Application Type	Original BLA
STN	125730/0
CBER Received Date	Jun 5, 2020
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Division / Office	DCEPT/OTAT
Committee Chair	Steven Bauer. PhD
Clinical Reviewer(s)	Rosa Sherafat-Kazemzadeh, MD
Project Manager	Candace Jarvis
Priority Review	Yes
Reviewer Name(s)	Stan Lin, Ph.D., FDA/CBER/OBE/DB/TEB
Review Completion Date / Stamped Date	
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	John Scott, Ph.D. Director, FDA/CBER/OBE/DB
Applicant	Stratatech Corp
Established Name	StrataGraft-Allogeneic Keratinocyte Cell Line (NIKS), Seeded on Rat Collagen ((b) (4)) Conditioned with Human Dermal Fibroblasts ((b) (4))]
(Proposed) Trade Name	Stratagraft
Pharmacologic Class	Viable allogeneic bi-layered tissue engineered skin replacement construct
Formulation(s), including Adjuvants, etc.	Single rectangular units (100 cm^2 surface per unit, ~8 x 12.5 cm).
Dosage Form(s) and Route(s) of Administration	Tissue patch
Dosing Regimen	100 cm^2
Proposed Indication(s) and Intended Population(s)	To promote durable wound closure & regenerative healing in the treatment of adult patients with (b) (4) thermal burns that contain intact dermal elements, and for which surgical intervention is clinically indicated

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GLOSSARY, ABBREVIATIONS AND DEFINITIONS OF TERMS

AE Adverse event
Baux Score Age + % TBSA
BSA Bovine serum albumin
CBER Center for Biologics Evaluation and Research
CFR Code of Federal Regulations
CI Confidence interval
CRF Case report form
CRMTS CBER Regulatory Meetings Tracking System
CSR Clinical study report
DNA Deoxyribonucleic acid
DPT Deep partial-thickness
FPRS FACES pain rating scale
GRAS Generally recognized as safe
HDE Humanitarian Device Exemption
HLA Human Leukocyte Antigens
IMM Independent medical monitor
IND Investigational new drug application
ISE Integrated Summary of Efficacy
ISS Integrated Summary of Safety
MHC Major Histocompatibility Complex
mITT Modified Intent-to-Treat
MM Medical monitor
NCS Not clinically significant
NHDF Normal human dermal fibroblasts
NK Natural killer
NIKS® Near-diploid human keratinocytes PBMC Peripheral blood mononuclear cells
PD Pharmacodynamic
PK Pharmacokinetic
POSAS Patient and Observer Scar Assessment Scale
PRA Panel reactive antibody
RMAT Regenerative Medicine Advanced Therapy
SAE Serious adverse event
SAP Statistical analysis plan
SD Standard deviation
SOC System organ class
STR Short tandem repeats
TBSA Total body surface area
TEAE Treatment-emergent adverse event

1. Executive Summary

This BLA seeks licensure of StrataGraft skin tissue for the treatment of adult patients with (b) (4) thermal burns that contain intact dermal elements, and for which surgical intervention is clinically indicated. Two clinical studies, Strata2016 and Strata2011, are used to support the efficacy of StrataGraft skin tissue for the treatment of DPT thermal burns.

Study Strata2016 was a prospectively designed phase 3 study with co-primary efficacy endpoints: 1) the difference in the percent area of the StrataGraft treatment site and control autograft treatment site that was autografted by Month 3, and 2) the proportion of subjects achieving durable wound closure of the StrataGraft treatment site at Month 3 without autograft placement. For the first co-primary endpoint, there was a mean difference of 97.8 percent area autografted by Month 3 between the two treatments (4.3 for StrataGraft site vs. 102.1 control autograft site). For the second co-primary endpoint, 59 (83.1%) subjects in the ITT population achieved durable wound closure of the StrataGraft treatment site at Month 3 without the need for autografting. The lower bound of the 95% CI was 74.4%, which was greater than the pre-defined success criterion of 50%. Consistent results were observed with the per-protocol population for both coprimary endpoints. Pre-specified secondary efficacy endpoints were also analyzed for the study, but these endpoints were essentially completely redundant with the first coprimary endpoint and do not add additional information.. Overall, the results of the study Strata2016 met the prespecified statistical success criteria of the efficacy endpoints.

Strata2011 was a small phase1b study whose intended purpose was primarily to assess the safety and tolerability of StrataGraft skin tissue compared to autograft in the deep partial-thickness component of complex skin defects due to thermal burns requiring surgical excision and autografting. For the three cohorts with 29 treated subjects, 27 achieved durable wound closure of the StrataGraft treatment site at Month 3 without the need for autografting (93.1%). Taken together, the results of the two studies support the applicant's proposed indication for StrataGraft skin tissue in this BLA.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

The product is intended as a treatment to promote durable wound closure and regenerative healing in the treatment of adult patients with (b) (4) thermal burns that contain intact dermal elements, and for which surgical intervention is clinically indicated. The product for this application is a viable allogeneic bi-layered tissue engineered skin replacement construct manufactured as single rectangular units (100cm^2 surface per unit, ~8 x 12.5 cm). Each manufacturing run produces (b) (4). Each unit is individually cryopreserved and packaged for shipment to clinical sites. Manufacturing utilizes two human cell lines, normal human dermal fibroblasts and an immortalized keratinocyte cell line which was isolated and expanded on mouse fibroblasts, making this a xenotransplantation product. This product has been under IND 10113 since 2002. It has Orphan and RMAT designations and has been granted priority review.

StrataGraft skin tissue, a viable and metabolically active allogeneic human NIKS® keratinocytes and human dermal fibroblasts, contains an epidermal layer comprising differentiated, multilayered, epidermal keratinocytes from a single human donor grown on a xenogeneic collagen matrix embedded with fibroblasts from a second human donor. StrataGraft skin tissue is not a subject-specific product; it is produced from well- characterized banks of keratinocytes and fibroblasts. StrataGraft skin tissue reproduces many of the structural and biological properties of normal human skin and is intended to provide immediate wound coverage, barrier

function, and sustained expression of wound healing factors to promote the healing of complex skin defects.

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

Currently, two medical products are approved by the FDA for the treatment of deep-dermal or full-thickness burns that provide definitive wound closure. Epicel® uses patient-specific keratinocytes obtained via biopsy and grown in culture over about 2 weeks, which are then applied in thin sheets of 2 to 8 cell layers thick to burns greater than or equal to 30% TBSA. Epicel is only available under a Humanitarian Device Exemption (HDE) from the FDA (Epicel, 2016) and is traditionally used as a life-saving measure when there is inadequate skin to cover very large burns. The RECELL® Autologous Cell Harvesting Device is also reliant upon the patient's own epidermal cells and is used to create and spray a cell suspension onto DPT wounds of less than 20% TBSA (RECELL, 2018). Both available treatment methods require the harvest of the patient's own skin cells, albeit smaller amounts than traditional donor site harvest.

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

N/A

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

Date	Type of Correspondence or Agency Agreements/Recommendations
7Nov2001	Original IND application
25Oct2001	Pre-IND Meeting Minutes
2Jul2002	Clinical Hold completed response
6May2011	End of Phase 1 Meeting Minutes (CRMTS #7916)
21May2012	FDA granted Orphan Drug designation
13Jan2015	Pre Phase 3 Meeting Minutes (CRMTS #9593)
16Jun2016	Pre Phase 3 Meeting Minutes (CRMTS #10256)
29Mar2017	Type C CMC Meeting Minutes (CRMTS #10586)
18Apr2017	Type C CMC Meeting Minutes (CRMTS #10626)
23Mar2018	CMC RMAT Meeting Minutes (CRMTS #11058)
23Mar2018	Clinical RMAT Meeting Minutes (CRMTS #11059)
18Jan2019	Type B CMC Meeting Minutes (CRMTS #11587)
27Aug2019	Proprietary name (StrataGraft) Conditionally Acceptable
4Oct2019	Pediatric Written Response (CRMTS #12038)
15Oct2019	Type B CMC Meeting Minutes (CRMTS #11198)
22Nov2019	Pre-BLA Meeting Minutes (CRMTS #12108)
24Mar2020	Correspondence regarding Rolling Review

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting an in-depth and complete statistical review without unreasonable difficulty.

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

NA

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The submission states that the primary evidence supporting the efficacy of StrataGraft skin tissue for the treatment of DPT thermal burns is derived from two studies, STRATA2016 and STRATA2011. Therefore, these two studies will be the focus of this review.

Both studies were designed as 12-month, open-label, multicenter, US, randomized, and controlled studies that evaluated the efficacy and safety of StrataGraft skin tissue for the treatment of DPT thermal burns. Eligible subjects were required to have 3% to 49% TBSA wounds including a thermal injury containing intact dermal elements for which surgical excision and autografting were clinically indicated. For each subject, two comparable treatment sites were prospectively identified and randomized to receive either a single topical application of StrataGraft skin tissue or autograft, such that each subject received both treatments.

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

The basis of this statistical memo is clinical study reports and data sets submitted in module 5 of the BLA submission.

5.3 Table of Studies/Clinical Trials (DPT thermal burns indication)

Table 1: List of studies pertinent to this BLA

Study Status	**Study Design**	**Objectives/Purpose**	**Study Treatment planned regimen** Route of administration	**Study Population**	**Country** (Number of Study Centers)
STRATA2016 Ongoing (n=71)	Phase 3, open-label, controlled, randomized multicenter; US, intra patient comparator = autograft First subject enrolled: May 17 BLA data cutoff date: 31 Jul 19	Assess the efficacy and safety of a single application of StrataGraft skin tissue in the treatment of complex skin defects caused by thermal burns and that contain dermal elements	Up to 1,000 cm^2 cryopreserved StrataGraft skin tissue (maximum used: 960 cm^2) Single topical application	71 subjects, aged ≥18 years with complex skin defects of 3% to 49% TBSA caused by thermal burns, with area(s) of deep partial-thickness wounds (ie, those containing intact dermal elements)	United States (12)
STRATA2011 Completed (n=30)	Phase 1b open-label, controlled, randomized, multicenter, US, dose escalation; intrapatient comparator = autograft First subject, first visit: 21 Sep 11 Last subject, last visit: 08 Oct 14	Assess the safety, tolerability, and efficacy of prolonged exposure to increasing amounts of a single application of StrataGraft skin tissue compared to autograft in the deep partial-thickness component of complex skin defects due to thermal burns requiring surgical excision and autografting	Cohort 1: up to 220 cm^2 of refrigerated StrataGraft skin issue (maximum used: 216 cm^2) Cohort 2: up to 440 cm^2 of refrigerated StrataGraft skin tissue (maximum used: 440 cm^2 Cohort 3: up to 440 cm^2 of cryopreserved StrataGraft skin tissue Single topical application maximum used: 440 cm^2)	30 subjects, aged ≥18 to 65 years with complex skin defects of 3% to 49% TBSA caused by thermal burns, with area(s) of deep partial-thickness wounds (ie, those containing intact dermal elements)	United States (6)

Data source : Module 5 of Tabular listing of clinical studies

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1 (Study STRATA2011)

6.1.1 Objectives

The primary objectives of this phase 1b, open-label, controlled, randomized, dosage-escalation study in adult volunteers were to evaluate the safety, tolerability, and efficacy of prolonged exposure to increasing amounts of a single application of StrataGraft skin tissue compared to autograft in the deep partial-thickness component of complex skin defects due to thermal burns requiring surgical excision and autografting.

6.1.2 Design Overview

The protocol specified 30 subjects with complex thermal burns involving 3% to 49% TBSA to participate in the study, with 10 subjects in each of 3 different cohorts, at 6 study sites. For each of the subjects, 2 wounds of comparable depth were identified, with 1 site randomized to treatment with StrataGraft skin tissue and the other site serving as a control (autograft) site. In Cohorts 2 and 3, the StrataGraft skin tissue treatment site could be up to twice the area of control (autograft) treatment site. Two donor sites were designated to provide a source of autograft skin for the control treatment site and, if needed, the StrataGraft skin tissue treatment site. Both the StrataGraft skin tissue and control (autograft) were placed on the treatment sites immediately after surgical excision of nonviable tissue.

6.1.3 Population

STRATA2011 enrolled 30 subjects with 3% to 49% TBSA complex skin defects including a deep partial-thickness component resulting from thermal injury that required surgical excision and autografting. Detailed inclusion and exclusion criteria are specified in the protocol. The

screening period for candidate study participants lasted for up to 4 days. Subjects who failed to satisfy all inclusion/exclusion requirements after the screening period were replaced and were not included in the final enrollment numbers.

6.1.4 Study Treatments or Agents Mandated by the Protocol

StrataGraft skin tissue was supplied as a sterile, cream-colored, circular, skin substitute that can be meshed and sutured, with a surface area of 44 cm^2 per unit. The sponsor provided both refrigerated and cryopreserved StrataGraft skin tissue to the clinical study sites. Refrigerated StrataGraft skin tissue was supplied in a shipping chamber containing a (b) (4) for storage at 2°C to 8°C. Cryopreserved StrataGraft skin tissue was supplied to the clinical site on dry ice for storage at -70°C to -90°C. StrataGraft skin tissue was shipped and maintained according to product storage conditions described in the IND for this product. The primary and secondary containers containing the StrataGraft skin tissue were appropriately sealed and labeled according to FDA requirements (21CFR 312.6). Final product labeling consisted of a large primary label that included study protocol number, lot number, product identity, and expiration date and 2 small, removable, and adhesive labels.

6.1.6 Sites and Centers

This study was conducted at 6 study centers in the US.

6.1.7 Surveillance/Monitoring

The Wake Forest School of Medicine (WFSM) IRB served as the coordinating IRB for the study. An I-DSMB (Institutional Data and Safety Monitoring Board) provided a source of independent oversight for the study. The clinical sites were monitored by the I-DSMB throughout the study. In addition to the board membership of the WFSM I-DSMB, an ad hoc member with expertise in trauma was included on the I-DSMB for this study. All members were to be independent of the study conduct.

6.1.8 Efficacy endpoints

6.1.8.1 Primary efficacy endpoints

- The proportion of injury treatment sites that achieved complete wound closure by Month 3, defined as at least 95% re-epithelialization in the absence of drainage
- Percent area of the StrataGraft treatment site requiring autografting by day 28

6.1.8.2 Secondary efficacy endpoints

- Proportion of treatment site wounds completely closed at Days 7, 14, and 28, and Months 3, 6 and 12.
- Percent wound closure (re-epithelialization) at Days 7, 14, and 28, and Months 3, 6, and 12.
- Appearance of treatment sites at Days 3, 7, 14, and 28.
- Pain of donor sites measured by FACES pain rating scale at Days 3, 7, 14, and 28.
- Cosmesis of treatment sites at Months 3, 6, and 12.
- Cosmesis of donor sites at Months 3, 6, and 12.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Study hypothesis:

As a phase 1b study, the focus was on safety and tolerability. Even though the study protocol listed efficacy endpoints, but no formal hypothesis testing was planned for the study and there was no power calculation for detecting statistically significance for any clinical endpoints.

Analysis populations

a. The Intent-to-Treat (ITT) population consists of all patients who received any amount of StrataGraft skin tissue, regardless of follow-up status. All safety and efficacy analyses will be performed on this population.
b. Per-protocol population includes any patients who received any amount of StrataGraft skin tissue and did not have major protocol violations. All primary and secondary efficacy analyses were also be performed on this population.

Statistical methods

Only descriptive statistics were planned. No formal hypothesis testing was planned for the study. But some inferential testing was done post-hoc in order to identify trends and for planning future studies. The lack of prespecification makes the statistical significance or non-significance of study results uninterpretable.

Sample size
The planned sample size was 30 subjects with complex thermal burns involving 3% to 49% TBSA, with 10 subjects in each of 3 different cohorts, at 6 study sites.

Interim analyses
No interim analyses of efficacy were planned for this study. One interim safety review by the DSMB was scheduled after the fifth subject in Cohort 1 completed the Month 3 session and prior to enrollment of Cohort 3.

Subgroup analysis
None planned.

Missing data
No imputations or other plans for missing data.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

6.1.10.1.1 Demographics

Table 2 Summary of Demographic Characteristics: Intent-to-Treat Population

	Cohort 1 (N=10)	Cohort 2 (N=10)	Cohort 3 (N=10)	Overall (N=30)
Age (yrs.)				
Mean	39.7	42.1	41.3	41.0
Median	40.5	38.5	37.5	38.0
STD	11.54	13.07	12.94	12.14
(Min, Max)	(22, 58)	(21, 63)	(23, 59)	(21, 63)
Sex, N (%)				
Male	7 (70.0)	5 (50.0)	9 (90.0)	21 (70.0)
Female	3 (30.0)	5 (50.0)	1 (10.0)	9 (30.0)
Race, N (%)				
White	9 (90.0)	9 (90.0)	10 (100)	28 (93.3)
Black or African American	1 (10.0)	1 (10.0)	0 (0.0)	2 (6.7)
Ethnicity, N (%)				
Hispanic or Latino	0 (0.0)	1 (10.0)	(30.0)	4 (13.3)
Not Hispanic or Latino	10 (100)	9 (90.0)	(70.0)	26 (86.7)
Height (cm)				
Mean	173.9	171.8	174.9	173.6
Median	173.7	171.5	176.5	173.7
STD	7.74	10.95	12.22	10.19
(Min, Max)	(160, 188)	(155, 190)	(157, 196)	(155, 196)
Weight (kg)				
N	10	10	10	30
Mean	82.9	92.2	88.6	87.9
Median	81.7	88.4	90.2	88.4
STD	21.91	28.06	17.78	22.50
(Min, Max)	(52.3, 129)	(46.3, 140)	(63.5, 120)	(46.3, 140)
Time Burn to Placement (days)				
N	10	10	10	30
Mean	7.9	6.9	6.8	7.2
Median	8.0	6.5	6.5	7.0
STD	3.38	2.96	2.86	3.01
(Min, Max)	(3.0, 13.0)	(3.0, 11.0)	(4.0, 12.0)	(3.0, 13.0)

Source: Table 14.1.1.4 of study report.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Baseline disease characteristics of subjects are summarized in the following table 2.

Table 3: Summary of Baseline Characteristics

	Refrigerated StrataGraft Skin Tissue		Cryopreserved StrataGraft SkinTissue	
	Cohort 1 (N = 10)	**Cohort 2 (N = 10)**	**Cohort 3 (N = 10)**	**Overall (N = 30)**
TBSA (%)				
N	10	10	10	30
Mean	9.2	16.0	16.5	13.9
Median	9.0	15.0	9.9	10.0
SD	5.93	9.45	12.59	9.96
(Minimum, Maximum)	(3.0, 21.8)	(6.0, 33.0)	(5.3, 43.0)	(3.0, 43.0)
Total 2° (%)				
N	10	10	10	30
Mean	5.5	11.3	14.4	10.4
Median	4.5	10.9	7.9	6.8
SD	3.93	7.57	12.20	9.11
(Minimum, Maximum)	(0.0, 13.3)	(2.3, 28.5)	(2.0, 38.5)	(0.0, 38.5)
Total 3° (%)				
N	10	10	10	30
Mean	3.8	4.7	2.1	3.5
Median	0.8	3.0	0.5	1.3
SD	4.70	6.69	2.50	4.90
(Minimum, Maximum)	(0.0, 12.0)	(0.0, 22.0)	(0.0, 6.0)	(0.0, 22.0)
Potential Treatment Sites				
Erythema	1 (10.0)	2 (20.0)	3 (30.0)	6 (20.0)
Swelling	1 (10.0)	1 (10.0)	2 (20.0)	4 (13.3)
Local Warmth	1 (10.0)	2 (20.0)	3 (30.0)	6 (20.0)
Areas Surrounding Potential Treatment Sites				
Erythema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Swelling	1 (10.0)	0 (0.0)	0 (0.0)	1 (3.3)
Local Warmth	0 (0.0)	0 (0.0)	1 (10.0)	1 (3.3)
Are potential treatment sites infected?	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Cohort 1 = Refrigerated StrataGraft skin tissue, up to 220 cm^2; Cohort 2 = Refrigerated StrataGraft skin tissue, up to 440 cm^2; Cohort 3 = Cryopreserved StrataGraft skin tissue, up to 440 cm^2; 2°, 3° denote second or third degree burns Source: Tables 14 1 1 5 and 14 2 1

6.1.10.1.3 Subject Disposition

Subject disposition is listed in table 4 below (all enrolled subjects). Of the 30 enrolled subjects, there were ten in each of the three cohorts. Comparable numbers (1 to 2) per cohort were lost to follow up; comparable numbers (0 to 1) per cohort had a major protocol deviation and were removed from the PP population, resulting in 26 (86.7%) completers.

Table 4: Subject Disposition

	Refrigerated StrataGraft Skin Tissue		Cryopreserved StrataGraft Skin Tissue	
	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 ITT population	10 (100.0)	10 (100.0)	10 (100.0)	30 (100.0)
Subjects who completed	9 (90.0)	9 (90.0)	8 (80.0)	26 (86.7)
Subjects who discontinued /due to lost to follow up	1 (10.0)	1 (10.0)	2 (20.0)	4 (13.3)

Cohort 1 = Refrigerated StrataGraft skin tissue, up to 220 cm^2; Cohort 2 = Refrigerated StrataGraft skin tissue, up to 440 cm^2;
Cohort 3 = Cryopreserved StrataGraft skin tissue, up to 440 cm^2
Source: Table 14 1 1 1 of study report

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoints

Wound Closure of Treatment Sites at Month 3

In the ITT population, across the three cohorts, the proportion of injury treatment sites that achieved complete wound closure by Month 3, defined as at least 95% re-epithelialization in the absence of drainage, were comparable: 93.1% in the StrataGraft treatment sites and100% in the autograft treatment sites. Table 5 displays the wound closure at month 3 for the ITT population.

Table 5: Wound Closure at Month 3 (ITT Population)

	Refrigerated StrataGraft Skin Tissue		Cryopreserved StrataGraft Skin Tissue	
	Cohort 1 (N = 10)	Cohort 2 (N = 10)	Cohort 3 (N = 10)	Overall (N = 30)[a]
ITT population at Month 3	**N = 10**	**N = 10**	**N = 9**	**N = 29**
StrataGraft treatment site closed?				
Yes	10 (100.0)	8 (80.0)	9 (100.0)	27 (93.1)
No	0 (0.0)	2 (20.0)	0 (0.0)	2 (6.9)
StrataGraft estimated % re-epithelialization				
Mean	100	93.5	100	97.8
Median	100	100	100	100
SD	0.00	15.99	0.00	9.60
(Min, Max)	(100, 100)	(50.0, 100)	(100, 100)	(50.0, 100)
Autograft treatment site closed?				
Yes	10 (100.0)	10 (100.0)	9 (100.0)	29 (100.0)
No	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Autograft estimated % re-epithelialization				
Mean	100	100	100	100
SD	0.00	0.00	0.00	0.00

[a]At Month 3 (Session 6), the total "n" for the ITT population was 29 One study subject was not treated with StrataGraft skin tissue

Cohort 1 = Refrigerated StrataGraft skin tissue, up to 220 cm^2; Cohort 2 = Refrigerated StrataGraft skin tissue, up to 440 cm^2; Cohort 3 = Cryopreserved StrataGraft skin tissue, up to 440 cm^2

Percent Area of StrataGraft Skin Tissue Treatment Site Requiring Autografting by Day 28

Overall, across the cohorts, the percent treatment area autografted by Day 28 was 0% for StrataGraft skin tissue and 100% for control autograft treatment sites. That is, no subjects required autograft at the StrataGraft skin tissue treatment site by Day 28.

6.1.11.2 Descriptive Results of Secondary Endpoints

- The wound closure rate across all 3 cohorts was lower at the StrataGraft treatment site through Day 28 for the ITT population, and Day 14 for the PP population, but was not different from the autograft treatment site by Month 3 in either population. For the ITT population subjects with data available at Month 6 and Month 12, there was 100% wound closure for all sites receiving either treatment.

- Within the ITT population compared per cohort, by Day 28 there were no substantial differences in either the percent closure (re-epithelialization) at the StrataGraft and autograft treatment sites, or the proportion of wounds achieving complete closure.

- Wound appearance was evaluated based on color (percent pinkness), percent adherence of the graft, and percent graft tissue remained intact. All overall mean scores (percntages) 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 the StrataGraft skin tissue 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 those for the StrataGraft skin tissue sites for each characteristic.

- No StrataGraft donor sites were harvested through Day 28. Accordingly, subjects reported less pain at the StrataGraft 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 skin tissue donor site at Day 3 to Day 28.

  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 skin tissue donor site and harvested autograft donor site.

- Scar scores were assessed with the POSAS (V2.0) where the total score is the sum of 6 different assessments. Mean total scores from observer assessments of scarring were not significantly different between the StrataGraft skin tissue and autograft treatment sites in any cohort and at any time point from Month 3 through Month 12 by Wilcoxon Signed-Rank test.

6.1.11.3 Subpopulation Analyses

This study did not plan or include the usual subgroup (e.g., sex, age, … etc.) analysis, perhaps due to it's a phase 1b study and the sample size was small.

6.1.11.4 Dropouts and/or Discontinuations

Section 6.1.10.1.3 above on subject disposition contains subject completion and early termination information.

6.1.12 Safety Analyses

This section summarizes safety results of Study STRATA2011.

6.1.12.1 Methods

All subjects were treated with 1 application of StrataGraft skin tissue and at least 1 application of autograft. The dosage of StrataGraft skin tissue applied ranged from 52 to 440 cm^2 per subject. Enrollment into subsequent cohorts began only after the I-DSMB had reviewed the interim safety data from Cohort 1 and recommended advancement to the next cohort. Based on review of

the interim analysis report, the I-DSMB recommended continuation to Cohort 2, and subsequently, Cohort 3.

6.1.12.2. Adverse Events

In total, 27 of 30 (90%) subjects had at least 1 TEAE. Five subjects (16.7%) had a TEAE that was possibly/probably related to the study drug, and 6 subjects (20%) had a total of 11 SAEs. One subject in Cohort 2 had a moderately severe SAE that the investigator considered possibly related to StrataGraft skin tissue, however, this event was associated with a major protocol deviation in which StrataGraft skin tissue was placed on a wound that did not meet eligibility criteria for inclusion in the study (full-thickness wound). The sponsor, MM, and IMM judged the event to be unrelated to StrataGraft skin tissue treatment, but rather was a function of the protocol deviation.

6.1.12.3 Deaths
No subjects died or discontinued the study because of a TEAE.

6.1.12.4 Non-fatal Serious Adverse Events
The study reported 104 of 117 (88.9%) TEAEs were mild or moderate in severity. Nine subjects reported 13 TEAEs that were considered severe. None of the severe TEAEs was considered related to study treatment, and all severe TEAEs resolved. Seven of the 13 severe TEAEs were considered SAEs.

6.2 Trial #2 (Study Strata2016)

6.2.1 Objectives

The primary objectives of the study were to evaluate whether treatment with StrataGraft skin tissue reduced the need for donor site harvest and autograft transplantation, and whether the StrataGraft-treated sites were durably closed at Month 3 without autografting.

The secondary objectives included the evaluation of additional efficacy endpoints including pain and cosmesis of the donor sites, cosmesis of the treatment sites, number of days of hospitalization due primarily to pain at the 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, physician and subject satisfaction with the healing of the study treatment sites, and the presence of allogeneic deoxyribonucleic acid (DNA) from StrataGraft skin tissue at Month 3.

6.2.2 Design Overview

Study Strata2016 was an open-label, controlled, randomized study of the efficacy and safety of StrataGraft skin tissue in promoting the healing of deep partial-thickness (DPT) wounds. Potential study treatment sites were excised to remove nonviable tissue and 2 areas of comparable depth were identified on each subject. These 2 areas were designated as study treatment sites A and B. Following surgical excision, the treatment sites were randomly assigned

to receive a single application of StrataGraft skin tissue on 1 treatment area and autograft on the other treatment area. Subjects could receive up to 1,000 cm^2 of StrataGraft skin tissue. The area of the StrataGraft treatment site was allowed to be up to twice that of the comparable autograft study treatment site to enable evaluation of larger treatment areas of StrataGraft skin tissue. StrataGraft skin tissue was left in place and wound closure was assessed during the course of the study.

6.2.3 Study Population

The population was subjects aged ≥18 years with acute wounds due to thermal burns and involving 3% to 49% total body surface area (TBSA). Detailed inclusion and exclusion criteria are listed in Section 8.3 of the clinical study report.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Subjects were treated with StrataGraft skin tissue, which is a cryopreserved, cream-colored, rectangular, viable, bioengineered regenerative skin construct with a surface area of approximately 100 cm^2.

Potential study treatment sites were excised to remove nonviable tissue and 2 areas of comparable depth on each subject were designated as study treatment sites A and B. The treatment sites were randomly assigned to receive a single topical application of StrataGraft skin tissue on 1 treatment area and autograft on the other treatment area. Subjects could receive up to 1,000 cm^2 StrataGraft skin tissue.

6.2.6 Sites and Centers

This study was conducted at 12 study centers in the U.S. James H. Holmes, IV, MD and Angela Gibson, MD, PhD, FACS, were the coordinating investigators.

6.2.7 Surveillance/Monitoring

A DSMB was chartered to monitor and evaluate the safety of all subjects in this study. Ongoing safety of study subjects was monitored by the Medical Monitor (MM) and the DSMB, which was independent of study conduct. In the event that an SAE as described above occurred, the FDA, local IRB, and DSMB were to be notified. The MM was to review the safety data associated with the adverse reaction with the clinical investigator and generate a summary narrative. The MM and DSMB were to then conduct a comprehensive review of the safety data and present their findings to the FDA prior to resumption of subject enrollment.

6.2.8 Endpoints and Criteria for Study Success

6.2.8.1 Co-Primary endpoints:

1) Percent Area of Study Treatment Sites Requiring Autografting by Month 3. This co-primary endpoint was selected to assess the efficacy of StrataGraft skin tissue for reducing the amount of autologous skin tissue surgically harvested.

Comment: Note that the autograft treated sites were initially treated with 100% autograft. Therefore, by design of the study, fewer StrataGraft sites would require autograft unless every single StrataGraft site required autograft.

2) Proportion of Wound Closure of the StrataGraft Treatment Site at Month 3 without autografting. This was the proportion of subjects that achieved durable wound closure of the StrataGraft treatment site at Month 3 without any autograft placement. Durable wound closure at Month 3 was defined as wound closure at 2 consecutive study sessions, at least 2 weeks but no greater than 5 months apart, and including or encompassing the Month-3 time point.

Wound closure of the treatment site was defined as complete skin re-epithelialization and the absence of drainage. A subject whose StrataGraft treatment site had achieved durable wound closure without autograft placement was classified as a responder. This endpoint was focused solely on the StrataGraft treatment site.

6.2.8.2 Ranked secondary efficacy endpoints:

a) Pain at Donor Site Through Day 14

Pain from each study donor site was evaluated using the FPRS. Scores were averaged through Day 14 for each donor site. The actual donor sites harvested were evaluated if the pre-identified site was not harvested. For the StrataGraft-treated wounds that did not require harvest of the donor site, the pre-identified site was evaluated. The difference between the average pain intensities through Day 14 between the StrataGraft donor site and the autograft donor site were analyzed with a 1-sided, 0.025 level paired t-test under the null hypothesis that the mean difference was 0. The average pain intensities were summarized descriptively by site.

b) Donor Site Cosmesis at Month 3

Donor site cosmesis was evaluated using the observer total POSAS score at Month 3. The difference between the total observer POSAS scores of the autograft donor site and the StrataGraft potential or harvested donor site were analyzed with a 1-sided, 0.025 level paired t-test under the null hypothesis that there was no difference between the 2 donor sites.

c) Study Treatment Site Cosmesis at Month 12

Treatment site cosmesis was evaluated using the observer total POSAS score at Month 12. The difference between the autograft treatment site and StrataGraft treatment site for the total observer POSAS score was analyzed with a 1-sided, 0.025 level paired t-test under the null hypothesis that there is no difference between the 2 treatment sites.

Because the time for the last ranked primary endpoint is 12 months and the database lock for the primary endpoint assessments reported in the study report was Month 4 (ie, database lock after last subject completes the Month 4 visit), the data for this endpoint are incomplete and the results

are not considered as final results. The final analysis and conclusion for the endpoint will be based on the final database once all subjects complete the Month-12 assessment.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Study hypothesis:

For the first co-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.

> **Note:** By the design of the study, autograft treatment sites had 100% area autografted at initial treatment, and this number could not go down (but could go up) over time. The StrataGraft treatment sites had no autograft at the initial treatment. Therefore, for this null hypothesis to be true, StrataGraft sites would require an average of at least 100% surface area autograft rescue between initial treatment and Month 3.

Because all control sites were autografted, the second co-primary endpoint of proportion of subjects whose StrataGraft treatment site is durably closed at Month 3 without autografting is an uncontrolled analysis. The null hypothesis was that at least 50% of the subjects' StrataGraft treatment sites were durably closed at Month 3 without autografting.

> **Note:** The null hypothesis of 50% was agreed to between the sponsor and FDA. After discussions with the clinical review team and searching relevant documents, I was unable to determine the scientific rationale for the 50% null hypothesis.
>
> Note also, if this null hypothesis was rejected, which it was, the results of this second coprimary endpoint would lend support for the first coprimary endpoint because it would establish that >= 50%of SG subjects do not require to be autografted, far greater than the 25% difference postulated for the alternative hypothesis for the first coprimary endpoint.

Analysis populations

a. The Intent-to-Treat (ITT) population consisted of all subjects with randomized study treatment sites, which was used for the co-primary efficacy evaluations.
b. Per-Protocol (PP) population: All subjects who had no major protocol violations during the study.

Statistical methods

As described in section 6.2.8, there were 2 co-primary endpoints analyzed for this study: 1) superiority in percent area of treatment site requiring autografting by Month 3, and 2) proportion of subjects that achieved durable wound closure of the StrataGraft treatment site at Month 3 without any autograft placement. The performance criterion for StrataGraft durable wound closure was set at 50%. Both endpoints were supposed to be shown to be statistically significant

in order to claim a study success. (The significance level for both analyses was set at 1- sided 0.025.)

Comment: Stated another way, the null hypothesis for the proportion P of durable wound closure of the StrataGraft treatment site without autografting is

H_0: $P \leq 0.5$ vs H_1: $P > 0.5$.

Note also, this endpoint was focused solely on the StrataGraft treatment sites because the whole control group was treated with autograft. FDA agreed with the 50% success criterion.

The secondary endpoints were tested at 1-sided with 0.025 Type I error rate as pre-specified, in a hierarchical rank order, with significance declared only if all previous endpoints were significant at 1-sided significance level of 0.025 Type I error.

Primary endpoints analysis

The null hypothesis on the percent area autografted was proposed to be compared between the StrataGraft and autograft treatment sites using the Wilcoxon Signed Rank test. The second co-primary endpoint was specified to be tested using a one-sided the normal approximation to the binomial proportion.

Secondary endpoints analysis: As mentioned, statistical tests for the ranked secondary efficacy endpoints were described along with the list of these endpoints in section 6.2.8.2 above.

Sample size

Assuming a difference of 75% between the two groups with a standard deviation of 0.75 for the first primary endpoint, a sample size of 20 subjects would provide greater than 90% power to reject the null hypothesis of no difference at one-sided Type I error of 0.025, using a Wilcoxon Signed Rank test of the paired difference.

For the proportion of subjects whose StrataGraft treatment site is durably closed at Month 3 without autografting, a sample size of 70 subjects would provide greater than 80% power to determine, at one-sided type I error rate of 0.025, that at least 50% of the subjects' StrataGraft treatment sites are durably closed at Month 3 without autografting, under the assumption that the actual proportion of subjects with closed StrataGraft treatment sites without autografting would be greater than 67%.

The sample size required was much larger with the second co-primary endpoint, the proportion of durable wound closure of the StrataGraft treatment site without autografting. With a sample size of 70 subjects the study achieves at least 80% power for both statistical tests. (The actual study enrolled 71 subjects.)

Interim analyses

No interim analysis was planned.

Subgroup analysis

Each co-primary endpoint outcome was summarized by the following demographic and baseline characteristics:

- Race (white, non-white).
- Ethnicity (Hispanic, non-Hispanic).
- Age (18-64, ≥65).
- Sex (female, male).
- Size of the StrataGraft treatment area (<250 cm^2, 250 to 500 cm^2, >500 cm^2).

Missing data approaches

a) Imputation of the difference in the percent area autografted co-primary Endpoint

For the co-primary endpoint of the difference in the percent area of the StrataGraft and autograft treatment sites autografted by Month 3, the primary method for imputing missing data is interpolation and extrapolation, as follows: For any given subject who was lost to follow-up, the cumulative sum of percent area of each study treatment site autografted for all non-missing sessions on or before Month 3 is used to impute the missing value after the follow-up for the same subject. Missing data were anticipated to occur only if the subject was lost to follow-up because the percent area autografted could be obtained for a missing session if the subject returned for a subsequent session. The primary imputation method assumed that no additional autografting was performed after the subject was lost to follow-up.

As a sensitivity analysis for missing values, a tipping point approach was used to assess a range of successively more severe imputation methods for missing StrataGraft treatment site data while using the primary imputation method for the autograft treatment site. For the first iteration, the percent area autografted at the StrataGraft treatment site for subjects with missing data was rounded up to the next decile percentage (eg, from 13% to 20%). Succeeding iterations increased the cumulative sum of percent area autografted at the StrataGraft treatment site by 10-point increments until 100% was imputed. At each iteration, the StrataGraft and autograft treatment sites were compared as described for the primary analysis.

b) Imputation of the durable wound closure Co-primary Endpoint

For the analysis of durable wound closure at Month 3, recall wound closure was confirmed at 2 consecutive study sessions at least 2 weeks but no more than 5 months apart and including or encompassing the Month 3 time point. 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.

6.2.10 Study Population and Disposition

A total of 88 subjects were screened for entry into the study, with 17 subjects failing screening. The remaining 71 subjects had wound sites randomized (within subject) to receive StrataGraft

skin tissue or autograft (control). All 71 subjects reached or went beyond the scheduled time (and window extension) for the Month 4 visit, and therefore had the data required to determine the co-primary endpoints.

6.2.10.1 Populations Enrolled/Analyzed

6.2.10.1.1 Demographics

The following table (Table 6) summarizes subject demographics for the ITT populations.

Table 6: Summary of Demographic and Baseline Burn Characteristics (ITT Population)

	Total (N=71)	
Age (years)		
Mean (SD)	43.9 (15.95)	
Median (Min, Max)	45.0 (19, 79)	
Age category (years), n (%)		
<65	63 (88.7)	
≥65	8 (11.3)	
Sex, n (%)		
Male	55 (77.5)	
Female	16 (22.5)	
BMI, kg/m2		
Mean (SD)	29.9 (6.38)	
Median (Min, Max)	29.2 (20.20, 52.31)	
Race, n (%)		
White	55 (77.5)	
Black or African-	14 (19.7)	
Asian	1 (1.4)	
Other	1 (1.4)	
Ethnicity, n (%)		
Hispanic or Latino	10 (14.1)	
Not Hispanic or Latino	61 (85.9)	
Degree of Burn (TBSA)		
1° (N)	6	
Mean (SD)	2.8 (4.0)	
Median (Min, Max)	1.3 (0.5, 11.0)	
2° (N)	29	
Mean (SD)	10.0 (7.0)	
Median (Min, Max)	8.0 (1.0, 30.5)	
3° (N)	36	
Mean (SD)	4.0 (3.5)	
Median (Min, Max)	2.8 (0.5, 13.8)	
Wound Area (cm^2) Covered	**StrataGraft Skin**	**Autograft**
Mean (SD)	239.8 (202.22)	219.8 (233.15)
Median (Min, Max)	162.0 (12, 960)	130.0 (20,

BMI=Body-Mass-Index; Max=maximum; Min=minimum; ITT=Intent-to-Treat; N=maximum number of subjects with data; n=number of subjects; SD=standard deviation; TBSA=Total Body Surface Area °= degree of burn Source: Table 8 of clinical study report

6.2.10.1.3 Subject Disposition

As mentioned above, a total of 71 subjects received StrataGraft skin tissue and autograft. All 71 subjects reached or went beyond the scheduled time for the Month 4 visit, and therefore had the data required to determine the co-primary endpoints.

Table 7: **Subject Disposition as of 31 July 2019 Data Cut-off (ITT Population)**

	Enrolled Subjects N=71 n (%)
Subjects Treated	71 (100.0)
Subjects who completed Study Session 7 (Month 3 ± 14 d)	64 (90.1)
Subjects who completed Study Session 8 (Month 4 ± 14 d)	58 (81.7)
Subjects who completed Study Session 10 (Month 12 ± 1 m)	22 (31.0)
Subjects who completed the study	22 (31.0)
Subjects who discontinued the study	7 (9.9)
Reason for discontinuation	
Lost to follow-up	5 (7.0)
Death*	2 (2.8)
Subjects ongoing in the study	42 (59.2)

N=maximum number of subjects with data; n=number of subjects. Source: table 6 of study report.
*Neither death was considered to be related to StrataGraft skin tissue
Source: Table 6 fo study report

6.2.11 Efficacy Analyses

6.2.11.1 Analysis of first Co-Primary Endpoint

The first of 2 co-primary endpoints was the difference in the percent area of the StrataGraft treatment site and control autograft treatment site that was autografted by Month 3. The difference in percent area autografted between the StrataGraft and autograft control treatment sites was statistically significant based on the Wilcoxon Signed Rank Test for the ITT population as shown in Table 8 (next page). Consistent results were observed with the per-protocol population (not shown here)

Table 8: Summary of Percent Area of Treatment Sites Requiring Autografting by Study Session 7/Month 3 (ITT Population)

	Percent Area Autografted by Study Session 7/Month 3[a]			
	StrataGraft (N=71)	**Autograft (N=71)**	**Difference[b] (N=71)**	**p-value[c]**
Mean (SD)	4.329 (21.5788)	102.099 (13.1432)	97.771 (16.5747)	<0.0001
Median (min, max)	0.000 (0.00, 138.54)	100.000 (100.00, 200.00)	100.000 (-38.54, 100.00)	

Max=maximum; Min=minimum; N=maximum number of subjects with data; SD=standard deviation
a: Percent area autografted by Study Session 7/Month 3 is the sum of the percent areas at each study session/visit, up to and including Study Session 7/Month 3 (± 14 d)
b: Difference is (percent area of Autograft treatment site requiring autografting by Month 3) – (percent area of StrataGraft treatment site requiring autografting by Month 3)
c: p-value from 1-sided Wilcoxon Signed Rank Test
Source: Table 9 of study re

6.2.11.2 Analyses of second Co-Primary Endpoint

The other co-primary endpoint was the proportion of subjects achieving durable wound closure of the StrataGraft treatment site at Month 3 without autograft placement. This endpoint is tested by Pearson Chi-square test and estimated by the normal approximation to the binomial distribution. There were 7 subjects from the study who were lost to follow-up or died and did not have data for this primary endpoint and were treated as “failures” in this analysis.

As summarized in table 9 below, fifty-nine (83.1%) subjects in the ITT population achieved durable wound closure of the StrataGraft treatment site at Month 3 without the need for autografting. The lower bound of the 95% CI was 74.4%, which was greater than 50% and, thus, this endpoint achieved statistical significance (Table 9). Consistent results were observed with the per-protocol population.

Table 9: 95% Confidence Interval for the Proportion of Subjects who Achieved Durable Wound Closure of the StrataGraft Treatment Site at Month 3 Without Autograft Placement (ITT Population)

	StrataGraft (N=71)
Subjects with durable wound closure	59 (83.1%)[b]
95% CI[a,c]	(74.4, 91.8)[a] (72.3, 91.0)[c]

[a]CI=confidence interval; N=maximum number of subjects with data. a: 95% CI is derived using the normal approximation to the binomial distribution. [c]Using binomial distribution.
[b]The null hypothesis H_0: P<0 5 (vs H_1: P>=0 5) was rejected with p-value < 0 00001

6.2.11.3 Analysis of the Secondary Endpoints

For ranked secondary efficacy endpoints, a sequential testing procedure was used, ie, the next test could only be performed after previous test was successful in a prespecified test order. The mean (SD) of the difference between the StrataGraft and autograft donor sites in the donor site pain through Day 14 was 2.4 (1.31) with p-value <0.0001.

> **Comment**: The highly significant difference in donor site pain is expected because grafts were not harvested from StrataGraft donor sites. This endpoint does not add any additional information to the fact that StrataGraft sites generally did not require autografts.

The mean (SD) of the difference in total POSAS score by observer between the StrataGraft and autograft on donor sites at Month 3 was 10.0 (7.92) with p-value <0.0001.

> **Comment**: Similarly, the highly significant difference in POSAS score can be explained by the lack of donor site surgery for StrataGraft sites. The third secondary endpoint, Study Treatment Site Cosmesis at Month 12 was not presented because at the time of BLA submission, the study had not reached complete 12-month data yet to be analyzed.

6.2.11.4 Dropouts and/or Discontinuations

Section 6.2.10.1.3 above on subject disposition contains subject completion and early termination information. Subjects who dropped out of the study were included in the analyses. Missing data for the primary endpoint including missing assessments, lost to follow up and death were imputed as non-responders.

6.2.11.5 Subgroup Analysis

There was no evidence of treatment effect difference by age, sex, or race.

6.2.12 Safety Analyses

6.2.12.1 Methods

Descriptive statistics are used to summarize safety data for study Strata2016. For data summary, the safety analysis set included all 71 enrolled (and treated) subjects.

6.2.12.3 Deaths

Two subjects (2.8%) died as of the data cut-off data of 31 July 2019. Subject (b) (6) experienced a severe SAE reported only as death (not otherwise specified) and Subject (b) (6) experienced severe SAEs of acute myocardial infarction, cardiac arrest, and sepsis, all of which were reported to be associated with the fatal outcome. Neither death was considered to be related to study treatments. For further details, please confer the clinical review of the BLA.

6.2.12.4 Non-fatal Serious Adverse Events

A total of 21 SAEs were reported by 10 subjects. No SAE was considered to be related to StrataGraft skin tissue. No SAE was reported at the StrataGraft- or autograft- treatment *site*.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

This BLA submits results from two studies, Strata2016 and Strata2011, for supporting the efficacy of StrataGraft skin tissue for the treatment of DPT thermal burns. Strata2011 was a 3-arm/cohort phase 1b study of 30 subjects, which was conducted entirely prior to Strata2016. Therefore, information derived from Strata2011 was informatively incorporated in designing the study Strata2016 which was a phase 3 study.

Study Strata2016 was designed with co-primary efficacy endpoints: 1) the difference in the percent area of the StrataGraft treatment site and control autograft treatment site that was autografted by Month 3, and 2) the proportion of subjects achieving durable wound closure of the StrataGraft treatment site at Month 3 without autograft placement. The first coprimary endpoint relates to whether StrataGraft treatment spares donor site surgeries; this has been amply demonstrated in both studies. The second coprimary endpoint provides assurance that this autograft-sparing effect does not prevent durable wound closure in the majority of StrataGraft-treated sites. As discussed above, results of the study met prespecified statistical success criteria in these efficacy endpoints, in favor of StrataGraft skin tissue.

Pre-specified secondary efficacy endpoints were also included and analyzed for the study. However, because these secondary endpoints relate to donor site effects and StrataGraft sites generally did not require donor site surgeries, the secondary endpoints do not add additional information beyond the coprimary endpoints.

10.2 Conclusions and Recommendations

Based on the collective evidence provided by the two studies included in this BLA submission, particularly study Strata2016, StrataGraft skin tissue demonstrate significant clinical benefit for

patients with DPT thermal burns, as measured by the co-primary endpoint. The secondary endpoints do not add additional information beyond the coprimary endpoints. The statistical analysis results provide evidence to support the applicant’s proposed indication for StrataGraft skin tissue in this BLA.