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3M™ Topical Tissue Adhesive Versus Commercially Available Tissue Adhesive for the Closure of Lacerations and Incisions

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ABBREVIATIONS/ACRONYMS

AE	adverse event
ADE	adverse device effect
CI	confidence interval
CIP	Clinical Investigation Plan
CRF	Case Report Form
EMA	European Medicines Agency
CSR	Clinical Study Report
EOT	end of treatment
FDA	U.S. Food & Drug Administration
IBIO	Independent Biostatistician
ICH	International Conference on Harmonization
ITT	intent-to-treat
LOS	length of stay
PI	Principal Investigator
PP	per protocol
SADE	serious adverse device effect
SAE	serious adverse event
SAP	Statistical Analysis Plan
WHO	World Health Organization

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1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) for the 05-015029 study is to outline the analyses planned to support the generation and completion of the Clinical Study Report (CSR). This SAP has been written to be in accordance with the clinical investigation plan (CIP) and relevant data collection documents. This SAP adheres to the requirements and guidelines identified by the ISO 14155 Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice, U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials.

The planned analyses identified in this SAP may be included in clinical study reports, regulatory submissions, or future manuscripts. Post-hoc exploratory analyses not identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned exploratory analysis will be identified as such. This document will be approved prior to the first interim analysis database lock. Changes made to the SAP prior to either interim or final database locks will be described in the document history. The SAP may be amended after the interim analyses but will not be amended after final database lock. Deviations from planned analyses, including additional exploratory analyses after interim and final database locks will be noted in the CSR.

2. STUDY OBJECTIVES

2.1. Primary Objective(s)

The primary objective of this study is to assess the efficacy of 3M™ Topical Tissue Adhesive on closure of minimum-tension wounds, including surgical incisions from minimally invasive surgery, low-tension incisions, superficial lacerations, and clean traumatic lacerations, when compared to the commercially available Control device.

2.2. Secondary Objective(s)

The secondary objectives of this study are to compare the safety and performance of 3M™ Topical Tissue Adhesive with the commercially available Control device when used to reapproximate minimum-tension wounds.

3. INVESTIGATIONAL PLAN

3.1. Study Design

This is a multicenter, prospective, open label, randomized, non-inferiority study that will enroll 452 Subjects requiring closure of superficial lacerations, clean traumatic lacerations, low-tension incisions, or surgical incisions from minimally invasive surgeries. The study will enroll Subjects from up to 10 sites in the USA with a maximum of 25% of randomized Subjects from anyone

site. Two interim analyses are planned for early stopping due to efficacy and will be conducted after 226 and 340 subjects are randomized and have reached their Day 10 follow-up visit (50% and 75% of the randomization goal, respectively). Subjects randomized but not treated cannot reach their Day 10 follow-up visit but will be included in the subject counts of 226 and 340. Subjects must have a single laceration or up to 4 surgical incisions requiring closure. Subjects with multiple lacerations are not eligible for the study.

3.2. Schedule of Events

A detailed schedule of events for the study is provided in Table 1.

Table 1: Schedule of Events

Procedure Description & Visit Windows	Visit 1 Screening & Enrollment Day -10 to 0	Visit 2 Treatment Application Day 0	Visit 3 Day 10 Follow-up (10 d ± 2 d)	Visit 4/EOS Day 30 Follow-up (30 d ± 5d)	Unscheduled
Informed Consent	X				
Inclusion/Exclusion Criteria	X	X[1]			
Demographics, Subject Characteristics, Medical and Surgical History	X	X[1]			
Vital Signs (Temperature)	X	X	X	X	X
Urine Pregnancy Test		X[2]			
Randomization		X			
Application of Tissue Adhesive		X			
Incision/Laceration Photographs		X[3]	X[4]	X[4]	X[4]
Assessment of Wound Apposition			X[5]	X[5]	X[5]
Assessment of Select ADEs and SADEs		X	X	X	X
Measurement of Remaining Tissue Adhesive			X		X[8]
Cosmesis Scoring				X	
Concomitant Medications		X	X	X	X
AEs / SAEs / ADEs / DDs		X[6]	X	X	X
End of Study				X	X[7]

[1] Confirm eligibility and update medical and surgical history if screening visit and treatment application occur on separate days.
[2] Before randomization, for WOCBP.
[3] After application of tissue adhesive but prior to application of any applicable dressings.
[4] After removal of any applicable dressings.
[5] Conducted by a blinded, independent assessor using photographs taken during the visit. Photograph assessments may occur after the visit.
[6] Starting at the time of randomization
[7] If the Subject is withdrawn early.
[8] If unscheduled visit is before Visit 3

3.3. Randomization

Subjects with wound(s) that meet all eligibility criteria will be eligible for randomization, which will occur immediately before closure of the wound(s). Eligible Subjects with multiple wounds will be randomized to the same treatment arm (ie, all wounds will be treated with the same tissue adhesive). Randomization of the Subjects, using a permuted block technique, will be centralized and electronic. Randomization will be stratified by study site, by whether the Subject has an existing diagnosis of diabetes mellitus, and by wound type – (1) single laceration, (2) single surgical incision, and (3) multiple surgical incisions. Subjects will be randomized to one of two treatment groups such that we target achieving a 1:1 ratio within the three stratification factors. Subjects with more than one laceration or more than four incisions will not be eligible for the study.

3.4. Blinding

Due to the nature of the investigative device, the duration of treatment application, and the study design, Subject and Investigator blinding is not feasible for the study. However, an independent assessor who is blinded to the treatment assigned will assess wound images to determine complete wound apposition of skin edges at the Day 10 and Day 30 follow-up visits.

The independent assessor will be selected by the lead Principal Investigator (PI), in consultation with the Sponsor, before enrollment begins and must meet the following criteria:

- Trained physician with an active medical license
- Minimum of 2-years of surgical experience using tissue adhesive
- Complete Financial Disclosure assessed by the Sponsor to insure he/she does not have serious scientific, financial, personal, or other conflicts of interest related to the conduct, outcome, or impact of the study
- Not listed on the FDA Debarment List or FDA Clinical Investigator – Disqualification Proceedings Database
- Not involved in any Subject-related activities (eg, enrollment, tissue adhesive application, follow-up visits).
- Not an employee of the Sponsor
- Not in a position susceptible to undue influence, either perceived or actual, by the lead PI (eg, a junior hierarchical member in relation to the lead PI)

The primary statistician, clinical operations members and the staff at the sites will be blinded to the final randomization schedule. The interim analyses will be conducted by an independent biostatistician (IBIO) of the Sponsor that is not involved in the operations or monitoring of the trial but will validate final analysis of the study. The IBIO will be the only person unblinded to

the treatment assignment at the interim analyses. Development and testing of SAS programs prior to interim and final data locks will occur using a dummy randomization schedule instead of the actual final randomization.

4. STUDY ENDPOINT(S)

4.1. Efficacy Endpoints

4.1.1. Primary Efficacy Endpoint

The primary endpoint is the percentage of wounds with 100% apposition of skin edges (ie, complete closure) at the Day 10 visit after application of the tissue adhesive.

4.1.2. Secondary Efficacy Endpoint(s)

1. The mean percentage (%) of the Subject's wound(s), in relation to the original incision/laceration length, with tissue adhesive remaining at the Day 10 visit after application of the tissue adhesive.
2. The percentage of wounds with 100% apposition of skin edges (ie, complete closure) at the Day 30 visit after application of the tissue adhesive.

4.1.3. Exploratory Endpoint(s)

An exploratory endpoint will be the cosmesis score at the Day 30 visit after adhesive application.

4.1.4. Health Economic Endpoint(s)

There are no Health Economic Endpoints.

4.2. Safety Endpoint(s)

The safety endpoint will be the incidence of all AEs and serious adverse events (SAEs). The incidence of all ADEs and SADEs will also be evaluated as part of the safety analysis for this study. Lastly, the Subject incidence of select treatment-emergent Adverse Device Events (ADEs) or serious ADEs (SADEs), will also be evaluated, including a composite and individual component incidence rates of:

- thermal injury
- well-defined to severe erythema
- well-defined to severe edema
- wound infection
- wound dehiscence, including:
  - dehiscence that does not require treatment
  - dehiscence that requires clinical intervention (and intervention type)

5. ANALYSIS POPULATIONS

The following analysis sets will be used throughout the course of analyses. The primary analysis will be conducted on the Per Protocol (PP) dataset and the Intent-to-Treat (ITT) dataset. The Safety Analysis Set will be used for safety analyses

5.1. Safety Population

The Safety Analysis Set will consist of all treated Subjects. Subjects will be analyzed in the group to which they were treated.

5.2. Intent-To-Treat Population

The Intent-to-Treat (ITT) Analysis Set will consist of all randomized Subjects. Subjects will be analyzed in the group to which they were randomized.

5.3. Per-Protocol Population

The PP Analysis Set may exclude Subjects from the ITT Analysis Set(s) that had major protocol deviation(s) that would impact the interpretation of the primary endpoint. Examples of exclusion from the various PP datasets are outlined below.

- PP analysis set for the primary endpoint: The following disqualifying protocol deviations will lead to exclusion from the per protocol data set for the analysis of the primary efficacy variable 100% wound apposition at the Day 10 visit:
    1. Subject who is missing the endpoint being analyzed. If there is 100% wound apposition at the Day 30 visit, 100% wound apposition at the Day 10 visit will have 100% wound apposition imputed as the Day 7 value. A Subject who is randomized but not treated will have this endpoint missing and will be excluded from the PP analysis set.
    2. Subject with endpoint measured outside the one-sided time window of minus two days.
    3. A Subject who receives the wrong or no treatment.
    4. A Subject for whom the wound was not approximated completely until the tissue adhesive cured.
- PP analysis set for the secondary endpoint #1: The following disqualifying protocol deviations will lead to exclusion from the per protocol data set for the analysis of the secondary endpoint #1, mean percent of subject's wound(s) with adhesive remaining at the Day 10 visit:
    1. Subject with at least one wound missing the endpoint being analyzed.

2. Subject with at least one wound with endpoint measured outside the two-sided time window of ± 2 days.
3. Subject with any wound which received the wrong or no treatment.

- PP analysis set for the secondary endpoint #2: The following disqualifying protocol deviations will lead to exclusion from the per protocol data set for the analysis of secondary endpoint #2, efficacy variable 100% wound apposition at the Day 30 visit:

1. Subject who is missing the endpoint being analyzed. However, if the wound was not 100% apposed at the Day 10 visit, that value will be carried forward for the 100% apposition response at the Day 30 visit.
2. Subject with endpoint measured outside the one-sided time window of minus five days.
3. A Subject who receives the wrong or no treatment.
4. A Subject for whom the wound was not approximated completely until the tissue adhesive cured.

All deviations not captured above that result in exclusion from the primary or secondary PP analyses will be defined and justified in a blinded review before data lock. In addition, documentation of these data classification decisions will be made prior to interim and final data locks.

6. GENERAL STATISTICAL CONSIDERATIONS

The following sections represent all the planned summaries and listings that will be carried out for the interim and final data analyses. These planned summaries may be supplemented with other summaries or figures as deemed appropriate by the data. Furthermore, the secondary efficacy, safety and cosmesis endpoints will not be summarized for the interim analysis.

The critical analysis for the interim analyses and interim decisions will be based on the primary efficacy analysis which will be interpreted considering the summaries of Subject disposition, demographics, baseline characteristics, medical history, and treatment compliance using the interim data.

Summaries of continuous variables will show the number of non-missing values [n], along with the mean, median, standard deviation, minimum, and maximum. Summaries of categorical (qualitative) variables will include the frequency and percentage of Subjects who are in the category of each possible value.

Other post hoc data analyses to characterize safety and/or efficacy activity of 3M™ Topical Tissue Adhesive may be conducted. These additional post hoc analyses will be decided at the

time of analysis and will be labeled as such. Due to the exploratory nature of the analyses, no adjustment for multiplicity will be made in these post hoc analyses.

All statistical analyses will be performed using SAS version 9.4 or above (SAS Institute, Cary, NC). Any changes to the methods proposed in this SAP will be justified and documented in the "Changes to Planned Analyses" section of the final Clinical Study Report (CSR).

If the study is terminated and the study data will not be used for a submission, the analysis may be limited to safety analysis only.

6.1. Interim Analysis

There will be two, unblinded interim analyses conducted after 226 and 340 Subjects have been randomized and have reached their Day 10 follow-up visit. These interim analyses correspond to 50% and 75% of expected total enrollment. Subjects randomized but not treated cannot reach their Day 10 follow-up visit but will be included in the subject counts of 226 and 340. The interim analyses will be conducted by an independent biostatistician (IBIO) of the Sponsor that is not involved in the operations or monitoring of the trial but will validate final analysis of the study. The IBIO will be the only person unblinded to the treatment assignment at interim. The IBIO will conduct the interim analysis and prepare the interim report. The results will be reviewed by an internal committee consisting of the biostatistics manager, clinical operations manager, and safety officer not connected with the day-to-day operations of the study. This committee will then decide whether the study will be stopped early due to efficacy or continue as planned. Enrollment will continue to occur during the interim analyses. The interim reports will be provided to the FDA along with the final report at submission of the 510k application.

The analysis of the primary endpoint will be conducted at adjusted alpha values of 0.0015 at the first interim analysis; 0.0092 at the second interim analysis and 0.022 at the final analysis. The boundary conditions were obtained using SAS PROC SEQDESIGN and are shown below.

```
proc seqdesign boundaryscale=pvalue
   errspend;

   onesidedobrienfleming: design nstages=3 info=cum(50 75 100)
   method=errfuncobf alpha = 0.025 beta = 0.2 alt = upper;
   samplesize model=inputnobs (n = 416);
   ods output boundary=bnd_ldl;
run;
```

Table 6.1.1

Boundary Information (p-Value Scale)
Null Reference = 0

Stage	Information Level Proportion	Alternative Reference Upper	Boundary Values Upper Alpha
1	0.5000	2.00037	0.00153
2	0.7500	2.44995	0.00916
3	1.0000	2.82896	0.02200

Table 6.1.2

Sample Size Summary

Input	One-Sample N
Fixed-Sample N	416
Information (Percent of Fixed Sample)	101.9633
Max Sample Size	424.1673
Expected Sample Size (Null Ref)	422.9823
Expected Sample Size (Alt Ref)	349.0936

The decisions rules are as follows:

At interim analysis #1, if alpha < 0.0015 for the PP population and <0.0015 for the ITT population, the study will be stopped for efficacy. Otherwise, the study will continue and interim analysis #2 conducted after enrollment and Day 10 visits for 340 Subjects.

At interim analysis #2, if alpha < 0.0092 for the PP population and <0.0092 for the ITT population, the study will be stopped for efficacy. Otherwise, the study will continue until completion of the study with 452 Subjects randomized.

Data for the interim analysis will be source verified and cleaned. All protocol deviations will be subjected to a blinded evaluation to assess if the deviation is major and should not be included in the per protocol dataset.

All planned interim statistical analyses will be documented in this SAP, finalized, and approved prior to conducting the first interim analysis.

6.2. Determination of Sample Size

The mean percent dehiscence for the RCT studies reported in the Summary of Safety and Efficacy Data for Histoacryl, whereby dehiscence is used as an indicator of incomplete wound

apposition, is 3%. However, the wounds in those previous studies were generally less than 5 cm in length, and the rate of incomplete apposition has been reported to be greater than the rate of dehiscence in some studies. Therefore, an incomplete apposition rate above this, at 10%, is used for the sample size calculation, with the 100% wound apposition rate assumed to be 90% for the comparator adhesive. A non-inferiority margin of 10% will be used, the same as that used by Blondeel et al in a previous trial.[1]

A non-inferiority test for the difference in two proportions yielded a total sample size requirement of 416 assuming that the observed proportions will be 85% in both treatment groups and using a non-inferiority margin of 10%, an overall one-sided alpha of 0.025 and a power of 80%. See Appendix B for the nQuery® PTE19 (Non-Inferiority test for the difference of two proportions) output that supports the sample size computation.

The initial sample size estimate of 416 was inflated to 424 to account for the group sequential design with two interim analyses conducted at 50% and 75% information fractions (see "Max Sample Size" in Table 6.1.2 in Section 6.1 Interim Analysis for the SAS® output supporting this inflation). The sample size was further inflated to a final sample size of 452 to account for a potential attrition rate of 6%.

The sample size goal for this study will be 452 subjects.

6.3. Handling of Dropouts and Missing Data

6.3.1. General Missing Data

Missing data will not be imputed for the PP dataset(s) except in the scenarios described below.

6.3.2. Imputations for PP Dataset(s)

In general. data will not be imputed for the PP dataset used to analyze the primary endpoint of 100% wound apposition at the Day 10 visit except:

- If wound apposition data is not available at the Day 10 visit any wound apposition of less than 100% at any time prior to the Day 10 visit will be carried forward and used as the apposition data for the Day 10 visit.
- If wound apposition data is not available at the Day 10 visit, but there is 100% wound apposition at the Day 30 visit, these data will be used as the apposition data for the Day 10 visit.

For the PP dataset analysis of the secondary endpoint of 100% wound apposition at the Day 30 visit, if wound apposition data is not available at the Day 30 visit any wound apposition of less than 100% at any time prior to the Day 30 visit will be carried forward.

6.3.3. Imputations for ITT Dataset

In cases where apposition data is missing from the primary endpoint (Day 10 100% apposition) or secondary endpoint #2 (Day 30 100% apposition), the following imputation process will be used to create the ITT analysis sets. Logical imputation will be conducted first. Missing data points for Subjects in which prior study visits indicated that the study wound was not 100% apposed will be imputed to reflect that the wound is not apposed at the missing timepoint. This method can be seen as a conservative application of last observation carried forward. Secondly, if Day 30 data is available and the wound(s) were 100% apposed, the wound(s) on Day 10 will be imputed as 100% apposed. Thirdly, the partially imputed data set created in the first two steps will have multiple imputations applied to all other instances of missing data to complete the dataset. The multiple imputation method will be a model-based approach that includes the fixed effects of treatment, site, wound type/number, diabetes status, age, and sex. Five (5) simulated datasets will be created through imputation. A tipping point analysis will be conducted. Multiple imputation datasets will be created independently for the primary endpoint and for secondary endpoint #2.

If there is $\leq$ 5% missing data for an efficacy endpoint being imputed in an ITT dataset, a single imputation will be used. There will be no imputation of safety endpoints.

6.3.4. Conventions/Imputations for Adverse Events (AE) and Concomitant Medications (CM)

If the Adverse Event/Concomitant Medication start date is partially missing [e.g. the month of the start date is missing, or the day of the date is missing], the following conventions will be applied:

- If only the day is missing then the imputed day will be: The day of the initial treatment application if the month is the same, or the first day of the month will be used if the month differs or the imputed day results in a start date after the end date.
- If only the month is missing then the imputed month will be the month of the initial treatment application if the year is the same, or 'January' if the year differs.
- If both month and day are missing, then the month is imputed as the month and day of the initial treatment application. If the imputed day results in a start date after the end date, then the first day of the month will be used.

If the AE start date is missing and the end date is complete

- If the end date is on or after the date of the treatment, the start date will be imputed as the date of the treatment date.
- If the start date is completely missing and the end date is completely missing then the AE/CM will assume to be "on-study", then the start date will be set to the date of the treatment.
- If the start date is completely missing and end date is prior to the treatment, the AE/CM will assume to be 'prior to study' and not be included in any summaries.

6.4. Validation Plan

The validation level of each program will use a risk-based approach.

Risk is comprised of:

- complexity of the program
- novelty of the method
- impact/importance of the results
- likelihood of an error occurring

Not all programs within a study need to be the same validation level.

As much as possible, one set of SAS programs will be written and used for both interim and final data analyses. The SAS programs will be validated prior to creating interim output and this validation may serve for both interim and final runs if there are no modifications to the programs. Separate validation of SAS outputs will occur for both interim and final outputs since they will be different.

7. SUMMARY OF STUDY POPULATION

7.1. Subject Disposition

The disposition summary will include the following:

- All Subjects screened by sites and overall.
- All Subjects who failed screening along with reasons for screen failure.
- All randomized Subjects by sites and overall.
- All treated Subjects by sites and overall.
- All Subjects who completed the study.
- All Subjects who discontinued from the study along with reasons for discontinuation.
- All subjects in each analysis set.
- Supporting Subject data listings for the above summaries will also be provided.

7.2. Clinical Investigation Plan Deviations

All deviations will be summarized by categories, treatment group and overall. Listing of protocol deviations will also be provided. Protocol deviations that affect the evaluability of subjects will be reviewed for evaluability during a blinded review process and documented before interim and final database locks.

7.3. Baseline and Demographic Characteristics

7.3.1. Demographics

Baseline demographics and other characteristics (e.g. age, race, sex, ethnicity, height, weight, body mass index (BMI)) will be summarized by treatment and overall using the ITT, Safety (if different from the ITT dataset), and PP datasets.

7.3.2. Baseline Characteristics

Key baseline characteristics variables will be summarized by treatment arm and overall, separately for ITT and PP analysis sets. These may include but are not limited general health status, overall comorbidities, and any specific factors related to each of the surgeries of interest

7.3.3. Medical History

Collected medical and surgical history will be presented as Subject level listings. Medical and surgical history events will be coded using MedDRA version v22.0 or higher. The number and percentage of Subjects with at least one medical or surgical history event in each system organ class by preferred term will be summarized. In any given category (eg, system organ class or preferred term), a Subject will be counted only once. The denominator for the calculation of percentages will be the number of Subjects in the Safety analysis set. The test for significant between-treatment differences will be carried out using the Fisher's exact test.

7.4. Treatment/Device Use Duration and Compliance

Treatment duration will be computed as the number of days from day of surgery: Visit Date - Surgery Day Date +1.

8. EFFICACY ANALYSIS

8.1. Primary Efficacy Analysis

This is a non-inferiority study for the percentage of Subjects with wounds with 100% apposition of skin edges (ie, complete closure) at the Day 10 visit after application of the tissue adhesive using a ten (10) percentage point non-inferiority margin. The relevant null and alternate hypotheses are specified below:

$$H_0: \pi_{c10} - \pi_{t10} \geq \delta$$

$$H_a: \pi_{c10} - \pi_{t10} < \delta$$

Where δ is the non-inferiority margin δ=10%

where π_{c10} is the percentage of Subjects with 100% wounds apposed for the control device at the Day 10 visit and π_{t10} is the percentage of Subjects with 100% wounds apposed for the investigational device at the Day 10 visit.

The randomization will be stratified by site, by diabetes mellitus status, and by wound type (ie, single laceration, single surgical incision, and multiple surgical incisions). Multiple lacerations will not be included in the study.

The analysis will be on a Subject basis. For Subjects with multiple surgical incisions, all wounds must be 100% apposed for that Subject to be considered 100% apposed at the Day 10 visit.

A Farrington-Manning (Score) Test will be used to conduct the non-inferiority analyses for the difference in proportions of Subjects with apposed wound(s). Analyses will be conducted on both the Day 10 PP dataset and the ITT dataset. At the final analysis, non-inferiority will be declared if the null hypothesis is rejected at $\alpha = 0.022$ level for the analyses conducted for both the PP and ITT datasets. The primary endpoint data will then be presented at the stratum level for each of the three stratification variables separately. The Breslow-Day test will also be carried out for each stratification variable. A p-value of < 0.15 for the overall strata effect will be considered significant for this purpose. Individual stratum level tests will not be conducted.

There is a single primary endpoint, and the only multiplicity adjustment necessary is due to the use of interim analyses. A one-sided $\alpha = 0.0015$ will be used for the first interim analysis, a one-sided $\alpha = 0.0092$ will be used for the second interim analysis, and a one-sided $\alpha = 0.022$ will be used at the final analysis. Refer to Section 6.1 (ie, the interim analysis section) for justification of these alpha levels,

Summary tables will be produced for the percentage of Subjects with 100% of wounds apposed as well as the percentage of wounds with 100% apposition. These summary tables will be for all data and by stratification factors for both the PP and ITT datasets.

8.2. Secondary Efficacy Analysis

There are two secondary endpoints.

1. The percentage (%) of the sum of the subject's wound length(s), in relation to the sum of the original incision/laceration length(s), with tissue adhesive remaining at the Day 10 visit after application of the tissue adhesive.

   $$Secondary\ Endpoint\ \#1 = \left\{\frac{\sum wound\ length(s) with\ adhesive\ remaining\ at\ Day\ 10\ visit}{\sum original\ wound\ length(s)}\right\} x100\%$$

2. The percentage of Subjects with wounds with 100% apposition of skin edges (ie, complete closure) at the Day 30 visit after application of the tissue adhesive.

If the primary objective is successful using both the ITT and the Day 10 PP datasets, the full alpha will be passed to the set of secondary endpoints. The alpha will be passed sequentially to secondary endpoint #1 and then to secondary endpoint #2 if the null hypothesis for secondary endpoint #1 is rejected.

Summary tables will be produced for the secondary endpoints by Subject and by wound. These summary tables will also be produced by stratification factor and by PP and ITT datasets.

Secondary Endpoint #1:

This is a nonequality study for secondary endpoint #1

The null and alternative hypotheses are specified below:

$$H_0: \text{Median } \pi_{cw10} - \text{Median } \pi_{tw10} = 0$$

$$H_a: \text{Median } \pi_{cw10} - \text{Median } \pi_{tw10} \neq 0$$

where π_{cw10} is the percent of the sum of wound length(s) with adhesive remaining for the control device at the Day 10 visit in relation to the sum of the original incision/laceration length(s), and π_{tw10} is the percent of the sum of the wound length(s) with adhesive remaining for the investigational device at the Day 10 visit in relation to the sum of the original incision/laceration length(s).

A non-parametric Wilcoxon Rank Sum test will be used to test for differences between treatment groups. The Day 10 PP dataset listed previously for this endpoint as well as the ITT dataset will be used for the analysis. Summary tables will be produced by strata within each stratification factor.

Secondary Endpoint #2:

This is a non-inferiority trial for secondary endpoint #2 – the percentage of wounds with 100% apposition of skin edges (ie, complete closure) at the Day 30 visit after application of the tissue adhesive using a 10% margin.

The analysis is on a Subject basis. For Subjects with multiple wounds, all wounds must be 100% apposed for that Subject's wounds to be considered 100% apposed. Both the Day 30 PP dataset and the ITT datasets will be used for the analysis.

The null and alternative hypotheses are specified below:

$$H_0: \pi_{c30} - \pi_{t30} \geq \delta$$

$$H_a: \pi_{c30} - \pi_{t30} < \delta$$

Where δ is the non-inferiority margin δ=10%

where π_{c30} is the percentage of Subjects with 100% wound apposition for the control device at the Day 30 visit and π_{t30} is the percentage of Subjects with 100% wound apposition for the investigational device at the Day 30 visit.

A Farrington-Manning (Score) Test will be used to conduct the non-inferiority analyses for the difference in proportions of Subjects with apposed wound(s) using all data. Analyses will be conducted on both the Day 30 PP dataset and the Day 30 ITT datasets. At the final analysis, non-inferiority will be declared if the null hypothesis is rejected at $\alpha = 0.022$ level for the analyses conducted for both the PP and ITT datasets. The secondary endpoint #2 data will then be presented at the stratum level for each of the three stratification variables separately. The Breslow-Day test will also be carried out for each stratification variable. A p-value of < 0.15 for the overall strata

effect will be considered significant for this purpose. Individual stratum level tests are not being conducted.

8.3. Exploratory Analysis

The cosmesis endpoint will be measured using the Vancouver Scar Score.[2] Four (4) components of this subset score along with the total score, will be summarized by treatment.
The Day 30 follow-up visit ITT and PP populations will be used as the analysis sets.

8.4. Health Economic Analysis

Not applicable

9. SAFETY ANALYSIS

9.1. Adverse Events

The analysis of safety endpoints will consist of summary statistics. The summary tables will be produced for the composite endpoint listed below as well as for the individual components of the composite, by treatment and overall.

A composite of treatment-emergent Adverse Device Events (ADEs) or serious ADEs (SADEs) will be generated of the list below and summarized by treatment.

- thermal injury
- well-defined to severe erythema
- well-defined to severe edema
- wound infection
- wound dehiscence, including:
    - dehiscence that does not require treatment
    - dehiscence that requires clinical intervention (and intervention type)

The Subject incidence of AEs will be reported by MedDRA system organ class and preferred term. AEs will also be presented by severity (mild, moderate, severe). A listing of SAEs including death(s), Subjects who died of any cause during study, will also be presented along with their relatedness to treatment, severity, and action taken.

9.2. Other Safety Variables

Listings for concomitant medications will be presented by subject. All the analyses and summaries of concomitant medications will be based on descriptive statistics. All subjects in the Safety analysis set will be accounted for in the summation.

10. CHANGES FROM PLANNED ANALYSIS

Any required changes to the SAP will be made prior to interim and final database locks and will be documented in Appendix A Revision History section of this SAP. Documentation will include the change and its corresponding reason.

11. REFERENCES

1. Blondeel PN, Murphy JW, Debrosse D, et al. Closure of long surgical incisions with a new formulation of 2-octylcyanoacrylate tissue adhesive versus commercially available methods. *Am J Surg.* Sep 2004;188(3):307-13. doi:10.1016/j.amjsurg.2004.04.006

2. Baryza MJ, Baryza GA. The Vancouver Scar Scale: an administration tool and its interrater reliability. *Journal of Burn Carte and Rehabilitation. 9/1/1995 1995;16(5):535-538*

12. APPENDICES

12.1. Appendix A – Revision History

REVISION HISTORY

The purpose of this appendix is to describe modifications made to this document.

Revision History Table		
Version #	**Description of change including section number impacted**	**Reason for change**
1		To Establish

12.2. Appendix B – Sample Size Documentation



12.3. Appendix C – Example SAS Code



