that the StrataGraft treatment site requires autografting. • Clinical expectation that study donor site will heal without grafting. • Complex skin defects of 3 to 49% TBSA. – Total burn may consist of more than one area.	• Thermal burn(s) with intact dermal elements for which excision and autografts are clinically indicated. • Total of both study treatment areas can be up to 2000 cm^2. • First excision and grafting of study treatment sites. • Thermal burn(s) on the torso, and upper or lower extremities.

EXCLUSION CRITERIA

Subject-specific criteria	Treatment site-specific criteria
• Pregnant women. • Prisoners. • Subjects receiving systemic immunosuppressive therapy. • Subjects with a known history of malignancy. • Preadmission insulin-dependent diabetic subjects. • Subjects with concurrent conditions that in the opinion of the investigator may compromise subject safety or study objectives. • Expected survival of less than 3 months. • Participation in the treatment group of an interventional study within 90 days prior to enrollment.	• Full-thickness burns. • Chronic wounds. • The face, head, neck, hands, feet, buttocks, and areas over joints. • Treatment sites immediately adjacent to unexcised eschar. • Clinical or laboratory determination of infection at the anticipated treatment sites.

NUMBER OF SUBJECTS

Targeted enrollment for this study is approximately 70 study subjects who have complex skin defects due to thermal burns that contain intact dermal elements and for which excision and autografts are clinically indicated.

ESTIMATED DURATION OF CLINICAL STUDY

Open Enrollment Period	24 months
Planned Subject Contact Duration	12 months

Screening Period (Within 7 Days Prior to Treatment)

Subjects with complex skin defects containing intact dermal elements who after surgical excision of an area of thermal burn meet all eligibility criteria would qualify for this study.

TEST PRODUCT

StrataGraft skin tissue contains an epidermal layer comprising differentiated, multilayered, epidermal keratinocytes from a single human donor grown on a collagen matrix embedded with fibroblasts from a second human donor. StrataGraft skin tissue is not a patient-specific product but an allogeneic human skin substitute. StrataGraft skin tissue is produced from well-characterized cell banks of pathogen-free human keratinocytes and fibroblasts. StrataGraft skin tissue reproduces many of the structural and biological properties of normal human skin and is intended to provide immediate wound coverage, barrier function, and sustained expression of wound healing factors to promote the healing of complex skin defects.

TEST PRODUCT ROUTE OF ADMINISTRATION AND DOSE REGIMEN

Following excision of nonviable tissue, 2 treatment sites that contain intact dermal elements and are up to 1,000 cm^2 each on the upper or lower extremities or torso will be prospectively identified. The treatment sites should be of comparable depth and have similar potentials for experiencing mechanical shear forces post-grafting. Prior to randomization, the 2 identified treatment sites must be labeled as sites A and B. Treatment site A will always be anterior, superior/proximal, lateral or to the subject's right. Treatment site B will always be posterior, inferior/distal, medial or to the subject's left. After identification, the sites will be randomized to receive up to 1,000 cm^2 StrataGraft skin tissue or up to 1,000 cm^2 autologous skin graft. Though sites A and B need not be contiguous to each other, each individual treatment site must be a single, contiguous area. The StrataGraft treatment site may be the same size as or up to twice the area of the autograft control site. Any remaining wound outside the identified study treatment sites will be treated according to the institutional SOC for that type of wound.

REGULATORY INFORMATION AND QUALITY STATEMENT

The study will be conducted under an active investigational new drug application (IND) which has been prepared and submitted to the Center for Biologics Evaluation and Research (CBER), United States Food and Drug Administration (FDA) to support the evaluation of safety and efficacy of StrataGraft skin tissue in the management of complex skin defects.

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