BLA Clinical Review Memorandum

Application Type	Original Application
STN	125730/0
CBER Received Date	Rolling submission: March 31, 2020 Final submission: June 5, 2020
PDUFA Goal Date	February 3, 2021
Division / Office	DCEPT/OTAT
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Rosa Sherafat-Kazemzadeh, MD
Review Completion Date / Stamped Date	February 12, 2021
Supervisory Concurrence	Lei Xu, MD, PhD Tejashri Purohit-Sheth, MD
Applicant	Stratatech Corp.
Established Name	Allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen - dsat
(Proposed) Trade Name	STRATAGRAFT
Pharmacologic Class	Allogeneic cellularized scaffold product, xenograft
Formulation(s), including Adjuvants, etc.	Allogeneic keratinocyte cell line (NIKS), seeded on rat collagen ((b) (4)) conditioned with human dermal fibroblasts ((b) (4))
Dosage Form(s) and Route(s) of Administration	An approximately 100 cm^2 (approximately 8 cm by 12.5 cm) rectangle, which may be trimmed to fit the shape and size of the wound area. For topical application to a surgically prepared wound bed.
Dosing Regimen	One-time application
Indication(s) and Intended Population(s)	Treatment of adults with thermal burns containing intact dermal elements, for which surgical intervention is clinically indicated (deep partial-thickness burns).
Orphan Designated (Yes/No)	Yes

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Glossary

ABA	American Burn Association
AE	Adverse event
BARDA	Biomedical Advanced Research and Development Agency
BLA	Biologics License Application
BSA	Bovine serum albumin
BUN	Blood urea nitrogen
CRF	Case report form
CSR	Clinical study report
DE	Donor Eligibility
DPT	Deep partial-thickness
FDA	Food and Drug Administration
FPRS	FACES pain rating scale
HLA	Human leukocyte antigen
I-DSMB	Intuitional Data Safety Monitoring Board
IND	Investigational New Drug Application
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major Histocompatibility Complex
mITT	Modified Intent-to-Treat
PeRC	Pediatric Review Committee
PI	Prescribing Information
POSAS	Patient and Observer Scar Assessment Scale
PRA	Panel reactive antibodies
PREA	Pediatric Research Equity Act
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SCE	Summary of Clinical Efficacy
SOC	System organ class
	Standard of care
TBSA	Total body surface area
TEAE	Treatment-emergent adverse event
WHO	World Health Organization

1. Executive Summary

STRATAGRAFT (allogeneic cultured keratinocytes and fibroblasts in murine collagen - dsat) is an allogeneic cellularized scaffold product that contains a fully-stratified epithelial layer comprised of differentiated, multilayered, epidermal keratinocytes from a single human donor. STRATAGRAFT is considered to be a xenotransplantation product because the keratinocyte component of STRATAGRAFT was originally derived in the presence of a mouse cell line.

STRATGRAFT is indicated for treatment of adults with thermal burns containing intact dermal elements (deep partial-thickness burns), for which surgical intervention is clinically indicated.

The safety and efficacy of STRATAGRAFT in adults with thermal burns containing intact dermal elements for which surgical intervention is clinically indicated (deep partial-thickness (DPT) burns) was evaluated in two randomized, open-label, intra-patient controlled, multicenter clinical studies of 12 months duration: STRATA2016 and STRATA2011. In both studies, two comparable wound sites of each subject were selected and randomized to receive either topical application of STRATAGRAFT or autograft. Autograft serves as the intra-subject control. Results from STRATA2016 provided the primary evidence of effectiveness. Results from STRATA2011 provided supportive evidence of effectiveness, because the early-phase, dose-escalation safety study is not sufficiently powered, and different primary efficacy endpoints and different definitions of wound closure were used in STRATA2011.

STRATA2016 enrolled 71 adult subjects with acute DPT thermal burns involving 3 to 37% total body surface area (TBSA). The time from burn to study treatment was 1 to 18 days. The range of the STRATAGRAFT treated wound area was 12 to 960 cm^2. The mean age was 44 years (19 to 79 years). Seventy-eight percent of subjects were White and 20% were Black or African-American. Male accounted for 70% of the population.

Efficacy was established on the basis of (1) difference in the percent area of the STRATAGRAFT treatment site and the control autograft treatment site that required autografting by 3 months after STRATAGRAFT or autografting, and (2) the proportion of subjects achieving durable wound closure of the STRATAGRAFT treatment site at 3 months without autograft placement. The endpoint of durable wound closure at 3 months without autograft placement at the STRATAGRAFT treatment site was deemed successful if the lower bound of the 95% confidence interval (CI) was ≥ 50% in the STRATAGRAFT treatment sites. Durable wound closure at 3 months was defined as wound closure at two consecutive study visits at least 2 weeks but no more than 5 months apart and including or encompassing the time point of 3 months. Wound closure of the treatment site was defined as complete skin re-epithelialization and the absence of drainage.

Among the 71 STRATAGRAFT-treated sites, three required autografting to achieve wound closure. Among the 71 autograft-treated sites, two needed repeated autografting to achieve wound closure. Therefore, 4.3% (3/71) of the STRATAGRAFT treatment sites and 102.1% (73/71) of the autograft treatment sites autografted by 3 months. The difference in the percent area of STRATAGRAFT and control autograft treatment sites that required autografting by 3 months was 97.8% ± 16.6% ($p<0.0001$). Two subjects had STRATAGRAFT treatment site autografted, and autograft control study site re-

grafted. Donor site harvest was eliminated in 96% of STRATAGRAFT-treated DPT burns.

The proportion of subjects achieving durable closure of the STRATAGRAFT treatment site at 3 months without autograft placement was 83.1% (95% CI: 74.4, 91.8). The lower bound of the 95% CI was above the pre-defined null threshold of 50%. The proportion of subjects achieving durable closure of the autograft control treatment site at 3 months without additional autograft placement was 86% (95% CI: 77.8, 94.0).

STRATA2011 enrolled 30 adult subjects with acute DPT thermal burns involving 3 to 49% TBSA. The time from burn to study treatment ranged from 3 to 13 days. The size of the STRATAGRAFT treated wound was 52 to 440 cm^2. The mean age was 41 years (21 to 63 years). Ninety-three percent of subjects were White and 7% were Black or African-American. Males accounted for 78% of the population.

Efficacy was evaluated on the basis of (1) the percent area of STRATAGRAFT treatment site requiring autograft by 28 days after STRATAGRAFT treatment, and (2) the proportion of treatment sites that achieved complete wound closure by 3 months. Complete wound closure was defined as ≥95% re-epithelialization in the absence of drainage.

No STRATAGRAFT treatment site required autograft by 28 days. Between 28 days and 3 months, one subject had both the STRATAGRAFT treatment site and the autograft site treated with autograft, and a second subject had 25% of the STRATAGRAFT treatment site autografted. At 3 months, 93.1% of STRATAGRAFT treatment sites and 100% of autograft treatment sites achieved complete wound closure. All STRATAGRAFT treatment sites remained closed when evaluated at 6 months and 12 months after treatment.

The safety database for STRATAGRAFT consists of 119 adult subjects in four randomized, within-subject controlled studies conducted in the United States. Among the 119 subjects, 101 subjects with DPT thermal burn received STRATAGRAFT topically in Studies STRATA2016 and STRATA2011 and 18 subjects with full-thickness complex skin defects received STRATAGRAFT topically in studies STRATA2014 and STRATA2001. The patient population ranged in age from 19 to 79 years (mean age 43 years). Each subject received topical application of STRATAGRAFT at one wound site and either autografting (104 subjects) or cadaver allografts (15 subjects) at the other wound site that serves as the intra-subject control.

The most frequent adverse reactions (incidence ≥ 2%) observed in the 4 studies include pruritus (11%), blister (4%), hypertrophic scar (3%) and impaired healing (3%). No subjects discontinued study participation due to adverse reactions. Overall, the safety profile of STRATAGRAFT with regard to wound-related events, including erythema, swelling, local warmth and wound site infections, was similar to that of autografting in these studies. There were no reports of rejection reaction to STRATAGRAFT. The safety of STRATAGRAFT beyond 12 months was not evaluated in the clinical studies.

STRATAGRAFT is produced from well-characterized human keratinocyte and fibroblast cell banks that contain no detectable pathogens. STRATAGRAFT is considered a xenotransplantation product. STRATAGRAFT may cause hypersensitivity reactions to murine collagen or products containing ingredients of bovine or porcine origin because

STRATAGRAFT product manufacture includes reagents derived from animal materials including rat-tail collagen type I, calf serum, porcine trypsin and purified bovine serum albumin. The layer of NIKS (neonatal foreskin keratinocytes) human keratinocytes in STRATAGRAFT has a known and well characterized chromosomal abnormality that is found to be karyotypically stable during manufacture. *In vivo* evaluation of NIKS keratinocytes in mice demonstrated no tumor formation. There was no persistence of cells of STRATAGRAFT in treated subjects and there have been no documented clinical or histological reports of tumor formation at the site of application. Although the risk of malignancy after use of STRATAGRAFT is thought to be low, this remains a potential risk. However, transmission of infectious diseases or agents by STRATAGRAFT or other potential risks have not been reported in clinical studies.

The reviewed safety data do not warrant a Risk Evaluation and Mitigation Strategies (REMS), or a safety postmarketing requirement (PMR) clinical study. Due to inadequate information regarding viral clearance and inactivation during manufacturing of rat tail collagen, a CMC safety-related PMR is proposed to conduct a more adequate viral inactivation study to more accurately quantify the viral log reduction of the collagen manufacturing process and to ensure the safety of STRATAGRAFT. In addition, the postmarketing risk mitigation plans include product labeling and enhanced pharmacovigilance plan with expedited reporting of serious adverse events. To facilitate tracking of serious adverse event(s) potentially related to the xenotransplantation nature of the product, the Applicant will maintain a patient tracking system to maintain information for all STRATAGRAFT recipients. This information will be provided to the FDA in the periodic safety reports (Periodic Adverse Experience Reports (PAERs)) at quarterly intervals for 3 years from the date of issuance of the biologics license, and then at annual intervals.

In conclusion, thermal burns containing intact dermal elements for which surgical intervention is clinically indicated (deep partial thickness burns) is a serious condition and represents an unmet medical need. The submitted data from an adequate and well-controlled trial (STRATA 2016) and an early-phase controlled trial (STRATA2011) provide substantial evidence of effectiveness for treatment of adults with deep partial thickness thermal burns containing intact dermal elements for which surgical intervention is clinically indicated. Efficacy was demonstrated with respect to rate of complete wound closure at STRATAGRAFT treated sites, and significantly decreased need for autograft in STRATAGRAFT treated sites. The potential serious risks associated with topical application of STRATAGRAFT include hypersensitivity reaction to murine collagen or products containing ingredients of bovine or porcine origin, transmission of infectious diseases and dermatological malignancy. None of these potential risks were observed in clinical studies. The risks can be mitigated through enhanced pharmacovigilance plan, medical management, adequate PI and additional postmarketing measures associated with xenotransplantation nature of STRATAGRAFT without requiring other regulatory measures such as REMS or clinical PMR. The efficacy and safety data in the BLA support a favorable benefit-risk profile for adults with thermal burns, containing intact dermal elements (deep partial-thickness burns), for which surgical intervention is clinically indicated. Therefore, the Clinical Reviewer recommends regular approval of STRATAGRAFT for topical application to a surgically prepared wound bed. The number of STRATAGRAFT constructs applied will vary depending on the size of the wound bed.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Demographic information for subjects in Studies STRATA2016 and STRATA2011 is shown in Table 1.

Table 1. Demographics for STRATA2011 and STRATA2016

	STRATA2011 N = 30	**STRATA2016 N = 71**
Age, mean (SD), year	41.0 (12.10)	43.9 (16.0)
Age range, year	21, 63	19, 70
Age <65 years, n (%)	30 (100)	63 (88.7)
Age ≥65 years, n (%)	0	8 (11.3)
Sex, n (%)		
Male	21 (70.0)	55 (77.5)
Female	9 (30.0)	16 (22.5)
Race, n (%)		
White	28 (93.3)	55 (77.5)
Black or African American	2 (6.7)	14 (19.7)
Asian and Other	0	2 (2.8)
Ethnicity, n (%)		
Hispanic or Latino	4 (13.3)	10 (14.1)
Not Hispanic or Latino	26 (86.7)	61 (85.9)

(Source: BLA 125730/0, Summary of Clinical Efficacy, page 21)

1.2 Patient Experience Data

Patient experience data relevant to this submission are summarized in Table 2.

Table 2 Patient Experience Data Relevant to this Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☒	Patient-reported outcome	6.2.11 Efficacy Analyses 6.2.11.1 Analyses of Primary Endpoint(s) 6.2.11.2 Analyses of Secondary Endpoints Table 12. Summary of Pain at Donor Site through Day 14
☒	Observer-reported outcome	6.1.11.2 Analyses of Ranked Secondary Efficacy Endpoints
☒	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Thermal burns are caused by contact with flames, hot liquids, hot surfaces, and other sources of high heat. Burns are common causes of skin loss/destruction leading to loss of the functions of intact skin and subsequent serious morbidity and mortality. Intact skin serves as an effective barrier to prevent the loss of water vapor from the body, while impeding the entry of chemicals, including toxins or irritants, and to inhibit local infection of the dermis or other underlying tissues. With intact skin, microbes attempting to invade through the skin are captured in and among dying squames that are then sloughed. In addition, the differentiating keratinocytes produce host defense peptides that act locally within the skin to protect against a broad range of microorganisms, fungi, and viruses, and serve as a critical component of innate defenses against infection. The loss of skin leaves the underlying tissues susceptible to infection, which can quickly disseminate and become life-threatening. In addition, significant loss of skin can result in marked disruption of homeostatic function, necessitating continuous fluid resuscitation.

Burns are a leading cause of accidental injury and death in the United States and worldwide. According to the American Burn Association (ABA) data, annually, approximately one million people in the United States seek medical care for burns, over 450,000 serious burn injuries require medical treatment, and approximately 40,000 hospitalizations are related to burn injury. Approximately one third of patients requiring hospitalization for severe skin loss due to burn-related incidences, require surgical intervention, i.e., skin grafting (McDermott, 2016). Between 2011 and 2015, approximately 486,000 fire or burn injuries were seen at Emergency Departments. For burn-related hospital inpatient stays, a considerably higher number of people and also a higher percentage of people die from their burn-related injuries (2.2% of 53,220 total burned inpatients) compared to all other diagnosis requiring hospital inpatient stays (1.9% of 35,544,572 total inpatients; McDermott, 2016).

The depth of the tissue injury and the cutaneous structures involved determine the classification of the burn. Cutaneous burns are commonly classified as: superficial, superficial partial-thickness, deep partial-thickness, full-thickness, and fourth degree burns (Figure 1).

- Superficial or epidermal burns involve only the epidermis and typically heal without medical intervention within one week.

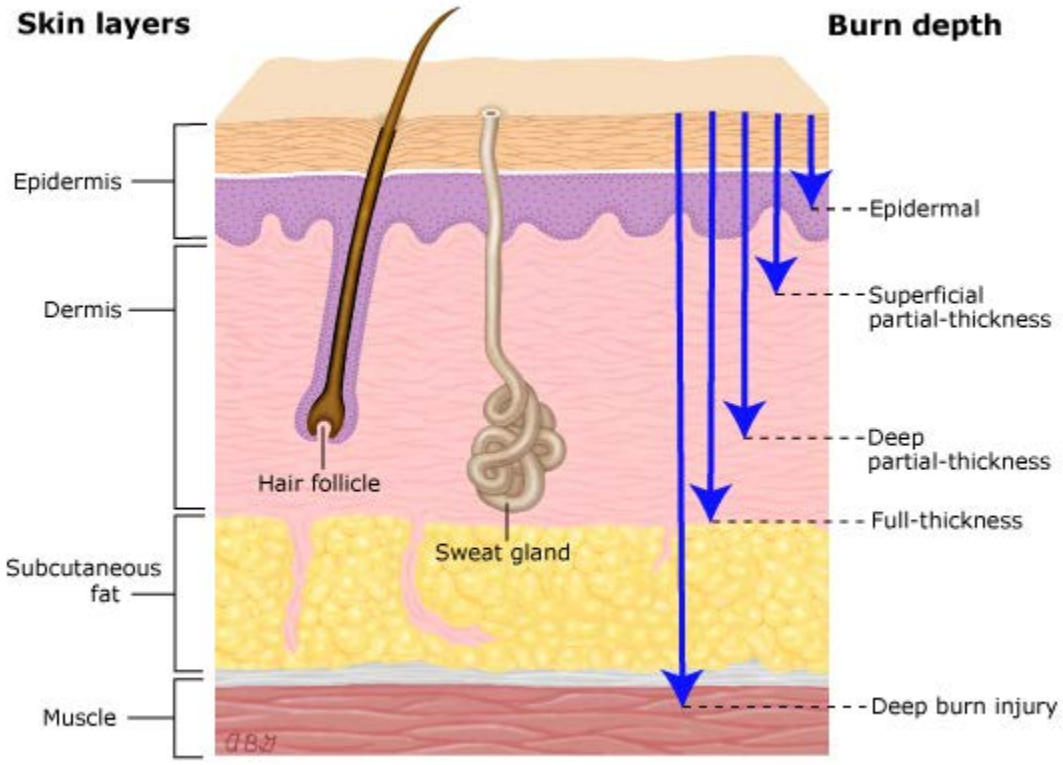
- Superficial partial-thickness burns involve the entire epidermis and approximately the top one-third of the dermis. These burns are painful to both temperature and air, and typically heal within one to three weeks.

- Deep partial-thickness (DPT) burns involve the entire epidermis and approximately the top two-thirds of the dermis. Sensation to pressure, and not temperature or air, remains. These wounds usually require surgical treatment and typically take more than three weeks to heal.

- Full-thickness wounds involve the entire epidermis and dermis. Only sensation to deep pressure remains, and healing without surgical intervention is rare.

- Fourth degree burns are the most severe burns and involve all layers of the dermis and extend into the subcutaneous soft tissue. Current belief is that these types of burns never heal without surgical intervention. Burn wounds typically are not uniform in depth and can evolve over time.

Figure 1. Cutaneous Burn Classification



Epidermal (superficial; first degree) burns involve only the epidermal layer of skin. Partial-thickness burns (second degree) involve the epidermis and portions of the dermis. They are characterized as either superficial or deep. Full-thickness burns (third degree) extend through and destroy all layers of the dermis and often injure the underlying subcutaneous tissue. Deep burn injury (fourth degree) extends into underlying soft tissue and can involve muscle and/or bone.
(Source: UpToDate; Emergency care of moderate and severe thermal burns in adults)

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

For decades the standard treatment for burn wound closure has been early excision of necrotic material and grafting of the burn site. The standard closure of full-thickness burns is a split thickness skin graft from an uninjured donor site on the same patient (autograft). The autograft includes the epidermal layer which regenerates, and a very thin portion of the dermal layer which does not regenerate. In a larger total body surface area (TBSA) burn (usually > 30%), the donor skin has to be meshed and expanded in an attempt to cover a larger surface area with a smaller amount of available skin (Pripotney, 2017).

Deep partial-thickness (DPT) burns extend deep into the dermis and retain intact dermal elements. Without autografting, a DPT wound requires more than 3 weeks to heal. These wounds are often autografted in order to achieve wound closure in a reasonable

timeframe with acceptable functional and cosmetic outcomes. As a result, the treatment of choice for DPT wounds is often the same as that for full-thickness wounds, i.e., excision and autografting.

If a patient does not have enough donor skin to cover the burn wound(s), the physician has limited options. Temporary or partial wound closure may be attempted with a variety of products, including allografts, xenografts and bio-membrane devices, such as Alloderm, Integra, and Biobrane.

2.3 Safety and Efficacy of Pharmacologically Related Products

Currently, two devices are FDA-approved for the treatment of DPT thermal burns.

RECELL Autologous Cell Harvesting (PMA BP170122):

RECELL Autologous Cell Harvesting device is indicated for the treatment of acute thermal burn wounds in patients 18 years of age and older. The RECELL device is a point-of-care device used to produce a cell suspension that can be applied directly to acute partial-thickness thermal burn wounds or in combination with meshed autografting for acute full-thickness thermal burn wounds. The labeling includes precautions stating that the safety and effectiveness of RECELL used alone (i.e., without meshed autograft) have not been established for treatment of partial-thickness burn wounds >320 cm^2, or in patients with >20% TBSA.

Patients with extensive burns may have limited donor sites. RECELL allows for a split thickness autograft to be distributed across a greater surface area than a conventional meshed autograft. RECELL relies on an autograft skin sample that is immediately processed and completely consumed in order to make a single treatment.

Epicel (HDE # BH990200):

Epicel is an aseptically processed wound dressing composed of autologous keratinocytes grown ex vivo in the presence of proliferation-arrested, murine (mouse) fibroblasts. Epicel consists of sheets of proliferative, autologous keratinocytes, ranging from 2 to 8 cell layers thick, referred to as a cultured epidermal autograft. Each graft of Epicel is attached to petrolatum gauze backing with titanium surgical clips and measures approximately 50 cm^2 in area.

Epicel is defined by the Public Health Service (PHS) Guideline on Infectious Disease Issues in Xenotransplantation and FDA as a xenotransplantation product, because it is manufactured by co-cultivation with proliferation-arrested mouse, 3T3 fibroblast feeder cells.

In 2007, Epicel received marketing approval under Humanitarian Device Exemption (HDE) regulations, for use in pediatric and adult patients who have deep dermal or full thickness burns in ≥30% of total body surface area. It may be used in conjunction with split-thickness autografts, or alone in patients for whom split-thickness autografts may not be an option due to the severity and extent of their burns.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

The product is not approved in any country. No foreign clinical data were submitted in the Biologics License Application (BLA).

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Major regulatory milestones for the BLA are summarized in Table 3.

Table 3. Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Date	Milestones
25Oct2001	Pre-IND meeting
7Nov2001	IND 10113 submitted
6May2011	End-of-Phase 1 Type B meeting
21May2012	Orphan Drug designation granted
16Jun2016	Pre-Phase 3 Type B meeting
6Jul2017	RMAT designation granted
23Mar2018	Post-RMAT designation Type B meeting to discuss CMC and clinical issues
4Oct2019	Pediatric Written Response
22Nov2019	Pre-BLA Meeting
5Jun2020	BLA 125730 submitted
31Jul2020	BLA filed, Priority Review
2Oct 2020	BLA 120-day Safety and Efficacy Update received
18Dec 2020	Xenotransplantation product exemption request denied
3Feb2021	PDUFA Action Due Date

BLA, Biologics License Application; CMC, Chemistry, Manufacturing, and Controls; IND, Investigational New Drug application; PDUFA, Prescription Drug User Fee Act; RMAT, Regenerative Medicine Advanced Therapy
(Source: FDA clinical review and BLA 125730 submission)

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The BLA submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty. The BLA was filed on 31 July 2020; no filing issues were identified by any of the review disciplines.

3.2 Compliance with Good Clinical Practices and Submission Integrity

All four studies were conducted in the United States under the Investigational New Drug application (IND) 10113, in accordance with the regulations specified in 21 CFR 312, and were compliant with Good Clinical Practice (GCP) international ethical and scientific quality standards for the design, conduct, recording, and reporting of clinical trials involving human subjects. The clinical trials included provisions for informed consent by all study subjects, and for ethical treatment of study subjects.

During the BLA review, routine Bioresearch Monitoring (BIMO) inspections were conducted at five clinical study sites that participated in Studies STRATA2011 and STRATA2016 (Table 3). Site 5 that participated in Study STRATA2011 was issued a Form FDA 483. The inspections did not reveal any significant problems that impact the integrity of data submitted in the BLA.

Table 4. List of Inspected Clinical Investigator Sites

Entity	Protocol ID	Site #	Study Site Name and Location	Final Classification
Clinical Investigators	STRATA2011	5	University of Colorado Department of Surgery Aurora, CO	Voluntarily Action Indicated
Clinical Investigators	STRATA2011	4	JBSA-Fort Sam Houston in TX	NAI
Clinical Investigators	STRATA2016	1	University of Wisconsin Hospital and Clinics Madison, WI	NAI
Clinical Investigators	STRATA2016	10	Tampa General Hospital Tampa, FL	NAI
Clinical Investigators	STRATA2016	12	University of California Irvine Orange, CA	NAI

NAI: No action indicated
(Source: BLA 125730, Bioresearch Monitoring Final Review Memorandum)

3.3 Financial Disclosures

No significant issues with financial disclosures were identified that could lead to undue bias in the data submitted in support of this BLA (Table 5).

Table 5. Financial Disclosure STRATA2001, STRATA2011, STRATA2014, STRATA2016

Covered clinical studies: 4 • STRATA2001 • STRATA2011 • STRATA2014 • STRATA2016
Was a list of clinical investigators provided? ☒ Yes ☐ No (Request list from applicant)
Total number of investigators identified: 135
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0 Is an attachment provided with details of the disclosable financial interests/arrangements? ☐ Yes ☐ No Is a description of the steps taken to minimize potential bias provided? ☐ Yes ☐ No
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0 Is an attachment provided with the reason? ☐ Yes ☒ No

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

SRATAGRAFT is a viable, bioengineered, allogeneic cellularized scaffold product that contains a fully-stratified epithelial layer comprised of differentiated, multilayered, epidermal keratinocytes from a single human donor. The keratinocytes are grown on a murine collagen matrix (rat-tail collagen type I) embedded with fibroblasts from a second human donor. STRATAGRAFT is produced from well-characterized human keratinocyte and fibroblast cell banks that contain no detectable pathogens. The cells are metabolically active allogeneic NIKS® keratinocytes and dermal fibroblasts.

STRATAGRAFT contains cells from human donors and may potentially transmit infectious diseases or infectious agents, e.g., viruses, bacteria, or other pathogens, including the agent that causes transmissible spongiform encephalopathy (TSE, also known as Creutzfeldt-Jakob disease (CJD) or variant CJD).

STRATAGRAFT is a xenotransplantation product because of an historic exposure of the keratinocyte cells to well-characterized mouse cells. The cell banks have been tested and found to be free of detectable adventitious agents and mouse cells are no longer used in the manufacture of STRATAGRAFT; however, these measures do not entirely eliminate the risk of transmitting infectious diseases and disease agents. Transmission of infectious diseases or agents by STRATAGRAFT has not been reported.

Consultation from the Division of Human Tissue (DHT), Office of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research, FDA, was requested to review donor eligibility (DE) for the cell lines used to manufacture STRATAGRAFT. Both cell lines were generated using neonatal foreskin tissues that were recovered before May 25, 2005. Because NIKS and NHDF are highly processed cell lines from human cells, NIKS and NHDF do not meet the definition of human tissue according to 21 CFR part 1270.3(j). Therefore, 21 CFR part 1270 does not apply to these cell lines recovered before May 25, 2005. As neither part 1270 nor part 1271 applies to these two cell lines, DE requirements are not applicable.

Reviewer Comment

The submission does not include information related to any donor screening or donor testing performed for the skin tissue donors that were used for generating the NIKS and NHDF cell lines.

Although the cell banks have been tested and found to be free of detectable adventitious agents, the product may carry a potential risk of transmitting infectious agents as there may be unknown adventitious agents that were not tested. In addition, there is no FDA approved donor test for transmissible spongiform encephalopathy (TSE, also known as Creutzfeldt-Jakob disease (CJD) or variant CJD). According to the *FDA Guidance for Industry, Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), 2007*, until suitable donor screening laboratory tests become available, donor screening by asking questions to identify donors at increased risk for CJD, is required for HCT/Ps recovered after May 25, 2005. For this product, two donors of skin tissue were not screened for TSE (no donor eligibility (DE) requirement applies to these two donors). Potential risk of transmission of infectious diseases is included in Warnings and Precautions section of the Prescribing Information (PI).

Due to inadequate information regarding viral clearance and inactivation during manufacturing of rat tail collagen, a CMC safety-related PMR was proposed. Please see section 4.6 for details of the CMC PMR.

STRATAGRAFT is considered to be a xenotransplantation product because the NIKS keratinocyte cell line was originally cultured in the presence of the (b) (4) . The cell banks have been tested and found to be free of detectable adventitious agents and mouse cells are no longer used to manufacture STRATAGRAFT.

STRATAGRAFT product manufacture includes reagents derived from animal materials including rat-tail collagen type I, calf serum, porcine trypsin and purified bovine serum albumin. STRATAGRAFT construct is loosely adherent to a supportive polycarbonate

membrane insert and treated in glycerin-containing media. Each cryopreserved STRATAGRAFT construct is supplied with Hold Solution and Hold Dish, which are used for preparing STRATAGRAFT. The Hold Solution is a cell-culture medium that is not supplemented with growth factors.

Reviewer Comment
Allergies to murine collagen or products containing ingredients of bovine or porcine origin is listed as Contraindication in PI. Potential risk of hypersensitivity reaction is included in Warnings and Precautions section of the PI.

4.2 Assay Validation

Please see the CMC review for details.

4.3 Nonclinical Pharmacology/Toxicology

No significant safety or effectiveness issues were identified by the Pharmacology/Toxicology reviewer. Please see the Pharmacology/Toxicology review for details.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

STRATAGRAFT contains metabolically active cells that produce and secrete a variety of growth factors and cytokines which may help healing. STRATAGRAFT does not remain permanently engrafted but is replaced by the patient's own cells over time, reducing the need for autografting to attain definitive closure of the majority of treated wounds.

4.4.2 Human Pharmacodynamics (PD)

The pharmacodynamic effects of STRATAGRAFT are tied to the mechanism of action and the treatment effect of STRATAGRAFT was evaluated in clinical trials as discussed elsewhere in this review.

4.4.3 Human Pharmacokinetics (PK)

The pharmacokinetic effects of STRATAGRAFT are not known; however, given the product type, PK data are not applicable.

4.5 Statistical

The Statistics review team confirmed the results of safety and efficacy endpoints. Please see the statistical review memo for details.

4.6 Pharmacovigilance

As indicated in the FDA Xenotransplantation Exemption Denial Letter to Stratatech dated 18 Dec 2020, the following routine and expanded pharmacovigilance activities will be conducted by the Applicant:

a. Spontaneous adverse event reports received will be reported per 15-day reporting requirements

b. Linkage of electronic medical record and medical claims data to identify events of special interest, and hospitalizations

c. Linkage to the National Death Index (NDI) to obtain mortality data (e.g., date and cause of death)

d. There will be linkages to other databases such as data from the North American Association of Central Cancer Registries (Virtual Pooled Registry)

e. Stratatech will maintain a database to collect comprehensive patient and product information and will provide updates on its database of STRATAGRAFT patient and product information in the periodic safety reports at quarterly intervals for 3 years post-licensure and annually thereafter.

The reviewed safety data do not warrant the need for a Risk Evaluation and Mitigation Strategy (REMS) or a safety clinical postmarketing requirement (PMR) study.

As noted in Section 4.1 above, CMC review team will be requesting the following post-marketing studies as follow:

a. Safety CMC PMR: collagen viral inactivation/clearance
b. PMCs:
    i. (b) (4) testing for final product impurity
    ii. Cell bank issues,(b) (4) test for contaminating cell lines, identity tests for cell banks
    iii. Replacement for (b) (4) assay for (b) (4)
    iv. Replace (b) (4) test with (b) (4)
    v. Annual reporting of lot release testing
c. Future inspectional issues: none identified as of 1/8/2021, but PLI has not been scheduled

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

For evaluation of efficacy, this reviewer focused on data from Study STRATA2016 to provide primary evidence of effectiveness. Efficacy data from Study STRATA2011 are supportive. Because different primary efficacy endpoints and different definitions of wound closure were used in the two studies, integrated evaluation of efficacy was not performed.

For evaluation of safety, data from four completed studies, including studies in adult subjects with DPT thermal burn (Studies STRATA2016 and STRATA2011), and studies in adult subjects with full-thickness complex skin defects (STRATA2014 and STRATA2001) were analyzed and integrated.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The sources for this review are: (1) the licensing application, which includes data from four US studies (Table 6); and (2) Publicly available literature, including PubMed, WHO, UpToDate and American Burn Association (ABA) website.

5.3 Table of Studies/Clinical Trials

Table 6. Summary of Clinical Studies and Data Sources Evaluated in BLA

Study	Study Design	Objectives/ Purpose	Study Treatment	Study Population	Number of Study Sites
STRATA2016 (NCT# 03005106) Completed (n=71)	Phase 3, open-label, controlled, randomized multicenter; US, intra-subject comparator (autograft)	Assess the efficacy and safety of a single application of STRATAGRAFT in the treatment of DPT caused by thermal burns	Up to 1,000 cm^2 cryopreserved STRATAGRAFT (maximum used: 960 cm^2) Single topical application	Subjects aged ≥ 18 years with complex skin defects of 3% to 49% TBSA of DPT caused by thermal burns	12
STRATA2011 (NCT# 01437852) Completed (n=30)	Phase 1b open-label, controlled, randomized multicenter, dose escalation; intra-subject comparator (autograft)	Assess the safety, tolerability, and efficacy of prolonged exposure to increasing amounts of a single application of STRATAGRAFT compared to autograft in the DPT component of complex skin defects due to thermal burns requiring surgical excision and autografting	Cohort 1: up to 220 cm^2 of refrigerated STRATAGRAFT (maximum used: 216 cm^2) Cohort 2: up to 440 cm^2 of refrigerated STRATAGRAFT (maximum used: 440 cm^2 Cohort 3: up to 440 cm^2 of cryopreserved STRATAGRAFT Single topical application maximum used: 440 cm^2)	30 subjects, age ≥18 to 65 years with complex skin defects of 3% to 49% TBSA of DPT caused by thermal burns	6
STRATA2001* (NCT#00618839) Completed (n=15)	Phase-1/2a, open-label, controlled, randomized, comparative, dose-escalation study in full-thickness complex skin defects; intra-subject comparator (cadaver allograft)	First in human study to evaluate the safety and efficacy of temporary placement of STRATAGRAFT as an alternative to cadaver allograft prior to autograft placement	Cohort 1: up to 220 cm^2 refrigerated STRATAGRAFT (maximum used: 60 cm^2) Cohort 2: up to 748 cm^2 refrigerated STRATAGRAFT (maximum used: 232 cm^2) Cohort 3: up to 2244 cm^2 refrigerated STRATAGRAFT (maximum used: 400 cm^2) STRTAGRAFT Single topical application with removal after 7 days	Subjects aged ≥ 18 years with complex skin defects of ≥5% TBSA	2
STRATA2014* (NCT# 03005054) Terminated (n=3 from Cohort 1) Study was closed after completion of Cohort 1 due to difficulty enrolling subjects and limited wound closure.	Phase 2, open-label, controlled, randomized, multicenter, dose escalation in full-thickness complex-skin defects; intra-subject comparator (autograft)	Assess the safety, tolerability, and efficacy of a single or multiple applications of STRATAGRAFT In promoting the healing of excised full thickness complex skin defects resulting from acute traumatic full thickness skin loss, such as thermal burns and degloving injuries	Cohort 1 = Up to 200 cm^2 of STRATAGRAFT; total cumulative dose of up to 600 cm^2 (maximum used [cumulative]: 525 cm^2) Cohort 2 = Up to 400 cm^2 of STRATAGRAFT; total cumulative dose of up to 1200 cm^2. Single or multiple topical applications of STRATAGRAFT.	Subjects aged 18 to 65 years with complex skin defects of up to 49% TBSA	4

* STRATA2001 and STRATA2014 assessed safety and efficacy in subjects with full-thickness complex skin defects; only safety data from these studies are relevant to this submission of STRATAGRAFT for the treatment of deep partial-thickness burns.
(Source: Adapted from BLA 125730/0 Section 5.3)

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

No Advisory Committee meeting was held because initial review of information submitted in the BLA did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

5.4.2 External Consults/Collaborations

No external consultation was requested for the completion of clinical review.

5.5 Literature Reviewed (if applicable)

During review of the BLA, this reviewer consulted FDA regulatory guidance documents, as well as academic literature, for background and context regarding the targeted disease and the mechanism of action of the product. The literature consulted is provided in *References*.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: STRATA2016 (Completed Phase 3 Trial)

Study Title: Phase 3 Open-Label, Controlled, Randomized, Multicenter Study Evaluating the Efficacy and Safety of STRATAGRAFT in Promoting Autologous Skin Tissue Regeneration of Complex Skin Defects due to Thermal Burns that Contain Dermal Elements and for which Excision and Autografts are Clinically Indicated

First subject enrolled: 30 May 2017
Last subject, last visit: 27 Mar 2020
Study database lock date: 01 May 2020

6.1.1 Objectives (Primary, Secondary, etc.)

Primary Efficacy Objective:

- To evaluate whether STRATAGRAFT treatment reduces the need for donor site harvest and autograft transplantation, and whether the STRATAGRAFT-treated sites are durably closed at 3 months.

Secondary Efficacy Objective:

- To evaluate additional efficacy endpoints including: pain and cosmesis of the donor sites, cosmesis of the treatment sites, number of days of hospitalization due primarily to the pain of donor sites, donor site sequelae, scar manipulation therapy of the treatment sites, wound closure of the treatment sites, histologic analyses of the treatment site wound beds, and physician and subject satisfaction of study treatment sites, presence of allogeneic DNA from the STRATAGRAFT at 3 months.

Safety Objective:

- To monitor treatment-emergent AEs (TEAEs) and treatment-emergent serious AEs (SAEs), vital signs, and incidence of wound infection throughout the study duration.

6.1.2 Design Overview

This study was an open-label, multicenter, intra-subject controlled, randomized study to evaluate the efficacy and safety of STRATAGRAFT in the treatment of acute DPT thermal burns that contain intact dermal elements for which surgical excision and autografting are clinically indicated. A total of 71 adult subjects (≥ 18 years old) with DPT thermal burns, involving 3 to 49% of TBSA, were enrolled. Following surgical debridement of nonviable tissues, two areas of comparable depth and similar potential for experiencing mechanical shear forces were identified on each subject and randomized to receive either a single topical application of STRATAGRAFT on one treatment area or autograft on the other area.

In addition, two areas of healthy skin of each subject were identified and designated to provide a source of autograft for the autograft treatment site and, if needed, for the STRATAGRAFT treatment site. An autologous skin graft was surgically harvested from one of the donor sites and was meshed up to 4:1 per standard of care (SOC) and secured in place at the autograft treatment site using staples, sutures, or tissue adhesive.

For STRATAGRAFT treatment sites, the STRATAGRAFT construct was meshed 1:1, trimmed to fit the wound as necessary, and secured in place using staples, sutures, or tissue adhesive.

The following co-primary efficacy endpoints were evaluated:

a. The percent area of the STRATAGRAFT treatment site that is autografted by 3 months,

b. The proportion of subjects achieving durable wound closure of the STRATAGRAFT treatment site at 3 months without autograft placement. Durable wound closure at 3 months was defined as wound closure at 2 consecutive study visits at least 2 weeks but no more than 5 months apart and including or encompassing the Month 3 time point.

Ranked secondary efficacy endpoints included the difference between the donor site for STRATAGRAFT treatment site and the donor site for autograft treatment site in:

a. The average pain intensity [score] through Day 14 based on the FACES pain rating scale (FPRS),

b. The cosmesis at 3 months based on observer Patient and Observer Scar Assessment Scale (POSAS) total score,

c. The cosmesis at 12 months based on observer POSAS total score.

The study follow-up duration was 12 months.

6.1.3 Population

Subjects were considered for enrollment after surgical excision, and confirmation of burn depth and the presence of intact dermal elements.

Inclusion Criteria:

- Men and women aged at least 18 years.
- Complex skin defects of 3 to 49% TBSA due to Thermal burn(s) with intact dermal elements for which excision and autografts are clinically indicated.
- First excision and grafting of study treatment sites.
- Total of both study treatment areas can be up to 2000 cm^2.
- Thermal burn(s) on the torso, and upper or lower extremities.

Exclusion Criteria:

- 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.
- Subjects receiving systemic immunosuppressive therapy.
- Subjects with a known history of malignancy.
- Preadmission insulin-dependent diabetic subjects.
- Expected survival of less than 3 months.

Reviewer Comment:
The effectiveness of STRATAGRAFT for treatment of DPT thermal burns in diabetic or immune-suppressed patients was not assessed.

6.1.4 Study Treatments or Agents Mandated by the Protocol

For each subject, following excision of nonviable tissue, two treatment sites that contained intact dermal elements and were up to 1,000 cm^2 each on the upper or lower extremities or torso were identified. The selected treatment sites were of comparable depth and had similar potential for experiencing mechanical shear forces post-grafting.

Prior to randomization, the two identified treatment sites were labeled as sites A and B. Treatment site A was always anterior, superior/proximal, lateral or to the subject's right. Treatment site B was always posterior, inferior/distal, medial or to the subject's left. The two sites were randomized to receive:

1. up to 1,000 cm^2 STRATAGRAFT, or
2. up to 1,000 cm^2 autologous skin graft.

The STRATAGRAFT treatment site could be the same size as the autograft control site or up to twice the size of the autograft control site.

6.1.5 Directions for Use

STRATAGRAFT construct is an approximately 100 cm^2 (approximately 8 cm by 12.5 cm) rectangle. It is for topical application to a surgically prepared wound bed.

STRATAGRAFT construct may be trimmed to fit the shape and size of the wound area. The surface area of the construct to be applied should be equal to the surface area of the wound to be treated. Multiple constructs may be applied to cover large wound areas. If multiple constructs are required to cover the wound area, the STRATAGRAFT constructs should abut without overlapping. Each construct is for application to a single subject only.

6.1.6 Sites and Centers

Study STRATA2016 was conducted at 12 study sites in the United States.

6.1.7 Surveillance/Monitoring

The following wound assessments were completed by the clinician throughout the study as outlined below:

- Treatment site assessment: The primary dressing will be removed on Day 7 ± 1 and may be reapplied per clinician judgment. Secondary dressings will be changed on Days 3, 7 ± 1, 14 ± 2, and 28 ± 3, and as needed for as long as deemed clinically necessary.
- Donor site assessment

A summary of study assessments and the timeline of study procedures are provided in Table 7 and Table 8.

Table 7. Study Assessments, STRATA2016

Assessments	Methods	Schedule of Assessments
Wound closure of the treatment sites	Clinician assessment supported by photo documentation	Day 28 as well as 2, 3, 4, 6 and 12 months
Percent area of the treatment sites autografted	Clinician assessment supported by photo documentation	Days 3, 7, 14, 28 as well as 2, 3, 4, and 6 months
Pain of donor sites	Wong-Baker FACES pain rating Scale (FPRS)	Days 3, 7, 14 and 28
Cosmesis of donor sites	POSAS supported by photodocumentation	Days 3, 4, 6 and 12 months
Cosmesis of treatment sites	POSAS supported by photodocumentation	Days 3, 4, 6 and 12 months
Adverse events, including treatment-emergent adverse-events	Standard	Throughout study duration
Vital signs	Blood pressure, temperature and pulse rate	Every study session
Incidence of infection	Clinical signs and symptoms; laboratory evidence as needed	Every study session
Concomitant medications	Standard	Every study session
Safety laboratory values	Comprehensive metabolic panel (CMP) & complete blood count (CBC) with differential	Baseline, days 7 and 28
Immunological evaluations	Panel reactive antibodies (PRA)	Baseline, days 28 and month 3
Immunological evaluations	Anti-bovine serum albumin (BSA) antibodies	Baseline and month 3
Histologic wound bed analysis	For cellular integrity and tissue architecture	Study session #1
Donor site complications	Clinician assessment	Days 3, 7, 14, 28, month 2, 3, 4, 6, 12
Archival plasma and leukocytes	Whole blood processed to collect plasma and leukocytes	Baseline and month 3
Presence of allogeneic DNA	(b) (4)	Baseline and 3 months

(Source: Adapted from STRATA2016, phase 3 Clinical Protocol, Version 2.0, May 30, 2019)

Table 8. Procedures Schedule, STRATA2016

Study Session	**Screening**	**Study Session #1**	**Study Session #2**	**Study Session #3**	**Study Session #4**	**Study Session #5**	**Study Session #6**	**Study Session #7**	**Study Session #8**	**Study Session #9**	**Study session #10**
Treatment Period		**Day 0**	**Day 3**	**Day 7 +/- 1 day**	**Day 14 +/- 2 days**	**Day 28 +/- 3 days**	**Month 2 +/- 7 days**	**Month 3 +/-14 days**	**Month 4 +/- 14 days**	**Month 6 +/- 1 month**	**Month 12 +/- 1 month**
Informed consent	X										
Medical history & physical	X										
Pregnancy test	X										
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Infection assessment	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Concomitant procedures		X	X	X	X	X	X	X	X	X	X
Reason for hospitalization [a]		X	X	X	X	X	X	X	X	X	X
Impediments to wound healing			X	X	X	X	X	X	X	X	X
Safety laboratory tests		X		X		X				X	
PRA screen		X				X		X			
Anti-BSA antibody screen		X						X			
Archival blood samples		X						X			
Allogeneic DNA samples		X						X			
Histological wound bed assessment		X									
STRATAGRAFT application		X								X	
AE/SAE assessment	X	X	X	X	X	X	X	X	X	X	
Photography of treatment sites		X	X	X	X	X	X	X	X	X	X
Photography of donor sites		X						X	X	X	X
Autografting assessment			X	X	X	X	X	X	X	X	X
Pain of study donor sites			X	X	X	X					
Donor site sequalae and complications			X	X	X	X	X	X	X	X	X
Wound closure						X	X	X	X	X	X
Pain of donor sites			X	X	X	X					
Cosmesis of treatment and donor sites								X	X	X	X
Subject satisfaction survey				X				X	X	X	X
Physician satisfaction survey								X	X	X	X
Scar manipulation therapy										X	X
Consent for contact											X

[a] To be performed on each day of inpatient hospitalization starting at treatment Day 0.
(Source: Adapted from STRATA2016, phase 3 Clinical Protocol, Version 2.0, May 30, 2019)

6.1.8 Endpoints and Criteria for Study Success

Co-primary efficacy endpoints:

- The difference in the percent area of the STRATAGRAFT treatment site and control autograft treatment site that is autografted by 3 months

- The proportion of subjects achieving durable wound closure of the STRATAGRAFT treatment site at 3 months without autograft placement. Durable wound closure at 3 months was defined as wound closure at 2 consecutive study visits at least 2 weeks but no more than 5 months apart and including or encompassing the Month 3 time point. (Note: The 5-month window allows for flexibility in scheduling the study visit at Month 6.) Wound closure of the treatment site was defined as complete skin re-epithelialization and the absence of drainage.

Ranked secondary efficacy endpoints:

1. The difference between the STRATAGRAFT and autograft donor sites in the average pain intensity through Day 14 based on the FPRS,
2. The difference between the STRATAGRAFT and autograft donor site cosmesis at 3 months based on observer POSAS total score,
3. 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 STRATAGRAFT at 3 months.

Exploratory Efficacy Endpoints:

- The difference between the number of days of hospitalization due primarily to pain of the STRATAGRAFT donor site as compared to autograft donor site.
- The difference in the proportion of subjects experiencing donor site sequelae at the STRATAGRAFT donor site as compared to the autograft donor site as classified by the investigator.
- Subject satisfaction with the treatment sites at Day 7 and 3, 4, 6, and 12 months.
- Physician satisfaction with the treatment sites at 3, 4, 6, and 12 months.
- The need for manual manipulation at each treatment site at 6 and 12 months.
- The difference in the proportion of subjects with wound closure at the STRATAGRAFT treatment site and the autograft treatment site irrespective of the need for subsequent autografting at 3, 4, 6, and 12 months.
- Summary of donor and treatment site patient and observer POSAS assessments at 3, 4, 6 and 12 months.

Reviewer Comment:
For the efficacy assessment, this review primarily focused on the co-primary efficacy endpoints.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Study Hypothesis:
For the first primary endpoint of percent area of the STRATAGRAFT treatment site and the autograft treatment site that was autografted by month 3, the null hypothesis was

there was no treatment difference. The null hypothesis was proposed to be compared between the STRATAGRAFT and autograft treatment sites using the Wilcoxon Signed Rank test.

For the second primary endpoint of proportion of subjects whose STRATAGRAFT treatment site is durably closed at Month 3 without autografting. Because the control subjects were all autografted, the null hypothesis is that at least 50% of the subjects' STRATAGRAFT treatment sites are durably closed at Month 3 without autografting. The lower confidence bound of this proportion is postulated to be ≥50%.

Both primary endpoints have to be statistically significant in order to succeed. (The significance level for both analyses was set at 1-sided 0.025.)

Sample Size:
The sample size was based on the goal of detecting the difference in the percent area of the STRATAGRAFT treatment site and control autograft treatment site that was autografted by Month 3, and the proportion of subjects whose treatment site was durably closed at Month 3 without autografting.

The sample size assumptions and calculations were based on data from STRATA2011. It was estimated that a total sample size of approximately 70 subjects was needed in order to achieve at least 80% power for both statistical tests.

Missing Data:
For the first primary endpoint, the primary method for imputing missing data used the cumulative sum of percent area of each study treatment site autografted for all non-missing sessions on or before Month 3.

For the second primary endpoint, subjects who did not provide evaluable data for 2 wound evaluations meeting these criteria were imputed as having failed both on the autograft treatment site and on the STRATAGRAFT treatment site. This provided a conservative estimate of the success rate of treatment.

6.1.10 Study Population and Disposition

Subjects with DPT thermal burns, containing intact dermal elements for which surgical intervention is clinically indicated, were enrolled and treated.

6.1.10.1 Populations Enrolled/Analyzed

The Intent-to-Treat (ITT) population comprised all subjects with randomized study treatment sites.

Since randomization occurs intraoperatively following excision of the burn site, treatment misallocations could occur. In the event that the randomization code received was not followed, the modified Intent-to-Treat (mITT) population was defined by wound sites as treated. In the event that donor sites other than those prespecified were harvested, mITT was defined by donor sites as harvested. All efficacy analyses were performed on the mITT population.

The safety population consisted of all study subjects who received any amount of STRATAGRAFT, regardless of follow-up status. All safety analyses were performed on this population.

Per-Protocol (PP) population: All subjects who had no major protocol violations during the study.

6.1.10.1.1 Demographics
The majority of subjects were male (77.5%) and White (77.5%). Eight subjects were 65 years of age and older. Key demographic characteristics are summarized in Table 9.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Baseline treatment site characteristics of STRATA2016 are summarized in Table 9.

Table 9. Summary of Key Demographic and Baseline Treatment Site Characteristics and Baux Scores STRATA2016

Characteristic	**STRATA2016 N=71**
Age, mean (SD), year	43.9 (16.0)
Age range, year	19, 70
Age <65 years, n (%)	63 (88.7)
Age ≥65 years, n (%)	8 (11.3)
Sex, n (%)	
Male	55 (77.5)
Female	16 (22.5)
Race, n (%)	
White	55 (77.5)
Black or African American	14 (19.7)
Asian and Other	2 (2.8)
Ethnicity, n (%)	
Hispanic or Latino	10 (14.1)
Not Hispanic or Latino	61 (85.9)
TBSA of 2nd and 3rd degree burns combined (%), Mean (SD)	12 (8.4)
Baux score, Mean (SD)	55.9 (17.7)
Size of STRATAGRAFT treatment area, n (%)	
<250 cm^2	47 (66.2)
≥250 to <500 cm^2	18 (25.4)
≥500 cm^2	6 (8.5)
STRATAGRAFT wound area (cm^2), Mean (SD)	240 (202.2)
Autograft wound area (cm^2), Mean (SD)	220 (244.2)

(Source: Adapted from BLA125730; Summary of Clinical Efficacy, page 22)

Concomitant usage of silver-containing antimicrobials, sulfamylon (mafenide acetate) and other investigational agents were prohibited.

6.1.10.1.3 Subject Disposition
A total of 71 subjects were enrolled and received STRATAGRAFT (Table 10):

- 51 subjects completed 12-month study,
- 20 subjects discontinued the study.

All 71 subjects were included in the Intent-to-Treat (ITT), modified ITT (mITT), and Safety Populations.

The randomization code received was followed, therefore the ITT and mITT Populations are identical for the co-primary efficacy evaluations.

Not all donor sites used were those that were prespecified and, therefore, the ITT and mITT Populations are not identical for those endpoints assessing donor site characteristics.

Table 10 Subject Disposition

	STRATA2016 N=71 n (%)
Subjects Screened	88
Subjects Who Failed Screening	17
Subjects Enrolled in the Study (ITT)	71
Subjects in the mITT Population	71 (100)
Subject in the PP population	65 (91.5)
Subjects who Completed Durable Wound Closure Assessment at Month 3	64 (90.1)
Subjects who Completed Durable Wound Closure Assessment at Month 6	59 (83.1)
Subjects who Completed Donor Site POSAS at Month 3	61 (85.9)
Subjects who Completed Durable Wound Closure Assessment at Month 12	51 (71.8)
Subjects who Discontinued the Study	20 (28.2)
Reason for Discontinuation	
Lost to follow-up	16 (22.5)
Death	2 (2.8)
Adverse Event	1 (1.4)
Investigator Decision	1 (1.4)

* Comparable numbers (0 to 1) per cohort had a major protocol deviation and were removed from the PP population.
(Source: Adapted from BLA 125730/0, Integrated Summary of Efficacy/Safety, page 77 and page 80)

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Co-Primary Endpoints

Co-Primary Endpoint #1 Analysis: The difference in the percent area of the STRATAGRAFT treatment site and control autograft treatment site that is autografted by 3 months

Table 11 summarizes the difference in the percent area of the STRATAGRAFT treatment and control autograft treatment sites that were autografted by 3 months. Among the 71 STRATAGRAFT-treated sites, three required autografting to achieve wound closure. Among the 71 autograft-treated sites, two required repeated autografting to achieve wound closure. Therefore, 4.3% (3/71) of the STRATAGRAFT treatment sites and 102.1% (73/71) of the autograft treatment sites autografted by 3 months. The mean

difference in percent area autografted by 3 months was 97.8%, with a standard deviation (SD) of 16.6%. Of note, two subjects needed autograft for the STRATAGRAFT treatment site, and additional autograft at the autograft treatment site. Donor site harvest was eliminated in 96% (68/71) of STRATAGRAFT-treated sites.

Table 11. Summary of Percent Area of Treatment Site Requiring Autografting by 3 Months

Percent area Autografted by 3 Months	STRATAGRAFT Treatment Site N=71	Autograft Treatment Site N=71	Difference (Autograft − STRATAGRAFT) N=71
Mean (SD)	4.3 (21.6)	102.1 (13.1)	97.8 (16.6)
95% CI	0, 9.4	99, 105.2	93.8, 101.7
		P value*	<0.0001

* P value from one-sided Wilcoxon Signed Rank Test.
(Source: Adapted from BLA125730/0; Summary of Clinical Efficacy, page 27)

Co-Primary Endpoint #2: The proportion of subjects achieving durable wound closure of the STRATAGRAFT treatment site at 3 months without autograft placement

Durable wound closure at 3 months was defined as wound closure at two consecutive study visits that were at least 2 weeks but no more than 5 months apart and including or encompassing the Month 3 timepoint. The co-primary endpoint of durable wound closure at 3 months without autograft placement at the STRATAGRAFT treatment site was deemed successful if the lower bound of the 95% confidence interval (CI) was ≥ 50% across the study population.

Fifty-nine subjects (83.1%; 95% CI: 74.4, 91.8) achieved durable wound closure of the STRATAGRAFT treatment site at 3 months without autografting. The lower bound of the 95% CI was above the pre-defined null threshold of 50%. Sixty-one subjects (86%; 95% CI: 77.8, 94.0) achieved durable closure of the autograft control treatment site at 3 months without additional autograft placement.

Reviewer Comment:
Assessment of durable wound closure at STRATAGRAFT treatment site was not based on comparison with the outcome at the control treatment site. However, the percentage of subjects that achieved durable wound closure seems comparable between STRATAGRAFT and autograft treatment sites.

6.1.11.2 Analyses of Ranked Secondary Efficacy Endpoints

Secondary Endpoint #1: Pain at Donor Site Through Day 14

Pain at the donor site was assessed using the 5-point Wong-Baker FACES pain rating scale (FPRS) (0=no pain to 5=worst pain) at Days 3, 7 and 14. One subject had no data collected at any of the three time points because the subject was intubated and sedated.

The difference between the STRATAGRAFT and autograft donor sites in the average pain intensity score through Day 14 based on the FPRS was 2.4 ±1.3 ($p<0.0001$). Table 12 summarizes the results.

Table 12. Summary of Pain at Donor Site through Day 14

N=70	STRATAGRAFT Donor Site	Autograft Donor Site	Difference (Autograft - STRATAGRAFT)
Mean (SD)	0.15 (0.54)	2.55 (1.3)	2.40 (1.31)
Median (Min, Max)	0 (0, 4.0)	2.44 (0, 5.0)	2.33 (0, 5.0)
		P value	<0.0001

(Source: Adapted from BLA125730; Summary of Clinical Efficacy, page 31)

Reviewer Comment:
All autograft donor sites were harvested on Day 0. The STRATAGRAFT donor site was the donor site prospectively identified as a source of tissue for potential autografting of the STRATAGRAFT treatment site if necessary. Only one subject required autografting of the STRATAGRAFT treatment site by Day 14 and the same subject required additional autografting of the autograft treatment site by Day 14. Otherwise, the comparison of the pain at the harvested autograft donor site was made to the pain at an intact skin area, allocated as a source of tissue for potential autografting of the STRATAGRAFT treatment site.

Secondary Endpoint #2: Donor Site Cosmesis at Month 3

Donor site cosmesis was assessed with the Patient and Observer Scar Assessment Scale (POSAS) by an observer. The scale consists of six items (vascularization, pigmentation, thickness, relief, pliability, and surface area). Each item is scored numerically on a 10-point scale to measure scar quality, where 1 is normal skin and 10 is the worst scar imaginable. The total score is the sum of the scores for 6 items.

Table 13 summarizes the difference between the STRATAGRAFT and autograft donor site cosmesis at Month 3 based on observer assessments using the POSAS. A lower number represents a more favorable outcome.

Table 13. Summary of Donor Site POSAS Score at Month 3

N=88	STRATAGRAFT Donor Site	Autograft Donor Site	Difference (Autograft - STRATAGRAFT)
Mean (SD)	1.1 (0.32)	2.8 (1.44)	1.8 (1.48)
		P value*	<0.0001

*P value from 1-sided, paired t-test on the difference (Autograft - STRATAGRAFT). Missing total score data were imputed using a multiple imputation analysis assuming a monotone missing data pattern. A linear regression model with ethnicity, race and age as predictive variables was used in the imputation.
(Source: Adapted from ISE/ISS STRATA2016 Addendum, table 14.2.4.1, page 77)

Reviewer Comment:
Donor site cosmesis assessed by patient and observer at Month 3 favored STRATAGRAFT. At month 12, the difference in cosmesis was not statistically significant anymore. Of note, only 3 STRATAGRAFT donor sites were harvested for autograft.

Secondary Endpoint #3: Treatment Site Cosmesis at Month 12

Treatment site cosmesis assessed by patient and observer at month 12 is summarized in Table 14. The cosmesis was similar between STRATAGRAFT treated sites and autograft treated sites.

Table 14: **Summary of Treatment Site POSAS Score at Month 12**

N=48	STRATAGRAFT Donor Site	Autograft Donor Site	Difference (Autograft - STRATAGRAFT)
Mean (SD)	2.6 (1.66)	2.7 (1.69)	0.1 (1.83)
		P value	0.319

(Source: Adapted from ISE/ISS STRATA2016 Addendum, table 14.2.4.2, page 80)

Reviewer Comment:
All three secondary endpoints assessed the difference between the potential donor site for STRATAGRAFT treatment site and the donor site for autograft treatment site. Since majority of the STRATAGRAFT treatment sites did not need autografting, those potential donor sites were intact.

6.1.11.3 Subpopulation Analyses

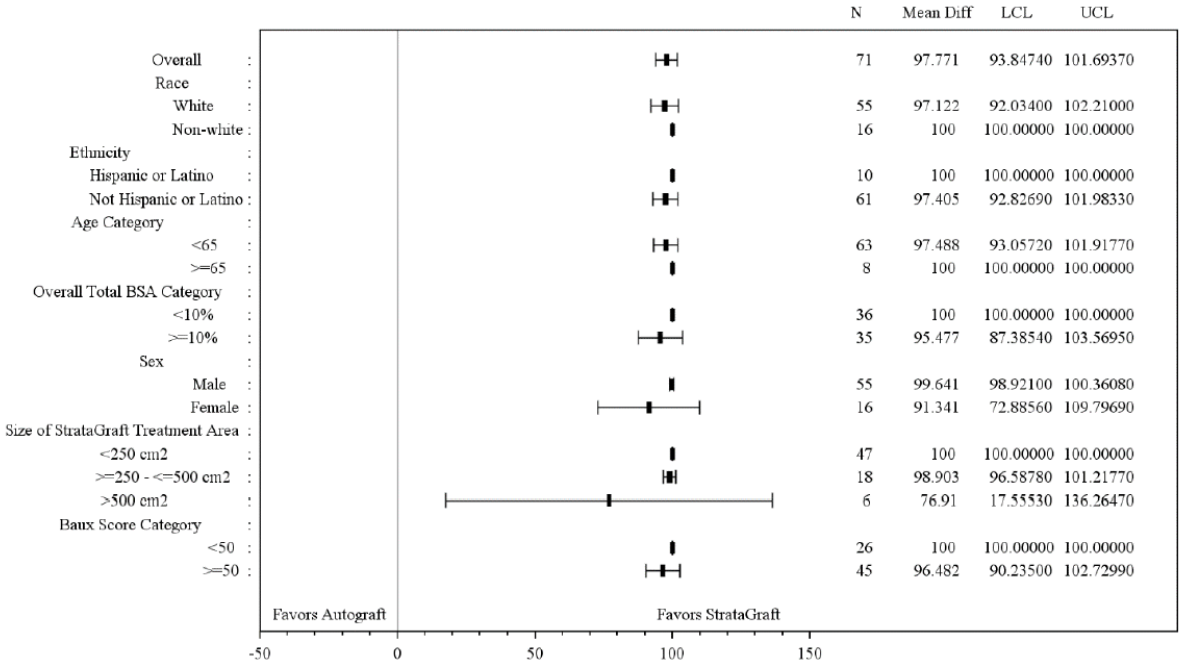
Each co-primary endpoint was analyzed for the following subgroups:

- Race (white, non-white),
- Ethnicity (Hispanic, non-Hispanic),
- Age (18-64, ≥65),
- Burn size in percentage of TBSA (<10%, ≥10%),
- Sex (female, male),
- Size of the STRATAGRAFT treatment area (<250 cm^2, 250 to 500 cm^2, >500 cm^2),
- Baux score (<50%, ≥50%)

Co-Primary Endpoint #1

A forest plot of the percent area of treatment sites requiring autografting by 3 months by different subgroups is provided in Figure 2.

Figure 2. Difference (Autograft – STRATAGRAFT) in Percent Area Autografted by Month 3

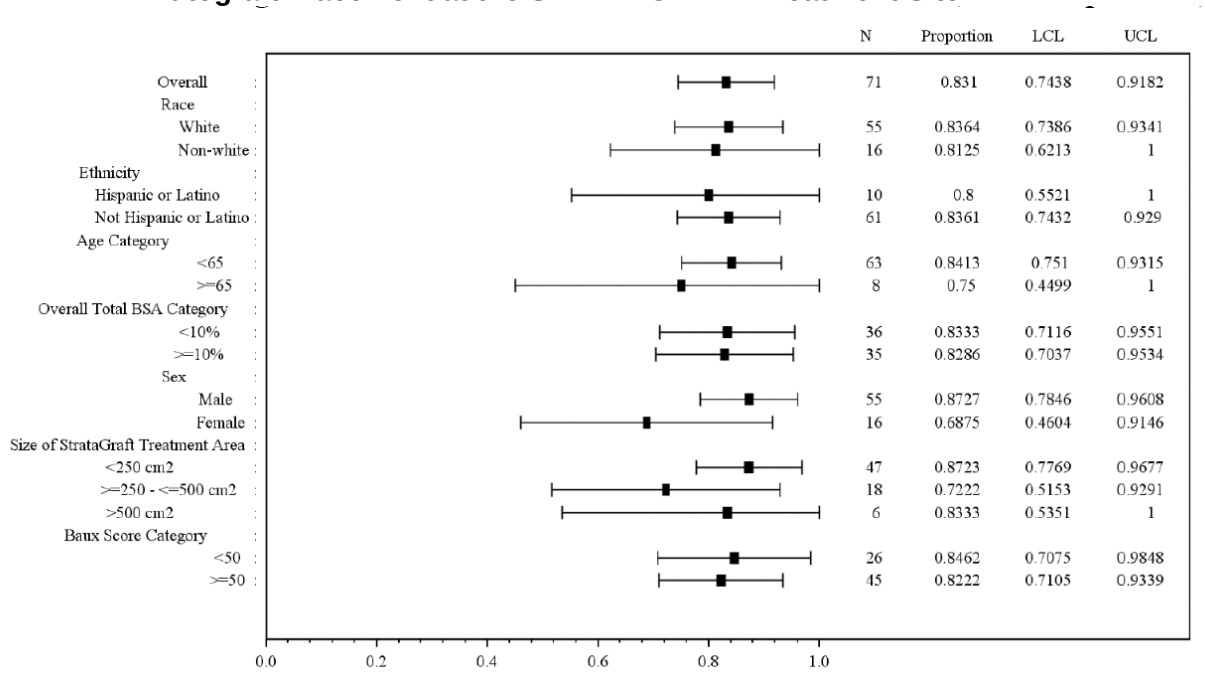


(Source: Adapted from BLA125730; STRATA2016 CSR, figure 4, page 55)

Co-Primary Endpoint #2:

A forest plot of durable wound closure at 3 months by different subgroup is shown in Figure 3.

Figure 3 Proportion of Subjects with Durable Wound Closure at Month 3 Without Autograft Placement at the STRATAGRAFT Treatment Site



(Source: Adapted from BLA125730; STRATA2016 CSR, figure 5, page 59)

Reviewer Comment

Durable wound closure at 3 months without autograft placement at the STRATAGRAFT treatment site was deemed successful if the lower bound of the 95% CI was ≥ 50% across the study population.

The lower bound of the 95% CI for subjects age 65 years and older was 0.449. The number of subjects aged 65 years and older (N=8) was not sufficient to determine whether they responded differently from younger subjects.

The lower bound of the 95% CI for female subjects was 0.460. The number of female subjects (N=16) was not sufficient to determine whether they responded differently from male subjects.

The proportion of subjects with durable wound closure at 3 months at STRATAGRAFT treatment sites without autograft placement in evaluable subgroups (race, sex, ethnicity, age, TBSA, STRATAGRAFT treatment area, and Baux scores), were in general consistent with the results in the overall STRATA2016 population.

6.1.11.4 Dropouts and/or Discontinuations

Twenty subjects discontinued study (Table 10).

6.1.11.5 Exploratory and Post Hoc Analyses

Subjects with Durable Wound Closure at Month 3 Assessed at Month 6

As part of the STRATA2016 exploratory analyses, 59 subjects were evaluated for wound closure at Month 6. Of these 59, 58 subjects (98.3%) had treatment sites that were completely closed at Month 6. One subject had 95% wound closure at Month 6.

However, not all of the 58 subjects with wound closure at Month 6 had achieved durable wound closure at Month 3 without autografting. In total, 54 subjects had durable wound closure at Month 3 without autografting and had evaluable data for Month 6. All 54 subjects had continued wound closure from Month 3 to Month 6 without autografting.

Of the three subjects who underwent autografting at the STRATAGRAFT treatment sites, two had durable wound closure, and one died before achieving durable wound closure.

6.1.12 Safety Analyses

6.1.12.1 Methods

Adverse events (AEs) were coded using MedDRA Version 19.1.

The Safety Population included all subjects who received STRATAGRAFT in the study, regardless of follow-up status.

All AEs analyzed in the safety database were treatment-emergent adverse events (TEAEs), which refer to AEs with an onset date and time equal to or after the placement of STRATAGRAFT or those events for which the onset date and time were before the placement of STRATAGRAFT but worsened after the placement of STRATAGRAFT.

TEAEs were considered related (i.e., adverse reactions) if they were possibly or probably related based on temporal sequence between administration and the event, a biologically plausible relationship, or the lack of an alternative explanation for the event.

The severity of AEs was graded according to the following definitions:

- Mild - The subject experiences awareness of symptoms but these are easily tolerated or managed without specific treatment.

- Moderate - The subject experiences discomfort enough to cause interference with usual activity, and/or the condition requires specific treatment.

- Severe - The subject is incapacitated with inability to work or do usual activity, and/or the event requires significant treatment measures.

6.1.12.2 Overview of Adverse Events

There were 71 subjects enrolled in this study, of which 57 (80.3%) reported 266 treatment emergent adverse events (TEAEs). Table 15 summarizes the TEAEs occurring in at least 2% of subjects at STRATAGRAFT, autograft or donor site.

Of the 57 subjects reporting TEAE(s), 10 (17.5%) experienced 21 serious adverse events (SAEs). None of the SAEs were assessed as related to STRATAGRAFT. There were 2 deaths (2.8%) reported during the study, both assessed by reviewer as unrelated to STRATAGRAFT.

Of subjects reporting a TEAE, 25 (43.8%) experienced a TEAE that was assessed as related to STRATAGRAFT. The most frequently reported adverse reactions by ≥5% of

subjects were pruritus (15.5%) and blister (5.6%). All other TEAEs were reported by 3 or fewer subjects.

Most TEAEs were mild or moderate in severity. One subject had a mild STRATAGRAFT treatment site infection that resolved with antibiotic treatment between study visits. One subject discontinued the study due to an SAE of craniocerebral injury more than 6 months after placement of tissue, which was assessed as unrelated.

Table 15. Treatment-emergent Adverse Events Reported by ≥2% of Subjects, Presented by Treatment Site Location

	STRATAGRAFT Treatment Site	Autograft Treatment Site	Other than STRATAGRAFT or Autograft Treatment Sites
# of Subjects with at least One TEAE	**43 (60.6%)**	**27 (38%)**	**51 (71.8)**
Pruritus	20 (28.2%)	12 (16.9)	11 (15.5%)
Hypertrophic scar	9 (12.7%)	3 (4.2%)	4 (5.6%)
Blister	6 (8.5%)	0 (0%)	4 (5.6%)
Pain	5 (7%)	3 (4.2%)	5 (7%)
Neuralgia	4 (5.6%)	3 (4.2%)	5 (7%)
Excessive granulation tissue	3 (4.2%)	0 (0%)	1 (1.4%)
Graft complication (STRATAGRAFT)	3 (4.2%)	0 (0%)	0 (0%)
Transplant complication (autograft)	0 (0%)	3 (4.2%)	1 (1.4%)
Folliculitis	1 (1.4%)	2 (2.8%)	3 (4.2%)
Impaired healing	2 (2.8%)	0 (0%)	0 (0%)
Contact dermatitis	2 (2.8%)	2 (2.8%)	2 (2.8%)
Rash	0 (0%)	0 (0%)	4 (5.6%)
Pyrexia	0 (0%)	0 (0%)	5 (7%)
Donor site complication	0 (0%)	0 (0%)	5 (7%)
Constipation	0 (0%)	0 (0%)	9 (12.7%)
Nausea	0 (0%)	0 (0%)	14 (19.7%)
Muscle spasm	0 (0%)	0 (0%)	6 (8.5%)
Insomnia	0 (0%)	0 (0%)	5 (7%)
Hypertension	0 (0%)	0 (0%)	6 (8.5%)
Anemia	0 (0%)	0 (0%)	4 (5.6%)

(Source: Adapted from BLA125730; Summary of Clinical Safety, page 31)

Reviewer Comment:
Due to intra-subject controlled design of the study, it is difficult to evaluate relatedness of systemic TEAEs to STRATAGRAFT.

Although, local TEAEs such as pruritus and hypertrophic scar seem to be reported more frequently in STRATAGRAFT treatment sites than autograft treatment sites, these events are common in DPT thermal burns. Overall, the safety profile of STRATAGRAFT

does not indicate an increase of severe or serious TEAEs in comparison to autografts and the benefit / risk profile of STRATAGRAFT is favorable.

6.1.12.3 Deaths

There were 2 deaths (2.8%) reported during the study, both assessed as unrelated to STRATAGRAFT. The narratives of deaths are discussed in section 8.4.1.

6.1.12.4 Nonfatal Serious Adverse Events

Ten subjects (17.5%) experienced 21 SAEs. None of the SAEs were assessed as related to STRATAGRAFT.

6.1.12.5 Adverse Events of Special Interest (AESI)

None.

6.1.12.6 Clinical Test Results

Eleven subjects experienced 17 TEAEs associated with laboratory abnormalities, including anemia (5), hypokalemia (4), hypoalbuminemia (1), hypocalcemia (1), hypoglycemia (1), hypomagnesaemia (1), hypophosphatemia (1), hyperkaliemia (1), hyperglycemia (1), and hepatic enzymes increased (1). These events were mild (12) or moderate (5) in severity, and none were considered by the investigator as related to STRATAGRAFT, and this reviewer concurs with the assessment.

6.1.12.7 Dropouts and/or Discontinuations

Three subjects discontinued from the study because of a TEAE:

- One subject in STRATA2016 (1.4%) discontinued study due to a TEAE. The subject had a serious adverse event (SAE) of craniocerebral injury more than 6 months after placement of STRATAGRAFT.

6.1.13 Study Summary and Conclusions

Results of STRATA2016, an adequate and well-controlled study, provide primary evidence of effectiveness and safety of STRATAGRAFT in the treatment of deep partial thickness (DPT) thermal burns:

- The difference in the percent area of STRATAGRAFT and control autograft treatment sites that required autografting by 3 months was 97.8% ± 16.6% ($p<0.0001$).

- Only three subjects (4.2%) had part of or the entire STRATAGRAFT treatment site autografted by 3 months, and two of the three subjects also had part or all of their autograft control site re-grafted.

- Donor site harvest was eliminated in 96% of STRATAGRAFT- treated DPT burns.

- Durable wound closure without additional autografting was achieved for 83.1% (95% CI: 74.4, 91.8) of the STRATAGRAFT treatment sites at 3 months. The

lower bound of the 95% CI for durable wound closure of STRATAGRAFT treatment site was 74.4%, which was greater than 50%.

- Durable wound closure without additional autografting was achieved for 86% (95% CI: 77.8, 94.0) of the autograft control treatment sites at 3 months.

- There were no increased serious or severe adverse events related to STRATAGARFT in comparison to autografts. The most frequently reported adverse reactions were pruritus, hypertrophic scar, and blister, at both STRATAGRAFT and autograft treatment sites as well as at other non-study burn wounds. No subjects discontinued study participation due to adverse reactions. Overall, the safety profile of STRATAGRAFT with regard to wound-related events, including erythema, swelling, local warmth and wound site infections, was similar to that of autografting in these studies. There were no reports of rejection reaction to STRATAGRAFT. These identified risks are labeled in Section 6.1 of the PI and will monitored in accordance with the proposed pharmacovigilance plan.

6.2 Trial #2: STRATA2011

Study Title: An Open-Label, Controlled, Randomized, Multicenter, Dose Escalation Study Evaluating the Safety and Efficacy of StrataGraft Skin Tissue in Promoting the Healing of the Deep Partial-Thickness Component of Complex Skin Defects as an Alternative to Autografting

First subject, first visit: 2 Sep 2011
Last subject, last visit: 08 Oct 2014

6.2.1 Objectives

The primary objectives were to evaluate the safety, tolerability, and efficacy of increasing amounts of a single application of STRATAGRAFT compared to autograft in the deep partial-thickness (DPT) component of complex skin defects due to thermal burns requiring surgical excision and autografting.

6.2.2 Design Overview

STRATA2011 was a 12-month, open-label, multicenter, intra-subject controlled, randomized, dose-escalation study in adult subjects with complex thermal burns involving 3% to 49% TBSA.

6.2.3 Population

Inclusion Criteria:

- Men and women aged 18 to 65 years, inclusive
- Complex skin defects of 3% to 49% TBSA requiring excision and autografting
- Had deep partial-thickness thermal burn(s) with total area of 88 to 880 cm^2 requiring excision and autografting

Exclusion Criteria:

- Full-thickness burns
- Chronic wounds

- Subjects receiving systemic immunosuppressive therapy
- Treatment sites on the face, head, neck, hands, feet, buttocks, or areas over joints or next to unexcised eschar
- Subjects with a known history of malignancy
- Subjects with insulin-dependent diabetes prior to admission
- Expected survival of less than 3 months
- There was clinical suspicion of burn wound infection at an anticipated treatment site

6.2.4 Study Treatments or Agents Mandated by the Protocol

After surgical excision to remove nonviable tissue, two DPT treatment sites of comparable area and depth were identified on each subject, with one site randomized to treatment with STRATAGRAFT and the other site serving as a control (autograft) site. Two donor sites were prospectively identified to provide sources of autografts for the control treatment site and STRATAGRAFT treatment site as needed. Both treatments were meshed 1:1 before application.

The study included three cohorts:

1. Cohort 1: 10 subjects received a single application of up to 220 cm^2 of STRATAGRAFT that was stored refrigerated (at 2°C to 8°C) and warmed prior to application.

2. Cohort 2: 10 subjects received up to 440 cm^2 of STRATAGRAFT that was stored refrigerated and warmed prior to application.

3. Cohort 3*: 10 subjects received up to 440 cm^2 of STRATAGRAFT that was stored cryopreserved (at -70°C to -90°C) and warmed prior to application.
   * The protocol was amended to include Cohort 3 to evaluate the safety and efficacy of cryopreserved STRATAGRAFT.

The area treated with STRATAGRAFT was permitted to be approximately twice that of the autograft control site in Cohorts 2 and 3. Safety and efficacy were assessed for 12 months after treatment.

Reviewer Comment:
Cryopreserved STRATAGRAFT, the to be marketed product, was used in Study STRATA2016 and Cohort 3 of STRATA2011. Each cryopreserved STRATAGRAFT construct will be supplied with Hold Solution and Hold Dish to prepare for STRATAGRAFT.

In addition, CMC has confirmed that the refrigerated STRATAGRAFT used in Cohorts 1 and 2 of STRATA2011 are comparable to the cryopreserved STRATAGRAFT. Therefore, data from STRATA2011 can be used to support the effectiveness and safety of STRATAGRAFT for treatment of DPT thermal burns.

6.2.5 Directions for Use

See section 6.1.5.

6.2.6 Sites and Centers

Study STRATA2011 was conducted at 6 study sites in the United States.

6.2.7 Surveillance/Monitoring

A summary of study assessments and the timeline of all study procedures are provided in Table 16 and Table 17.

Table 16. Study Assessments, STRATA2011

Assessments	Methods	Schedule of Assessments
Area of STRATAGRAFT treatment site requiring autografting	Clinician assessment supported by photo documentation	Days 3, 7, 14 and 28
Wound closure of treatment sites	Clinician assessment supported by photo documentation	Days 7, 14, 28 and month 3, 6 and 12
Histological wound bed assessment	Biopsy punch of treatment site wound beds	Day 0
Cosmesis of treatment sites	Clinician/patient assessment using POSAS supported by photo documentation	Month 3, 6 and 12
Cosmesis of donor sites	Clinician/patient assessment using POSAS supported by photo documentation	Month 3, 6 and 12
Pain of donor sites	Wong-Baker FACES pain rating scale (FPRS)	Days 3, 7, 14 and 28
Blood chemistry and hematological parameters	CMP, CBC with differential, additional analyses as needed per standard of care	Baseline, day 7 & 28, as per standard of care
Vital signs	Standard	Every study session
Immunological evaluations	Panel reactive antibodies (PRA)	Baseline, days 28 and month 3
Incidence of infection	Clinical signs & symptoms, laboratory evidence as necessary	Every study session
Presence of allogeneic DNA	(b) (4)	Baseline and month 3
Adverse events	Standard	Assessed throughout study duration

(Source: Adapted from STRATA2011, phase 1b Clinical Protocol, Version 3, April 17, 2013)

Table 17. Procedures Schedule STRATA2011

Study Session	**Screening**	**Study Session #1**	**Study Session #2**	**Study Session #3**	**Study Session #4**	**Study Session #5**	**Study Session #6**	**Study Session #7**	**Study Session #8**
Treatment Period		**Day 0**	**Day 3**	**Day 7 +/- 1 day**	**Day 14 +/- 2 days**	**Day 28 +/- 3 days**	**Month 3 +/-14days**	**Month 6 +/-1month**	**Month 12 +/-1month**
Medical history & physical	X								
Pregnancy test	X								
Vital signs	X	X	X	X	X	X	X	X	X
Infection assessment	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Blood chemistry		X[a]		X		X			
Immunological assessment		X				X	X		
Archival blood samples		X					X		
Histological wound bed assessment		X							
STRATAGRAFT application		X							
AE assessment	X	X	X	X	X	X	X	X	X
Photography of treatment sites	X	X	X	X	X	X	X	X	X
Photography of donor sites							X	X	X
Dressing changes			X	X	X	X			
Appearance of donor sites			X	X	X	X			
Pain of donor sites			X	X	X	X			
Presence of allogeneic DNA		X[b]							
Wound closure				X	X	X	X	X	X
Cosmesis of treatment sites							X	X	X
Cosmesis of donor sites							X	X	X

[a] Can be performed up to 4 days prior to treatment day 0.
[b] blood collected at study session #1 served as a patient-specific reference to assess the persistence of allogeneic DNA.
(Source: STRATA2011, Clinical Protocol, Version 3, April 17, 2013)

6.2.8 Endpoints and Criteria for Study Success

Primary Endpoints:

- The percent of the STRATAGRAFT and autograft treatment sites that received autograft by Day 28,
- Wound closure of treatment sites at Month 3. Complete wound closure was defined as at least 95% re-epithelialization in the absence of drainage.

Secondary Endpoints:

- Adverse events (AEs), incidence of infection, vital signs and clinical laboratories, immunology assessments (Baseline, Day 28, Month 3)
- Archival plasma and leukocyte collection (Baseline, Month 3),
- Persistence of allogenic DNA (Month 3),
- Donor site cosmesis (Months 3, 6, and 12),
- Donor site pain as measured by FACES pain rating scale (Days 3, 7, 14, and 28),
- Percent of subjects requiring autograft of the STRATAGRAFT treatment site (Day 28),
- Wound closure of the treatment sites (Days 7, 14, and 28, and Months 3, 6, and 12),
- Treatment site cosmesis (Months 3, 6, and 12),
- Treatment site appearance (Days 3, 7, 14, and 28).

6.2.9 Statistical Considerations & Statistical Analysis Plan

No formal hypothesis testing was planned for this early phase exploratory study, but some inferential testing was completed in order to identify trends and plan future studies.

This study was not powered to detect statistically significant differences in efficacy or safety. Data listings are provided for safety and efficacy data.

Overall summary descriptive statistics for the demographic variables of interest were used to provide a descriptive profile. For categorical variables, the numbers and percent for each demographic variable are presented. For continuous variables, summary statistics including number, mean, standard deviation (SD), median, minimum, and maximum values are presented. Analyses of safety and efficacy endpoints were performed on results from the ITT population, consisting of subjects who received any amount of STRATAGRAFT, regardless of follow-up status. The treatment sites in the STRATA2011 ITT Population were assessed “as treated” rather than as assigned, and therefore, the ITT population is the same as the mITT Population.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Adult subjects with DPT thermal burn meeting study eligibility criteria were enrolled.

6.2.10.1.1 Demographics

Demographics of Study STRATA2011 are summarized in Table 18.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Baseline treatment site characteristics of study subjects is summarized in Table 18.

Table 18. Summary of Key Demographic and Baseline Treatment Site Characteristics and Baux Scores STRATA2011

Characteristic	STRATA2011 N=30
Age, mean (SD), year	41.0 (12.10)
Age range, year	21, 63
Age <65 years, n (%)	30 (100)
Age ≥65 years, n (%)	0
Sex, n (%)	
Male	21 (70.0)
Female	9 (30.0)
Race, n (%)	
White	28 (93.3)
Black or African American	2 (6.7)
Asian and Other	0
Ethnicity, n (%)	
Hispanic or Latino	4 (13.3)
Not Hispanic or Latino	26 (86.7)
TBSA of 2nd and 3rd degree burns combined (%), Mean (SD)	13.9 (10)
Baux score, Mean (SD)	54.9 (15.3)
Size of STRATAGRAFT treatment area, n (%)	
<250 cm^2	19 (63.3)
>=250 to <500 cm^2	11 (36.7)
>=500 cm^2	0
STRATAGRAFT wound area (cm^2), Mean (SD)	223 (131.1)
Autograft wound area (cm^2), Mean (SD)	161 (95.8)

(Source: Adapted from BLA125730; Summary of Clinical Efficacy, page 22)

6.2.10.1.3 Subject Disposition

Subjects were sequentially enrolled and treated into Cohorts 1 to 3. There were 10 subjects enrolled in each cohort and total 4 subjects (13.3%) discontinued the study. None of the subjects discontinued study participation due to a TEAE. The reason for discontinuation was noted as lost to follow up. Subject disposition is provided in Table 19.

Table 19. Subject Disposition and Efficacy Analysis Populations in Dose Cohorts STRATA2011

	Refrigerated STRATAGRAFT		Cryopreserved STRATAGRAFT	
	Cohort 1 (N = 10) n (%)	**Cohort 2 (N = 10) n (%)**	**Cohort 3 (N = 10) n (%)**	**Overall (N = 30) n (%)**
Subjects enrolled	10 (100.0)	10 (100.0)	10 (100.0)	30 (100.0)
Subjects population (ITT)	10 (100.0)	10 (100.0)	10 (100.0)	30 (100.0)
Subjects who completed study	9 (90.0)	9 (90.0)	8 (80.0)	26 (86.7)
Subjects who discontinued	1 (10.0)	1 (10.0)	2 (20.0)	4 (13.3)
Lost to follow-up	1 (10.0)	1 (10.0)	2 (20.0)	4 (13.3)

(Source: Adapted from STRATA2011 CSR, Table 14.1.1.1)

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

(1) The percent of the STRATAGRAFT and autograft treatment sites that received autograft by Day 28

No STRATAGRAFT treatment sites received autograft by Day 28. All autograft treatment sites received autograft by Day 28.

(2) Wound Closure of Treatment Sites at Month 3

Of the STRATAGRAFT treatment sites, 93.1% achieved complete wound closure by Month 3. All (100%) of the autograft treatment sites achieved complete wound closure.

6.2.11.2 Analyses of Secondary Endpoints

Percent Wound Closure at Day 28

- At Day 28, 69.0% of the STRATAGRAFT-treated sites were closed versus 89.7% of the autograft-treated sites. The wound closure rate across all 3 cohorts was lower at STRATAGRAFT treatment sites through Day 28 for the ITT population, but was not different from the autograft treatment site by Month 3.

- For the ITT population subjects with data available at Month 6 and Month 12, there was 100% wound closure for all subjects receiving either treatment.

- Overall, re-epithelization occurred in 87.9% (± 24.88%) of the STRATAGRAFT-treated sites and 95.0% (± 18.13%) of the autograft- treated sites by Day 28.

Reviewer Comment:
The wound closure rate across all 3 cohorts was lower at the STRATAGRAFT treatment sites through Day 28 but was not different from the autograft treatment site by Month 3. For the subjects with data available at Month 6 and Month 12, there was 100% wound closure for all subjects receiving either treatment.

Wound Appearance characteristic

- Wound appearance was evaluated based on color (pinkness), adherence of the graft, and whether the graft tissue remained intact. All overall mean scores from the combined cohorts for pinkness, adherence, and intactness of grafted tissue were greater than 80% at all time points, regardless of treatment. In general, the overall mean scores for STRATAGRAFT and autograft treatment sites were comparable for each characteristic at Day 3. However, at all visits from Day 7 through Day 28, the overall mean scores for the autograft sites were approximately 10% higher than for the STRATAGRAFT sites for each.

Reviewer Comment:
Wound appearance characteristics such as color (pinkness), adherence of the graft, and whether the graft tissue remained intact, were not reported beyond Study Session #5 (Day 28).

Pain at Donor Sites

- No STRATAGRAFT donor sites were harvested through Day 28. Therefore, subjects reported less pain at the STRATAGRAFT (potential) donor sites compared with the autograft donor sites from Day 3 through Day 28, and the majority of subjects reported no pain at the STRATAGRAFT donor site from Days 3 to 28. Among the overall population, at each session, 57.1% to 89.3% of subjects reported no pain at the STRATAGRAFT donor site compared with 7.1% to 64.3% at the autograft donor site.

Reviewer Comment
It is possible that the source of reported pain at the unharvested STRATAGRAFT donor site is referred pain from another wound area. This is supported by subjects reporting more pain at the Day 3 and Day 7 evaluations for both unharvested STRATAGRAFT donor site and harvested autograft donor site.

Treatment Site Cosmesis

- Scar scores were assessed by POSAS (V2.0) where the total score is the sum of 6 different assessments. The STRATAGRAFT-treated site had significantly higher subject total scores compared with the autograft treatment site for Cohort 2 subjects at Month 6 and for Cohort 3 at Month 3.

- Mean total scores from observer assessments of scarring were not significantly different between the STRATAGRAFT and autograft treatment sites in any cohort and at any time point from Month 3 through Month 12.

Reviewer Comment
The unfavorable subject total scores of scarring in STRATAGRAFT-treated sites, is not consistent throughout the study and is not replicated by observer assessment of scarring. Due to the open-label design of the study, subject reported scores could be subject to bias.

6.2.11.3 Subpopulation Analyses

For a trial such as STRATA2011 with a small number of subjects, subgroup analysis by age, sex, race, or ethnicity was not done and is unlikely to be meaningful.

6.2.11.4 Dropouts and/or Discontinuations

A total of 26 subjects (86.7%) completed the study. Four subjects were lost to follow-up.

6.2.12 Safety Analyses

6.2.12.1 Methods

Safety Population included all subjects who received STRATAGRAFT in the study, regardless of follow-up status.

6.1.12.2 Overview of Adverse Events

There were 30 subjects enrolled in this study, of which 27 (90%) reported at least one TEAE. Of subjects reporting a TEAE, 5 (16.7%) experienced a TEAE that was assessed as related to STRATAGRAFT. Of 117 total TEAEs, 104 (88.9%) were mild to moderate in severity. Pruritus was the most frequently reported TEAE reported by 5 (16.7%) subjects.

Nine subjects (30%) reported 13 severe TEAEs, 7 of which were SAEs. None of the severe TEAEs were assessed as related to study treatment, and all 13 severe TEAEs resolved.

Six subjects (20%) reported 11 SAEs. One SAE out of the 11 reported was impaired healing (moderate severity) and was considered possibly related to STRATAGRAFT but was associated with a major protocol deviation involving a site excluded per protocol (neck), and a wound-specific exclusion criterion (full thickness burn). No other SAEs were assessed as related to STRATAGRAFT.

At Month 3 post treatment, 28 of the 30 subjects were evaluated for persistence of allogeneic DNA at the treatment site. None of the 28 samples showed evidence of residual DNA.

Of the 29 subjects who were tested for antibodies to human leukocyte antigens (HLA) expressed by the cells, 11 (38%) had developed HLA antibodies and of those, 4 (36%) had persistent antibodies. The clinical significance of persistent HLA antibodies is unknown.

No clinical signs of infection were reported for the STRATAGRAFT treatment sites.

There were no deaths reported, and none of the subjects discontinued the study participation because of a TEAE.

6.2.12.3 Deaths

There were no deaths reported in the study.

6.2.12.4 Nonfatal Serious Adverse Events

Six subjects (20%) reported 11 SAEs. One SAE was impaired healing (moderate severity) and was considered possibly related to STRATAGRAFT. The SAE was also associated with a major protocol deviation involving a site excluded per protocol (neck), and a wound-specific exclusion criterion (full thickness burn). No other SAEs were assessed as related to STRATAGRAFT.

6.2.12.5 Adverse Events of Special Interest (AESI)

None.

6.2.12.6 Clinical Test Results

In STRATA2011 (n=30), three subjects had five TEAEs associated with laboratory abnormalities (anemia, hypermetabolism, and hypoalbuminemia in one subject; anemia in one subject; and sepsis in one subject). None of these events was serious, and all resolved. None was considered as related to STRATAGRAFT.

6.2.12.7 Dropouts and/or Discontinuations

No subjects discontinued from the study because of a TEAE.

6.2.13 Study Summary and Conclusions

STRATA2011 was a 3-cohort early phase study in 30 subjects with DPT thermal burns. STRATA2011 was completed prior to initiation of STRATA2016. Therefore, the data derived from STRATA2011 were utilized in designing the phase 3 study, STRATA2016. Overall, the results from STRATA2011 support the safety and effectiveness of STRATAGRAFT.

7. Integrated Overview of Efficacy

7.1 Indication #1

An Integrated Overview of Efficacy (i.e., an analysis using pooled data from all subjects treated with topical application of STRATAGRAFT) was not performed, for the following reasons:

- Different primary efficacy endpoints were used for STRATA2016 and STRATA2011,
- Different definitions of complete wound closure were used for STRATA2016 and STRATA 2011.

Please refer to the individual study sections for discussion of efficacy results. Although the data were not pooled for an integrated review of efficacy, the study results from the individual studies provide substantial evidence of the effectiveness of STRATAGRAFT for the treatment of DPT thermal burns.

8. Integrated Overview of Safety

8.1 Safety Assessment Methods

The integrated overview of safety is based on pooled data from 119 adult subjects treated with STRATAGRAFT in four open-label US studies: STRATA2001, STRATA2011, STRATA2014 and STRATA2016 (Table 6).

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Please refer to Table 6, which summarizes the four studies contributing to the safety population.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Among the 119 subjects, 101 subjects with DPT thermal burns received STRATAGRAFT topically in Studies STRATA2016 and STRATA2011; and 18 subjects with full-thickness complex skin defects received STRATAGRAFT topically in studies STRATA2014 and STRATA2001. Study Populations Analyzed in these studies are listed in Table 20.

Table 20. Study Populations Analyzed in STRATAGRAFT Studies

Deep Partial-Thickness Burn Studies	**Analysis Set Relevant to SCS***
STRATA2016	Safety: All study subjects who received any amount of STRATAGRAFT, regardless of follow-up status.
STRATA2011	Intent-to-Treat: All subjects who received any amount of STRATAGRAFT regardless of follow-up status.
Full-Thickness Wound Studies	**Analysis Set Relevant to SCS***
STRATA2014	Modified Intent-to-Treat: Study subjects who received any amount of STRATAGRAFT based on the actual treatment sites, whether correctly assigned as randomized or misallocated.
STRATA2001	Safety: All subjects who received STRATAGRAFT. As all subjects completed the study through Day 77, all subjects were assessed for safety.

*SCS=Summary of Clinical Safety.
(Source: BLA 125730, Summary of Clinical Efficacy, Page 15)

The patient population ranged in age from 19 to 79 years (mean age 43 years). Each subject received topical application of STRATAGRAFT at one wound site and either autografting (104 subjects) or cadaver allografts (15 subjects) at the other wound site that serves as the intra-subject control. A summary of exposure to STRATAGRAFT is provided in Table 21.

Table 21. Summary of Exposure to STRATAGRAFT

Characteristic, Mean (SD)	**STRATAGRAFT Treatment Site (n=119)**
Study duration (days)	247.8 (124.6)
Total number of 44 cm^2 STRATAGRAFT constructs applied, n=45	4.6 (1.1)
Total number of 100 cm^2 STRATAGRAFT constructs applied, n=74	2.9 (2.0)
Total dosage of STRATAGRAFT (cm^2)* n=119	225 (179)

*Total dosage is rounded to the nearest tenth cm. Dosage determined by area calculated from wound length x width measurements, except for one subject in STRATA2001, who had a

triangular wound and area was calculated using Heron's formula where sides are a, b, and c, s =(a+b+c)/2, A = square root of [s(s-a)(s-b)(s-c)].
(Source: BLA 125730, Summary of Clinical Safety, page 16)

8.2.3 Categorization of Adverse Events

Adverse events (AEs) were coded using MedDRA Version 19.1.

Safety Population included all subjects who received STRATAGRAFT, regardless of follow-up status.

All AEs analyzed in the safety database were treatment-emergent adverse events (TEAEs), which refer to AEs with an onset date and time equal to or after the placement of STRATAGRAFT or those events for which the onset date and time were before the placement of STRATAGRAFT but worsened after the placement of STRATAGRAFT.

TEAEs were considered related (i.e., adverse reactions) if they were possibly or probably related based on temporal sequence between administration and the event, a biologically plausible relationship, or the lack of an alternative explanation for the event.

The severity of AEs was graded according to the following definitions:

- Mild - The subject experiences awareness of symptoms but these are easily tolerated or managed without specific treatment.

- Moderate - The subject experiences discomfort enough to cause interference with usual activity, and/or the condition requires specific treatment.

- Severe - The subject is incapacitated with inability to work or do usual activity, and/or the event requires significant treatment measures.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

The following limitations were identified in the assessment of the pooled safety population:

- The study population in STRATA2001 (15 subjects) and STRATA2014 (3 subjects) included subjects with full thickness complex skin defects; STRATA2016 and STRATA2011 included subjects with deep partial thickness skin defects.

- Subjects in STRATA2001 (15 subjects) received cadaver allograft as intra-subject comparator, and subjects in the three subsequent studies (104 subjects) all received autograft as intra-subject comparator.

- Due to intra-subject controlled design of all four studies, it is difficult to evaluate relatedness of systemic TEAEs to STRATAGRAFT.

8.4 Safety Results

8.4.1 Deaths

- No deaths were reported in STRATA2011, STRATA2014, or STRATA2001.
- Two deaths occurred in STRATA2016 (1.7%):
  - Subject (b) (6) experienced an SAE of death due to acute myocardial infarction (approximately 300 days after application of STRATAGRAFT).
  - Subject (b) (6) experienced SAEs of acute myocardial infarction, cardiac arrest, and sepsis, all of which were reported to have contributed to the fatal outcome (79 days after application of STRATAGRAFT).

Narratives of Deaths:

- Subject (b) (6) : A 50-year-old Black or African-American male who had suffered a 4% TBSA burn to head, face, and bilateral upper extremities, received 50 cm^2 STRATAGRAFT and a control autograft to two different sites on his right forearm. His Baux score was 54 (study range 23 to 91.75). At study session # 7 (Month 3), the wound treated with STRATAGRAFT was assessed as closed. On Day 300 post application, the study site learned that the subject had experienced a myocardial infarction and was found dead. This death was not considered to be related to STRATAGRAFT and was attributed to the underlying coronary artery disease. No autopsy was performed. The investigator assessment of the cause of death was unrelated to STRATAGRAFT and this reviewer concurs with the assessment.

- Subject (b) (6) : A 48-year-old morbidly obese white female with hypertension and fibromyalgia, who had suffered a 33.5% TBSA burn to her upper body, received 960 cm^2 STRATAGRAFT and control autograft treatment to the posterior trunk. She developed fever of 102.1°F and an infection of the STRATAGRAFT treatment site 11 days after STRATAGRAFT placement. The wound infection was considered to be resolved on Day 17 post-treatment and additional surgery for autografting of STRATAGRAFT treatment site was scheduled for the next day. She developed methicillin-resistant Staphylococcus aureus (MRSA), hypoxic respiratory failure, and a non-ST-elevation myocardial infarction (NSTEMI). On post-treatment Day 21 she underwent autografting of STRATAGRAFT treatment site and is considered a “treatment failure.” The events of pneumonia and sepsis were considered resolved on post-treatment Days 25 and 30, respectively. She was discharged from the hospital on Day 42 post-treatment. Following autografting of STRATAGRAFT treatment site on post-treatment Day 21, the wound was assessed as closed at Study Visit 6 (month 2). On Day 78 after application of STRATAGRAFT, the subject experienced an acute myocardial infarct and had a cardiac arrest at home. Cardiopulmonary resuscitation was performed. She was transferred to the hospital and was treated for gram positive sepsis. She died on day 79 post treatment. An autopsy was not performed. The investigator assessment of the cause of death was unrelated to STRATAGRAFT.

Reviewer Comment:

This reviewer agrees with the investigator assessment that the two reported deaths in STRATA2016 were likely due to the subjects' underlying conditions and unrelated to treatment with STRATAGRAFT.

8.4.2 Nonfatal Serious Adverse Events

Twenty of the 119 subjects (16.8%) had 36 serious TEAEs (Table 22). One SAE of impaired healing (moderate severity) was considered to be possibly related to STRATAGRAFT by the investigator. Table 22 summarizes the SAEs.

Table 22. Serious Treatment-emergent Adverse Events

System Organ Class Preferred Term	All Subjects (n=119)
Total number of serious TEAEs	**36**
Number of subjects with at least one serious TEAE	20 (16.8%)
General disorders and administration site conditions	**7 (5.8%)**
Impaired healing	2 (1.7%)
Concomitant disease progression	1 (0.8%)
Death	2 (1.7%)
Malaise	1 (0.8%)
Pain	1 (0.8%)
Pyrexia	1 (0.8%)
Injury, poisoning and procedural complications	**5 (4.2%)**
Transplant (STRATAGRAFT and autograft) failure	2 (1.7%)
Craniocerebral injury	1 (0.8%)
Graft complication	1 (0.8%)
Thermal burn	1 (0.8%)
Infection and infestation	**4 (3.4%)**
Cellulitis	1 (0.8%)
Enterobacter bacteremia	1 (0.8%)
Pneumonia	1 (0.8%)
Pneumonia bacterial	1 (0.8%)
Pseudomonal bacteremia	1 (0.8%)
Sepsis	1 (0.8%)
Respiratory, thoracic and mediastinal disorders	**3 (2.5%)**
Pulmonary embolism	2 (1.7%)
Acute respiratory failure	1 (0.8%)
Vascular disorders	**3 (2.5%)**
Deep vein thrombosis	2 (1.7%)
Migraine	1 (0.8%)
Cardiac disorders	2 (1.7%)
Acute left ventricular failure	1 (0.8%)
Acute myocardial infarction	2 (1.7%)
Atrial fibrillation	1 (0.8%)
Bundle branch block left	1 (0.8%)
Cardiac arrest	1 (0.8%)
Musculoskeletal and connective tissue disorders	**1 (0.8%)**
Joint effusion	1 (0.8%)
Nervous system disorders	**1 (0.8%)**
Seizure	1 (0.8%)
Psychiatric disorders	**1 (0.8%)**
Hallucination	1 (0.8%)

A subject may have had more than one SAE per system organ class/preferred term. If so, the SAE with the highest relationship to STRATAGRAFT was counted per system organ class/preferred term for this summary.
(Source: Adapted from BLA125730; Summary of Clinical Safety, page 34)

Impaired healing, transplant failure, pulmonary embolism and deep vein thrombosis were reported for two subjects each (1.7%), all other SAEs were reported for one subject each (0.8%).

Impaired Healing
One subject in STRATA2011, Cohort 2, had a moderately severe SAE of impaired healing (reported as delayed healing at the STRATAGRAFT treatment site), that was considered by the investigator to be possibly related to STRATAGRAFT. This SAE was considered by the medical monitor, independent medical monitor, and Sponsor to be related to placement of STRATAGRAFT on a wound that had a significant area of full-thickness injury and, therefore, did not meet eligibility criteria.

Graft Complication
One subject in STRATA2014, experienced one SAE, graft complication of the STRATAGRAFT treatment site. This SAE was of moderate severity and was considered by the investigator as not related to STRATAGRAFT.

Reviewer Comment:
This reviewer agrees with the assessment that impaired healing in one subject was possibly related to STRATAGRAFT. Overall, adverse events reported are expected in the burn patient population.

8.4.3 Study Dropouts/Discontinuations

Across the four studies, three subjects discontinued from the study because of a TEAE:

- One subject in STRATA2016 (1.4%) discontinued study due to a TEAE. The subject had a serious adverse event (SAE) of craniocerebral injury more than 6 months after placement of STRATAGRAFT.

- Two subjects died in STRATA2016 (See section 8.4.2 for more detail).

Reviewer Comment:
This reviewer's assessment is that the SAE of craniocerebral injury and two deaths are unlikely related to STRATAGRAFT.

8.4.4 Common Adverse Events

The most frequent TEAEs among 102 subjects were pruritis (28.5%), blister (11.8%), hypertrophic scar (10.1%), pain (9.2%) and neuralgia (9.2%), graft complication (6.7%), impaired healing (4.2%), excessive granulation tissue (4.2%), edema (4.2%) and tachycardia (3.3%). All other TAEAs were reported in less than 2% of subjects.

Thirty-one subjects (26%) had 39 adverse reactions (ARs). The most frequent ARs (incidence ≥ 2%) observed in the 4 studies include pruritus (10.9%), blister (4.2%), hypertrophic scar (2.5%) and impaired healing (2.5%).

8.4.5 Clinical Test Results

In STRATA2016 (n=71), 11 subjects experienced 17 TEAEs associated with laboratory abnormalities, including anemia (5), hypokalemia (4), hypoalbuminemia (1), hypocalcemia (1), hypoglycemia (1), hypomagnesaemia (1), hypophosphatemia (1),

hyperkaliemia (1), hyperglycemia (1), and hepatic enzymes increased (1). These events were mild (12) or moderate (5) in severity, and none were considered as related to STRATAGRAFT.

In STRATA2011 (n=30), three subjects had five TEAEs associated with laboratory abnormalities (anemia, hypermetabolism, and hypoalbuminemia in one subject; anemia in one subject; and sepsis in one subject). None of these events was serious, and all resolved. None was considered as related to STRATAGRAFT.

In STRATA2014 (n=3), one subject experienced two nonserious TEAEs (thrombocytopenia and hyperglycemia) assessed as unrelated to STRATAGRAFT.

STRATA2001 (n=15) collected and reported all laboratory abnormalities and assigned severity using a modified WHO grading scale. Values lower than Grade 1 were considered to be normal. Adverse events rated as Grade 3 (severe) and unexpected included lymphocytes and granulocyte bands (13.3%). In general, changes in the mean clinical laboratory evaluations did not demonstrate specific trends.

Reviewer Comment:
Safety data collected from four clinical studies with STRATAGRAFT does not indicate any association with laboratory-related AEs. Changes in subjects' laboratory values during the course of the studies were more likely related to the subjects' existing conditions. This reviewer agrees that these laboratory-related AEs are unlikely related to STRATAGRAFT.

8.4.6 Systemic Adverse Events

In STRATA2016, 9 subjects had 9 TEAEs associated with abnormal vital sign values, including hypertension (8) and hypotension (1). All events were assessed as mild (8) or moderate (1) in severity; none was considered related to STRATAGRAFT.

Additional 5 subjects had TEAEs of pyrexia. One of these events was considered moderate in severity and was reported as an SAE (Subject (b) (6)). The additional events of pyrexia were considered mild in severity and not serious, and all resolved. None were considered related to STRATAGRAFT.

There were no apparent treatment-related trends in changes from baseline of vital-sign measurements. Vital-sign measurements that were associated with TEAEs included hypertension, worsening of preexisting hypertension, hypotension, pyrexia, tachycardia, and hypothermia. With the exception of one episode of tachycardia, none of these TEAEs was considered related to STRATAGRAFT. The event of tachycardia was considered temporally related to STRATAGRAFT intraoperatively and resolved after one dose of beta-blocker administration.

Reviewer Comment:
This reviewer agrees with the assessment that observed changes in vital signs were not related to STRATAGRAFT.

8.4.7 Local Reactogenicity

Not applicable.

8.4.8 Adverse Events of Special Interest

Graft Site Infection

STRATAGRAFT treatment site infections occurred in 4 of the 119 subjects (3.4%). Autograft treatment site infections occurred in 5 of the 119 subjects (4.2%). There was no increased risk of infection at the STRATAGRAFT treatment site comparing to autograft treatment site (relative risk=1.25; 95% confidence interval 0.34, 4.54).

Persistence of Allogeneic DNA

STRATAGRAFT contains human keratinocytes from a single donor and dermal fibroblasts from a second donor. The presence of DNA from the allogeneic keratinocytes and fibroblasts of STRATAGRAFT was assessed using (b) (4) by evaluating (b) (4) that differ between STRATAGRAFT and each subject's cells. Samples to examine the persistence of allogeneic STRATAGRAFT DNA were collected at baseline and from the STRATAGRAFT treatment site at Month 3 (± 14 days). Subjects with informative alleles (those unique to cells of STRATAGRAFT and not represented in the DNA of the recipient) above the limit of detection for the test method were to be considered to have a positive result.

A total of 85 subjects in Studies STRATA2016 and STRATA2011 were evaluated at 3 months for persistence of allogeneic STRATAGRAFT DNA at the treatment site. STRATAGRAFT-associated DNA was not detected in any of these subjects.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

Overall dose dependency of STRATAGRAFT for adverse events could not be clearly determined, because each subject received different sizes of STRATAGRAFT based on their wound size.

8.5.2 Time Dependency for Adverse Events

Observed adverse reactions occurred in close proximity to surgical application of STRATAGRAFT.

8.5.6 Human Carcinogenicity

No human or animal studies were conducted to evaluate the effects of STRATAGRAFT on carcinogenesis, mutagenesis, or impairment of fertility, nor were they warranted based on the evaluation of tumorigenic potential in the following studies:

Karyotype Stability

The NIKS® keratinocytes and human dermal fibroblasts contained in STRATAGRAFT are karyotypically stable.

In Vitro Studies

The NIKS keratinocytes and human dermal fibroblasts cultured for 43 and 6 passages, respectively, did not exhibit anchorage independent growth (a standard assay that evaluates the potential for cellular transformation). STRATAGRAFT contains NIKS keratinocytes and human dermal fibroblasts that are at passage 40 and 7, respectively.

In Vivo Studies

A single subcutaneous injection of NIKS® keratinocytes into immunodeficient mice did not result in tumor formation by 23 weeks post-injection. Topical application of STRATAGRAFT on full-thickness excisional wounds in immunodeficient mice did not result in tumor formation by 20 weeks post-dose.

Reviewer Comment:
The layer of NIKS human keratinocytes which have a known and well characterized chromosomal abnormality are found to be karyotypically stable during manufacture. In vivo evaluation of NIKS keratinocytes in mice demonstrated no tumor formation. There was no persistence of cells of STRATAGRAFT in treated subjects and there have been no documented clinical or histological reports of tumor formation at the site of application. Although the risk of malignancy after use of this product is thought to be low, this remains a potential risk. An enhanced pharmacovigilance plan, including 15-day expedited reporting of any adverse events of dermal tumorigenicities/malignancies will be in place post-approval.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.5.8 Immunogenicity (Safety)

Anti-BSA Antibody
STRATAGRAFT is manufactured with media that contains purified bovine serum albumin (BSA). Anti-BSA antibody titers were assessed at baseline and at Month 3 in 58 subjects in STRATA2016.

Thirteen (13) subjects (22.4%) had an increase in anti-BSA antibody titer at Month 3.

Panel Reactive Antibodies (PRAs)
Blood samples were obtained at baseline, Day 28, and Month 3 for assessment of PRAs.

The median PRA at baseline was 0.0% (range, 0% to 65%), 0.3% at Day 28 (range, 0 to 100%), and 0.0% at Month 3 (range, 0 to 100%). The number of subjects with positive PRA values at each visit were 3 (4.3%) at baseline, 28 (43.8%) at Day 28, and 15 (24.2%) at Month 3.

Three subjects (4.3%) demonstrated reactivity at baseline to MHC Class I alleles found in STRATAGRAFT. The number of subjects demonstrating reactivity to MHC Class I alleles increased at Day 28 (28 subjects, 43.8%) and decreased again at Month 3 (15 subjects, 24.2%).

Reviewer Comment:
Transient immunological response to one-time application of STRATAGRAFT seems to occur in a subset of subjects and decline by Month 3. Clinical significance of this immunological response is unclear. No subjects developed rejection to STRATAGRAFT.

8.5.9 Person-to-Person Transmission, Shedding
Not applicable.

8.6 Safety Conclusions

The most frequent adverse reactions (incidence ≥ 2%) observed in the 4 studies include pruritus (11%), blister (4%), hypertrophic scar (3%) and impaired healing (3%) at the STRATAGRAFT treatment sites. No subjects discontinued study participation due to adverse reactions. Overall, the safety profile of STRATAGRAFT with regard to wound-related events, including erythema, swelling, local warmth and wound site infections, was similar to that of autografting in these studies. There were no reports of rejection reaction to STRATAGRAFT. The safety of STRATAGRAFT beyond 12 months was not evaluated in the clinical studies.

Reviewer Comment:
The potential serious risks associated with topical application of STRATAGRAFT include hypersensitivity reactions to murine collagen or products containing ingredients of bovine or porcine origin, and transmission of infectious diseases. However, hypersensitivity reactions were not observed in the clinical studies.

9. Additional Clinical Issues

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

There are no available data regarding STRATAGRAFT use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with STRATAGRAFT to assess whether it can cause fetal harm when administered to a pregnant woman.

In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

9.1.2 Use During Lactation

There is no information available on the presence of STRATAGRAFT in human milk, the effect on the breastfed infant, or the effect on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for STRATAGRAFT and any potential adverse effects on the breast-fed infant from STRATAGRAFT, especially considering the xenotransplant nature of STRATAGRAFT, or from the underlying maternal condition.

9.1.3 Pediatric Use and PREA Considerations

The safety and effectiveness of STRATAGRAFT in pediatric patients (< 18 years) have not been established. STRATAGRAFT is not subject to PREA, since the product received Orphan Drug designation.

9.1.4 Immunocompromised Patients

The safety and effectiveness of STRATAGRAFT in immunocompromised patients have not been established.

9.1.5 Geriatric Use

Eight subjects aged 65 years and older were enrolled in STRATA2016. Although no differences in safety or efficacy were observed between patients aged 65 years and older and younger subjects, the number of subjects aged 65 years and older was not sufficient to determine whether they responded differently from younger subjects.

10. CONCLUSIONS

The primary evidence of effectiveness is based on significant improvements in clinically meaningful efficacy outcomes following application of STRATAGRAFT observed in STRATA2016, an adequate and well-controlled study, for adults with deep partial thickness thermal burns containing intact dermal elements for which surgical intervention is clinically indicated. The effectiveness of STRATAGRAFT was supported by data from STRATA2011.

The safety database included 119 adult subjects from four clinical trials. The potential serious risks with topical application of STRATAGRAFT include hypersensitivity reaction to murine collagen or products containing ingredients of bovine or porcine origin, and transmission of infectious disease agents. These risks can be mitigated by adequate risk mitigation information in the PI and Patient Information Sheet, enhanced pharmacovigilance plan, and a CMC-related safety PMR.

Review of the submitted data indicates that STRATAGRAFT appears safe and effective for the treatment of deep partial thickness thermal burns, containing intact dermal elements for which surgical intervention is clinically indicated.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Risk-benefit considerations for STRATAGRAFT are summarized in Table 23: Benefit/Risk Considerations.

Table 23. Benefit/Risk Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Burns leading to skin loss are common causes of skin loss, which puts patients at increased risk of infection and death. • In the United States, annually, approximately 40,000 hospitalizations are related to burn injury and approximately 4,500 of these people die. Based on data from the American Burn Association 2011 National Burn Repository Report, an estimated 5-10,000 individuals with thermal burns require surgical excision and autograft placement each year in the US.	• DPT thermal burn is a serious and life-threatening condition.
Unmet Medical Need	• Available treatment options include autograft, allografts, xenografts and devices such as Recell and Epicel. • Major limitation is requirement for healthy donor sites to prepare sufficient skin (autograft, allograft, xenograft), or adequate amount of the cell suspension (Recell) or to produce sufficient amount of autologous keratinocyte sheets (Epicel) to cover large burn surface areas. • Available treatments may cause donor site wound complications, e.g., infection, pain, delayed healing, granulation tissue or additional cosmesis adverse events.	• There is an unmet medical need for treatment of DPT thermal burns with products that decrease the need to obtain autologous skin tissues or biopsies.
Clinical Benefit	• The efficacy of STRATAGRAFT in adults with DPT thermal burns, affecting up to 50% TBSA, for which surgical intervention is clinically indicated was evaluated in two randomized, open-label, intra-patient controlled, multicenter clinical studies of 12 months duration. In both studies, autograft served as the intra-subject comparator. • Study STRATA2016 enrolled 71 subjects, the difference in the percent area of STRATAGRAFT and control autograft treatment sites that required autografting by 3 months was 97.8% ± 16.6% ($p<0.0001$). Three subjects had STRATAGRAFT treatment site autografted. Donor site harvest was eliminated in 96% of STRATAGRAFT-treated DPT burns. The proportion of subjects achieving durable closure was 83.1% (95% CI: 74.4, 91.8), and 86% (95% CI: 77.8, 94.0) at the STRATAGRAFT treatment site and autograft treatment site, respectively, at 3 months without additional autografting. • Study STRATA2011 enrolled 30 subjects. No STRATAGRAFT treatment site required autograft by 28 days. Between 28 days and 3 months, 2 subjects had STRATAGRAFT site autografted. At 3 months, 93.1% of STRATAGRAFT treatment sites and 100% of autograft treatment sites achieved complete wound closure. All STRATAGRAFT treatment sites remained closed when evaluated at 6 months and 12 months after treatment.	• Overall, substantial evidence indicates clinical benefit of STRATAGRAFT for treatment of DPT thermal burn, based on data from one adequate and well-controlled study and one early phase study.
Risk	• The most frequent adverse reactions (incidence ≥ 2%) observed in 119 subjects across 4 studies include pruritus (11%), blister (4%), hypertrophic scar (3%) and impaired healing (3%). • STRATAGRAFT Manufacturing utilizes an immortalized keratinocyte cell line from culture of neonatal foreskin keratinocytes (NIKS) which were isolated and expanded on mouse 3T3 feeder line, thus, making STRATAGRAFT a xenotransplantation product. NIKS cells have well-characterized chromosomal abnormality. • Potential risks include hypersensitivity reactions, transmission of infectious diseases and dermatological malignancy. None were observed in study subjects after 12-month follow-up.	• The risk profile of STRATAGRAFT is similar to currently marketed products and is acceptable.
Risk Management	The risk management plan includes: • Enhanced pharmacovigilance plan, including expedited adverse event reports within 15 days to FDA regarding dermatological malignancy(ies), unexpected infection and any clinical events suspicious of a xenogeneic cause • Additional measures associated with xenotransplantation nature of STRATAGRAFT (Appendix 1) • Adequate information provided in Prescribing Information (PI) and Patient Instruction Sheet • CMC-related safety PMR to conduct a more adequate viral inactivation study to more accurately quantify the viral log reduction of the collagen manufacturing process.	• The risks can be mitigated through enhanced pharmacovigilance plan, medical management, adequate PI, CMC PMR and additional postmarketing measures associated with xenotransplantation nature of STRATAGRAFT. No clinical PMC/PMR is required. • The data do not support the need for a risk evaluation and mitigation strategy (REMS).

11.2 Risk-Benefit Summary and Assessment

The overall risk-benefit is favorable for administration of STRATAGRAFT as a single topical application to adults with deep partial thickness thermal burns containing intact dermal elements for which surgical intervention is clinically indicated.

An unmet medical need exists for the treatment of deep partial thickness thermal burns containing intact dermal elements for which surgical intervention is clinically indicated that does not rely on healthy donor sites. Two clinical studies provide substantial evidence of effectiveness of STRATAGRAFT with meaningful clinical benefit with regard to complete wound closure and minimization of the need for skin autografts.

Available evidence indicates that the major known and potential risks associated with STRATAGRAFT, including potential transmission of infectious diseases, potential hypersensitivity reactions and potential risks associated with xenotransplantation product, can be prevented or mitigated by the proposed enhanced pharmacovigilance plan, routine medical practice and suitable prescribing information.

The applicant has provided substantial evidence of effectiveness and safety from an adequate and well-controlled study supported by an early phase study, and the benefit/risk profile is favorable for STRATAGRAFT for the proposed indication.

11.3 Discussion of Regulatory Options

The regulatory options include (1) standard approval; or (2) Complete Response (CR).

Reviewer Comment:
Due to inadequate information regarding viral clearance and inactivation during manufacturing of rat tail collagen, a CR was a potential consideration. However, the review team concluded that the benefit/risk profile is favorable in support of a traditional (regular) approval provided a safety CMC PMR viral inactivation study is conducted to more accurately quantify the viral log reduction of the collagen manufacturing process

The following were critically considered in the benefit / risk analysis in support of a traditional approval of STRATAGRAFT with a safety CMC PMR study as opposed to a CR:

- The review team's assessment is that although there is a potential risk of viral transmission during the manufacturing process, the risk is small due to risk mitigation measures such as testing of the collagen and animal source of the product. Additionally, the Applicant has adequate animal source risk mitigation measures, which include closed animal source, animal health monitoring and adventitious virus surveillance/testing. A CMC safety-related PMR viral inactivation study is expected to more accurately quantify the viral log reduction of the collagen manufacturing process and to ensure the safety of STRATAGRAFT following approval.

- STRATAGRAFT addresses an unmet medical need for the treatment of deep partial thickness (DPT) thermal burns and was granted RMAT designation.

- STRATAGRAFT reduces the need for an autograft for the treatment of DPT thermal burns, and associated donor site morbidity.

- In comparison to the marketed device, Epicel, STRATAGRAFT poses lower potential risks. Epicel manufacturing uses mouse feeder cells while STRATAGRAFT manufacturing no longer uses mouse cell feeders. Based on the extensive cell-line testing for xenotransplantation-related viruses, lack of detectable mouse (b) (4) in the product, and the NIKS cell line subsequently being cultured without the mouse feeder cells, potential xenotransplantation related risks are likely low.

- There has been no evidence of STRATAGRAFT associated transmission of adventitious agents in the treatment of over 120 patients over approximately 20 years of product development.

- It was noted that Biomedical Advanced Research and Development Agency (BARDA) has supported development of STRATAGRAFT.

11.4 Recommendations on Regulatory Actions

Based on analyses of the clinical safety and efficacy data contained in the BLA submission, the Clinical Reviewer considers the benefit/risk profile favorable in support of traditional approval of STRATAGRAFT for the treatment of adults with thermal burns containing intact dermal elements for which surgical intervention is clinically indicated (deep partial-thickness burns).

11.5 Labeling Review and Recommendations
FDA made substantial changes to each section of the Prescribing Information (PI), based on available clinical trial data, as well as FDA guidance on product labeling. The Clinical Reviewer and APLB consider the revised PI to be acceptable.

The overall content of the PI suitably conveys known information regarding safety and efficacy results demonstrated in clinical studies of STRATAGRAFT, as well as additional safety information obtained from the expanded access program.

The overall content of the PI contains adequate warnings for medical practitioners, as well as for caregivers, considering STRATAGRAFT for treatment of adults with deep partial thickness thermal burns, containing intact dermal elements for which surgical intervention is clinically indicated.

11.6 Recommendations on Postmarketing Actions

Based on the review of the safety data submitted in the BLA, the Applicant's proposed postmarketing risk mitigation plans are acceptable, which include: adequate risk mitigation information in the PI and Patient Information Sheet, enhanced pharmacovigilance plan, and a CMC-related safety PMR.

In addition to the routine pharmacovigilance and adverse event reporting in accordance with 21 CFR 600.80, the Applicant will submit expedited 15-day adverse event reports to FDA for dermatological malignancy(ies), unexpected infection and any

clinical events that are suspicious of a xenogeneic cause. The Applicant will also provide updates on its database of STRATAGRAFT patient and product information in the periodic safety reports at quarterly intervals for 3 years post-licensure and annual intervals thereafter ((21CFR 600.80(c)(2)).

FDA will require a safety CMC PMR study under Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act to identify unexpected serious risk of patient exposure to murine (rat) virus and subsequent viral infection, in association with the use of STRATAGRAFT. The available data do not suggest a safety concern that would warrant either a Risk Evaluation and Mitigation Strategy (REMS) or a safety-related PMR clinical study.

APPENDIX 1

Xenotransplantation Risk Mitigation Plan:

STRATAGRAFT xenotransplantation product designation plan, in accordance with the FDA Guidance for Industry, Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans (2016), was communicated with the Applicant in the Exemption Request Denial Letter, dated December 18, 2020.

The plan includes the following:

a. Stratatech will archive samples of the final product from every other lot.

b. Stratatech will obtain baseline, i.e., pre-treatment, samples of the patient's blood for archiving.

c. STRATAGRAFT recipients, but not their intimate contacts, should defer from donating whole blood, blood components, source plasma, source leukocytes, tissues, breast milk, ova, sperm, or other body parts for use in humans.

d. The Prescription Information (PI) and patient instruction sheet will communicate to the patient, or through the treating physician, the xenogeneic nature of STRATAGRAFT.

e. Stratatech will ensure that the patient's medical record indicates that the patient has been treated with a xenotransplantation product. The record will state: This patient has been treated with STRATAGRAFT (allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen - dsat), a product manufactured with human cells previously exposed to murine cells.

f. The patient instruction sheet will communicate to the patient and through the treating physician that the patient should consider allowing an autopsy examination of their body upon death.

g. Stratatech will maintain a database to collect STRATAGRAFT patient and product information. This information will be provided to the FDA in the periodic safety reports (Periodic Adverse Experience Reports (PAERs)) at quarterly intervals, for 3 years from the date of issuance of the biologics license, and then at annual intervals ((21CFR 600.80(c)(2)).

h. Stratatech will provide expedited adverse event reports within 15 days to FDA regarding dermatological malignancy(ies), unexpected infection and any clinical events that are suspicious of a xenogeneic cause.

i. STRATAGRAFT recipients will be passively monitored. Stratatech will conduct active investigation of any suspicious clinical events reported to Stratatech.

On January 25, 2021, Stratatech proposed (b) (4) The Applicant's proposal is currently under review.

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