EM-05-015029

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

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Study Title	A Multi-Center, Prospective, Open-label, Randomized, Non-inferiority Study of 3M™ Topical Tissue Adhesive versus Commercially Available Tissue Adhesive for the Closure of Traumatic Lacerations and Surgical Incisions
Study Number	EM-05-015029
Release Date	02/08/2024 11:40:48 AM CST
Name of Device Under Investigation	3M™ Topical Tissue Adhesive
Sponsor Address	[redacted]
Manufacturer Address	[redacted]

ELECTRONIC SIGNATURES:

Signer	Role	Date Signed
[redacted]		

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Investigator Statements of Compliance

This clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

This clinical investigation shall be conducted in accordance with ISO-14155:2020, US FDA 21 CFR parts 812, 50, 54, 56, and any regional or national regulations, as appropriate.

The clinical investigation shall not begin until the required approval/favorable opinion from the Institutional Review Board (IRB) and regulatory authority (if applicable) has been obtained and permission to proceed has been received from the study Sponsor. Any additional requirements imposed by the IRB or regulatory authority shall be followed.

I have read the Clinical Investigation Plan (CIP), including all appendices, as well as supporting study-related documents and I agree that it contains all necessary details for me and my staff to conduct this study as described. I agree to record all adverse events/ deviations and report those adverse events/ deviations to the Sponsor per this CIP and IRB per local requirements. I always agree to maintain product accountability and ensure the security of study materials. I agree to comply with financial disclosure requirements.

All Subjects will sign and date the approved Informed Consent before any study procedures are conducted, as applicable.

I will ensure that all Subjects meet inclusion criteria before enrolling them in the study.

I agree to maintain and retain records as required by this Clinical Investigation Plan.

Investigator's Signature:	
Investigator's Name:	
Institution:	
Date of Signature:	

ABBREVIATIONS/ACRONYMS

AE	adverse event
ADE	adverse device effect
[redacted]	
CIP	Clinical Investigation Plan
CFR	code of federal regulations
cm	centimeters
cm^2	square centimeters
CP	conditional power
CRF	Case Report Form
[redacted]	
DD	device deficiency
DM	diabetes mellitus
DMP	Data Management Plan
eCRF	electronic Case Report Form
EOS	end of study
EU MDR	European Medical Device Regulation
FDA	U.S. Food & Drug Administration
GCP	Good Clinical Practice
hCG	Human Chorionic Gonadotropin
HEENT	head, eyes, ears, nose, and throat
HIPAA	Health Insurance Portability and Accountability Act
IBIO	independent biostatistician
ICF	Informed Consent Form
IDE	investigational device exemption

IRB	Institutional Review Board
mm	millimeters
MP	monitoring plan
[redacted]	
PHI	personal health information
PI	Principal Investigator
PP	Per Protocol
RCT	randomized controlled trial
SADE	serious adverse device effect
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	Standard of Care
SOP	standard operating procedure
UADE	unanticipated adverse device effect
USA or US	United States of America
WOCBP	Women of Child-Bearing Potential

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1 SUMMARY

Study Title	A Multi-Center, Prospective, Open-label, Randomized, Non-inferiority Study of 3M™ Topical Tissue Adhesive versus Commercially Available Tissue Adhesive for the Closure of Traumatic Lacerations and Surgical Incisions
Study Type	Pre-market
Coordinating Center Lead Principal Investigator (PI)	[redacted]
Device under Investigation Summary	The investigational device in this study is 3M™ Topical Tissue Adhesive, which aids in the approximation of skin edges, including surgical incisions from minimally invasive surgery, low-tension incisions, superficial lacerations, and clean traumatic lacerations. [redacted]
Sponsor	3M Company 3M Center St. Paul, MN. 55144
Purpose	The purpose of this study is to generate safety and performance data for 3M™ Topical Tissue Adhesive to support premarket submissions to the US FDA (510k), European Union Medical Device Regulation (EU MDR), and other countries.
Design	This is a multicenter, prospective, open-label, randomized, non-inferiority study that will include 452 randomized 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 any one 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 may have a single laceration or up to 4 surgical incisions requiring closure. Subjects with multiple lacerations are not eligible for the study. Subjects will be seen during Screening (no more than 10 days before application of tissue adhesive), on the day in which skin edges of wound(s) are reapproximated and tissue adhesive is applied (Day 0), 10 days (± 2 days) after application of the tissue adhesive, and 30 days (± 5 days) after application of the tissue adhesive.
Selection of Subjects	To be considered eligible for enrollment, Subjects must meet all of the eligibility criteria listed below. *Inclusion Criteria:* To be considered eligible for enrollment, Subjects must meet all of the following inclusion criteria: 1. Subject is at least 22 years of age on the date of informed consent 2. Subject or Subject's legally authorized representative can provide informed consent 3. Subject is willing and able to attend all scheduled study visits and abide by all study restrictions 4. Subject has a single laceration that is ≤ 100 mm (10.0 cm) in length **or** up to 4 surgical incision(s), each ≤ 100 mm (10.0 cm) in length, defined as Class I or Class II wound(s) (according to CDC definitions[1] – see Appendix 18.1), in which the use of a tissue adhesive (in combination with but not replacing deep dermal sutures, if applicable) is appropriate, including the following: • surgical incision from a minimally invasive surgery • low-tension incision • superficial laceration

	• clean, traumatic laceration with edges that can be easily approximated *Exclusion Criteria:* Subjects that meet any of the criteria listed below are excluded from participating in the study. 1. Subject has a positive pregnancy test within 48 hours prior to randomization at Day 0 or lactating prior to randomization at Day 0* *Women who have had surgical sterilization by a medically accepted method (eg, tubal ligation, hysterectomy, or oophorectomy) or are post-menopausal, defined as not having menstruation for > 12 months will not be required to undergo pregnancy testing 2. Subject is found to have any of the following before randomization: • a known peripheral vascular disease • a history of hypertrophic scarring and/or keloids • any Class III or Class IV wounds (according to CDC definitions[1] – see Appendix 18.1) • uncontrolled diabetes mellitus, defined as HbA1C ≥ 10% within 90 days before screening. If HbA1C data is unavailable or the Subject presents in an emergency situation, uncontrolled DM will be defined as blood glucose ≥ 250 mg/dL • a known blood clotting disorder • immunocompromised • a known systemic or local bacterial, viral, or fungal infection • critical injury • condition(s) that in the opinion of the Investigator will impact study results (eg, hemophilia or autoimmune disorder) or the ability of the Subject to remain compliant with study procedures, study restrictions, and/or visits

	3. Subject has a known hypersensitivity or allergy to any of the components of study products (eg, polyoxamides or cyanoacrylates) 4. Subject is concurrently participating in or was enrolled in another interventional clinical study within 30 days of randomization 5. Subject has a laceration or incision that is > 100 mm (10 cm) in length 6. Subject has any incision that is within 5 cm of any adjacent incision 7. Subject has one of the following: • a "burst" or stellate laceration • wound with exposed bone • wound with suspected skin edge ischemia due to extensive undermining • wound requiring drain(s) • wound requiring a conventional closure method (eg, subcuticular/intradermal suture, staples, adhesive strips) **OR** subcuticular stitch placement for enhanced wound support (ie, to further minimize tension) 8. Subject has a wound with any of the following etiologies: • human or animal bite • prolonged pressure (ie, decubitus) 9. Subject has a wound in any of the following anatomical locations: • on mucosal surfaces or across mucocutaneous junctions (eg, oral cavity, lips) • in or around the eyes • an anatomical area that is under tension or over a joint • on an area that may be regularly exposed to body fluids or with dense natural hair present, (eg, scalp)
Device Regulatory Classification	The 3M™ Topical Tissue Adhesive is categorized as a significant risk device as defined in 21 CFR 812.3(m), requiring a clinical study

	conducted under the Investigational Device Exemptions (IDE) regulation, 21 CFR part 812. The Sponsor is currently seeking 510(k) clearance for the 3M™ Topical Tissue Adhesive such that it is regulated as a Class II (special controls) device under product code MPN (tissue adhesive for the topical approximation of skin) under 21 CFR 878.4010. The special control for this device is FDA Guidance document, *Tissue Adhesive for the Topical Approximation of Skin – Guidance for Industry and FDA Staff*.
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.
Endpoint(s)	The primary endpoint is 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. The secondary endpoints will include the following: • 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 • 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 An exploratory endpoint will be the cosmesis score at the Day 30 visit. The safety endpoint will be the incidence of all adverse events (AEs) and serious adverse events (SAEs). The incidence of all adverse device effects (ADEs) and serious adverse device effects (SADEs) will also be evaluated as part of the safety analysis for this study. Lastly, the Subject incidence of select treatment-emergent 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)

Duration of the Study	The entire duration of enrollment is expected to last approximately 12 to 15 months, and the duration of participation for individual Subjects is expected to last up to 46 days.
Sponsor Study Contact	[redacted]
Medical Monitor Contact	

2 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

2.1 BACKGROUND

2.1.1 Tissue Adhesives

Topical tissue adhesives, which were first developed in the 1940s, provide an alternative to conventional methods of wound closure by primary intention (eg, sutures, clips, or staples).[2] Some of the advantages of tissue adhesives over conventional wound closure methods include the ease of application, less trauma to the wound site, and unnecessary return visits for subsequent removal.[3] Present-day, commercially available tissue adhesives can be separated into three categories: natural or biological adhesives (eg, fibrin-based or collagen-based adhesives); biomimetic adhesives (eg, mussel-inspired or gecko-inspired adhesives); and synthetic or polymer-based adhesives (eg, polycyanoacrylates).[4-6]

Polycyanoacrylates and other synthetic tissue adhesives, which undergo rapid polymerization to form a strongly adhesive film, have stronger adhesive properties than biological tissue adhesives due, in part, to the covalent bonding that occurs between the cyanoacrylate and functional groups (eg, amines) in the tissue.[4] A disadvantage to using polycyanoacrylate tissue adhesives is that polymerization occurs in an exothermic manner, which can cause skin damage.[3] In addition, degradation of the polymer into the monomeric cyanoacrylate and formaldehyde, a process that is mitigated by the addition of long-chain alkyl groups (-R) such as a butyl or octyl chain, can cause tissue inflammation.[3, 5]

[redacted]

2.1.2 Randomized Controlled Trials Assessing Wound Closure with Synthetic Tissue Adhesives

There have been over 20 publications related to randomized controlled trials (RCTs) assessing 100% wound apposition of closed incisions/lacerations (ie, complete closure), or the lack thereof (eg, dehiscence), wherein a synthetic adhesive was used in at least one study arm.[7-28] All of these publications pertained to cyanoacrylate tissue adhesives (CTA), and 17 were related to trials in which a 2-Octyl cyanoacrylate tissue adhesive (O-CTA) was applied in at least one arm.[7, 8, 10-13, 15-21, 23-26] Four publications were related to trials in which an *n*-Butyl cyanoacrylate tissue adhesive (B-CTA) was applied to the reapproximated skin edges of wounds in one study arm,[14, 22, 27, 28] and one publication was related to a study in which an adhesive comprised of separate *n*-Butyl cyanoacrylate and octyl cyanoacrylate components was applied to the

approximated skin edges of post-surgical incisions.[9] The vast majority of these studies compared wounds (ie, incisions or lacerations) that were closed using tissue adhesive with wounds closed using conventional methods (ie, sutures or staples).[7-14, 16-18, 20-28] One RCT compared the use of low-viscosity and high-viscosity O-CTAs for closure of lacerations,[19] and another compared closure of laparoscopic incisions using an O-CTA versus a blended tissue adhesive containing 90% butyl cyanoacrylate and 10% octyl cyanoacrylate.[15]

Dehiscence

Twenty publications related to RCTs have reported on the percentage of wound dehiscence after closure with a CTA.[7, 9-14, 16-28] In eight of these studies, no (0) dehiscence was observed in wounds closed using CTAs, including 54 facial incisions closed using O-CTA,[26] 20 incisions for blepharoplasty (eyelid surgery) closed using O-CTA,[12] 15 incisions after skin cancer surgeries closed using O-CTA,[23, 25] 54 incisions for implanted venous ports that were closed using O-CTA,[16] 21 groin incisions closed using B-CTA,[14] 65 supraclavicular incisions for thyroidectomies closed using B-CTA,[28] and 20 incisions for brain surgery that were closed using B-CTA.[9] In studies where incisions or lacerations were closed using O-CTA and dehiscence was reported, the incidence of dehiscence ranged from 1.6% to 17.14%.[7, 10, 13, 17-21, 24] This included a dehiscence rate of 1.6% (7/438) to 3.2% (2/63) following closure of lacerations or a combination of lacerations and incisions,[13, 19-21] 2.1% (1/48) after closure of laparoscopic port site incisions,[17] 3.125% (1/32) following closure of repeat Pfannenstiel incisions,[10] 7.1% (1/14) after closure of neck incisions for thyroidectomies,[18] 16.7% (4/24) following closure of inguinal herniorrhaphy incisions,[24] and 17.14% (6/35) following closure of laparoscopic cholecystectomy port incisions.[7] The incidence of dehiscence in studies where incisions or lacerations were closed using B-CTA and dehiscence occurred was 3.1% (2/77) for incisions related to port implantation[27] and 15% (3/20) following closure of hand incisions.[22]

Complete Apposition

The incidence of dehiscence can underestimate the true rate of incomplete apposition (ie, closure of less than 100%) since some studies do not categorize wounds as dehisced unless a clinical intervention is necessary. There have been two RCTs assessing complete apposition wherein O-CTA was used in one of the treatment arms.[8, 15] In 2004, Blondeel et al analyzed the healing rate of long surgical incisions when using a high-viscosity O-CTA (n = 106 Subjects and 145 wounds) or commercially available closure methods (n = 103 Subjects and 131 wounds) at the time of the study. The mean (± SD) total length of incision treated was 16 centimeters (cm) (± 14 cm) for wounds closed using O-CTA and 16 cm (± 13 cm) for wounds closed using commercially available methods.[8] Ten days after closure, 102 of the 106 Subjects (96.2%) that underwent wound closure using high-viscosity O-CTA had complete wound apposition, and 100 of the 103 Subjects (97.1%) that underwent wound closure using

commercially available devices, some of which included older O-CTA formulations, had complete wound apposition.[8] In 2014, Kent et al compared closure of laparoscopic port sites using either high-viscosity O-CTA (n = 216 Subjects and 636 total incisions) or a blended tissue adhesive containing 90% butyl cyanoacrylate and 10% octyl cyanoacrylate (n = 217 Subjects and 618 total incisions).[15] At two weeks after closure, 356 of 598 (59.5%) incisions that were closed using high-viscosity O-CTA had 100% apposition compared with 357 of the 593 (60.2%) incisions that were closed using the blended tissue adhesive being 100% apposed.[15] In this same study, only 1.7% (10/603) or 1.9% (11/593) of the incisions closed with high-viscosity O-CTA or the blended tissue adhesive, respectively, were reported to be dehisced,[15] supporting the notion that the incidence of dehiscence underestimates the true rate of incomplete apposition.

2.2 Rationale for Studying the Specific Population/Condition

Some of the suggested criteria for the use of tissue adhesive on skin include the wound (i) being non-infected or non-contaminated, (ii) not crossing a joint and/or not being under significant tension, (iii) not crossing a mucocutaneous junction, (iv) not resulting from an animal bite, which can increase the risk of infection, and (v) occurring in a person without a chronic condition that might impair wound healing.[29] In this study, low-tension Class-I or Class-II wounds (ie, a single laceration or up to 4 surgical incisions) will be assessed after closure using a tissue adhesive. Stellate wounds, wounds with evidence of infection, and wounds resulting from human or animal bites have been excluded from this study. In addition, Subjects with certain conditions that may impact wound healing have been excluded (see Section 6.2.1.2, Exclusion Criterion # 2).

Incisions and lacerations ≤ 100 millimeters (mm), or 10.0 cm in length, were selected for this study in an effort to have each Subject treated with a single vial of tissue adhesive. Of the previous RCTs where tissue adhesive was used in at least one study arm and wound length was reported, a mean or median wound length of less than 5 cm was reported in most studies,[7, 11, 13, 17, 19-21, 23, 27] although 3 RCTs reported a mean wound length of more than 8 cm.[8, 9, 14]

2.3 Scientific Rationale for Design

To have a high level of evidence, a multicenter, prospective, open-label, randomized, non-inferiority trial was designed for this study. In addition, stratification of Subjects during randomization was chosen as part of the study design to help control for wound type (ie, incision or laceration) and diabetes as confounding factors that may impact the primary endpoint (ie, complete closure).

Histoacryl® Blue Topical Skin Adhesive (Histoacryl®; Histoacryl® is a registered trademark of Aesculap, Inc) was selected as the comparator (Control product) for this trial because it is a well-known *n*-Butyl cyanoacrylate tissue adhesive,[4, 6] and four previous publications have described the usage of Histoacryl® and other *n*-Butyl cyanoacrylates in RCTs.[14, 22, 27, 28]

The primary endpoint of this study will be the percentage of wounds that are completely closed (ie, 100% apposition of skin edges) at the Day 10 visit after reapproximation with tissue adhesive. This duration was selected based on previous RCTs that assessed 100% apposition when CTAs were used for wound closure, which ranged from 10 days to two weeks,[8, 15] and on the duration that the polymerized Control product is expected to remain in place before natural sloughing.[30] The amount of polymerized tissue adhesive remaining at 10 days is being captured as part of the secondary endpoints in this study (see Section 5.4.2).

It is hypothesized that 3M™ Topical Tissue Adhesive will be at least as effective as the Control tissue adhesive in attaining 100% apposition of skin edges at the Day 10 visit.

3 IDENTIFICATION AND DESCRIPTION OF THE STUDY DEVICES

3.1 INVESTIGATIONAL DEVICE

The investigational device in this study is 3M™ Topical Tissue Adhesive, which aids in the approximation of skin edges, including surgical incisions from minimally invasive surgery, low tension incisions, superficial lacerations, and clean traumatic lacerations. [redacted]



3.1.1 Investigational Device Regulatory Classification

The 3M™ Topical Tissue Adhesive is categorized as a significant risk device as defined in 21 CFR 812.3(m), requiring a clinical study conducted under the Investigational Device Exemptions (IDE) regulation, 21 CFR part 812.

The Sponsor is currently seeking 510(k) clearance for the 3M™ Topical Tissue Adhesive such that it is regulated as a Class II (special controls) device under product code MPN (tissue adhesive for the topical approximation of skin) under 21 CFR 878.4010. The special control for this device is FDA Guidance document, *Tissue Adhesive for the Topical Approximation of Skin – Guidance for Industry and FDA Staff*.

3.1.2 Intended Use of the Investigational Device

The intended use of the device includes the following:

> *The 3M™ Topical Tissue Adhesive is intended for use on clean, easily approximated skin edges.*
>
> *The 3M™ Topical Tissue Adhesive is intended to provide skin closure on easily approximated, minimally invasive surgical incisions, low tension incisions, superficial, and clean traumatic lacerations.*
>
> *The 3M™ Topical Tissue Adhesive is delivered by an applicator.*
>
> *The intended users of the 3M™ Topical Tissue Adhesive are trained medical professionals in a clinical/surgical setting.*

3.1.3 Indications for Use for Investigational Device

The indications for use include the following:

> *The 3M™ Topical Tissue Adhesive is indicated for use as a skin closure on easily approximated, minimally invasive surgical incisions, low tension incisions, superficial, and clean traumatic lacerations. It is for use by medical professionals in a clinical/surgical setting. 3M Topical Tissue Adhesive can be used in combination with but should not replace deep dermal sutures. The product is not designed, sold, or intended for use except as indicated.*

3.2 CONTROL DEVICE

The Control device in this study will be Histoacryl® Blue Topical Skin Adhesive.

3.2.1 Control Device Regulatory Classification

The Control device in this study was most recently cleared (K140343) as a Class-II medical device under product code MPN (tissue adhesive for the topical approximation of skin) under 21 CFR 878.4010.

3.2.2 Indications for Use for Control Device

The indications for the Control device include the following:

> *Histoacryl® Blue Topical Skin Adhesives is intended for topical application to hold closed easily approximated skin edges of minimum-tension wounds from clean surgical incisions and simple, thoroughly cleansed, trauma-induced lacerations. Histoacryl® Blue may be used in conjunction with, but not in place of, deep dermal sutures.*

4 BENEFITS AND RISKS OF THE INVESTIGATIONAL DEVICE(S), CLINICAL PROCEDURE, AND CLINICAL INVESTIGATION

4.1 BENEFITS OF THE DEVICE(S), CLINICAL PROCEDURE, AND CLINICAL EVALUATIONS

Skin adhesives, including the Control device in this study (Histoacryl®), are intended for topical application to hold easily closed, approximated skin edges of minimum-tension wounds from clean surgical incisions and simple, thoroughly cleansed, trauma-induced lacerations.

The 3M™ Topical Tissue Adhesive aids in the approximation of skin edges, including surgical incisions after minimally invasive surgery, low tension incisions, superficial lacerations, and clean traumatic lacerations. All Subjects in this trial will undergo application of skin adhesive

to approximate skin edges, and the skin adhesive (Control device or Treatment device) will be provided by the Sponsor at no charge to the Investigator or Subject.

All Subjects will also undergo an assessment of their study wound(s) at the Day 30 follow-up visit, which may be an additional evaluation that would not normally occur as part of standard care. Subjects may experience increased monitoring, education, and evaluation of wound(s) and could lead to identification of complications. Subjects may benefit from increased engagement with healthcare professionals which may lead to increased awareness of wound care and wound healing and earlier detection of any complications. Study-related wound closure and wound evaluations will be provided at no charge to the Subject.

4.2 RISKS OF THE DEVICE(S), CLINICAL PROCEDURE, AND CLINICAL EVALUATIONS

Use of skin adhesives such as the Control device in this study and 3M™ Topical Tissue Adhesive include the following potential risks:

- dehiscence with the need for re-closure
- infection
- impaired healing
- erythema (redness)
- edema
- itching
- blister
- bonding to unintended tissues
- thermal discomfort during polymerization
- exposure-related reaction (eg, allergic reaction, rash, hives)
- irritation
- foreign body reaction
- tattooing (ie, skin pigmentation change)
- chronic non-healing of a wound
- pain or discomfort
- tissue necrosis

[redacted] The device components may present a risk of an adverse reaction, especially in patients who are allergic or hypersensitive to the device compounds. It should not be used in or around the eyes or mucous membranes. Lastly, good adhesion may not be obtained due to the presence of exudate, skin oils, moisture, or hair. Substrate failure may increase the risk of wound dehiscence.

4.3 Anticipated Adverse Device Effects

Skin adhesives, including the Investigational device and the Control device in this study, may cause an allergic reaction by skin contact in certain individuals who have hypersensitivity to substances in the devices. Certain incision site skin injuries are being captured as secondary endpoints in this study, and all skin injuries are being captured as adverse events. For example, thermal injury, wound infection, and wound dehiscence, all of which are potential risks for skin adhesives, are being captured as part of the safety endpoints in this study.

4.4 Residual Risks of the device(s)

Subjects in this study will undergo a single treatment of wounds (eg, a single laceration or up to 4 surgical incisions) with 3M™ Topical Tissue Adhesive (Treatment arm) or Histoacryl® (Control arm) and will be assessed approximately 10 days post-application and again 30 days post-application. Polyoxamides and cyanoacrylates are more inert (ie, less sensitizing or less toxic) than the monomeric non-polymerized compounds, and the polymerized tissue adhesive is expected to naturally slough off the skin during the treatment period. Therefore, any residual risks associated with long-term exposure to the polymerized tissue adhesive are expected to be minimal.

4.5 Risk of Interactions with Concomitant Medical Treatments

The manufacturer of the Control device in this study cautions to keep wounds dry following closure with Histoacryl® and not to apply topical medications following closure. Similarly, the study Sponsor cautions against applying topical solutions, ointments, or medications to the wound immediately after application of 3M™ Topical Tissue Adhesive.

4.6 Mitigation of Risk

Risk related to the devices may be mitigated or controlled through appropriate selection of study Subjects for inclusion in this study, adherence to this Clinical Investigation Plan (CIP), and reporting of adverse events (AEs), adverse device effects (ADEs), device deficiencies (DDs), and deviations to the Sponsor. For example, Subjects with known sensitivities to device components [redacted] are excluded

from participating in this study (see Section 6.2.1.2). If a patient has any signs of an allergic reaction, irritation, or hypersensitivity (eg, rash, hives, or significant itching), they should consult a physician immediately.

4.7 Risk to Benefit Rationale

The manufacturer has evaluated the 3M™ Topical Tissue Adhesive through bench testing, histopathology evaluations, risk analysis, biocompatibility evaluations, and pre-clinical evaluations. The results of these evaluations have identified no new risks associated with the proposed use of this device in this study. In addition, the design of this study attempted to minimize the occurrence of any foreseeable harm. Therefore, based on the risks and benefits listed above and adherence to this CIP, the study Subjects are at no greater risk of harm than individuals undergoing wound therapy who are not participating in this study.

5 OBJECTIVES OF THE CLINICAL INVESTIGATION PLAN

5.1 Purpose of the Clinical Investigation

The purpose of this study is to generate safety and performance data for 3M™ Topical Tissue Adhesive to support premarket submissions to the US FDA (510k) and European Union Medical Device Regulation (EU MDR), and other countries.

5.2 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.

5.3 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.

5.4 Endpoint(s)

5.4.1 Primary Endpoint(s)

The primary endpoint is 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.

5.4.2 Secondary Endpoint(s)

The secondary endpoints will include the following:

- 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
- 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

5.4.3 Exploratory Endpoint(s)

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

5.4.4 Safety Endpoints

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 (see Section 13). 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)

6 DESIGN OF CLINICAL INVESTIGATION

6.1 DESIGN

This is a multicenter, prospective, open-label, randomized, non-inferiority study that will include 452 randomized 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 any one 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 must have a single laceration or up to 4 surgical incisions requiring closure. Subjects with multiple lacerations are not eligible for the study.

6.1.1 Study Duration

The entire duration of enrollment is expected to last approximately 12 to 15 months, and the duration of participation for individual Subjects is expected to last up to 46 days.

Subjects will be seen during Screening (no more than 10 days before application of tissue adhesive), on the day in which skin edges of wound(s) are reapproximated and tissue adhesive is applied (Day 0), 10 days (± 2 days) after application of the tissue adhesive, and 30 days (± 5 days) after application of the tissue adhesive. Subjects may participate in additional unscheduled visits as required during the study if evaluation of the wound(s) is required outside of the scheduled study visits. Unscheduled visits may be initiated by either the Investigator or the Subject.

6.1.2 Minimization of Bias

To help minimize bias and help account for potential confounding variables in the study, multiple sites will randomize Subjects in a permuted-block-randomized manner. In addition, each site will enroll Subjects with both wound types (ie, lacerations or surgical incisions) when feasible, and each site will randomize Subjects to both arms. Lastly, randomization will be stratified by study site, by pre-existing diabetes mellitus, and by wound type.

Due to the nature of the investigational 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 assigned treatment 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 Coordinating Center 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 1 year of surgical experience using tissue adhesives
- Completed Financial Disclosure assessed by the Sponsor to ensure 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

6.1.3 Investigational Use of Device(s)

3M™ Topical Tissue Adhesive will be applied to the approximated skin edges of lacerations or incisions of Subjects in the Treatment arm immediately upon closure, and then covered with a dressing (if applicable per the SOC) for 10 ± 2 days. Lacerations or incisions of Subjects in the Control arm will be covered with Histoacryl®, which may be covered with a dressing (if applicable per the SOC) for 10 ± 2 days.

6.2 SUBJECT ENROLLMENT

A total of 452 Subjects (226 subjects in each treatment arm) will be randomized. Subjects with a single laceration or up to 4 surgical incisions may be eligible, with all of the surgical incisions assigned to the same treatment arm. Of the randomized Subjects, a minimum of 25% will have 2 to 4 surgical incisions, a minimum of 10% will have a single laceration, and a minimum of 15% will have a single surgical incision.

6.2.1 Enrollment Criteria

To be considered for this study, a Subject must meet all eligibility criteria listed in Sections 6.2.1.1 and 6.2.1.2. For Subjects in which the initial eligibility assessment and the date of wound closure occur on different dates, the eligibility criteria will be confirmed before randomization on Day 0. Subjects who do not meet all eligibility criteria will not be eligible for either arm and will be considered a screen failure.

6.2.1.1 INCLUSION CRITERIA

Subjects that meet all the criteria listed in Table 6.2.1.1-1 may be included in this study:

Table 6.2.1-1: Inclusion Criteria for Subjects and Subject Wounds

Number	Inclusion Criteria
1	Subject is at least 22 years of age on the date of informed consent
2	Subject or Subject's legally authorized representative can provide informed consent

Number	Inclusion Criteria
3	Subject is willing and able to attend all scheduled study visits and abide by all study restrictions
4	Subject has a single laceration that is ≤ 100 mm (10.0 cm) in length **or** up to 4 surgical incision(s), each ≤ 100 mm (10.0 cm) in length, defined as Class I or Class II wound(s) (according to CDC definitions[1] – see Appendix 18.1), in which the use of a tissue adhesive (in combination with but not replacing deep dermal sutures, if applicable) is appropriate, including the following: • surgical incision from a minimally invasive surgery • low tension incision • superficial laceration • clean, traumatic laceration with edges that can be easily approximated

6.2.1.2 EXCLUSION CRITERIA

Subjects that meet any of the criteria listed in Table 6.2.1.2-1 are excluded from participating in this study.

Table 6.2.1.2-1: Subject Exclusion Criteria

Number	Exclusion Criteria
1	Subject has a positive pregnancy test within 48 hours prior to randomization at Day 0 or is lactating prior to randomization at Day 0.* *Women who have had surgical sterilization by a medically accepted method (eg, tubal ligation, hysterectomy, or oophorectomy) or are post-menopausal, defined as not having menstruation for > 12 months will not be required to undergo pregnancy testing
2	Subject is found to have any of the following before randomization: • a known peripheral vascular disease • a history of hypertrophic scarring and/or keloids • any Class III or Class IV wounds (according to CDC definitions[1] – see Appendix 18.1) • uncontrolled diabetes mellitus (DM), defined as HbA1C ≥ 10% within 90 days before screening. If HbA1C data is unavailable or the Subject presents in an emergency situation, uncontrolled DM will be defined as blood glucose ≥ 250 mg/dL • a known blood clotting disorder • immunocompromised

Number	Exclusion Criteria
	• a known systemic or local bacterial, viral, or fungal infection • critical injury • condition(s) that in the opinion of the Investigator will impact study results (eg, hemophilia or autoimmune disorder) or the ability of the Subject to remain compliant with study procedures, study restrictions, and/or visits
3	Subject has a known hypersensitivity or allergy to any of the components of study products (eg, polyoxamides or cyanoacrylates)
4	Subject is concurrently participating in or was enrolled in another interventional clinical study within 30 days of randomization
5	Subject has a laceration or incision that is > 100 mm (10 cm) in length
6	Subject has any incision that is within 5 cm of any adjacent incision
7	Subject has one of the following: • a “burst” or stellate laceration • wound with exposed bone • wound with suspected skin edge ischemia due to extensive undermining • wound requiring drain(s) • wound requiring a conventional closure method (eg, subcuticular/intradermal suture, staples, adhesive strips) **OR** subcuticular stitch placement for enhanced wound support (ie, to further minimize tension)
8	Subject has a wound with any of the following etiologies: • human or animal bite • prolonged pressure (ie, decubitus)
9	Subject has a wound in any of the following anatomical locations: • on mucosal surfaces or across mucocutaneous junctions (eg, oral cavity, lips) • in or around the eyes • an anatomical area that is under tension or over a joint • on an area that may be regularly exposed to body fluids or with dense natural hair present (eg, scalp)

6.3 PROCEDURES AND ASSESSMENTS

6.3.1 Obtaining Informed Consent

Informed Consent must be obtained for each Subject before any study activities are performed or data is collected. The Investigator or designee will review all relevant aspects of the study with the potential study Subject (or legally authorized representative) that are relevant to the Subject's decision to participate throughout the study. To minimize pressure and undue influence on Subjects, the Investigator or designee who is obtaining informed consent should ensure appropriate communication techniques (eg, visual aids and avoidance of jargon). The Investigator or designee should also provide ample time for the Subject (or legally authorized representative) to read and understand the Institutional Review Board (IRB)-approved Informed Consent Form (ICF) and to consider participation in the study.

The study Subject (or legally authorized representative) and the Investigator or designee must sign and date the ICF. The Investigator or designee must file the original ICF and provide the Subject with a copy of the signed and dated ICF and any other written documentation per local IRB requirements.

The Informed Consent Process must be documented by the Investigator or designee. The Informed Consent Process includes documentation of the discussion regarding study procedures, Subject concerns, that the Subject was provided ample time to consider participation, and that all questions were answered before participation in any research activity.

Upon signing the ICF, the Subject will be enrolled in the study. Subjects will be assigned a unique Subject identification number, and study data will be reported according to this identification number. The unique Subject identification number will not contain information that could identify the Subject.

6.3.2 Demographics and Subject Characteristics

After a Subject signs the ICF (see Section 6.3.1) but before the application of the tissue adhesive, the following demographic data and Subject characteristics will be collected and documented:

- Date of birth
- Biological Sex
- Height
- Weight
- Tobacco use – smoking and non-smoking (never, former, current)

- Race
- Ethnicity
- Fitzpatrick Skin Type[31]
- Comorbidities
- Study wound(s) characteristics, including:
    - type and location
    - wound etiology (ie, reason for the wound)
    - duration of wound
    - incision/laceration length (not to exceed 10 cm)
- Procedures conducted per wound, including:
    - use of local anesthesia – yes/no
    - cleansing – yes/no and if yes, type of cleansing agent
    - debridement – yes/no and if yes, list method (eg, sharp, mechanical, enzymatic, other)
    - use of deep dermal sutures – yes/no
- Date of reapproximation and tissue adhesive application

6.3.3 Vital Signs

Body temperature will be assessed and recorded for Subjects at all visits.

6.3.4 Medical and Surgical History

As part of screening procedures, the Investigator or designee will collect a complete medical and surgical history for each Subject. For example, anticoagulant medications (eg, warfarin, aspirin, clopidogrel, or Factor Xa inhibitors) being used by a Subject at the time of screening will be documented. If the screening visit and randomization (Visit 2 / Day 0) occur on different days, the medical and surgical history should be reviewed and updated on Day 0 prior to randomization.

6.3.5 Laboratory Assessments

Urine human chorionic gonadotropin (hCG) assessment to determine pregnancy status in female Subjects of child-bearing potential will be conducted within 48 hours prior to randomization at Day 0. If the Subject's pregnancy test is positive, the Subject will not be eligible to continue in the study and will be considered a screen failure. Women who have had surgical sterilization by a medically accepted method (eg, tubal ligation, hysterectomy, or oophorectomy) or are post-menopausal, defined as not having menstruation for > 12 months will not be required to undergo pregnancy testing.

6.3.6 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.

6.3.7 Application of Tissue Adhesive and Wound Imaging

6.3.7.1 WOUND CLOSURE AND TISSUE ADHESIVE APPLICATION

For wounds resulting from a traumatic laceration, cleansing (eg, irrigation using sterile normal saline) and debridement of any non-viable tissue may occur according to the Investigator's standard practices. For surgical incisions, surgical procedures, including cleaning the surgical site, should be performed in accordance with the Investigator's standard practice.

At the time of primary closure of the clean wound(s) (ie, clean traumatic lacerations or clean surgical incision), hemostasis and dermal closure (as needed) should be attained. In addition, the wound edges, as well as periwound skin, should be dry, and the skin edges should be easily apposable. Tissue adhesive – 3M™ Topical Tissue Adhesive (Treatment arm) or Histoacryl® (Control arm) – should then be applied, avoiding heavy application, to the entire length of the approximated skin edges (ie, closed incision/laceration) according to the manufacturers' instructions. The Investigator or designee should document that the entire length of the approximated skin edges was fully covered (ie, sealed) with tissue adhesive. Neither tissue adhesive is to be applied below the skin surface, and additional topical medications should not

be applied following closure. After allowing the tissue adhesive to polymerize, the wound may be covered with an appropriate dressing according to the Investigator's standard practice. The type of secondary dressing (eg, gauze, non-adherent pad, transparent film, etc) used to cover the wound and polymerized tissue adhesive should be documented and should not contain antimicrobial agents (eg, silver or chlorhexidine gluconate) or other topical medications.

6.3.7.2 WOUND IMAGING

Wound images will be captured for each study visit using a commercially available imaging system (eKare, Inc). Imaging guidelines, equipment, and supplies will be provided to the investigational sites by eKare Inc. The eKare inSight imaging system is CE-marked and registered with the FDA – the system allows for single image capture that is synchronized to a secure HIPAA, GDPR, and 21 CFR Part 11-compliant environment. The system provides real-time image quality feedback that facilitates standardized and optimized image quality with validated inter- and intra-rater reliability (ie, accurate and consistent image capture). Each wound image should encompass the entire wound length, and all images should be captured such that they are of high quality with the wound clearly visible. Each image file will contain the Subject identification number, wound number (if multiple wounds), visit number, and date. Images should not contain protected health information.

At the time of wound closure (Day 0), an image, with a ruler visible and parallel to the wound, should be captured after polymerization of the tissue adhesive but before applying any dressing, if applicable. At the Day 10 follow-up visit, an image should be captured after removal of the dressing, if applicable, and after assessment of tissue adhesive remaining (see Section 6.3.8.3). At the Day 30 follow-up visit, an image should be captured after removal of the dressing, if applicable. The images captured at Day 10 and Day 30 visits will be analyzed by an independent assessor (see Section 6.3.8.1). Wound images should not be used to guide patient treatment.

6.3.8 Post-Procedure Assessments

6.3.8.1 WOUND APPOSITION

The percentage of wounds with 100% apposition of skin edges (ie, complete closure) will be determined based on an assessment of wound images by an independent assessor. For primary endpoint analysis, the Investigator or designee will capture wound images (see Section 6.3.7.2) at the Day 10 visit, which will then be analyzed by an independent assessor for 100% apposition. Images captured by the Investigator or designee at the Day 30 follow-up visit will be analyzed by an independent assessor to make a determination for the secondary endpoint related to 100% wound apposition. Categories for complete closure will be either "yes" for

100% apposition (ie, complete closure) or "no" for anything less than 100% apposition. The independent assessor will document whether the skin edges are completely apposed.

6.3.8.2 COSMESIS SCORING

Cosmesis scoring will be reported based on the Vancouver Scar Scale (see Appendix 18.2).[32] Assessment of scar quality will be performed on each wound by the Investigator or designee using a pocket-sized (3 in x 5 in) piece of plexiglass, as described in Sullivan et al and Baryza et al.[32, 33] The overall composite score (0 to 13) and the individual component scores (ie, pigmentation, pliability, height, and vascularity) will be recorded.

6.3.8.3 TISSUE ADHESIVE REMAINING

The presence of tissue adhesive remaining at the Day 10 follow-up visit will be documented by the Investigator or designee upon assessment using a flexible metric ruler (see Appendix 18.3 for example). For Subjects with multiple study wounds, all wounds will be assessed for the presence of tissue adhesive remaining, and the results for each wound will be documented.

At the Day 10 visit, a metric ruler will be placed adjacent to the incision/laceration, with the zero point of the ruler aligned with the wound apex. Sites should use a permanent marker (provided by sponsor) to fill in any segments along the ruler that correspond to segments along the wound with tissue adhesive remaining. Rulers should contain a label with Subject identification number, wound number (if multiple wounds), visit number, and date and should be retained in the Subject source file. Total wound length (mm) and total length of segments with tissue adhesive present (mm) for each wound should be recorded in the eCRF.

6.3.9 Concomitant Medications

Concomitant medications will be collected for all Subjects from the day of wound closure through the end of the study. The medication name, start date, end date, and indication will be reported.

Medications required to be reported include:

- local anesthetics (see Section 6.3.2)
- medications required to treat pre-existing health conditions that are active during the study period
- medications used to treat AEs during the study
- all medications that are used as prophylactic agent(s) related to the study wound(s), including antimicrobial medications

6.3.10 Adverse Events and Adverse Device Effects

AEs, SAEs, and DDs will be collected from the time of randomization through the end of the study. ADEs and SADEs will be collected from the time of tissue adhesive application through the end of the study. AEs and ADEs will be reported according to Section 13.

Select ADEs and SADEs (ie, components of wound and periwound skin injury) will be assessed based on the below criteria by the Investigator or designee, including thermal injury, erythema, edema, wound infection, and/or wound dehiscence. Each of these components will be categorized as either "yes" or "no," with a categorization of "yes" based on the following criteria:

- thermal injury – signs of a first- or second-degree burn or a noticeable burning smell from the wound area
- erythema – well-defined (pale red), moderate (definite red), or severe (beet or crimson) discoloration with definable area
- edema – well-defined edema (definable area but not raised > 1mm), moderate edema (well-defined area and raised approximately 1mm), or severe edema (well-defined area, raised > 1mm, and extended beyond exposure area)
- wound infection – a wound requiring antimicrobial treatment (local or systemic) or an area of blanching redness around the wound, with or without discharge
- dehiscence – any wound dehiscence regardless of need for treatment

Treatment for any of the aforementioned ADE/SADE components should also be recorded if it is categorized as "yes," including the need for hospitalization, subsequent wound treatment (eg, debridement and irrigation) and closure (yes/no and method), the need for antibiotic (oral or topical) or other medications (type and dose), or other treatments.

6.3.11 Prohibited Procedures and Treatments and On-Study Restrictions

No other treatments for the study wound other than those described in Section 6.3.7 are permitted during the treatment period of this study. Any divergence from these treatment conditions will be captured as a protocol deviation (see Section 10) and the reason for selecting alternative treatments in the absence of an AE or device defect should be documented. Day 10 or Day 30 follow-up visits that occur outside of the study visit windows will also be documented as protocol deviations. In addition, Subjects should avoid the following from the time of tissue adhesive application until completion of the study: (i) topical application of any additional products on the wound; (ii) prolonged submersion of the wound in water (eg, swimming or soaking in a hot tub or bathtub); and (iii) any activity that may contribute to increased

friction/rubbing at the wound site. Non-conformity with these on-study restrictions should be assessed and documented as a protocol deviation at the subsequent follow-up visit. Subjects may shower or bathe the wound site gently as directed by their physician. However, the wound site should not be scrubbed, soaked, or exposed to prolonged wetness.

Any deviation(s) from the CIP that diminishes the integrity of the data, results in non-adherence to the eligibility criteria, or impacts the Subject's rights, safety, or welfare will be documented as major protocol deviation(s) (see Section 10).[34] Failure to completely cover the entire length of the reapproximated wound with tissue adhesive and/or the use of conventional wound closure devices (eg, intradermal sutures, staples, or adhesive strips) will be considered major protocol deviations. These and other major protocol deviations should be documented.

6.3.12 End of Study Documentations

Subjects may withdraw or be discontinued from this study at any time. The Investigator may discontinue a Subject's study participation if the Investigator determines it is in the best interest of the Subject or the integrity of the study.

The following information will be documented at the End of Study:

- Last day of study participation
- Completion status – Did the Subject complete the study (Yes/No)?
- Reason for study discontinuation

6.4 VISIT SCHEDULE AND DESCRIPTION OF STUDY VISITS

6.4.1 Point of Enrollment

A Subject is considered enrolled in the study following signing the ICF.

6.4.2 Visits

Informed consent will be conducted at the time of screening. Upon enrollment of Subjects scheduled to undergo surgery, Subjects will return within 10 days for surgery (and randomization), although enrollment of surgical patients may occur on the day of surgery in some cases. In cases of traumatic lacerations, Subject enrollment and randomization may occur on the same day. All Subjects will return for a Day 10 (± 2 days) follow-up visit and a Day 30 (± 5 days) follow-up visit after wound closure. All applicable data are to be recorded in the applicable Case Report Form (CRF).

6.4.2.1 SCHEDULE OF EVENTS

A schedule of events for Subjects is in Tables 6.4.2.1-1 below:

Table 6.4.2.1-1. Schedule of procedures and assessments by study visit.

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 Images		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] Images, which will be captured by the Investigator, will be analyzed by an independent assessor who is blinded to the assigned treatment. NOTE: image assessments by independent assessor 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.

6.4.2.2 VISIT 1 – SCREENING & ENROLLMENT VISIT (STUDY DAY -10 TO 0)

The following procedures and assessments will be completed at Visit 1:

1. Obtain informed consent (see Section 6.3.1)
2. Document Subject demographic, Subject characteristics, and wound characteristics (see Section 6.3.2)
3. Review and record medical and surgical history (see Section 6.3.4)
4. Assess and record vital signs (see Section 6.3.3)
5. Assessment of eligibility (see Section 6.2)

6.4.2.3 VISIT 2 – APPLICATION OF TISSUE ADHESIVE (DAY 0)

The following procedures and assessments will be completed at Visit 2:

1. Confirmation that Subject meets eligibility criteria (see Section 6.2) and update of medical and surgical history (see Section 6.3.4) and concomitant medications (see Section 6.3.9) if Visit 2 occurs on a different day than Visit 1 (rescreen if Visits 1 and 2 are > 10 days apart)
2. Document wound characteristics (see Section 6.3.2) if Visit 2 occurs on a different day than Visit 1.
3. Assess and record results of urine pregnancy test in female Subjects of childbearing potential (see Section 6.3.5)
4. Assessment and recording of vital signs (see Section 6.3.3)
5. Randomization (see Section 6.3.6)
6. Reapproximation of wound edges and application of tissue adhesive (see Section 6.3.7.1)
7. Capture of wound image after closure (see Section 6.3.7.2)
8. Documentation of concomitant medications (see Section 6.3.9)
9. Assessment and documentation of AEs, SAEs, ADEs (including select components of skin and periwound skin injury), and DDs (see Section 6.3.10)

6.4.2.4 VISIT 3 – (DAY 10 ± 2 DAYS)

The following procedures and assessments will be completed at Visit 3:

1. Documentation of concomitant medications (see Section 6.3.9)
2. Assessment and recording of vital signs (see Section 6.3.3)
3. Capture of wound image (see Section 6.3.7.2) – wound image will be analyzed by the independent assessor to determine 100% wound apposition (see Section 6.3.8.1). NOTE: image assessments may occur after the visit
4. Assessment and recording of remaining tissue adhesive (see Section 6.3.8.3)
5. Assessment and documentation of AEs, SAEs, ADEs (including select components of skin and periwound skin injury), and DDs (see Section 6.3.10)

6.4.2.5 VISIT 4 – END OF STUDY (DAY 30 ± 5 DAYS)

The following procedures and assessments will be completed at Visit 4:

1. Documentation of concomitant medications (see Section 6.3.9)
2. Assessment and recording of vital signs (see Section 6.3.3)
3. Capture of wound image (see Section 6.3.7.2) – wound image will be analyzed by the independent assessor to determine 100% wound apposition (see Section 6.3.8.1). NOTE: image assessments may occur after the visit
4. Cosmesis scoring (see Section 6.3.8.2)
5. Assessment and documentation of AEs, SAEs, ADEs (including select components of skin and periwound skin injury), and DDs (see Section 6.3.10)
6. Documentation of end of study (see Section 6.3.12)

6.4.2.6 UNSCHEDULED VISIT

The following procedures and assessments will be completed at all unscheduled visits that are related to the study wound:

1. Assessment and recording of vital signs (see Section 6.3.3)
2. Capture of wound image (see Section 6.3.7.2) – wound image will be analyzed by the independent assessor to determine 100% apposition (see Section 6.3.8.1). NOTE: image assessments may occur after the visit

3. Assessment and recording of remaining tissue adhesive (see Section 6.3.8.3), if unscheduled visit occurs before Visit 3
4. Documentation of concomitant medications (see Section 6.3.9)
5. Assessment and documentation of AEs, SAEs, ADEs (including select components of skin and periwound skin injury), and DDs (see Section 6.3.10)
6. Documentation of end of study, as described in Section 6.3.12, if applicable

6.4.3 Point of Exit

Study Subjects may exit the study for a variety of reasons. The Investigator shall record the reason for withdrawal and discontinuation of the study in the applicable CRF. These reasons include, but are not limited to:

- Study completion (all study-related visit(s) are completed)
- Withdrawal by the Subject
- Withdrawal by Investigator
- Lost to follow-up
- Death
- Study Termination

In the event of Subject withdrawal or discontinuation from the Treatment arm before study completion (Visit 4 – Day 30 ± 5 days), study Subjects will not be replaced. In addition, data collected until the last known contact of the study Subject may be used in the analyses.

For study Subjects lost to follow-up, the Investigator shall make 3 documented attempts before confirming the Subject is lost to follow-up. If the study Subject withdraws from the study for any reason and there is an ongoing safety event, additional safety event information may need to be collected by the Investigator and shared with the Sponsor.

6.5 ROLE OF SPONSOR REPRESENTATIVE

6.5.1 Monitoring

Study monitoring is conducted to ensure that (i) the rights, safety, and well-being of study participants are protected, (ii) the reported study data are accurate, complete, and verifiable, and (iii) the conduct of the study is in compliance with the currently approved CIP, with good clinical practice (GCP) principles, and with applicable regulatory requirement(s). 3M, as Sponsor of this clinical investigation, is responsible for study oversight and for providing the

PIs and study staff with training regarding the proper conduct of the clinical investigation with regard to CIP adherence and validity of the data recorded on the CRFs. 3M has therefore assigned study monitor(s) to this clinical investigation. The progress of the clinical investigation will be monitored by:

- Periodic in-person and/or remote review of study documents
- Telephone and electronic communications with the study staff and PI
- Review of CRFs and source documents (eg, Subject records)

The study monitor(s), other authorized representatives of the Sponsor, representatives of the IRB, or regulatory authorities may inspect all documents and records required to be maintained by the Investigator, including but not limited to Subject records (office, clinic, or hospital) for the participants in this study. The clinical study site personnel will permit access to such records. The Investigator will give 3M study monitor(s) direct access to source documents that support data on the CRFs, including any electronic records. If site policies restrict access to Subjects' files to site personnel, the PI will designate a staff member to work with the Sponsor's monitor to verify source documents on an as-needed basis. This verification will be conducted in a way that will ensure that only study-related information is examined.

Details of clinical site monitoring are documented in a Monitoring Plan (MP). The MP describes who will conduct the monitoring, the planned frequency of monitoring visits, records to be reviewed, and the distribution of monitoring reports.

Independent audits may be conducted by 3M personnel or an independent party to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the MP.

6.5.2 Other Sponsor Oversight

In addition to study monitoring, the Sponsor, or their representatives may conduct the following tasks during this study:

- Audits of the Investigator
- Provision of technical support/product specific training for the study device

Investigator non-compliance of required study responsibilities will require Sponsor involvement to alleviate the non-compliance, including corrective and preventative actions up to and including disqualification.

7 DATA MANAGEMENT

Data collected for this study will be analyzed and stored at 3M or an approved supplier for use by researchers, including those outside of the study. Permission to transmit, store, and use data outside of the study will be included in the ICF. Details of data management for this investigation are documented in a Data Management Plan (DMP), which describes the procedures for CRF tracking, data review, database cleaning, query management, coding, and data reconciliation.

7.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible, and permanent (ie, non-editable) manner to ensure accurate interpretation of data. Data recorded in the electronic case report form (eCRF) that is derived from source documents must be consistent with the information in the source documents.

All data, including AEs and expected AE data, will be entered into a 21 CFR Part 11-compliant data capture system provided by the Sponsor. The data system includes password protection and internal quality checks (eg, automatic range checks) to identify data that appear inconsistent, incomplete, or inaccurate.

The Sponsor is responsible for compilation and verification of the clinical study data, retention of the clinical study database, performance of statistical analysis, and preparation of the clinical study report.

7.2 STUDY RECORDS RETENTION

Information for each study participant will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location in accordance with policies from the reviewing IRBs, Institutions, regulatory authorities, and Sponsor requirements.

No records will be destroyed without the written consent of the Sponsor. It is the responsibility of the Sponsor to inform the Investigator when study documents no longer need to be retained.

7.3 SPONSOR OVERSIGHT

The Investigator will allow access to clinical study records for periodic on-site or remote monitoring visits by a designated Sponsor representative, with the understanding that the

representative is bound by professional secrecy and will not disclose the identity of any Subject or personal medical information. The Sponsor representative will review source documentation for completeness during monitoring visits and verify against the eCRFs; any discrepancies will be resolved with the Investigator, as appropriate. The data will be entered into the clinical study database and verified for accuracy.

In addition to on-site or remote monitoring, routine review of submitted study information will be conducted by the Sponsor to ensure compliance with the CIP. Items reviewed include but are not limited to AEs, deviations, and the number of withdrawn/terminated Subjects, all of which may impact completion of the study. Appropriate measures may be taken to ensure Investigator compliance with the CIP.

8 STATISTICAL DESIGN AND ANALYSIS

The sections below provide a brief overview of the statistical elements pertinent to the study. Full details of statistical analysis will be documented in a Statistical Analysis Plan (SAP). The formal SAP will be completed prior to an interim analysis.

8.1 PASS/FAIL CRITERIA

The null hypothesis of interest for this study is that the percentage of Subjects with Treatment-arm wounds closed using 3M™ Topical Tissue Adhesive that achieve 100% apposition (complete closure) at the Day 10 visit is at least 10% lower than the percentage of Subjects with complete closure for Control-arm wounds closed using Histoacryl® (ie, the investigational device is inferior to the control). The associated alternative hypothesis is that this same Subject level complete closure rate is strictly no more than 10% lower than that of Control-arm wounds (ie, the investigational device is non-inferior to the control). The non-inferior margin is 10% of the complete closure rate.

The relevant null and alternate hypotheses are specified below:

$$H_0: P_{c10} - P_{t10} \geq 10\%$$

$$H_a: P_{c10} - P_{t10} < 10\%$$

where P_{c10} is the percentage of Subjects with 100% wounds apposed for the control device at the 10-day visit and P_{t10} is the percentage of Subjects with 100% wounds apposed for the investigational device at the 10-day visit. The primary hypothesis should be rejected using both the ITT and the PP dataset to be considered passing.

8.2 SAMPLE SIZE DETERMINATION

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 (see Section 2.1.2). Therefore, an incomplete apposition rate above this, at 15%, is used for the sample size calculation, with the 100% wound apposition rate assumed to be 85% for the comparator adhesive. A non-inferiority margin of 10% will be used as was used by Blondeel et al in a previous trial.[8]

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

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 18.4 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 8.6.2 in Section 8.6 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%.

8.3 ANALYSIS POPULATIONS

The following analysis sets will be used throughout the course of analysis. 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.

- Intent-to-Treat (ITT) Analysis Set – This dataset will consist of all randomized Subjects. Subjects will be analyzed in the group to which they were randomized.
- Safety Analysis Set – The Safety Analysis Set will consist of all treated Subjects. Subjects will be analyzed in the group to which they were treated.
- PP Analysis Set(s) – 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 10-day visit:
  1. Subject who is missing the endpoint being analyzed
  2. Subject with endpoint measured outside the one-sided time window of minus two days.
  3. A Subject who receives the wrong treatment.
- 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, percent of subject's wound(s) with adhesive remaining at the 10-day visit:
  1. Subject with at least one wound missing the endpoint being analyzed.
  2. Wounds from Subject with endpoint measured outside the two-sided time window of $\pm$ 2 days.
  3. Wounds from Subject who received the wrong 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 30-day visit:
  1. Subject who is missing the endpoint being analyzed. However, if the wound was not 100% apposed at the 10-day visit, that value will be carried forward for the 100% apposition response at the 30-day visit.
  2. Subject with endpoint measured outside the one-sided time window of minus five days.
  3. A Subject who receives the wrong treatment.

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.

8.4 HANDLING MISSING DATA

In cases where apposition data is missing from the primary endpoint (10-day 100% apposition) or secondary endpoint #2 (30-day 100% apposition), the following imputation process will be

used to create the ITT analysis set. First, missing datapoints 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, the partially imputed data set created in the first step will have multiple imputation 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: site, wound type/number, and diabetes status. Twenty (20) 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 < 5% missing data for an efficacy endpoint being imputed in an ITT dataset, a single imputation will be used in the second stage. There will be no imputation of safety endpoints.

8.5 STATISTICAL ANALYSES

8.5.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics for the study will be generated and displayed. Key baseline characteristics variables besides age, sex, race, ethnicity, and Fitzpatrick Skin Type may include but are not limited to general health status, overall comorbidities, and any specific factors related to each of the surgeries of interest.

8.5.2 Analysis of Primary Endpoints

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 margin. The relevant null and alternate hypotheses are specified below:

$$H_0: P_{c10} - P_{t10} \geq 10\%$$

$$H_a: P_{c10} - P_{t10} < 10\%$$

where P_{c10} is the percentage of Subjects with 100% wounds apposed for the control device at the 10-day visit and P_{t10} is the percentage of Subjects with 100% wounds apposed for the investigational device at the 10-day 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 10-day 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 10-day 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 are not being 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 8.6 (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.

8.5.3 Analysis of Secondary Endpoints

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

   $$2^{o}\ Endpoint\ \#1 = \left\{\frac{\sum wound\ length(s) with\ adhesive\ remaining\ at\ Day\ 10\ visit}{\sum original\ wound\ length(s)}\right\} x100\%$$

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 10-day PP dataset, 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:

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

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

where P_{cw10} is the percent of the sum of wound length(s) with adhesive remaining for the control device at the 10-day visit in relation to the sum of the original incision/laceration length(s), and P_{tw10} is the percent of the sum of the wound length(s) with adhesive remaining for the investigational device at the 10-day 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 10-day 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 30-day PP dataset and the ITT datasets will be used for the analysis.

The null and alternative hypotheses are specified below:

$$H_0: P_{c30} - P_{t30} \geq 10\%$$

$$H_a: P_{c30} - P_{t30} < 10\%$$

where P_{c30} is the percentage of Subjects with 100% wound apposition for the control device at the 30-day visit and P_{t30} is the percentage of Subjects with 100% wound apposition for the investigational device at the 30-day 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 30-day PP dataset and the ITT dataset. Non-inferiority will be declared if the null hypothesis is rejected for the analyses conducted for both the 30-day 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.

8.5.4 Analysis of Safety Endpoints

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.

8.6 Planned Interim Analyses and Criteria for Clinical Investigation

There will be two unblinded interim analyses conducted after 226 and 340 Subjects are randomized and have reached their Day 10 follow-up visit. These interim analyses correspond to 50% and 75% of the randomization goal. 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. 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 an 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 and "max sample size" were obtained using SAS PROC SEQDESIGN and are shown below in Tables 8.6.1 and 8.6.2, respectively.

```
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 8.6.1

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

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

Table 8.6.2

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, continue the study and conduct interim analysis #2.

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, continue the study until completion of the study with 452 Subjects randomized.

8.7 PROCEDURES FOR REPORTING DEVIATIONS FROM STATISTICAL PLAN

In general, any deviations from the statistical plan outlined in the SAP will be justified and described in the final report.

8.8 VALIDATION PLAN

A risk-based approach depending upon statistical program complexity, the likelihood of an error occurring, and the potential impact will be used in determining the level of SAS program validation required on a per-program basis. Full details of the validation plan can be found in the SAP.

9 AMENDMENTS TO THE CIP

In the event that modifications to this CIP are necessary (eg, to protect the safety of the Subjects and/or the integrity of the data), the CIP will be amended and approved by the Sponsor. All changes will be evaluated for impact per the Sponsor's standard operating procedures (SOPs). In collaboration with the Investigator(s), the CIP modifications will then be documented and submitted for ethical and regulatory approval (as required) before implementation. Modifications will be considered implemented after all ethical and regulatory approvals (as required) are received and all key Sponsor personnel, Investigators, and key site staff, have been trained regarding the modified CIP.

10 DEVIATIONS FROM THE CIP

The Investigator is not allowed to deviate from the CIP except as specified in Section 5.6.4 of the International Standard, ISO/FDIS 14155:2020. Briefly, deviations from the CIP to protect the rights, safety, and well-being of human Subjects under emergency circumstances may proceed without prior approval of the Sponsor and the IRB; however, such deviations shall be documented and reported to the Sponsor and the IRB in accordance with IRB requirements. All deviations shall be documented on a deviation report form or appropriate CRF, and a deviation report form shall be completed for each event per individual Subject. The Investigator is responsible for reporting all deviations to the Sponsor and reviewing IRB, per local requirements.

10.1 DEVIATION REPORTING TIMELINES

The timelines and methods for reporting the different types of deviations to the Sponsor are provided in Table 10.1-1.

Table 10.1-1. Deviation reporting timelines and methods

Type of Deviation	Report to Sponsor	Method
Major Subject safety, rights, or welfare; OR Compromise the data integrity or statistical analysis of the study; OR Non-adherence to Inclusion/Exclusion criteria	Within 24 hours of study staff becoming aware of the event	Initial: Phone/Email to Sponsor Complete CRF
Minor All other protocol deviations	Per protocol visits	Complete CRF

11 DEVICE ACCOUNTABILITY

The device(s) under investigation will not be distributed to the investigational site until all agreements between the site and the Sponsor are finalized and IRB approval has been obtained. 3M requires that Investigators maintain device accountability and security of the devices at all times. The Investigator will:

- maintain and account for devices at the Investigator site, including:
  - the name(s) of the person(s) who received, used, returned, or disposed of the device;
  - the date of receipt, identification, and quantity of each investigational device (batch number/serial number or unique code);
  - the expiration date of the device, if applicable.
- keep devices in a secure storage area, accessible only to authorized individuals.
- dispense devices only to Subjects properly enrolled in and eligible for the study, including the following:
  - Subject identification;
  - the date or dates of use;
  - the date on which the investigational device was returned/explanted from Subject, if applicable.

- return all unused investigational materials to the Sponsor at the end of the study or dispose of as agreed upon, including:
    - the date-of-return for unused, expired, or malfunctioning investigational devices, if applicable;
    - the date and documentation of disposal of the investigational devices as per instructions of the Sponsor, if applicable.

The Sponsor shall have instructions in place and make packaging materials available, if applicable, for the safe return or disposal of investigational devices.

11.1 Labeling for Device(s) Under Investigation

The device(s) under investigation in this study will be labeled for investigative clinical use only. A sample label, along with other study-related documents, will be retained at the sites in an Investigator Site File.

11.2 Additional Study-specific Equipment/Device(s)

Additional study-specific equipment/devices used in this study shall be maintained, calibrated (if applicable), and ensured to be functioning correctly during the study, in accordance with this CIP or applicable site policy and regulatory requirements. The Sponsor should be notified of any anticipated or known issues with the device functionality that may impact the study conduct or outcome. Any equipment provided to the site by the Sponsor should be returned upon malfunction or at the end of site participation.

12 STATEMENTS OF COMPLIANCE

12.1 Ethical Considerations

This study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. In addition, this clinical investigation shall be conducted in accordance with ISO-14155:2020, US FDA 21CFR parts 812, 50, 54, 56, and any regional or national regulations, as appropriate.

Approving IRBs will be provided all relevant study documentation to safeguard the rights, safety, and well-being of Subjects as mandated. The participating Investigator will obtain IRB approval of the study prior to initiation of the study at the site. The protocol, Instructions for Use, Informed Consent Form, written information given to Subjects, safety updates, and any revisions to these documents will be provided to the IRB by the Investigator.

12.2 PERIODIC REVIEWS

Ongoing reviews by IRB are required for the duration of the clinical study. The Investigator will comply with local IRB requirements for ongoing reviews, at a minimum annually. The Sponsor may provide an annual study report to participating Investigators.

12.3 PARTICIPANT CONFIDENTIALITY

Participant confidentiality and privacy is strictly held in trust by the participating Investigators, their staff, and the Sponsor(s) and their authorized representatives. Information collected about Subjects during the study will be kept confidential and managed according to the requirements of the IRB and Health Insurance Portability and Accountability Act of 1996 (HIPAA). This confidentiality is extended to cover the testing of biological samples and other clinical information relating to participants (eg, images related to the study wound). Therefore, the CIP, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without the prior written approval of the Sponsor.

In the event that a Subject revokes authorization to collect or use personal health information (PHI), the Investigator retains the ability to use all information collected prior to the revocation of Subject authorization.

Study data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at 3M or an approved supplier. This data will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number (see Section 6.3.1). The electronic data capture system used by clinical sites and by 3M research staff will be secured and password protected. At the end of the study, all study databases will be archived at 3M or an approved supplier.

12.4 CONFLICT OF INTEREST

The independence of this study from any actual or perceived influence, such as by the medical device industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The Sponsor has established procedures for all Investigators to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

12.5 INSURANCE

The Sponsor shall provide clinical study-related insurance covering the reasonable and necessary costs of diagnostic, therapeutic, and medical treatment including hospitalization costs (treatment costs) for such participant injuries following the administration or use of the study device(s) in accordance with this Clinical Investigation Plan (CIP) and accordance with the national regulations. The Sponsor may reimburse the institution and/or study participants for treatment costs depending on who incurred such treatment costs. The Sponsor will not be responsible for paying for or reimbursing treatment costs if (i) the injury is attributable to the negligence or misconduct of any agent or employee of the institution or Investigator, or the failure of such persons to comply with a study protocol, (ii) the treatment costs are covered by the study participant's medical or hospital insurance coverage, or (iii) the treatment costs arose as a result of the treatment of normal progression of the study participant's disease or injuries resulting from interventions that the study participants would have incurred had they not participated in the study.

13 ADVERSE EVENTS, ADVERSE DEVICE EFFECTS, AND DEVICE DEFICIENCIES

Investigators are responsible for ensuring that all safety events are recorded in the Subject record(s). Events defined in Section 13.1 will be reported to the Sponsor, as applicable, per the timelines in Section 13.3.

13.1 SAFETY AND EVENT REPORTING DEFINITIONS

This study utilizes the terms and definitions related to safety and event reporting listed in Table 13.1-1.

Table 13.1-1: Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in Subjects, users, or other persons, whether or not related to the investigational medical device. This includes, but is not limited to, events related to the investigational device or the comparator and to procedures involved in this study.

Term	Definition
Adverse Device Effect (ADE)	An adverse event related to the use of an investigational medical device. This includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This includes any event that is a result of a user error or intentional misuse of the investigational device.
Unanticipated Adverse Device Effect (UADE)	A UADE is any SAE on health or safety, or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of Subjects.
Serious Adverse Event (SAE)	An AE is considered serious if it results in any of the following outcomes: • Death • Life-threatening • Hospitalization (initial or prolonged) • Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions • Congenital anomaly/birth defect • Required intervention to prevent permanent impairment or damage • Other important medical events may be considered serious when, based upon appropriate medical judgment, they may jeopardize the Subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. ***Note:*** *Planned hospitalization for a pre-existing condition, or a procedure required by the Clinical Investigation Plan without serious deterioration in health, is not considered an SAE.*

Term	Definition
Serious Adverse Device Effect (SADE)	An adverse device effect that has resulted in any of the consequences that are characteristic of a serious adverse event
Device Deficiency (DD)	An inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance, such as malfunctions, use errors, and inadequate labeling.
Complaint	Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a **device** after it is released for distribution. ***Note:*** *Device-related adverse events would meet this definition.*
Serious Health Threat	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in Subjects, users or other persons, and that requires prompt remedial action for other Subjects, users or other persons.

13.2 CLASSIFICATION OF EVENTS

13.2.1 Severity Ratings

The severity ratings for events are defined in Table 13.2.1-1. The Investigator shall ensure rating of reportable events on the applicable CRF.

Table 13.2.1-1: Severity Ratings Definitions

Term	Definition
Mild	asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention indicated
Moderate	minimal, local, or non-invasive intervention indicated
Severe	medically significant but not immediately life-threatening or hospitalization or prolongation of hospitalization indicated or disabling

13.2.2 Relatedness to Study Device or Study Treatment

Table 13.2.2-1 defines the relatedness definitions for events. The Investigator shall ensure rating of reportable events on the applicable CRF.

Table 13.2.2-1: Relatedness Definitions

Term	Definition
Not Related	Relationship to the device or procedure can be excluded
Possible	Relationship with the use of the study device is weak but cannot be ruled out completely.

Causal	The event is associated with the study device or with the procedures beyond a reasonable doubt when:
	• The event is a known side effect of the device
	• The event has a temporal relationship with the study device/application procedures
	• The event involves a body/site or organ that
	  ○ The device or procedures are applied to;
	  ○ The device or procedure affects
	• The event follows a known response pattern to the device

13.3 Details Concerning Safety Recording and Reporting Requirements

13.3.1 Investigator Responsibilities

It is the responsibility of each participating Investigator to ensure all safety events (eg, AEs, SAEs, device effects, or DDs) are recorded in the Subject's record. The collection/reporting period for safety events will begin from the time of randomization through the end of the study. Investigators should assess for AEs at each visit after randomization, and study Subjects should be instructed to report any AE that they experience to the Investigator. All AEs, regardless of perceived relationship to study product, will be documented in a timely manner and reported according to the methods and timelines in Section 13.4. In addition, the worsening of an underlying medical condition should also be recorded as an AE. The AE description will include the nature of the experience (AE term), the start date, the end date, the severity of each sign or symptom, the seriousness of the event or experience, the relationship to study treatment, the course of action taken, and the outcome of the experience. It will be indicated if the AE caused the Subject to be discontinued from the study.

SAEs, SADEs, and UADEs must be reported by the Investigator to the Sponsor and the reviewing Institutional Review Board (IRB) and/or Ethics Committee (EC) according to their reporting requirements within 24 hours of becoming aware of the event (see Table 13.4-1). In addition to submitting SAEs, SADEs, and UADEs to the IRB/EC, the Investigators will, along with the Sponsor, make a determination to continue, suspend, or terminate the study.

13.3.2 Sponsor Responsibilities

Safety oversight will be under the direction of the Medical Monitor and Safety Monitor of 3M, which both have appropriate expertise. The Clinical Trial Safety Officer and Senior Medical Director will routinely review and assesses the safety data of the study. Emergency contact information for reporting SAEs, SADEs, and UADEs will be provided to the Investigator, as well as the IRB, before initiating the study.

The Sponsor will evaluate the received AEs/SAEs and if an event is confirmed to be an SAE/SADE/UADE, will then immediately conduct an evaluation and report the results of the evaluation to the FDA and participating Investigators, if required, within 5 working days after the Sponsor first receives notice of the event. (21 CFR 812.46(b), 812.150). If the Sponsor determines that the event presents an unreasonable risk to the study Subjects, the Sponsor will adapt or terminate all clinical studies presenting risk as soon as possible.

13.4 REPORTING TIMELINES

Safety events are to be recorded in a timely manner, as described in Table 13.4-1. The study Sponsor may request additional information from the Investigator, including but not limited to medical records, laboratory testing, or radiological results regarding the event.

Table 13.4-1. Reporting Timelines for AEs and Adverse Device Effects

Type of event	Report to Sponsor	Method
AEs, regardless of perceived relationship to study product	Per protocol visits	Complete CRF
Adverse Device Effects (ADE)	Per protocol visits	Complete CRF
Serious Adverse Event (SAE)/Serious Adverse Device Effect (SADE)	Within 24 hours of study staff becoming aware of event	Initial: Phone/Email to Medical Monitor Followed by: Complete CRF and complete 3M SAE Report Form. This form should be completed by the Investigator and submitted (e-mail) to [redacted]
Unanticipated Adverse Device Effect (UADE)	Within 24 hours of study staff becoming aware of event	Initial: Phone/Email to Medical Monitor Followed by: Complete CRF and complete 3M SAE Report Form. This form should be completed by the Investigator and submitted (e-mail) to [redacted]
Serious Health Threat	Within 24 hours of study staff becoming aware of event	Initial: Phone/Email to Medical Monitor Followed by: Complete CRF and complete SAE Report Form. This form should be completed by the Investigator,

Type of event	Report to Sponsor	Method
		or designee, and submitted (e-mail) to [redacted].
Device Deficiency (DD)	Within 3 business days of becoming aware of event	Complete CRF
Product Complaints on 3M Marketed Product	Within 3 business days of becoming aware of event	Complete CRF

13.5 FOLLOW-UP PERIOD FOR ONGOING AES

Any AEs that are not device-related and are ongoing at the end of the study should be marked as "persistent" per the eCRF. Any AEs that are device-related and ongoing at the end of the study will be followed until stabilization or resolution. Events reported by Subjects after the last study visit may be reported to the Sponsor up to 30 calendar days from the date of the last visit.

14 VULNERABLE POPULATION

This study is intended to be conducted using a non-vulnerable adult population (ie, 22 years of age or older) with no expectations of benefits associated with participation or of a retaliatory response from senior hierarchical members in case of refusal to participate. In addition, informed consent will be obtained directly from the Subject or a legally authorized representative when the Subject is not capable of providing informed consent. However, the study does not exclude economically or educationally disadvantaged persons. The protection of rights, well-being, and safety of vulnerable populations is the most important consideration and should take precedent over the interests of the study. In addition, the protection of rights, well-being, and safety of vulnerable populations, and ascertaining appended safeguards, are the prerogative of the IRB, and the Investigator should comply with all institutional guidelines related to vulnerable populations.

In the recruitment process, the Investigator will ensure that Subject recruitment is free from pressure and will respect the Subject's expectations of privacy. Participation will be presented as a voluntary option. In addition, the screening process will contain procedures to assess the pregnancy status of females of childbearing age as well as the decisional capacity of potential study Subjects. The study will be described to all potential Subjects by the Investigator in non-technical terms, and the ICF will be written in an essentially non-technical manner to suit the solicited community. The study will be presented in a manner that permits ample time for consideration of participation, with no undue pressure related to the timing of the request.

15 SUSPENSION OR PREMATURE STUDY TERMINATION

The study will be terminated in the event of any Subject death that is related to the investigative device or any device-related, life-threatening wound complication that requires hospitalization. This study may also be suspended or prematurely terminated by either the Sponsor or the PI at any time if there is sufficient reasonable cause, including the occurrence of UADEs. Should this be necessary, the procedures will be arranged on an individual basis after review and consultation by both parties. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, participating Investigators, IRBs, and regulatory authorities. Upon termination or suspension, the PIs at each site will promptly inform study participants and provide reason(s) for the termination or suspension. If applicable, regulatory authorities and the Subject's physician and other health care providers will also be informed. In terminating or suspending the clinical investigation, the 3M study team personnel and the PI will assure that adequate consideration is given to the protection of the Subjects' interests.

Other circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of early efficacy – to be defined in the SAP
- Determination of futility – see Section 8.6 for details
- Insufficient compliance with CIP requirements
- Data that are not sufficiently complete and/or evaluable

Suspended studies may resume once concerns about safety, Clinical Investigation Plan compliance, and data quality are addressed and satisfy the Sponsor, IRB, and regulatory authorities. Study participants will be contacted, as applicable, and be informed of changes to the study visit schedule.

15.1 BY SPONSOR

The Sponsor reserves the right to discontinue the clinical study for business or ethical reasons at any time, such as, but not limited to:

- Information regarding the study product causes doubt as to the benefit/risk ratio.
- Changes in medical practice limit utility of the data obtained from the study.
- Investigator(s) lack of compliance with the approved CIP, lack of oversight, and/or not following applicable regulatory or IRB guidelines in conducting the study
- Incidence or severity of AEs indicates a potential health hazard or poses an unreasonable risk to the study participants

- Subject enrollment is unsatisfactory
- Fraud or misconduct

15.2 BY IRB

The IRB may choose to discontinue the study at the site for which they granted approval. If the IRB discontinues the study, the Investigator will report a withdrawal of IRB approval to the study Sponsor within 5 business days.

16 REGISTRATION AND PUBLICATION POLICY

16.1 PUBLIC REGISTRATION

The Sponsor shall ensure that the study is conducted in accordance with applicable publication and data sharing policies and complies with any national registration requirements. A description of this study will be publicly available at the website, http://www.ClinicalTrials.gov, as required by U.S. law. The online study description will include a summary of the study results but will not include information that identifies Subjects.

16.2 PUBLICATIONS RESULTING FROM STUDY

When applicable, attempts will be made to publish the results of the study. Details regarding publication policies, including publication rights and timing, are addressed in the study contracts between the Sponsor and the study sites.

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18 APPENDICES

18.1 APPENDIX 1 – CDC DEFINITIONS FOR SURGICAL WOUND CLASSIFICATIONS

Class I – Clean: An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tract is not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow nonpenetrating (blunt) trauma should be included in this category if they meet the criteria.

Class II – Clean-contaminated: An operative wound in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category, provided no evidence of infection or major break in technique is encountered.

Class III – Contaminated: Open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique (e.g., open cardiac massage) or gross spillage from the gastrointestinal tract, and incisions in which acute, non-purulent inflammation is encountered are included in this category.

Class IV – Dirty-infected: Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation.

18.2 APPENDIX 2 – VANCOUVER SCAR SCALE

Pigmentation (upon blanching with plexiglass):

0. Normal – color that closely resembles color over the rest of the body
1. Hypopigmentation
2. Hyperpigmentation

Vascularity:

0. Normal – color that closely resembles color over the rest of the body
1. Pink
2. Red
3. Purple

Pliability:

0. Normal
1. Supple – flexible with minimal resistance
2. Yielding – giving way to pressure
3. Firm – Inflexible, not easily moved, resistant to manual pressure
4. Banding – rope-like tissue that blanches with extension of scar
5. Contracture – permanent shortening of scar producing deformity or distortion

Height:

0. Normal – flat
1. < 2 mm
2. < 5 mm
3. > 5 mm

18.3 FLEXIBLE METRIC RULER



18.4 SAMPLE SIZE DETERMINATION PARAMETERS

[redacted]