AN OPEN-LABEL, CONTROLLED, RANDOMIZED, MULTICENTER, DOSE ESCALATION STUDY EVALUATING THE SAFETY, TOLERABILITY, AND EFFICACY OF SINGLE OR MULTIPLE APPLICATIONS OF STRATAGRAFT® SKIN TISSUE AS AN ALTERNATIVE TO AUTOGRAFTING FULL-THICKNESS COMPLEX SKIN DEFECTS

STRATA2014
PHASE II CLINICAL PROTOCOL

Version 3
March 23, 2017

Corporation, except that this document may be disclosed to appropriate institutional review boards/ethical committees so long as they are requested to maintain its confidentiality.

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 Investigator Statement (FORM FDA-1572), the Clinical Investigators agree to abide by US federal regulations and the study protocol during the course of the clinical trial conducted under an IND application.

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

Approved by: [redacted] **Date:** 23MAR2017

Vice President of Regenerative Medicine

LIST OF ABBREVIATIONS/DEFINITIONS

AE	Adverse event
ALT	Alanine transaminase/SGPT
Allograft	Transplant from one person to another person
AST	Aspartate transaminase/SGOT
Autograft	Transplant from one anatomical location to another within the same person
BSA	Bovine serum albumin
BSE	Bovine spongiform encephalopathy
CBC	Complete blood count
CBER	Center for Biologics Evaluation and Research
CFR	Code of Federal Regulations
CMP	Comprehensive metabolic panel
CRF	Case report form
CRO	Contract research organization
DoD	Department of Defense
DSMB	Data and safety monitoring board
FDA	Food and Drug Administration
FPRS	Wong-Baker FACES pain rating scale
GCP	Good clinical practice
HgB	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HRPO	Human Research Protection Office
IB	Investigator's brochure
ICH	International Conference on Harmonisation
IND	Investigational new drug
IRB	Institutional review board
MHC	Major histocompatibility complex
MM	Medical monitor
NIKS®	Near-diploid human keratinocytes
ORP	Office of Research Protections
PHI	Protected health information
POSAS	Patient and observer scar assessment scale
PRA	Panel reactive antibodies
QA	Quality assurance
QC	Quality control
SAE	Serious adverse event
SD	Standard deviation
SOC	Standard of care
TBSA	Total body surface area
UPIRTSO	Unanticipated problem involving risks to subjects or others
USAMRMC	U. S. Army Medical Research and Materiel Command
WBC	White blood cells

SUMMARY OF STRATA2014 PROTOCOL

TITLE OF STUDY

Open-label, controlled, randomized, multicenter, dose escalation study evaluating the safety, tolerability, and efficacy of single or multiple applications of StrataGraft® skin tissue as an alternative to autografting full-thickness complex skin defects

CLINICAL PHASE

Phase II

STUDY OBJECTIVE

The objective of this study is to assess the safety, tolerability, and efficacy of increasing dosages of a single or multiple applications of StrataGraft skin tissue in the treatment of full-thickness complex skin defects on the arms, legs, and torso.

STUDY RATIONALE

The current standard of care (SOC) for severe burns and other complex skin defects is surgical harvesting of a sheet of healthy skin from an uninjured site on the patient and transplantation of this autologous skin graft to the wound after excision of non-viable tissue. While this process can be effective in providing closure of the original wound, it has significant limitations related to the iatrogenic donor site wounds created during surgical removal of autologous skin tissue. These donor site wounds are extremely painful, prone to infection and scarring, and can themselves convert to full-thickness wounds that must then be managed to promote healing. In addition, the amount of healthy skin available for harvesting is frequently limited in large burns, necessitating sequential re-harvesting of available donor sites. As a result, there is an urgent need for alternatives to donor site harvesting for treatment of severe burns and other complex skin defects.

This range-finding study is designed to evaluate StrataGraft skin tissue as an alternative to autografting in promoting autologous tissue regeneration of the full-thickness component of complex skin defects resulting from acute traumatic skin loss (e.g., burn or degloving injuries). StrataGraft skin tissue is an off-the-shelf, biologically active human skin substitute which is anticipated to provide immediate wound coverage and aid in wound bed conditioning and tissue regeneration. Based on over 25 years of clinical experience with human skin substitutes containing living allogeneic cells,[1] as well as prior clinical experience with StrataGraft skin tissue, 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 StrataGraft skin tissue in subjects with complex skin defects of 5-73% total body surface area (TBSA) resulting from thermal injury, trauma, or necrotizing fasciitis. This study showed that autograft take in wound beds temporized with StrataGraft skin tissue was comparable to autograft take in wounds temporized with cadaver allograft. No product-related adverse events (AE) were seen following application of StrataGraft skin tissue to the full-thickness component of these complex skin defects for seven days. There was no change in the types of AE as the total

[1] Rennert RC, Rodrigues M, Wong VW, et al. *Biological therapies for the treatment of cutaneous wounds: phase III and launched therapies*. Expert Opin Biol Ther. 2013;13(11):1523-1541.

dosage of StrataGraft skin tissue increased 5-fold across the three cohorts from 44 cm^2 to 220 cm^2. StrataGraft skin tissue remained intact and viable throughout the seven day placement period, suggesting the potential for continued biological activity during longer exposure.

The STRATA2011 study, a follow-up to the STRATA2001 trial, has been conducted as an open-label, dose-escalation, multicenter study evaluating the safety, tolerability, and efficacy of prolonged exposure to increasing dosages of a single application of StrataGraft skin tissue in promoting the healing of complex skin defects with intact dermal elements. In STRATA2011, a single application of StrataGraft tissue was applied to the deep partial-thickness portion of thermal burns and left in place to evaluate whether StrataGraft could promote autologous tissue regeneration thereby reducing or eliminating the need for the surgical harvesting of a donor site for autografting.

The STRATA2011 study included subjects with complex skin defects whose total injury areas range from 3-43% TBSA due to thermal injury. Each subject had two comparable wound areas containing intact dermal elements that were identified and randomized to receive StrataGraft or an autologous skin graft. Thirty subjects were enrolled in this dose escalation study and those in cohort 1 received up to 220 cm^2 while those in cohorts 2 and 3 received up to 440 cm^2 of StrataGraft skin tissue. None of the study sites treated with StrataGraft skin tissue required autografting by day 28 (primary efficacy endpoint). No safety signal was seen following application of StrataGraft skin tissue, and 27 of the 28 per-protocol subjects had complete wound closure of treatment sites at the 3 month study session (primary safety endpoint). The presence of DNA from StrataGraft tissue was assessed after three months to evaluate whether StrataGraft tissue had permanently engrafted. Molecular analysis of patient biopsy samples found no evidence of DNA from cells of StrataGraft tissue.

The STRATA2001 and STRATA2011 studies provided several important clinical findings that have informed the development of this phase II STRATA2014 protocol:

- StrataGraft remains intact, adherent, and viable in complex skin defects for at least seven days, during which time it is anticipated to act as a continuous source of factors that are involved in promotion of autologous tissue regeneration.
- StrataGraft tissue does not permanently engraft and is replaced by the patient's own cells by three months.
- None of the complex skin defects containing intact dermal elements treated with StrataGraft tissue required autografting by day 28 eliminating the need for autografting. These results exceeded the expectations established prior to the study that a 50% reduction in the StrataGraft-treated area that ultimately requires autografting would be clinically meaningful.
- The absence of donor site harvest for areas treated with StrataGraft tissue resulted in significantly less pain and other morbidities as well as improved cosmesis associated with the prospective donor site wounds.

The STRATA2014 study builds upon the data generated in the STRATA2001 and STRATA2011 studies in the same patient population as that for STRATA2001. The proposed study is designed as an open-label, controlled, randomized, multicenter, dose-escalation study evaluating the safety, tolerability, and efficacy of single or multiple applications of StrataGraft skin tissue as an

alternative to donor site harvesting and autografting in promoting the healing of full-thickness complex skin defects. The proposed study population will include subjects with up to 49% TBSA complex skin defects including a full-thickness component. Targeted enrollment for this study is up to 20 subjects with full-thickness complex skin defects requiring surgical excision and autografting. Subjects will be sequentially enrolled in two cohorts of increasing dosage of StrataGraft skin tissue (treatment area per surgical application). Subjects will be eligible to receive up to three applications of StrataGraft skin tissue in the treatment of full-thickness skin defects. In the first cohort, up to 10 subjects will receive an initial surgical application of up to 200 cm^2 of StrataGraft skin tissue. The second cohort will enroll up to 10 subjects who will receive an initial treatment of up to 400 cm^2 of StrataGraft skin tissue. The treatment site will be evaluated to assess the progress of wound healing. Per the clinical judgment of the Clinical Investigator and as necessary to promote complete wound closure, wounds may be treated with up to two additional applications StrataGraft tissue. The cumulative study dosage for cohort 1 may be up to 600 cm^2 and for cohort 2 may be up to 1200 cm^2.

Two comparable wounds in each subject will be identified and the wounds randomized to receive StrataGraft skin tissue or a surgically harvested autologous skin graft. The intrapatient comparator design allows for a matched control to eliminate significant underlying immunologic, physiologic, and scarring variables inherent in this population. Two donor sites will be prospectively designated to provide a source of autograft skin for the control treatment site and, if needed, the StrataGraft treatment site. Both the StrataGraft skin tissue and autograft control will be placed on the treatment sites immediately following surgical excision of non-viable tissue. After the fifth subject in cohort 1 reaches the three month study session, an interim safety report will be generated and reviewed by the Data and Safety Monitoring Board (DSMB). Progression to cohort 2 will take place only after a favorable review of the safety information by the DSMB.

Efficacy will be assessed by evaluating the percent area of the StrataGraft treatment site requiring autografting by 3 months, pain of the donor sites through day 28, and the incidence of complete wound closure at three months supported by clinical photography. Cosmesis of the treatment sites will be evaluated at 3, 6, and 12 months. Additional assessments will include persistence of allogeneic DNA in the StrataGraft-treated sites as well as cosmesis and pain of the donor sites. Safety assessments will include monitoring of AE, vital signs, laboratory safety values, incidence of wound infection, and immunologic responses to StrataGraft tissue.

In addition to routine safety monitoring by the study's medical monitor (MM) and the DSMB, the study will have a Department of Defense (DoD) research monitor whose sole responsibility will be to assess safety. The decision to advance to cohort 2 will be based on an interim safety analysis by the DSMB after the fifth subject in the first cohort has completed the 3 month visit. This time frame will allow for the evaluation of acute, sub-acute, and early chronic AE resulting from prolonged exposure and multiple applications of StrataGraft skin tissue in these subjects. Enrollment into the second cohort will begin only after the DSMB has reviewed the interim safety data and recommended progression. A copy of the interim analysis will also be submitted to the Investigational New Drug (IND) on file for StrataGraft skin tissue.

STUDY DESIGN
Primary clinical endpoints

- Percent area of the StrataGraft treatment site requiring autografting by 3 months
- Wound closure of the treatment sites at 3 months

Secondary clinical efficacy assessments

- Percent of subjects requiring autografting of the StrataGraft treatment site by 3 months
- Incidence of complete wound closure of the treatment sites at 3, 6, and 12 months
- Percent wound closure at 3, 6, and 12 months
- Cosmesis of treatment sites at 3, 6, and 12 months
- Cosmesis of donor sites at 3, 6, and 12 months
- Pain of donor sites measured at days 3, 7, 14, 21, and 28

Secondary clinical safety assessments

- Treatment-emergent AE assessed throughout study duration
- Incidence of infection assessed at all study sessions
- Vital signs assessed at all study sessions
- Safety laboratory values at baseline, day 7, and day 28
- Immunology assessments at baseline, day 28, and 3 months
- Archival plasma and leukocyte collection at baseline and 3 months
- Persistence of allogeneic DNA at 3 months

Statistical methods

- Standard statistical measures
- SAS statistical program

Study Assessments (efficacy)

Assessments	Methods	Schedule of Assessments
Percent area of treatment site requiring autografting	Clinician assessment supported by photodocumentation	Days 3, 7, 14, 21, 28 and 3 months
Wound closure of treatment sites	Clinician assessment supported by photodocumentation	3, 6, and 12 months
Cosmesis of treatment sites	POSAS supported by photodocumentation	3, 6, and 12 months
Cosmesis of donor sites	POSAS supported by photodocumentation	3, 6, and 12 months
Pain of donor sites	Wong-Baker FACES pain rating scale (FPRS)	Days 3, 7, 14, 21, and 28

Study Assessments (safety)

Assessments	Methods	Schedule of Assessments
Blood chemistry and safety laboratory parameters	CMP and CBC with differential	Baseline, 7 and 28 days and as per SOC
Vital signs	Blood pressure, temperature and pulse	Every study session

Immunological evaluations	Panel reactive antibodies (PRA)	Baseline, 28 days, and 3 months
	Anti-bovine serum albumin (BSA) antibodies	Baseline and 3 months
Incidence of infection	Clinical signs and symptoms; laboratory evidence as necessary	Every study session
Presence of allogeneic DNA	PCR of short tandem repeats	Baseline and 3 months
Adverse events	Standard	Throughout study duration

NUMBER OF SUBJECTS

Targeted enrollment for this study is up to 20 study subjects who have full-thickness complex skin defects.

ESTIMATED DURATION OF CLINICAL STUDY

Open Enrollment Period	18 months
Planned Subject Conduct Duration	12 months

Screening period (up to 7 days prior to treatment)

Subjects with full-thickness complex skin defects who meet all inclusion and exclusion criteria would qualify for this study.

INCLUSION CRITERIA

Subject-specific criteria	Study site-specific criteria
• Men and women aged 18-65 years, inclusive • Written informed consent • Sufficient healthy skin identified and reserved as a donor site in the event that the StrataGraft treatment site requires autografting • Complex skin defects of up to 49% TBSA requiring excision and autografting o Total skin defect may consist of more than one wound area	• Full-thickness complex skin defect(s) requiring excision and autografting • Study treatment sites on the torso and limbs may be up to 200 cm^2 in cohort 1 and 400 cm^2 in cohort 2 • For thermal burns only, first excision and grafting of treatment sites

EXCLUSION CRITERIA

Subject-specific criteria	Study site-specific criteria
• Pregnant women and prisoners • Subjects receiving systemic immunosuppressive therapy • Subjects with a known history of malignancy	• Chronic wounds • The face, head, neck, hands, feet, buttocks, perineum, and area over joints

• 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 < 3 months • Participation in the treatment group of an interventional study within the 90 days prior to enrollment	• Treatment sites with exposed tendon or bony prominences • Chemical and electrical burns • Treatment sites directly adjacent to unexcised eschar • Clinical determination of infection at the anticipated treatment sites

TEST PRODUCT

StrataGraft skin tissue contains an epidermal layer comprised of 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 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

Two full-thickness wound areas of comparable depth and area (contiguous or non-contiguous with each other) on the arms, legs, or torso in subjects with complex skin defects will be prospectively identified as treatment 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 excision, the two sites will be randomized to be treated with StrataGraft skin tissue or autograft. Each treatment site must be a single contiguous full-thickness wound area. Any wound outside the study treatment sites will be treated according to the institutional standard of care for that wound.

Subjects in cohort 1 may receive an initial dosage of up to 200 cm^2 each of StrataGraft skin tissue and autograft. Subjects in cohort 2 may receive an initial dosage of up to 400 cm^2 each of StrataGraft skin tissue and autograft. StrataGraft skin tissue is to be meshed 1:1 prior to application. Autograft may be meshed up to 4:1 as per SOC prior to application.

Subjects in both cohorts are eligible to receive up to two additional applications of StrataGraft skin tissue days 6 through 31, inclusive at the discretion of the Clinical Investigator as deemed clinically necessary to promote complete wound closure. The subsequent applications of StrataGraft tissue will be applied to wounds after surgical or non-surgical debridement of the wound areas consistent with standard practice.

REGULATORY INFORMATION AND QUALITY STATEMENT

This study will be conducted under an active IND application 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).