Official Title: A Phase 1/2a, Controlled, Randomized, Multicenter Study Evaluating the Efficacy, Safety, and Tolerability of StrataGraft Overlay of Meshed Autograft (SOMA) in Treatment of Full-Thickness Thermal Burns

NCT Number: NCT04765202

Document Date: Statistical Analysis Plan (Version 1): 26 July 2024

STATISTICAL ANALYSIS PLAN

Protocol Number: **MNK01062117**

A Phase 1/2a, Controlled, Randomized, Multicenter Study Evaluating the Efficacy, Safety, Tolerability of StrataGraft Overlay of Meshed Autograft (SOMA) in Treatment of Full-Thickness Thermal Burns

Product: StrataGraft® Construct

Regulatory Agency Identification Number: IND #010113

Original Protocol Date: **11 Mar 2020**
Final Protocol Date: 28 September 2023
Version: 5
Study Phase: 1/2a

Original Drafted SAP Date: 26 Aug 2020
Final SAP Date: 26 July 2024
SAP Version: 1.0

Author: [redacted] Ph.D.

Mallinckrodt Pharmaceuticals
440 US-22 Suite 302,
Bridgewater, NJ 08807
United States of America

Statistical Analysis Plan Approval

Title:	A Phase 1/2a, Controlled, Randomized, Multicenter Study Evaluating the Efficacy, Safety, Tolerability of StrataGraft Overlay of Meshed Autograft (SOMA) in Treatment of Full-Thickness Thermal Burns
Protocol Number:	MNK01062117
Author:	[redacted] Mallinckrodt Pharmaceuticals, [redacted]
Version Number	Version 1
Version Date:	26 July 2024

[redacted] Digitally signed by [redacted]
Date: 2024.07.29 18:10:29 -04'00'

[redacted] Ph.D. Date
[redacted]
Mallinckrodt Pharmaceuticals

The undersigned have reviewed and hereby approve this document and find that it meets the requirements with respect to the protocol.

[redacted] 07/29/2024

[redacted] M.D. Date
[redacted]
Mallinckrodt Pharmaceuticals

[redacted]

Digitally signed by [redacted]
DN: postalCode=63042, o=Mallinckrodt Inc, street=675 McDonnell Boulevard, st=Missouri, c=US, cn=[redacted] email=[redacted]
Reason: I am approving this document
Date: 2024.07.29 11:52:25 -05'00'

[redacted] Ph.D.
[redacted]
Mallinckrodt Pharmaceuticals

Date

[redacted]

[redacted] Ph.D.
[redacted]
Mallinckrodt Pharmaceuticals

[redacted]

TABLE OF CONTENTS

LIST OF TABLES

ABBREVIATIONS

Abbreviation or Special Term	Explanation
AE	Adverse event
AG	Autograft –a transplant from 1 location to another on same person
AG Tx	Autograft treatment – the control study treatment arm receiving the tissue application of meshed autograft alone
allograft	A transplant from 1 person to another person
anti-BSA	Anti-bovine serum albumin
CI	Confidence interval
CBC	Complete Blood Count
CMP	Complete Metabolic Panel
CRF	Case report form
DPT	Deep partial-thickness
DSMB	Data and safety monitoring board
eCRF	Electronic case report form
FDA	Food and Drug Administration
FSA	Full analysis set
FT	Full-thickness
GCP	Good Clinical Practice
HCRU	Health care resource utilization
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional review board
POSAS	Patient and Observer Scar Assessment Scale
PRA	Panel reactive antibodies
PSAQ	Patient Scar Assessment Questionnaire
PPS	Per protocol set
SAE	Serious adverse event

SAF	Safety analysis set
SOMA	StrataGraft Overlay of Meshed Autograft
SOMA Tx	SOMA treatment - StrataGraft **O**verlay of **M**eshed **A**utograft (SOMA), where meshed autograft is covered with StrataGraft and applied to a burn area
Study Tx	SOMA Tx and the control AG Tx
TBSA	Total body surface area
TEAE	Treatment-emergent adverse event

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis for Mallinckrodt Pharmaceuticals protocol MNK01062117 (A Phase 1/2a, Controlled, Randomized, Multicenter Study Evaluating the Efficacy, Safety, Tolerability of StrataGraft Overlay of Meshed Autograft (SOMA) in Treatment of Full-Thickness Thermal Burns). This study is being conducted in order to evaluate safety and clinical outcomes associated with the use of StrataGraft as an overlay to meshed autograft to promote wound closure and reduced area of donor site harvest in the treatment of full-thickness (FT) thermal burns in a population of subjects with thermally-induced FT burns.

The following documents were reviewed in preparation of this SAP:

- Protocol MNK01062117, Version 5, issued on 28 September 2023.
- Case report form (CRF), version 2.0, issued on 15 March 2023.
- ICH (E9) Guidance on Statistical Principles for Clinical Trials.

The purpose of the SAP is to ensure the credibility of the study results by pre-specifying the statistical approaches for the study analysis prior to database lock. The analyses outlined in this SAP supports the completion of the Clinical Study Report (CSR) and may be included in regulatory submissions and/or future manuscripts. Unplanned, exploratory analyses performed to support the clinical development program may not necessarily be identified in the SAP and will be identified in the CSR.

2 PROTOCOL SUMMARY

2.1 Study Design

This is a Phase 1/2a, multicenter, open-label, randomized, within-patient controlled study in subjects with 2% to 49% (inclusive) TBSA thermal burn. The overall objective of this study is to evaluate the efficacy, safety, and tolerability of StrataGraft as an overlay for meshed autograft to promote complete wound closure and reduce the area of donor site harvested in the treatment of FT thermal burns.

The targeted enrollment for this study is 40 subjects with FT thermal injury. On each subject, 2 wounds, comparable in area, wound bed composition (fat, fascia, or muscle), and kinesiologic stressors will be identified, designated as Sites A and B, and randomized to receive either AG Tx (control) or SOMA Tx, such that each subject receives both treatments. Following excision, the control autograft treatment site will receive meshed split-thickness skin graft, while the SOMA treatment site will receive autograft that is meshed at 1 or 2 mesh ratio(s) greater than the control treatment site and overlaid with StrataGraft meshed up to 1:1.

Cohort 1 will consist of 20 subjects randomized to one of 2 groups: Group 1 (n=10) will receive AG Tx consisting of autograft alone (mesh ratio "m", per clinical judgment) compared to SOMA Tx in which m+1:1 meshed autograft is overlaid with StrataGraft, while Group 2 (n=10) will receive AG Tx with autograft (mesh ratio "m" per clinical judgment) compared to SOMA Tx in which m+2:1 meshed autograft is overlaid with StrataGraft, applied to wounds of 100 to 400 cm^2 in area. Subjects will be followed and assessments performed per the Schedule of Activities (Table 1). Each subject will be determined to be a success or failure based upon the criteria below, and one of the 2 treatments, m+1 or m+2, will be determined to meet the *a priori* established criteria within the algorithm to move forward:

- Percent closed (re-epithelialization) at Day 28, with success declared if the difference between paired wounds < 10%.
- Total score of Observer assessment of the POSAS at Day 28, with success declared if the difference between paired wounds < 20%.

Cohort 2 will consist of 20 subjects, all of whom will receive the SOMA Tx (with autograft meshed at m+1 or m+2) identified following assessment of Cohort 1 and the AG Tx control, applied to wounds of 400 to 1,900 cm^2 in area. Subjects will be followed, and assessments performed per the Schedule of Activities (Table 1).

- **Advancement to Cohort 2**

Following excision, a total of 20 subjects (Cohort 1) will be randomized into one of 2 groups, Group 1 and Group 2.

Following completion of the Day 28 assessments, each subject will be determined to be a success or failure based upon the criteria below:

  - % closed at Day 28, with success declared if the difference between paired wounds < 10%, and
  - Total score of Observer assessment of the POSAS at Day 28, with success declared if the difference between paired wounds < 20%.

Group success will be declared if ≥ 80% subjects are determined to have treatment success within that group. Only one of the 2 SOMA Txs, m+1 or m+2, will be determined to meet the *a priori* established criteria above and become the SOMA Tx in Cohort 2.

- **Treatment Groups and Duration:**

This study is open-label. Subjects will serve as their own control. Subjects will be randomized to receive autograft, meshed at a ratio per clinician judgment at 1 treatment site (m), and StrataGraft overlay of autograft at either m+1 (i.e., group 1) or m+2 (group 2), relative to the control autograft mesh ratio.

It is anticipated that each subject will participate in this study for up to 14 months: up to 2 weeks of screening followed by up to 12 months (± 4 weeks) of post-treatment observation.

- **Estimated Duration of Study**

Enrollment ~36 months.

Duration of subject participation up to 60 weeks.

Total study duration ~96 months.

- **Study Was Terminated Early by Sponsor**

Study enrollment was terminated on 12 January 2024 due to a decision to voluntarily discontinue sale and manufacture of StrataGraft for business reasons. A total of 13 subjects were randomized, all in Cohort 1, at the time of termination of enrollment. Follow up for enrolled subjects was completed in April 2024.

- **Scientific Rationale for Study Design**

The current standard of care for closure of FT burns is autografting, i.e., the surgical harvest of healthy skin from an uninjured site and subsequent transplantation of the donor tissue to the wound following surgical excision of nonviable tissue from the burn. While this method is effective in achieving closure of the original wound, optimal sites for the harvest of donor skin are often limited, and closure of large areas of injury may necessitate sequential re-harvest of available donor sites. Additionally, the donor site is painful, susceptible to infection and scarring,

and can convert to a FT wound. As a result, there is an urgent need for treatment alternatives that reduce donor site harvesting for treatment of severe burns.

Table 1: Schedule of Activities

Assessments	Day -14 to Day -1	Day 1	Day7± 1d	Day 14± 2d	Day 21 ± 2d	Day 28± 3d	Day 42± 4d	Month 2 ± 4d	Month 3 ± 7d	Month 6 ± 2Wks	Month 12± 4Wks
Informed consent[a]	√										
Physical examination and medical history review	√										
Laboratory tests (CMP and CBC with differential)[b]		√				√					
Pregnancy test (women of childbearing potential)[b]	√										
Blood samples for immunogenicity (PRA & anti-BSA)[c]		√							√		
Vital signs	√	√	√	√	√	√	√	√	√	√	√
Archival blood sample collection[c]		√									
Study Tx application		√									
Photograph Study Tx sites[d]		√	√	√	√	√	√	√	√	√	√
Study site surveillance[e]		√	√	√	√	√	√	√	√	√	√
Blinded wound assessments[f]			√	√	√	√	√	√	√	√	√
Concomitant medications		√	√	√	√	√	√	√	√	√	√
Concomitant procedures		√	√	√	√	√	√	√	√	√	√
Assessment and reporting of AEs	√	√	√	√	√	√	√	√	√	√	√

Assessments	Day -14 to Day -1	Day 1	Day7± 1d	Day 14± 2d	Day 21 ± 2d	Day 28± 3d	Day 42± 4d	Month 2 ± 4d	Month 3 ± 7d	Month 6 ± 2Wks	Month 12± 4Wks
Quality of healed Study Tx sites (POSAS/PSAQ)[g]						√		√	√	√	√
Biopsy of healed SOMA Tx site and adjacent uninjured skin[h]									√		

[a] Study Tx consent, including consent for photos, biopsy and for direct contact by sponsor post-study.
[b] Processed by local laboratory. Obtain within 48 hours prior to application of StrataGraft.
[c] Processed by central laboratory. Collected BEFORE StrataGraft placement.
[d] Photos will be taken of the Study Tx sites prior to excision, following excision and hemostasis, and following placement of the Study Txs. During hospital stay, photos will be taken weekly. Following hospital discharge, the subject will have the option to submit photographs of the Study Tx sites each week until Month 3, every other week until Month 6, and then monthly until the Month 12 visit.
[e] Study site surveillance includes assessment of local wound area for signs of infection, site adverse events, and graft loss.
[f] Blinded assessor will assess all treatment sites for percent epithelialization beginning at Day 7 then and daily, or as often as possible, during dressing changes until complete closure is observed. A second observation of complete closure at least 2 weeks after the initial observation is required to confirm closure. Thereafter maintenance of closure will be assessed at each study visit, to assess durability of closure.
[g] All POSAS Observer assessments will be performed by blinded assessor, first at the time of closure, and at Day 28, Months 2, 3, 6 and 12.
[h] Biopsies will be collected from subjects in Cohort 1 and processed by the central laboratory.

CMP = complete metabolic panel; CBC = complete blood count; PRA = panel reactive antibodies; anti-BSA = anti-bovine serum albumin; Study Tx = study treatment; AE = adverse event; POSAS = Patient and Observer Assessment Scale; PSAQ = Patient Scar Assessment Questionnaire; SOMA Tx = StrataGraft Overlay of Meshed Autograft treatment

2.2 Study Objectives and Endpoints

The overall objective of this study is to evaluate the efficacy, safety, and tolerability of StrataGraft when used as an overlay of meshed autograft to facilitate wound closure and reduce donor site harvest in the treatment of FT thermal burns.

The two comparative study treatment sites per subject are as follows:

1. The study treatment that is **S**trataGraft **O**verlay of **M**eshed **A**utograft (SOMA), where meshed autograft is applied to the burn area and covered with StrataGraft and applied to a burn area, hereafter will be referred to as "SOMA Tx."
2. The study treatment that is autograft alone as applied to a burn area hereafter will be called "AG Tx."

When collectively referring to both study treatments (i.e., the SOMA Tx and the comparator AG Tx), we will hereafter refer to "Study Tx."

2.2.1 Efficacy Primary Objective and Co-primary Endpoints

The primary efficacy objective is to evaluate the efficacy of SOMA treatment by assessing two co-primary efficacy endpoints. The definitions of the two co-primary efficacy endpoints are as follows:

- Calculated percent reduction of donor skin (as defined by [1-(AG Tx mesh ratio/SOMA Tx mesh ratio)× 100]) at Month 2.
- Difference in percent of SOMA Tx sites and AG Tx sites with confirmed complete wound closure without additional autografting at Month 2.
    - Confirmed complete wound closure is defined as complete skin re-epithelialization without drainage confirmed at 2 visits at least 2 weeks apart but no later than Week 20. Complete wound closure will be considered to have occurred at the earlier of the two observations of complete skin re-epithelialization without drainage.
    - Confirmed complete wound closure without additional autografting at Month 2 is determined by Mallinckrodt's biostatistics and programming team based on the above definition. The first wound closure needs to have occurred before Month 2.

2.2.2 Efficacy Secondary Objectives and the Secondary Efficacy Endpoints

The 2nd efficacy secondary objective is to evaluate the efficacy of SOMA Treatment by assessing the following 2nd efficacy endpoints:

- Incidence of confirmed complete wound closure of the study Tx sites at Days 14, 21, 28, and 42, Month 2, and Month 3.
- Percent re-epithelialization of the study Tx sites at Day 14, 21, 28, and 42, Month 2 and Month 3.
- Percent subjects with durable wound closure of study Tx sites at Months 3, 6, and 12.
    - Durable wound closure is defined as persistence of closure, maintained for at least 3 months after the initial observation of closure. The blinded assessor will evaluate the wound sites at each visit subsequent to wound closure to assess the maintenance of the closure.
- Patient and Observer Scar Assessment Scale/Patient Scar Assessment Questionnaire (POSAS/PSAQ) scores of Study Tx sites at Day 28, Months 2, 3, 6, and 12.

2.2.3 Efficacy Tertiary / Exploratory Objectives and Endpoints

The tertiary efficacy objective is to evaluate Health Care Resource Utilization (HCRU) and explore other efficacy endpoints.

Health Care Resource Utilization (HCRU) endpoints are defined as follows:

- Location of care for StrataGraft application (e.g., inpatient hospital, outpatient/ambulatory hospital, clinic, etc.).
- Treatments used for all other non-study burn areas following excision and % total body surface area (TBSA) treated with each (i.e., other than Study Tx sites).
- Number and duration of operating room procedures required for study burn treatment.
- Length of hospital stay.
- Prescription drugs given for pain control.
- Antibiotics given for outpatient use at discharge.
- Re-admission within 30 days after discharge.
- Whether a re-admission is planned.
- Length of hospital stay after re-admission.

The efficacy exploratory endpoints are as follows:

- Calculated total area of autologous (donor) skin applied to study treatment sites by Month 6.
- Time to first confirmed complete wound closure without additional autograft by Month 2.

2.2.4 Safety Objectives

The safety objective is to evaluate the safety of SOMA treatment. At the same time, the safety of control treatment, i.e., autograft, site will also be displayed for reference, where applicable. The safety measurements are as follows:

- Incidence of treatment-emergent AEs (TEAEs) throughout study.
- Incidence of TEAEs related to each of the Study Tx's.
- Incidence of wound infection-related events at Study Tx sites.
- Clinically significant changes in vital signs throughout study compared to Baseline.
- Clinically significant changes in laboratory values between Baseline and Day 28.
- Clinically significant changes in panel reactive antibodies (PRA) and anti-bovine serum albumin (BSA) levels between Baseline and Month 3.
- Concomitant medication use.

2.2.5 Additional Outcome Measures

- Number of treatment sites with complete wound closure without additional autografting at Month 2.
- Number of subjects with durable wound closure of the study treatment sites without additional autografting at Month 12.

2.2.6 Adverse Events of Special Interest

An Adverse Event of Special Interest (AESI), whether serious or nonserious, is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. AESI will be reported using the SAE/AESI Report Form and observe the same reporting timeline (within 24

hours of first knowledge of an event or receipt of follow up information). For this study, AESI include:

- Unexpected or unusual infections.
- Dermatological malignancy.

2.2.7 Modification from the Statistical Section of the Final Protocol

The amendments to the statistical section and relevant endpoints of the final protocol are displayed here. The final analyses are based on this final SAP. The amendments are as follows:

- In protocol section 4, objectives and endpoints (p. 19):

The exploratory endpoint, "Effect of total wound burden on rate of wound closure," is listed. However, no data has been collected on overall donor site closures. Consequently, no analysis will be performed for this endpoint.

- The protocol does not mention the endpoint 'Time to First Confirmed Wound Closure Without Additional Autograft by Month 2.' (see Section 2.2.3) However, this endpoint and its results were outlined in the briefing document (see the References: Type B Meeting Briefing Materials submitted in IND 010113 Sequence 0151 on 27 November 2023), leading to its inclusion.

- In protocol section 10.3.2 Efficacy Analyses (p36):

The original analyses for the first co-primary endpoint as stated in the clinical protocol were as follows:

> *For calculated percent reduction of donor skin (as defined by [1-(AG Tx mesh ratio/SOMA Tx mesh ratio) × 100]) at Month 2, the log-transformation of the endpoint will be performed, and geometric mean ratio percent reduction of donor skin between treatment site will be presented.*
>
> *A mixed-effect model repeated measures method with covariates, including subject treatment site, mesh ratio on SOMA Tx site, and cohort will be used for this log-transformed primary endpoint.*

If the mixed-effect model repeated measures model does not converge or violates the model assumptions, the paired t-test will be used. If parametric statistics models are not appropriate, the Wilcoxon signed-rank test will be performed.

The updated statistical analysis will not use log-transformation, to facilitate easier clinical interpretation. Additionally, the mixed-effect model for repeated measures will not be used due to the small number of subjects and the existence of only one cohort. To ensure robustness of the method, the non-parametric Wilcoxon signed-rank test, as originally planned last method, will be used (see Section 3.7.1).

2.3 Sample Size Considerations

The sample size for the study is based on clinical experience. No calculations were performed to estimate sample size. Up to 40 subjects will be enrolled in 2 cohorts (details in Section 2.1).

2.4 Randomization and Blinding

This is a randomized, open-label study.

There will be a total of 40 subjects enrolled in the study. On each subject, two wounds, comparable in area, wound bed composition (fat, fascia, or muscle), and kinesiologic stressors will be identified, designated as Sites A and B, and randomized to receive either AG Tx (control) or SOMA Tx, such that each subject receives both treatments.

There are two cohorts, as described in Section 2.1, based on the size of wound areas. Cohort 1 treatment sites are 100 to 400 cm^2, whereas Cohort 2 treatment sites are 400 to 1,900 cm^2.

2.5 Ad-hoc Data Review

Due to slow enrollment, the sponsor performed a preliminary assessment of the efficacy and safety of the product in April 2023 to determine the appropriateness of amending the ongoing Phase 1/2a StrataSOMA clinical study to a seamless Phase 1/2/3 study design. To this end, the sponsor performed an ad-hoc data analysis for the first 10 subjects enrolled in Cohort 1 after 1st 10 subjects completed primary endpoints assessments. Results of this data review were included

in Sponsor Meeting Materials for a Type B meeting with FDA to discuss the proposed clinical study amendment.

The ad-hoc data review demonstrated that all of the first 10 subjects enrolled in the StrataSOMA study achieved confirmed complete wound closure by or before Month 2 without additional autografting on both SOMA and AG treatment sites, regardless of whether they were randomized to the m+1 or m+2 group (i.e., 100% of the SOMA treatment sites achieved confirmed complete wound closure by or before Month 2 without additional autografting).

Additionally, SOMA treatment decreased the amount of donor tissue required to close treated sites relative to the control AG treatment site by 35% and 57% for autograft mesh ratios m+1 and m+2, respectively, without sacrificing cosmetic outcomes, as evidenced by comparable POSAS scores at Months 2 and 3.

For safety, ad hoc analyses of TEAEs or SAEs for the first 10 patients through the data cutoff showed that most TEAEs and SAEs were typical of what is observed in burn wounds and during wound healing. The safety profile at the StrataGraft treatment sites was similar to that of the control treatment sites, and no new safety signals were identified.

For details of the ad-hoc analyses, see the Type B Meeting Briefing Materials submitted in IND 010113 Sequence 0151 on 27 November 2023 (see References).

This ad-hoc data analysis will not alter the screened significance level of the entire study.

2.6 Pharmacokinetics

Pharmocokinetic parameters are not evaluated in this study.

2.7 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

2.8 Pharmacoeconomics

Pharmacoeconomics parameters are not evaluated in this study.

3 STATISTICAL METHODS AND CONVENTIONS

3.1 General Conventions

- Unless otherwise noted, the number of subjects (n), mean, standard deviation, median, minimum, and maximum will be presented for continuous variables and frequency and percentage of subjects in each category will be presented for discrete variables.
- Unless otherwise noted, confidence intervals (CIs) will be 2-sided 95% CIs.
- Listings will be sorted by subject identification.
- Statistical analyses will be done using Statistical Analysis Software (SAS®) version 9.3 or higher.
- All statistical tests will be two-sided with a final significance level of 0.05, unless stated otherwise.

3.1.1 Handling of Missing Data

No imputation for missing values will be conducted. All observed values (i.e., excluding missing values for visit) will be used for the analyses except for the second co-primary endpoint, missing data will be imputed as non-responder.

3.1.2 Date/Time Derived Variable Conventions

Study Day 1 when Study Tx is applied will be considered as baseline for the endpoint calculations.

3.2 Analysis Populations

- All Enrolled Population.
- Full Analysis Set (FAS).
- Per-Protocol Set (PPS).
- Safety Analysis Set (SAF).

3.2.1 All Enrolled Population

The All Enrolled Population is defined as all subjects who signed the Informed Consent Form (ICF).

3.2.2 Full Analysis Set (FAS)

The Full Analysis Set is defined as all subjects who are randomized and treated with at least one area of SOMA Tx and one area of AG Tx. Efficacy analyses will be based on treatment applied (as treated).

3.2.3 Per-Protocol Set (PPS)

The Per-Protocol Set is defined as all subjects in the FAS except for those who are excluded because of major protocol deviation. A major protocol violation is one that may affect the interpretation of study results. The criteria of major protocol deviations may include but is not limited to deviation from:

- A patient who does not have primary endpoint value.
- Any major violations of efficacy-related entry criteria.
- Deviation of an inclusion or exclusion criterion.

Major protocol deviations will be reviewed case by case on a regular basis during the conduct of the study by the Medical Monitor and clinical trial management team and adjudicated before database lock.

3.2.4 Safety Population (SAF)

The safety population is defined as all subjects who sign the ICF and are treated with the investigational treatment; these subjects are considered evaluable as the safety population.

3.3 Demographics and Baseline Characteristics

All variables concerning demographic, and baseline characteristics will be summarized by cohort, relative autograft mesh ratio group at the SOMA Tx site (m+1 and m+2) and all subject to describe the study population. Continuous variables will be summarized by number of subjects (n), mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized by frequency and percentage. Summaries will be presented for all subjects in the FAS populations.

3.4 Medical History

Medical history terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 23.0. The frequency and percentage of subjects with medical history within each system organ class will be summarized by all subjects and by cohort, and relative autograft mesh ratio group at the SOMA Tx site (m+1 and m+2).

3.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHODRUG dictionary B, version September 2019 (i.e., WHODDSEP19B3). The frequency and percentage of subjects with prior and concomitant medications by using Anatomical-Therapeutic-Chemical (i.e., ATC 4) classification and preferred term name will be summarized all subjects and by cohort, and sites.

3.6 Treatment and Exposure

The number of subjects with sites allocated to AG Tx and SOMA Tx in Cohort 1 and Cohort 2 and their autograft mesh ratio will be summarized. The size of area treated with AG Tx, SOMA Tx, AG donor and SOMA donor will also be summarized with the area categories of up to 400 cm^2 or 400 to 1,900 cm^2. The treatment placement location and position, and treatment measurements will be summarized by cohort and sites.

The duration from Day 1 to the end of study will be summarized by cohorts, sites and all subjects.

3.7 Efficacy Analysis

Efficacy analyses will be performed comparing the differences between treatments within subjects, where appropriate. Descriptive summaries will be reported by treatment site, relative autograft mesh ratio group at the SOMA Tx site (m+1 and m+2), cohort and all subjects.

For continuous variables, descriptive statistics will include the following: the number of patients reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category. The definition of primary and secondary endpoints is described in Section 2.2.1 and 2.2.2.

Safety assessments will include monitoring of TEAEs, vital signs, laboratory safety values, incidence of wound infection-related events, and potential immunologic responses to StrataGraft.

3.7.1 Co-Primary Endpoints Analysis

There is no formal hypothesis test for primary efficacy variables. All p-values provided in the tables are considered as screened p-values for signal exploration.

The primary efficacy analysis will be performed on the FAS and PPS (details in Section 3.2.2 and 3.2.3, respectively). If the difference in the number of subjects between the FAS and the PPS is less than or equal to 2, no analysis will be performed on the PPS.

For the first co-primary endpoint, which is the calculated percent reduction of donor skin (as defined by [1-(AG Tx total mesh ratio/SOMA Tx total mesh ratio) × 100]) harvested at Month 2, the Wilcoxon Signed Rank test will be used.

If autografting occurs by Month 2 at either treatment site, the total autograft mesh ratio with additional re-autografting is calculated as follows:

The total autograft mesh ratio is calculated as $1/(1/mr_0+p\_area\%/mr_1)$.

Where:

- mr_0 is initial mesh ratio
- mr_1 is re-graft mesh ratio
- p_area% is percent wound area autografted after initial study treatment (additional autografting).

In addition, the areas of treatment and donor sites will be summarized by treatment site and by relative autograft mesh ratio group at the SOMA Tx site (m+1 and m+2).

For the paired binary 2nd co-primary endpoint of the difference in percent of SOMA Tx sites and AG Tx sites with confirmed complete wound closure without additional autografting at Month 2, 95% confidence intervals (CIs) of difference are derived by fitting a repeated measures model with PROC GENMOD that adjusts for the correlation with pairs, and then the 95% CI of difference can be estimated using the Margins Macro, provided by SAS. The P-value will be derived from McNemar's test.

The descriptive statistics will also be determined by treatment site and by relative autograft mesh ratio group at the SOMA Tx site (m+1 and m+2). The missing binary data will be imputed as non-responders.

3.7.1.1 SUBGROUP ANALYSES FOR CO-PRIMARY ENDPOINTS

The two Co-primary endpoints will be summarized by the following demographic and baseline characteristics:

- Race (white, non-white).
- Ethnicity (Hispanic, non-Hispanic).
- Age (<65, ≥ 65).
- Sex (Male, Female).
- SOMA treatment area (≤ 500 cm^2, > 500 cm^2).
- Overall TBSA (< Median, ≥Median)

3.7.2 Secondary Endpoint Analysis

The secondary endpoints of this study are:

- Incidence of confirmed complete wound closure of the Study Tx sites at Days 14, 21, 28, and 42, Month 2, and Month 3.

Confirmed complete wound closure will be assessed at Days 14, 21, 28, and 42, Month 2, and Month 3. The incidence will be calculated at the time point and covered the time period (table below):

Time Point	Time period covered	Denominator
Day 14	Day 14 to <Day 21	Subjects with Day 14 assessment
Day 21	Day 21 to <Day 28	Subjects with Day 21 assessment
Day 28	Day 28 to <Day 42	Subjects with Day 28 assessment
Day 42	Day 42 to <Month 2	Subjects with Day 42 assessment
Month 2	Month 2 to <Month 3	Subjects with Month 2 assessment
Month 3	Month 3 to <Month 6	Subjects with Month 3 assessment
Month 6	Month 6 to EOS	Subjects with Month 6 assessment

No P-value is to be provided for difference of percent of complete wound closure between treatment sites.

- Percent re-epithelialization of the Study Tx sites at Day 14, 21, 28, and 42, Month 2 and Month 3

The percent re-epithelialization values of both AG Tx and SOMA Tx at Day 14, 21, 28, and 42, Month 2 and Month 3 will be summarized with n, mean, standard deviation, median, minimum, and maximum. If the wound is closed, it is assumed to have 100% re-epithelialization.

The screened P-value is derived from paired t-test.

- Percent subjects with durable wound closure of Study Tx sites at Months 3, 6, and 12

Durable wound closure is defined as persistence of closure, maintained for at least 3 months after the initial observation of closure.

The proportion and 95% confidence interval of subjects who have durable wound closure at Month 6 and Month 12 will also be presented. The proportion and 95% CI will be calculated using the exact method to the binomial distribution.

- Patient and Observer Scar Assessment Scale/Patient Scar Assessment Questionnaire (POSAS/PSAQ scores of Study Tx sites at Day 28, Months 2, 3, 6, and 12.

The POSAS/PSAQ scores will be summarized with number of subjects (n), Mean, Median, Standard deviation, Minimum, and Maximum at Day 28, Month 2, 3, 6, and 12 for AG Tx and SOMA Tx sites.

The screened P-values on total score of POSAS between treatment sites is derived from paired t-test.

3.7.3 Tertiary/Exploratory Endpoints

3.7.3.1 Health Care Resource Utilization (HCRU)

- Location of care for StrataGraft application (e.g. inpatient hospital, outpatient/ambulatory hospital, clinic, etc.).
- Treatment used for all other non-study burn areas following excision and % total body surface area (TBSA) treated with each.
- Number and duration of operating room procedures required for study burn treatment.
- Length of hospital stay.
- Prescription drug given for pain control.
- Antibiotics given for outpatient use at discharge.
- Re-admission within 30 days after discharge.
- Whether a re-admission is planned.
- Length of hospital stay of re-admission.

The above endpoint variables will be summarized with the number of subjects (n), mean, standard deviation, median, minimum, and maximum for continuous variables and frequency and percentage of subjects in each category will be presented for discrete variables.

3.7.3.2 Exploratory Endpoints

- Calculated total area of autologous (donor) skin applied to Study Tx sites by Month 6

The cumulative total area of donor skin applied to both AG Tx and SOMA Tx sites will be summarized with number of subjects, mean, median, standard deviation, minimum, and maximum up to Month 6 by treatment sites, by relative autograft mesh ratio group at the SOMA Tx site (m+1 and m+2), and all subjects The calculated total donor area is determined by dividing the treatment area by the relevant total mesh ratio up to Month 6. If a subject undergoes re-grafting, the area of the donor site used for the re-graft is included in the total calculation. Calculation of the total mesh ratio is detailed in Section 3.7.1.

- Time to First Confirmed Complete Wound Closure Without Additional Autograft by Month 2

The event for the Kaplan-Meier method is defined as the first occurrence of confirmed complete wound closures without additional autograft by Month 2. The time to first complete wound closure by treatment site will be analyzed using the Kaplan-Meier estimation method. The time period for this analysis is calculated as (the date of the first event - the date of Day 1 + 1). Treatment sites that do not experience any event during the study will have their time censored at the last available date in the study.

The Kaplan-Meier estimate will be used to determine the median time to first confirmed complete wound closure without additional autograft by treatment site.

3.8 Safety

The safety analysis, including adverse events (AEs), treatment-emergent adverse events (TEAEs), laboratory results, and vital signs, will be based on the safety population (SAF).

3.8.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment.

All adverse events (AEs) will be assessed and recorded before and after first placement of study product. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 23.0. The number of TEAE/AEs, and the number of subjects reporting TEAE/AEs will be listed and summarized by body system, preferred term, severity, and relationship, and by relative autograft mesh ratio group at the SOMA Tx site (m+1 and m+2), cohort and treatment sites or "other"). All serious AEs (i.e., SAEs) will be summarized by relative autograft mesh ratio group at the SOMA Tx site (m+1 and m+2), cohort and location, and narratives will be created. The incidence of wound infection-related events will be listed and summarized overall by subject, by relative autograft mesh ratio group at the SOMA Tx site (m+1 and m+2), cohort, and treatment sites, and if applicable, by subject.

The focus of the AE data summaries will be on treatment-emergent adverse events (TEAE). Treatment emergent AEs are defined as AEs for which the AE start date is on or after the start of

study drug administration date. For AEs with missing onset dates, the first day of study treatment will be used as the onset date.

If a subject has more than one TEAE coding to the same preferred term, the subject will be counted only once for that preferred term. Similarly, if a subject has more than one TEAE within a system organ class category, the subject will be counted only once in that system organ class category.

The following TEAEs will be summarized by frequency and percentage of subjects by SOC and PT and by cohort, by relative autograft mesh ratio group at the SOMA Tx site (m+1 and m+2), by treatment sites, if applicable, and all subjects:

- All TEAEs.
- TEAEs by SOC and PT.
- TEAEs by Relationship.
- TEAE by Maximum Severity.
- TEAEs by Relationship and Maximum Severity.
- TEAEs by Location.
- TEAEs Location and Relationship.
- TEAEs leading to Withdrawals by Relationship.
- Infection Assessment (Yes/No) at Study treatment Sites by Clinician.
- TEAEs of Special Interest (AESIs) by SOC and PT.
- Serious Treatment-Emergent Adverse Events (TEAEs) by SOC and PT.
- Serious TEAEs by Relationship.
- Serious TEAEs by Location.
- Serious TEAEs by Location and Relationship.
- Serious TEAEs of Special Interest by SOC and PT.

The listing of AEs with relative autograft mesh ratio group at the SOMA Tx site (m+1 and m+2), TEAE flag, location of the AE, SOC/PT/Verbatim Term, Outcome, Wound Infection Related, Relationship, Action Taken, and Serious etc. will be presented by subject.

3.8.2 Laboratory Assessments

Laboratory assessments of Complete Metabolic Panel (CMP) and Complete Blood Count (CBC) as well as urine pregnancy tests for women of childbearing potential will be performed at the local clinical laboratory of the clinical site. CMP and CBC will be collected at screening, Day 1 and Day 28. Summaries of baseline assessment and change from baseline for laboratory assessments will be summarized by number of subjects, mean, standard deviation, median, minimum and maximum and by cohort, relative autograft mesh ratio group at the SOMA Tx site (m+1 and m+2), and for all subjects.

CMP and CBC laboratory results will be classified as status of 'Low', 'Normal' and 'High' as defined at the local clinical laboratory of the clinical site. Shift tables summarizing status of changes from baseline at Day 28 according to baseline status will be provided for subjects with both baseline and Day 28 results by cohort, relative autograft mesh ratio group at the SOMA Tx site (m+1 and m+2), and for all subjects.

CMP and CBC parameters will be categorized as normal, non-clinical significance and clinical significance at Baseline and Day 28 by the clinician. Shift tables of change from baseline to Day 28 will be created for laboratory results using clinical significance categories by cohort, relative autograft mesh ratio group at the SOMA Tx site (m+1 and m+2), and for all subjects.

3.8.3 Vital Signs

Subjects vital sign data was collected at each visit and the visit for confirmation of healing (closure). The averages value and change from baseline in vital signs of body temperature, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and respiratory rate, will be summarized by number of subjects, mean, standard deviation, median, minimum and maximum, and by cohort, relative autograft mesh ratio group at the SOMA Tx site (m+1 and m+2), and for all subjects.

3.8.4 Immunologic Responses to StrataGraft: Panel Reactive Antibodies (PRA) and Anti-Bovine Serum Albumin (anti-BSA) Antibody

Blood samples will be collected prior to placement of StrataGraft and again at Month 3 to assess changes in Panel Reactive Antibodies (PRA) and anti-Bovine Serum Albumin (anti-BSA) levels. PRA is a measure of antibody formation to non-self human proteins such as those found in StrataGraft. The cells in StrataGraft are cultured in media containing BSA and anti-BSA antibodies may be formed with exposure to StrataGraft.

PRA and anti-BSA antibody (IgG) assessments will be performed by a central laboratory. PRA will be screened and tested for HLA class I and II allelic reactivity at Day 1 (baseline) and Month 3. The number and percentage of subjects that are HLA class I and II positive will be provided for Baseline (Day 1) and for Month 3 by cohort, relative autograft mesh ratio group at the SOMA Tx site (m+1 and m+2), and for all subjects.

Additionally, the number and percentage of subjects that are HLA allele positive will be provided for each visit and for each allele by cohort, relative autograft mesh ratio group at the SOMA Tx site (m+1 and m+2), and for all subjects.

PRA parameters and anti-BSA IgG will be categorized as normal, of non-clinical significance, and of clinical significance at Baseline and Month 3 by the central laboratory. Shift tables indicating changes from Baseline to Month 3 for PRA results will be created using clinically significant categories by cohort, relative autograft mesh ratio group at the SOMA Tx site (m+1 and m+2), and for all subjects.

4 AMENDMENTS TO THE SAP

This is the final SAP (version 1) based on the latest protocol Amendment 5 which was approved on 28 September 2023. The drafted SAP (version 0.1) was created on 26 Aug 2020.

5 PROGRAMMING SPECIFICATIONS AND CONSIDERATIONS

The corresponding programming specifications for variables for this SAP will be provided in a separate document.

6 TABLE, LISTING, AND FIGURE (TLF) SHELLS

The corresponding TL shells for this SAP will be provided in a separate document. Figures will not be provided for the abbreviated CSR.

7 APPENDIX

None.

8 REFERENCES

Type B Meeting Briefing Materials: Full-Thickness Burn Indication Pre-Phase 3 Meeting for STRATAGRAFT® by Mallinckrodt, Inc (dated 22 November 2023).