CLINICAL STUDY PROTOCOL

A Randomized, Open-label, Multi-center, Controlled Clinical Study to Compare MAR-CUTIS with Dermabond Advanced in Closure of Surgical Incisions and Lacerations ≤15cm

Protocol Number:	KF7021-04
ClinicalTrials.gov Identifier:	NCT03688880
EudraCT Number:	Not applicable
Syneos Health Study Number:	1012937
Investigational Product:	MAR-CUTIS topical tissue adhesive
Phase:	Pivotal
Investigational Device Management Category:	European Union: IIb; United States: II
Sponsor:	Grünenthal GmbH Zieglerstraße 6 52078 Aachen Germany
Contract Research Organization:	Syneos Health 3201 Beechleaf Court Suite 600 Raleigh, NC 27604-1547 United States
Protocol Date:	25 Feb 2019
Protocol Version:	Version 4.0

SUMMARY OF CHANGES

Amendment Type: Substantial

Rationale for Amendment: The protocol tries to avoid the inclusion of patients who are on chronic treatment with drugs known to interfere with wound healing and/or are known to trigger wound healing complications like haematoma. Unfortunately, the chosen phrase in Version 3.0 of the protocol prohibits the application of steroids, immunosuppressants, chemotherapy, or anticoagulants with the exception of anti-platelet therapies pre-operation and also post-operatively. This was never intended and indeed would be against established deep vein thrombosis prophylaxis regimens, neo-adjuvant chemotherapies etc.
The proposed amendment of the protocol corrects this aspect.

Summary of Amendment: See below.

Section	Change Made	Rationale for Change
Cover page and header	Protocol version and date changed to v4.0, 25 Feb 2019.	
Protocol Approval Signature page	Change of one of the CRO signatories from [redacted] to [redacted]	
Synopsis and Section 7.3.3	Exclusion Criterion #8 Subjects requiring suturing with sutures >~~**5-0**~~ **0.5** mm thickness Exclusion Criterion #12 Subjects receiving **chronic, pre-operative** steroids, immunosuppressants, chemotherapy, or anticoagulants; only **chronic** anti-platelet therapies like ASA and clopidogrel are accepted. **Chronic is to be interpreted as long term or "for more than acute treatment". Pre-operative standard of care, like a single dose of an anticoagulant, for the aforementioned treatments is allowed along with standard of care post-operative anticoagulant and chemotherapy regimen including application of steroids and immunosuppressants.**	Clarification to avoid confusion which arose from the use of a USP and metric combination to describe the suture thickness. To allow application of steroids, immunosuppressants, chemotherapy, or anticoagulants with the exception of anti-platelet therapies pre-operatively and post-operatively, to be in line with established deep vein thrombosis prophylaxis regimens, neo-adjuvant chemotherapies, etc.
Section 7.4.8.1	Prohibited medications are **chronic,**	To allow application of

Section	Change Made	Rationale for Change
Prohibited Medication/Therapy	**pre-operative** steroids, immunosuppressants, chemotherapy, and anticoagulants; only **chronic** anti-platelet therapies like acetylsalicylic acid (ASA) and clopidogrel are accepted. **Chronic is to be interpreted as long term or "for more than acute treatment". Pre-operative standard of care, like a single dose of an anticoagulant, for the aforementioned treatments is allowed along with standard of care post-operative anticoagulant and chemotherapy regimen including application of steroids and immunosuppressants.**	steroids, immunosuppressants, chemotherapy, or anticoagulants with the exception of anti-platelet therapies pre-operatively and post-operatively, to be in line with established deep vein thrombosis prophylaxis regimens, neo-adjuvant chemotherapies etc.
Throughout protocol	Corrections to typographical and grammatical errors.	To improve readability.

1 PROTOCOL APPROVAL SIGNATURES

Protocol Title: A Randomized, Open-label, Multi-center, Controlled Clinical Study to Compare MAR-CUTIS with Dermabond Advanced in Closure of Surgical Incisions and Lacerations ≤15cm

Protocol Number: KF7021-04

This study will be conducted in compliance with the clinical study protocol (and amendments), International Standard ISO 14155:2011: Clinical investigation of medical devices for human subjects, Good Clinical Practice, and Declaration of Helsinki.

Sponsor Signatory

[redacted]
Grünenthal GmbH

[redacted]
25-Feb-2019
Signature
Date

[redacted]
Grünenthal GmbH

[redacted]
25-Feb-2019
Signature
Date

Contract Research Organization Signatory

[redacted]
Syneos Health

[redacted]
25 Feb 2019
Signature
Date

[redacted]
Syneos Health

[redacted]
25 Feb 2019
Signature
Date

Principal or Coordinating Investigator

[redacted]

[redacted]

Signature

27/2/19.

Date

2 SYNOPSIS

Protocol Number:

KF7021-04

Title:

A randomized, open-label, multi-center, controlled clinical study to compare MAR-CUTIS with Dermabond Advanced in closure of surgical incisions and lacerations ≤15 cm.

Investigational Device:

MAR-CUTIS topical tissue adhesive

Study Centers:

Up to 22 study centers located in the European Union

Phase:

Pivotal

Investigational Device Management Category:

European Union: IIb; United States: II

Study Design:

This is a randomized, open-label, multi-center, comparator-controlled clinical study to compare MAR-CUTIS with Dermabond Advanced in closure of surgical incisions ≥6 to ≤15 cm and lacerations ≤15 cm. Eligible subjects will be randomized 2:1 to MAR-CUTIS or Dermabond Advanced.

Number of Subjects:

A total of 189 subjects will be treated (defined as study product applied to the wound). Only subjects that are withdrawn from the study due to product failure at the time of application will be replaced. Re-screening is not allowed in the study.

Treatment:

MAR-CUTIS or Dermabond Advanced topical tissue adhesive will be applied to surgical incisions ≥6 to ≤15 cm and lacerations ≤15 cm as a last dermal closing layer on Day 0 once wounds have been prepared in a standard manner.

Study Duration:

The overall study duration for each subject is up to 4 months:

- Day -21 to Day 0: screening, presurgical examination.
- Day 0: presurgical examination, surgery, final eligibility, allocation to treatment group, treatment.
- Follow-up visits: Day 1, Day 10, Month 1, and Month 3 or Early Discontinuation.

Study Population:

Inclusion Criteria

For subjects with surgical incisions:

1. Subject undergoing closure of surgical incision ≥6 to ≤15 cm following a laparotomy, abdominal hysterectomy, inguinal hernia repair, or laparoscopic intervention.

For subjects with lacerations:

2. Subject requiring closure of a laceration on face (avoiding the immediate area around the eye or lips/mouth) or extremities, ≤15 cm. In subjects with multiple lacerations, one will be selected as the target wound (ie, greatest length and meets the study entry criteria).

For all subjects:

3. Subject has the ability to consent and has given written informed consent/assent to participate.
4. Male and female subjects ≥2 years of age and body weight ≥10 kg.
5. Subject willing and capable of following instructions for wound care provided by the investigator and agreeing to return for all treatment control visits specified in this clinical study.

Exclusion Criteria

For subjects with lacerations:

1. Wounds on mucosal surfaces or across mucocutaneous junctions (eg, oral cavity, lips, eyes).
2. Wounds which may be regularly exposed to body fluids or with dense natural hair (eg, scalp); wounds on ears.
3. Wounds on palms and feet.
4. Animal or human bites.
5. Lacerations that are heavily contaminated.
6. Punctured or crushed wounds.
7. Subjects with lacerations having wound treatment >6 hours after the trauma.

For all subjects:

8. Subjects requiring suturing with sutures >0.5 mm thickness.
9. Subject with documented skin disease or skin conditions (eg, excessive hair at the site of surgery, scar tissue, wound, tattoo, coloration, or pre-existing open sores at the site of surgery that would interfere with the application of investigational medical device [IMD] or the skin assessment, as judged by the investigator).
10. Subject with any factors that may have an adverse effect on wound healing (eg, previous history of keloid formation or hypertrophy [including family history]), other general risk factors for dehiscence (need of premature post-surgery exercise/heavy lifting, expected conditions leading to recurrent vomiting, coughing, or constipation), history of immunosuppression, chronic systemic infection, or poor general health.
11. Subjects with known blood clotting disorders.
12. Subjects receiving chronic, pre-operative steroids, immunosuppressants, chemotherapy, or anticoagulants; only chronic anti-platelet therapies like acetylsalicylic acid (ASA) and clopidogrel are accepted. Chronic is to be interpreted as long term or “for more than acute treatment”. Pre-operative standard of care, like a single dose of an anticoagulant, for the aforementioned treatments is allowed along with standard of care post-operative anticoagulant and chemotherapy regimen including application of steroids and immunosuppressants.
13. Subject having known or suspected allergy or sensitivity to polyurethane, cyanoacrylates, formaldehyde, tapes or adhesives, or benzalkonium chloride.
14. Subject participating in any current clinical study with a non-Conformité Européenne–marked device or investigational product.
15. Subject who is pregnant or breastfeeding.
16. Subject with history of a significant dermatologic disease or condition, such as atopic dermatitis, psoriasis, lichen ruber planus, vitiligo or conditions known to alter the skin appearance or physiologic response (eg, decompensated diabetes mellitus, porphyria) that involves the investigative site.

Withdrawal Criteria:

Subjects will be withdrawn from the study if the adhesive does not adhere appropriately at the time of application as assessed by the investigator and the event will be reported as device deficiency.

Objectives and Endpoints:

Objectives	Endpoints
Primary Efficacy Objective: • To compare the dehiscence rate between MAR-CUTIS and Dermabond Advanced between Day 1 and Day 10.	**Primary Efficacy Endpoint:** • Total dehiscence rate of target incision/laceration assessed at the Day 10 visit.
Main safety objective: • To compare the incidence of adverse events between MAR-CUTIS and Dermabond Advanced.	**Main safety endpoint:** • Adverse events within 1 month after treatment classified by severity and relatedness to the treatment.
Secondary	
• To compare the dehiscence rate between MAR-CUTIS and Dermabond Advanced at the Month 1 visit.	• Total dehiscence rate of target incision/laceration assessed at the Month 1 or Early Discontinuation visit (if Early Discontinuation occurs before Month 1).
• To compare the incidence of adverse events between MAR-CUTIS and Dermabond Advanced at additional study time points.	• Adverse events classified by severity and relatedness to the treatment.
• To evaluate the subject satisfaction with the cosmetic outcome after treatment of the surgical incision/laceration with MAR-CUTIS versus Dermabond Advanced	• Subject-completed Patient and Observer Scar Assessment Scale (POSAS) done at the Month 1 and Month 3 visits or at the Early Discontinuation visit (if Early Discontinuation occurs before Month 1).
• To compare the wound infection incidence between both treatment groups.	• Wound infection incidence assessed at the Day 10, Month 1, and Month 3 visits or at the Early Discontinuation visit (diagnosed according to the Centers for Disease Control and Prevention criteria for surgical site infection). • Wound infection assessed on a binary scale ("1 - yes" or "0 - no") for the following criteria: o Presence of erythema o Presence of edema o Presence of pain at rest o Presence of elevated temperature A total score will be calculated for each subject.
• To evaluate the investigator satisfaction with the cosmetic outcome after the closure of the target surgical incision/laceration with MAR-CUTIS versus Dermabond Advanced.	• Investigator-completed POSAS done at the Month 1 and Month 3 visits or at the Early Discontinuation visit. • Investigator-completed Modified Hollander Cosmesis Scale (mHCS) done at the Day 10 and Month 1 visits or at the Early Discontinuation visit (if Early Discontinuation occurs before Month 1).
• To evaluate the subject comfort with the device during and after treatment with MAR-CUTIS versus Dermabond Advanced.	• A questionnaire related to subject experience and satisfaction with the device completed by the subject at the Day 10 and Month 1 visits or at the Early Discontinuation visit (if Early Discontinuation occurs before Month 1). • A subject-related questionnaire to be completed by investigators at the Day 0 and Month 1 visits or at the Early Discontinuation visit (if Early Discontinuation occurs before

Objectives	Endpoints
	Month 1).
• To evaluate the investigator overall satisfaction and ease of use with the device during and after the closure of the target surgical incision/laceration with MAR-CUTIS or Dermabond Advanced.	• A product-related questionnaire completed by investigators at the Month 1 or Early Discontinuation visit (if Early Discontinuation occurs before Month 1).

Statistical Analysis:

Assuming dehiscence rates of 3.05% for MAR-CUTIS and 0.85% for Dermabond Advanced, 189 subjects (2:1, 126 MAR-CUTIS versus 63 Dermabond Advanced) ensure a power of 85% to show noninferiority of MAR-CUTIS compared with Dermabond Advanced using a one-sided significance level of $\alpha = 0.05$ and a Farrington-Manning test given a noninferiority margin of 8%.

The assumed dehiscence rates of 3.05% and 0.85% were derived based on the assumption to have 15% of subjects in the trial with lacerations that have a dehiscence rate of 0.5% for MAR-CUTIS and 0% for Dermabond Advanced and 85% of subjects in the trial with incisions, with dehiscence rates of 3.5% for MAR-CUTIS and 1% for Dermabond Advanced.

The assumed noninferiority margin of 8% is based on an average of dehiscence rates observed in previous studies eg, Siddiqui et al 2013 (dehiscence between 2%-13%), Muncie et al 2018 (dehiscence rates between 0.8-7.5%), and Eymann et al 2010 (dehiscence rates between 2%-24%). Noninferiority versus a placebo would not be ethical in the context of this trial, and thus has been set conservatively versus an approved IMD (Dermabond).

Descriptive statistics for the efficacy parameters will be based on the Full Analysis Set and for the safety and tolerability parameters based on the Safety Analysis Set. Summaries will be provided by treatment and time point (if applicable).

For the primary efficacy endpoint, Maximum-Likelihood estimates will be obtained fitting a logistic regression model to the dehiscence rates using the skin type (types I to III/types IV to VI), age group (2 to 21 years and ≥22 years), type of wound (incision/laceration) and treatment as explanatory variables. The method of Farrington-Manning (FM) will be applied to determine the variance estimator. Based on the derived Maximum-Likelihood estimates for the dehiscence rates and the FM estimate for the variance, the p-value of the FM test regarding noninferiority and the 90% confidence interval for the difference in dehiscence rates will be determined. The noninferiority of MAR-CUTIS compared with Dermabond Advanced will be established if the upper limit of this confidence interval is below the noninferiority margin of 8%.

A sensitivity analysis will be performed considering the length of incision/laceration in the logistic regression model instead of the wound type. Other sensitivity analyses will be performed as well.

All endpoints other than the primary efficacy endpoint will only be investigated descriptively in an exploratory manner.

3 TABLE OF CONTENTS

SUMMARY OF CHANGES 2

1 PROTOCOL APPROVAL SIGNATURES 4

2 SYNOPSIS 6

3 TABLE OF CONTENTS 11

4 LIST OF ABBREVIATIONS 14

5 INTRODUCTION 15

6 STUDY OBJECTIVES 18

7 INVESTIGATIONAL PLAN 20

7.1 Overall Study Design and Plan: Description 20

7.1.1 Study Design 20
7.1.2 Schedule of Assessments 21

7.2 Discussion of Study Design 23

7.2.1 Study Design 23

7.3 Selection of Study Population 24

7.3.1 Number of Planned Subjects 24
7.3.2 Inclusion Criteria 24
7.3.3 Exclusion Criteria 25
7.3.4 Removal of Subjects From Therapy or Assessments 26

7.4 Investigational Medical Device 27

7.4.1 Investigational Medical Device Applied 27
7.4.2 Identity of Investigational Medical Device 27
7.4.3 Manufacturing, Packaging, and Labeling 28
7.4.4 Method of Assigning Subjects to Treatment Groups 28
7.4.5 Application in the Study 28
7.4.6 Timing of Application for Each Subject 29
7.4.7 Blinding 29
7.4.8 Prior and Concomitant Therapy 29
7.4.9 Treatment Compliance 30
7.4.10 Device Deficiencies Reporting 30

8 TIMING OF STUDY PROCEDURES 30

8.1 Treatment 30

8.1.1 Screening Visit (Day -21 to 0) 30
8.1.2 Baseline Visit (Day 0) 30

8.2 Follow-up Period 31

8.2.1 Day 1 31
8.2.2 Day 10 and Month 1 31

8.2.3 End-of-treatment Visit (Month 3) 32
8.2.4 Early Discontinuation Visit 32

9 EFFICACY, SATISFACTION QUESTIONNAIRES, AND SAFETY 33

9.1 Efficacy Assessments 33

9.2 Satisfaction Questionnaires 33

9.3 Safety Assessments 34

9.3.1 Safety Definitions 35
9.3.2 Safety Reporting 37
9.3.3 AE Assessments 38
9.3.4 Pregnancy 40
9.3.5 Laboratory Assessments 40
9.3.6 Other Safety Assessments 40

9.4 Data Safety Monitoring Board 40

9.5 Appropriateness of Measurements 40

10 STATISTICAL METHODS 40

10.1 Statistical and Analytical Plans 40

10.1.1 Datasets or Populations Analyzed 40
10.1.2 Demographic and Other Baseline Characteristics 41
10.1.3 Efficacy Variables 41
10.1.4 Safety Variables 43
10.1.5 Handling of Missing Data 43

10.2 Determination of Sample Size 45

10.3 Protocol Deviations 45

11 QUALITY ASSURANCE AND QUALITY CONTROL 45

11.1 Audit and Inspection 45

11.2 Monitoring 46

11.3 Data Management and Coding 46

12 RECORDS AND SUPPLIES 47

12.1 Investigational Medical Device Accountability 47

12.2 Financing and Insurance 47

13 ETHICS 48

13.1 Independent Ethics Committee or Institutional Review Board 48

13.2 Regulatory Authorities 48

13.3 Ethical Conduct of the Study 48

13.4 Informed Consent 48

13.5 Subject Confidentiality 49

13.6 Reporting and Publication, Including Archiving 49

14 REFERENCES 50

15 APPENDICES 51

15.1 Centers for Disease Control and Prevention Surgical Site Infection Criteria 52

15.2 Dermabond Advanced Instructions for Use 57

15.3 Patient and Observer Scar Assessment Scale 60

15.4 Modified Hollander Cosmesis Scale 62

15.5 Product-related Questionnaire for Investigators 63

15.6 Subject-related Questionnaire for Investigators 66

15.7 Subject-completed Questionnaire 67

15.8 Contact Information for Safety Reporting 70

15.9 Investigator Signature Page 71

4 LIST OF ABBREVIATIONS

LIST OF ABBREVIATIONS

ADE	Adverse device effect
AE	Adverse event
CDC	Center for Disease Control and Prevention
CMH	Cochran-Mantel-Haenszel
DD	Device deficiency
eCRF	Electronic case report form
FAS	Full Analysis Set
FM	Farrington-Manning
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Council for Harmonisation
ID	Identifier
IEC	Independent Ethics Committee
IMD	Investigational medicinal device
IRB	Institutional Review Board
ISO	International Organization for Standardization
mHCS	Modified Hollander Cosmesis Scale
POSAS	Patient and observer scar assessment scale
PPS	Per Protocol Set
SAE	Serious adverse effect
SAP	Statistical analysis plan

5 INTRODUCTION

The goal of wound closure is to achieve hemostasis, avoid infection, and restore function to the affected skin area with minimal scarring. The most commonly used methods for wound closure after surgical procedures or traumatic injuries employ staples or sutures. Alternative methods for wound closure include the use of skin adhesives. The application of skin adhesives offers potential advantages over standard staple/suture methods (Smith et al. 2010, Sajid et al. 2009, Dumville et al. 2014):

- Simpler and shorter application procedure.
- Reduced pain intensity.
- Less trauma and disruption of wound's microcirculation.
- No painful injection of local anesthetic.
- Barrier function against microbial penetration into the wound bed.
- No risk of accidental needle stick injury.
- No need for follow-up for removal of sutures.
- Good cosmetic results.

Adhesives have been used in various forms for many years since the first cyanoacrylate adhesives were synthesized (Coover 1959). These early adhesives were appropriate for small superficial lacerations and incisions, but their limited physical properties prevented use in the management of other wounds. In addition, acute and chronic inflammatory reactions were reported to occur (Houston 1969). Further development led to the introduction of the n-2-butylcyanoacrlyates that were purer and stronger, but those did not receive widespread acceptance, because their clinical performance was limited by their low tensile strength and brittleness (Bruns 1996; Quinn 1993). More recently, stronger skin adhesives have been developed to increase flexibility and reduce toxicity by combining plasticizers and stabilizers (Quinn 1997). Skin adhesives have been used primarily in emergency rooms and there is increasing support in the literature for their effectiveness in the closure of various traumatic lacerations (Dumville et al. 2014, Farion 2002). Surgeons now also use skin adhesives in the operating room for the closure of surgical skin incisions.

Although skin adhesives may offer some of the advantages listed above, a Cochrane Systematic Review concluded that there is insufficient evidence as to whether covering surgical wounds healing by primary intention with cyanoacrylates adhesives reduces the risk of infections, improves scarring, pain control, subject acceptability or ease of dressing removal. Apart from that, the review showed that sutures are significantly better than cyanoacrylate adhesives for minimizing dehiscence (Dumville et al. 2014). As such, the development of a skin adhesive that affords dehiscence comparable with sutures would offer subjects an alternative method of wound closure which is less burdensome than the use of sutures or staples.

Wound dehiscence is one of the most common complications of surgical wounds and it involves the breaking open of the surgical incision along the suture. Typically, the sutures or closures around wound edges stay intact while new tissue, known as "granulation tissue," starts forming to help heal the wound. However, when wound dehiscence occurs, the edges starts to separate and the wound reopens instead of healing.

Wound dehiscence can be caused by poor surgical techniques such as improper suturing, overtightened sutures, or inappropriate type of sutures. Wound dehiscence can also be caused by increased stress to the wound area as a result of strenuous exercise, heavy lifting, coughing, laughing, sneezing, vomiting, or bearing down too hard with a bowel movement. In some cases, wound dehiscence could be secondary to wound infection or poor healing as seen in patients with chronic diseases, malnutrition, or weak immune systems. Secondary wound dehiscence can also occur in patients with AIDS, renal disease, diabetes mellitus, and those undergoing chemotherapy or radiotherapy.

Every person who has a surgical wound has a risk of dehiscence, especially in the first 2 weeks after surgery when the tissue is still weak and not completely healed. The 2 most important factors controlling the risk of wound dehiscence are:

- The patient's health status – the risk is higher in patients with a weak immune system, malnutrition, or chronic medical illness.
- The surgical procedure – the risk of dehiscence increases with overtightening of sutures, poor suturing technique, inappropriate surgery site, or suturing material.

The risk is also greater with smoking, obesity, premature postsurgery exercise, heavy lifting, recurrent vomiting, coughing, or an improper diet that leads to constipation.

Any wound dehiscence needs to be treated as a new wound and is a surgical emergency that requires immediate attention. Surgical debridements, antibiotic therapy, reclosure with the appropriate surgical technique, and sutures represent the most appropriate treatments. Finally, the patient's wound should be closely monitored to prevent dehiscence from recurring.

For all the above mentioned reasons, wound dehiscence always needs to be prevented as much as possible.

Therefore, a new, polyurethane-based topical skin adhesive has been developed: MAR-CUTIS. MAR-CUTIS is intended for topical application to close wounds of the skin, such as cuts and wounds from surgical incisions. It consists of a polyurethane-based prepolymer and an amino acid-based hardening agent which are provided in prefilled, double syringes with a mixing cannula and spreader tip.

Information about the preclinical testing as well as known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of MAR-CUTIS are to be found in the Investigator’s Brochure.

In particular, there are some predictable AEs (rates) that have been observed with other skin adhesives and can be possibly associated with the use of MAR-CUTIS:

- Infection (3.6%) after wound closure; this also applies to sutures and is not limited to adhesives.
- Dehiscence (2.5%) which is greater in wounds closed with skin adhesive as compared to other methods of wound closure (namely sutures, staples and strips).
- Improper application of the skin adhesive (unknown).

- Allergic reactions (11.5%).
- Other additional risks mentioned in risk management file, eg, pain (6.1%), edema (9.7%), and warmth (1.3%).

Such novel polyurethane-based medical adhesive differs from existing technologies due to its unique composition. The adhesive technology is:

- Fully Synthetic
- Easy to use
- Flexible

Based on polyurethane, it is completely different from existing skin adhesives based on cyanoacrylate. This new component is adhering to the tissue via mechanical and physical adhesion**,** forming a strong, yet flexible film**.** There is no reaction with the tissue itself; a strong polymer network is quickly formed and full polymerization is completed after a few minutes.

6 STUDY OBJECTIVES

Objectives	Endpoints
Primary Efficacy Objective: • To compare the dehiscence rate between MAR-CUTIS and Dermabond Advanced between Day 1 and Day 10.	**Primary Efficacy Endpoint:** • Total dehiscence rate of target incision/laceration assessed at the Day 10 visit.
Main safety objective: • To compare the incidence of AEs between MAR-CUTIS and Dermabond Advanced.	**Main safety endpoint:** • Adverse events within 1 month after treatment classified by severity and relatedness to the treatment.
Secondary	
• To compare the dehiscence rate between MAR-CUTIS and Dermabond Advanced at the Month 1 visit.	• Total dehiscence rate of target incision/laceration assessed at the Month 1 or Early Discontinuation visit (if Early Discontinuation occurs before Month 1).
• To compare the incidence of AEs between MAR-CUTIS and Dermabond Advanced at additional study time points.	• Adverse events classified by severity and relatedness to the treatment.
• To evaluate the subject satisfaction with the cosmetic outcome after treatment of the surgical incision/laceration with MAR-CUTIS versus Dermabond Advanced.	• Subject-completed Patient and Observer Scar Assessment Scale (POSAS) done at the Month 1 and Month 3 visits or at the Early Discontinuation visit (if Early Discontinuation occurs before Month 1).
• To compare the wound infection incidence between both treatment groups.	• Wound infection incidence assessed at the Day 10, Month 1, and Month 3 visits or at the Early Discontinuation visit (diagnosed according to the Centers for Disease Control and Prevention [CDC] criteria for surgical site infection [Section 15.1]). • Wound infection assessed on a binary scale (“1 - yes” or “0 - no”) for the following criteria: o Presence of erythema o Presence of edema o Presence of pain at rest o Presence of elevated temperature A total score will be calculated for each subject.
• To evaluate the investigator satisfaction with the cosmetic outcome after the closure of the target surgical incision/laceration with MAR-CUTIS versus Dermabond Advanced.	• Investigator-completed POSAS done at the Month 1 and Month 3 visits or at the Early Discontinuation visit (if Early Discontinuation occurs before Month 1).

	• Investigator-completed Modified Hollander Cosmesis Scale (mHCS) done at the Day 10 and Month 1 visits or at the Early Discontinuation visit (if Early Discontinuation occurs before Month 1).
• To evaluate the subject comfort with the device during and after treatment with MAR-CUTIS versus Dermabond Advanced.	• A questionnaire related to subject experience and satisfaction with the device completed by the subject at the Day 10 and Month 1 visits or at the Early Discontinuation visit (if Early Discontinuation occurs before Month 1). • A subject-related questionnaire completed by the investigator at the Day 0 and Month 1 visits or at the Early Discontinuation visit (if Early Discontinuation occurs before Month 1).
• To evaluate the investigator overall satisfaction and ease of use with the device during and after the closure of the target surgical incision/laceration with MAR-CUTIS or Dermabond Advanced.	• A product-related questionnaire completed by investigators at the Month 1 or Early Discontinuation visit (if Early Discontinuation occurs before Month 1).

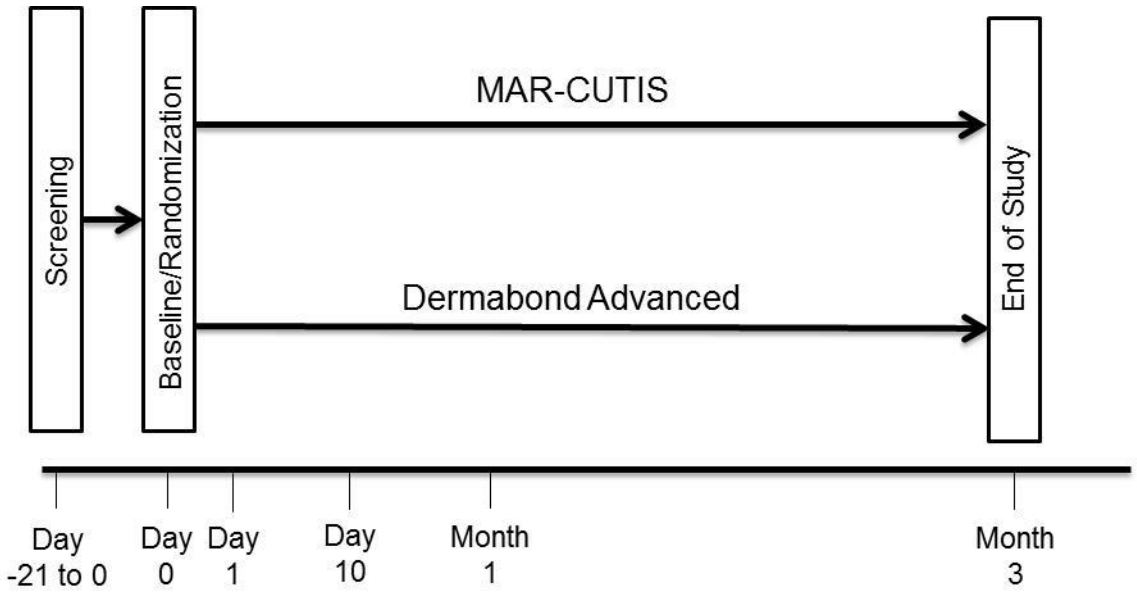
7 INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan: Description

This is a randomized, open-label, multi-center, comparator-controlled clinical study to compare MAR-CUTIS with Dermabond Advanced in closure of surgical incisions ≥6 to ≤15 cm and lacerations ≤15 cm. A total of 189 subjects will be treated (defined as study product applied to the wound). Only subjects that are withdrawn from the study due to product failure at the time of application (see Section 7.3.4) will be replaced. Subjects will be randomized 2:1 to MAR-CUTIS or Dermabond Advanced. Screening and baseline (randomization) can occur on the same day. Application of the investigational medical device (IMD) occurs on Day 0 with wound evaluation occurring on Day 1, Day 10, Month 1, and Month 3/Early Discontinuation. Training on the application of both devices will be provided.

7.1.1 Study Design

Figure 8.1 Study Design



7.1.2 Schedule of Assessments

	D -21 to 0	D0	D1	D10	Month 1	Month 3	ED
Visit Window			12 hours up to 36 hours after application	±2 days	±7 days	±14 days	
Obtain written informed consent/assent	X						
Check inclusion/exclusion criteria	X	X					
Record demographic data and medical/surgical history[a]	X						
Perform a urine ß-hCG pregnancy test (if applicable)		X					
Allocate subject to treatment and issue a diary		X					
Application of device		X					
Document prior (within the last 2 weeks) and concomitant medication intake (including steroids, immunosuppressants, chemotherapy, anticoagulants, antibiotics. Excluding related to intraoperative anesthesia)	X	X	X	X	X	X	X
Record of adverse events	X	X	X	X	X	X	X
Record of incidents and device performance, device-related complaints		X	X	X	X	X	X
Evaluation of incision/laceration (incidence and grading)		X					
Evaluation of dehiscence			X	X	X		X[d]
Evaluation of wound infection				X	X	X	X
mHCS completed by investigator				X	X		X[d]
POSAS completed by subject and investigator					X	X	X[d]
Subject-completed satisfaction questionnaire				X	X		X[d]
Subject-related questionnaire completed by investigator[c]		X			X		X[d]
Product-related questionnaire completed by investigator					X[b]		X[d]
Subject diary collection					X		X[d]

Abbreviations: ß-hCG=beta human chorionic gonadotropin; D=Day; ED=early discontinuation; mHCS= Modified Hollander Cosmesis Scale; POSAS= Patient and Observer Scar Assessment Scale.

.

[a] In particular, the following information will be collected: body mass index, medical history (including diabetes mellitus, chronic obstructive pulmonary disorder, hematological and vascular disorders, disorders of immune system, congestive heart failure, cardiovascular disease), concomitant medications (excluding related to intraoperative anesthesia), smoking, alcohol abuse.
[b] The product-related questionnaire is completed by the investigator only once per site when the last subject randomized at the site completes the Month 1 visit.
[c] Also completed if there is premature removal of the adhesive.
[d] Only to be performed if Early Discontinuation is before the Month 1 Visit or if the questionnaire has not previously been completed/if the diary has not previously been collected.

7.2 Discussion of Study Design

7.2.1 Study Design

The study will include 3 levels of stratification:

- By wound type (lacerations and incisions): approximately 40 subjects with lacerations will be randomized.
- By skin type according to the Fitzpatrick classification (types I to III versus types IV to VI): approximately 40 subjects with skin types IV to VI will be randomized; approximately 20 subjects from this cohort will have skin types V to VI.
- By age group (2 to 21 years of age and ≥22 years of age): approximately 30 subjects in the 2 to 21 age group will be randomized. To ensure that the pediatric population is not dominated by an adolescent sub-group, approximately 5 subjects aged 15 to <22 years will be included.

Screening and Randomization

Only one incision/laceration will be treated with the IMD. If a subject has more than one incision/laceration, the target wound will be the one with the greatest length (ie, the longest) that meets the study entry criteria. If the length of 2 or more wounds is equal, the investigator can chose either of them to be the target wound.

The incision/laceration will be prepared for closure as per the standard of care at a treating hospital. The investigator will assess the need and perform closure of deep tissue layers as necessary before proceeding with the closure of the last (dermal) layer with the IMD.

All lacerations will first be assessed for the need of deep suturing and/or debridement; this information will be recorded in the electronic case report form (eCRF). Wounds that require debridement and/or deep suturing will be treated according to the local practice of the investigator and only at the time of skin closure will the lacerations be randomized into 1 of the 2 study treatment arms. Wounds that do not require deep suturing and/or debridement will be randomized immediately.

Re-screening is not allowed in the study.

Treatment Phase

Use of Dermabond Advance will be according to Instructions for Use (Section 15.2). Wounds closed with Dermabond Advanced will be prepared in a standard manner. They will be cleaned with an antiseptic solution (which will be recorded in the eCRF), patted dry with dry, sterile gauze, and hemostasis will need to be achieved prior to wound closure (eg, by pressure application or use of local vasoconstrictors). Wound edges will be approximated by fingers of forceps and Dermabond Advanced will be applied in one continuous layer onto a dry wound through painting motions, taking care not to apply adhesive between the wound edges. Applying a second layer is not required or recommended. If a second layer of Dermabond Advanced is applied, or if large droplets of liquid are not spread thinly, the subject may experience an increased sensation of heat or discomfort. The wound will be held for 60 seconds to allow for complete polymerization. The wound may or may not be covered with a protective dressing thereafter.

Wounds closed with MAR-CUTIS will be prepared in a standard manner. They will be cleansed with an antiseptic solution (which will be recorded in the eCRF), patted dry with dry, sterile gauze, and hemostasis will need to be achieved prior to wound closure (eg, by pressure application or use of local vasoconstrictors). The use of peroxide-containing antiseptics is not recommended to be applied directly on the MAR-CUTIS strip as they may provoke cracking of the strip. These products however may be used for preparing the wound for closure. In addition, iodine-containing products may be used as necessary but they may stain the glue strip making it non-transparent. Wound edges will be approximated by fingers of forceps and MAR-CUTIS will be applied in one 1 to 2 mm thick layer ensuring that at least 1 cm of the glue is applied over the length of the wound on each side. The amount of the glue applied will be calculated such that one 5-mL syringe covers up to 8 cm of wound length (giving a total of 10 cm per syringe). For wounds >8 cm, 2 syringes will be needed. The wound will be held for approximately 30 seconds to allow for initial polymerization. Only for the pediatric population, the maximum number of syringes per day is limited based on the body weight as shown in the table below:

Body Weight	Number of MAR-CUTIS Syringes
10 to <15 kg	Maximum of 1 syringe
15 kg and above	Maximum of 2 syringes

A protective dressing may be applied after 3 minutes and instructions will be given to the subject on wound protection and showering as MAR-CUTIS requires moisture protection during showering.

If necessary, further dressing and wound management will be performed in accordance with the local practice.

Evaluation of all wounds will occur on Day 1, Day 10, Month 1, and Month 3/Early Discontinuation.

All subjects (or subject legal guardians in case of a pediatric subject) will be issued a subject's diary to record any wound exposure to water and any complaints. The diaries will be collected at the Month 1 study visit and analyzed descriptively.

7.3 Selection of Study Population

The study population will include subjects with surgical incisions from ≥6 to ≤15 cm or lacerations ≤15 cm who meet the criteria specified below.

7.3.1 Number of Planned Subjects

A total of 189 subjects will be treated (defined as study product applied to the wound). Only subjects that are withdrawn from the study due to product failure at the time of application (see Section 7.3.4) will be replaced.

7.3.2 Inclusion Criteria

For subjects with surgical incisions:

1. Subject undergoing closure of surgical incision ≥6 to ≤15 cm following a laparotomy, abdominal hysterectomy, inguinal hernia repair, or laparoscopic intervention.

For subjects with lacerations:

2. Subject requiring closure of a laceration on face (avoiding the immediate area around the eye or lips/mouth) or extremities, ≤15 cm. In subjects with multiple lacerations, one will be selected as the target wound (ie, greatest length and meets the study entry criteria).

For all subjects:

3. Subject has the ability to consent and has given written informed consent/assent to participate.
4. Male and female subjects ≥2 years of age and body weight ≥10 kg.
5. Subject willing and capable of following instructions for wound care provided by the investigator and agreeing to return for all treatment control visits specified in this clinical study.

7.3.3 Exclusion Criteria

Subjects will be excluded from the study if one or more of the following criterion is applicable:

For subjects with lacerations:

1. Wounds on mucosal surfaces or across mucocutaneous junctions (eg, oral cavity, lips, eyes).
2. Wounds which may be regularly exposed to body fluids or with dense natural hair (eg, scalp); wounds on ears.
3. Wounds on palms and feet.
4. Animal or human bites.
5. Lacerations that are heavily contaminated.
6. Punctured or crushed wounds.
7. Subjects with lacerations having wound treatment >6 hours after the trauma.

For all subjects:

8. Subjects requiring suturing with sutures >0.5 mm thickness.
9. Subject with documented skin disease or skin conditions (eg, excessive hair at the site of surgery, scar tissue, wound, tattoo, coloration, or pre-existing open sores at the site of surgery that would interfere with the application of IMD or the skin assessment, as judged by the investigator).
10. Subject with any factors that may have an adverse effect on wound healing (eg, previous history of keloid formation or hypertrophy [including family history]), other general risk factors for dehiscence (need of premature post-surgery exercise/heavy

lifting, expected conditions leading to recurrent vomiting, coughing, or constipation), history of immunosuppression, chronic systemic infection, or poor general health.

11. Subjects with known blood clotting disorders.
12. Subjects receiving chronic, pre-operative steroids, immunosuppressants, chemotherapy, or anticoagulants; only chronic anti-platelet therapies like acetylsalicylic acid (ASA) and clopidogrel are accepted. Chronic is to be interpreted as long term or "for more than acute treatment". Pre-operative standard of care, like a single dose of an anticoagulant, for the aforementioned treatments is allowed along with standard of care post-operative anticoagulant and chemotherapy regimen including application of steroids and immunosuppressants.
13. Subject having known or suspected allergy or sensitivity to polyurethane, cyanoacrylates, formaldehyde, tapes or adhesives, or benzalkonium chloride.
14. Subject participating in any current clinical study with a non-Conformité Européenne–marked device or investigational product.
15. Subject who is pregnant or breastfeeding.
16. Subject with history of a significant dermatologic disease or condition, such as atopic dermatitis, psoriasis, lichen ruber planus, vitiligo or conditions known to alter the skin appearance or physiologic response (eg, decompensated diabetes mellitus, porphyria) that involves the investigative site.

7.3.4 Removal of Subjects From Therapy or Assessments

Subjects may stop the study for any of the following reasons:

- Subject request
- Use of nonpermitted concurrent therapy
- Lost to follow-up (considered lost to follow-up only before Day 10)
- Occurrence of AEs not compatible with the continuation of subject participation in the study, in the investigator's opinion, or unacceptable to the subject to continue
- Investigator request
- Intercurrent illness

Subjects are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal will be documented in the eCRF.

Subjects withdrawing from the study will be encouraged to complete the same final evaluations as subjects completing the study according to this protocol, particularly safety evaluations. The aim is to record data in the same way as for subjects who completed the study.

Reasonable efforts will be made to contact subjects who are lost to follow-up. These efforts must be documented in the subject's file.

The sponsor has the right to terminate the study at any time in case of SAEs or if special circumstances concerning the IMD or the company itself occur, making further treatment of subjects impossible. In this event, the investigator(s) will be informed of the reason for study termination.

Removal of Subjects Based on Device Performance
Subjects will be withdrawn from the study if the adhesive does not adhere appropriately at the time of application as assessed by the investigator and the event will be reported as device deficiency.

Pregnancy
Subjects will be instructed that known or suspected pregnancy occurring during the study, in subjects or female partners of male subjects, should be confirmed and reported to the investigator. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject is subsequently found to be pregnant after inclusion in the study, the pregnancy will be followed to term and the status of mother and child will be reported to the sponsor after delivery.

Full details will be recorded on the withdrawal page of the eCRF and a pregnancy report will be completed.

7.4 Investigational Medical Device

7.4.1 Investigational Medical Device Applied

MAR-CUTIS is a polyurethane-based skin adhesive. At the time of use, the 2 components in the syringe are mixed in the mixing cannula. Complete hardening occurs about 5 minutes after application to the skin. The adhesive result can be corrected in the first 30 seconds. MAR-CUTIS is distributed sterile and is intended for single use. The product is used for topical closure of incisions and surgical wounds, replacing the last dermal suture line. It is not intended for intra-abdominal use and/or as a substitute for subcutaneous sutures. It should not be used after the expiration date and/or if the sterile packaging has been opened or damaged.

Dermabond Advanced is a topical skin adhesive used to hold closed easily approximated skin edges of wounds from surgical incisions, including incisions from minimally invasive surgery, and simple, thoroughly cleansed, trauma-induced lacerations.

7.4.2 Identity of Investigational Medical Device

The prepolymer component of MAR-CUTIS is made with hexamethylene diisocyanate, benzoyl chloride, and trifunctional polyol with primarily short alkylene oxide units. The curing agent is composed of diethyl maleate, 1,5-diamino-2-methylpentane, and polyethylene glycol 200. MAR-CUTIS should be stored at room temperature (15 to 25°C) and should be protected from moisture and humidity.

The active ingredient in Dermabond Advanced is 2-octyl cyanoacrylate. The recommended storage conditions are below 30°C (86°F), and away from moisture, direct heat, and direct light.

7.4.3 Manufacturing, Packaging, and Labeling

Manufacturing, labeling, packaging, and shipment of MAR-CUTIS will be performed by Syneos Health. All manufacturing, packaging, and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements. Details of packaging and labeling will be on file in the trial master file.

Dermabond Advanced adhesive is supplied sterile, in a prefilled, single-use applicator. The pen-style applicator consists of a crushable ampoule contained within a plastic applicator. The applicator contains the liquid adhesive. The applicator is supplied in a blister package to maintain the sterility of the device until opened or damaged. Dermabond Advanced adhesive is available in boxes of 6 or 12 applicators.

7.4.4 Method of Assigning Subjects to Treatment Groups

Subjects (ie, the unique subject identifier [ID] consisting of center ID and subject ID) will be randomly allocated to treatment according to a randomization scheme designed using the covariate-adjusted dynamic allocation method as implemented in Balance (Medidata, 2015). The algorithm combines complete randomness with a minimization method (Pocock and Simon, 1975), not only looking at marginal balances, but also considering the treatment balances overall and within individual strata, to ensure a balanced treatment allocation. Based on the expected clinical relevance of the explanatory variables for incision and laceration closure, the algorithm is implemented by assigning a different weight to the stratification factors to be included in the trial and minimize unbalances (ie, wound type having more importance than the other 2 factors, and age group having more importance than skin type). Further details regarding the parameters used to implement the randomization in balance are documented in the form “Balance Study Configuration Requirements”.

The incision/laceration will be prepared for closure as per the standard of care at a treating hospital. The investigator will assess the need and perform closure of deep tissue layers as necessary before proceeding with the randomization and subsequently with the closure of the last (dermal) layer with the IMD.

Eligible subjects will be randomized 2:1 to MAR-CUTIS or Dermabond Advanced.

The study will include 3 levels of stratification as randomization factors:

- By wound type (lacerations and incisions).
- By skin type according to the Fitzpatrick classification (types I to III versus types IV to VI).
- By age group (aged 2 to 21 years and ≥22 years).

The primary efficacy analysis will consider the stratification factors as explanatory variables in the model. Additionally, center will be considered as a further randomization factor as recommended by International Council for Harmonisation (ICH) E9.

7.4.5 Application in the Study

Detailed instruction and a training video on the application of MAR-CUTIS will be provided to each investigational site. MAR-CUTIS will be applied in one 1 to 2 mm thick layer, ensuring that at least 1 cm of the glue is applied over the length of the wound on each side.

The amount of the glue applied will be calculated such that one 5-mL syringe covers approximately 8 cm of wound length (giving a total of 10 cm per syringe). For wounds >8 cm, 2 syringes will be required. The wound will be held for approximately 30 seconds to allow for initial polymerization. Only for the pediatric population, the maximum number of syringes per day is limited based on the body weight as shown in the table below:

Body Weight	Number of MAR-CUTIS Syringes
10 to <15 kg	Maximum of 1 syringe
15 kg and above	Maximum of 2 syringes

Detailed instruction and a training video on Dermabond Advanced application will also be provided to each investigational site. Use of Dermabond Advanced will be according to Instructions for Use (Section 15.2). Dermabond Advanced will be applied in one continuous layer onto a dry wound through painting motions, taking care not to apply adhesive between the wound edges. Applying a second layer is not required or recommended. If a second layer of Dermabond Advanced is applied or if large droplets of liquid are not spread thinly, the subject may experience an increased sensation of heat or discomfort. The wound will be held for 60 seconds to allow for complete polymerization.

7.4.6 Timing of Application for Each Subject

The IMD will be applied only on Day 0 as instructed in Section 7.4.5.

7.4.7 Blinding

Blinding is not applicable as this is an open-label study.

In the given context, a blinding of investigators, site staff, and subjects is not feasible due to visual differences between the two adhesives, and therefore the possibility to distinguish both products. The assessment of the dehiscence and other endpoints might be prone to bias given the open-label trial design. To minimize the potential bias, sites will provide adequate training to all device users and further site staff involved in the trial in cooperation with the Sponsor.

7.4.8 Prior and Concomitant Therapy

Medication taken within the two weeks before screening will be documented in the eCRF. Allowed medications include those not listed in Section 7.4.8.1. Intraoperative anesthesia is not considered concomitant medication and does not require capturing in the eCRF.

7.4.8.1 Prohibited Medication/Therapy

Prohibited medications are chronic, pre-operative steroids, immunosuppressants, chemotherapy, and anticoagulants; only chronic anti-platelet therapies like acetylsalicylic acid (ASA) and clopidogrel are accepted. Chronic is to be interpreted as long term or “for more than acute treatment”. Pre-operative standard of care, like a single dose of an anticoagulant, for the aforementioned treatments is allowed along with standard of care post-operative anticoagulant and chemotherapy regimen including application of steroids and immunosuppressants.

7.4.8.2 Rescue Medication

Not applicable.

7.4.9 Treatment Compliance

The IMD will only be applied on Day 0 by the investigator. The timing of the glue detachment will be noted and recorded in the eCRF (day of application). Early glue removal and reason for removal will also be recorded in the eCRF.

7.4.10 Device Deficiencies Reporting

Device deficiencies (complaints and malfunctions) will be recorded in the subject diary. The investigator shall record all observed device deficiencies together with an assessment in the eCRF. If the device deficiency leads to an SAE, an SAE form must also be completed (see Section 9.3.2).

The Sponsor will ensure that the device can be inspected for defects in the event of procedural complications and root cause analysis will be done.

8 TIMING OF STUDY PROCEDURES

Subjects/legal guardians will provide written informed consent/assent before any study-related procedures are performed. The planned study assessments are in Section 7.1.2.

8.1 Treatment

8.1.1 Screening Visit (Day -21 to 0)

- Review and sign informed consent/assent form.
- Assess for eligibility (against the inclusion and exclusion criteria).
- Collect medical and surgical history (including diabetes mellitus, chronic obstructive pulmonary disease, hematological and vascular disorders, disorders of immune system, congestive heart failure, cardiovascular disease, smoking, and alcohol abuse).
- Record demographic data, such as ethnic origin, race, age, and sex.
- Record prior and concomitant medication (including steroids, immunosuppressants, chemotherapy, anticoagulants, and antibiotics. Excluding related to intraoperative anesthesia).
- Record adverse events (if applicable and if not recorded as medical history).

8.1.2 Baseline Visit (Day 0)

Screening and baseline can occur on the same day. The following procedures will be performed at the Baseline Visit:

- Reassess for eligibility against the inclusion and exclusion criteria if baseline is not on the same day as screening.
- Record concomitant medication (Excluding related to intraoperative anesthesia).

- Record adverse events.
- Record of incidents and device performance, device-related complaints
- Perform a urine beta-human chorionic gonadotropin (ß-HCG) pregnancy test (in all female subjects of childbearing potential [post-menarchal and pre-menopausal]).
- Issue a subject diary.
- Subject-related questionnaire completed by investigator.
- Evaluation of incision/laceration (incidence and grading).

When all the baseline procedures have been performed, subjects will be randomized (the 3 stratification factors of age group, wound type, and skin type will be recorded). All wounds, including those that require debridement and/or deep suturing, will be prepared for closure as per the standard of care at a treating hospital. The investigator will assess the need and perform closure of deep tissue layers as necessary before proceeding with the closure of the last (dermal) layer with the IMD. Once the IMD has been applied to the wound, the investigator will complete the specified portion of the subject-related questionnaire.

8.2 Follow-up Period

Subjects treated for lacerations may not be able to attend the Day 1 visit since they are usually not hospitalized. In this case, all attempts should be made to obtain information on potential dehiscence and AEs by phone. The reason for non-attendance should also be reported.

In case a subject is not able to attend the Day 10 visit, a telephone call can be done to capture the primary endpoint variables information. However, this is only allowed for exceptional cases and the reason for non-attendance and potential dehiscence and AEs should be recorded.

8.2.1 Day 1

The following procedures will be performed at Day 1:

- Record concomitant medication.
- Record AEs.
- Record of incidents and device performance, device-related complaints.
- Evaluation of dehiscence (incidence and grading).

8.2.2 Day 10 and Month 1

The product-related questionnaire will be completed by the investigator only once per site when the last subject randomized at the site completes the Month 1 visit.

The following procedures will be performed at both Day 10 and Month 1:

- Record concomitant medication
- Record AEs
- Record of incidents and device performance, device-related complaints

- Evaluation of dehiscence (incidence and grading)
- Evaluation of wound infection, if an infection occurred (incidence and criteria score)
- Modified Hollander Cosmesis Scale (mHCS) completed by investigator
- Subject-completed satisfaction questionnaire

Additional procedures performed at Month 1 include:

- Patient and Observer Scar Assessment Scale (POSAS), completed by subject and investigator
- Subject-related questionnaire completed by investigator
- Collect subject diary

8.2.3 End-of-treatment Visit (Month 3)

The following procedures will be performed at the Month 3 visit:

- Record concomitant medication
- Record AEs
- Record of incidents and device performance, device-related complaints
- Evaluation of wound infection, if an infection occurred (incidence and criteria score)
- Patient and Observer Scar Assessment Scale completed by subject and investigator

8.2.4 Early Discontinuation Visit

The following procedures will be performed at the Early Discontinuation Visit:

- Record concomitant medication
- Record AEs
- Record of incidents and device performance, device-related complaints
- Evaluation of wound infection, if an infection occurred (incidence and criteria score)
- Patient and Observer Scar Assessment Scale completed by subject and investigator
- Subject-completed satisfaction questionnaire (completed if Early Discontinuation is before the Month 1 visit or if the questionnaire has not previously been completed)
- Modified Hollander Cosmesis Scale (mHCS) completed by investigator (completed if Early Discontinuation is before the Month 1 visit or if the questionnaire has not previously been completed)
- Subject-related questionnaire completed by investigator (completed if Early Discontinuation is before the Month 1 visit or if the questionnaire has not previously been completed)
- Product-related questionnaire completed by the investigator (completed if Early Discontinuation is before the Month 1 visit or if the questionnaire has not previously been completed)

- Evaluation of dehiscence (completed if Early Discontinuation is before the Month 1 visit)
- Collection of subject diary (collected if the diary has not previously been collected)

The overall study duration for each subject is up to 4 months.

9 EFFICACY, SATISFACTION QUESTIONNAIRES, AND SAFETY

The planned schedule of assessments is in Section 7.1.2.

9.1 Efficacy Assessments

- Total dehiscence rate assessed at the Day 1, Day 10, Month 1, and Early Discontinuation (if earlier than Month 1) study visits.
- Classification of dehiscence:
  - Partial dehiscence not requiring re-treatment;
  - Dehiscence to original depth/length not requiring re-treatment (eg, closure with secondary intention);
  - Any dehiscence requiring re-treatment (including draining, debridement, closure, management of infection, etc.).
- Classification of dehiscence according to their grade (World Union of Wound Healing Societies Scale):
  - Dermal layer only
  - Subcutaneous layer exposed, fascia not visible
  - Subcutaneous layer and fascia exposed
  - Any area of fascial dehiscence with organ space, viscera or bone exposed

9.2 Satisfaction Questionnaires

- Patient and Observer Scar Assessment Scale (Section 15.3) will be completed by the subject and investigator at the Month 1 and Month 3 visits or the Early Discontinuation visit (Section 7.1.2).
  - The POSAS is a questionnaire that was developed to assess scar quality. It consists of 2 separate 6-item scales (Observer Scale and Patient Scale), both of which are scored on a 10-point rating scale.
  - Each scale has an overall “opinion” with 1 being no pain, no itching, or normal skin and 10 being worst scar imaginable with pain and itching.
- Modified Hollander Cosmesis Scale (Section 15.4) is completed by investigator at the Day 10, Month 1, and Early Discontinuation (if earlier than Month 1 or if the questionnaire has not previously been completed) visits (Section 7.1.2).
  - The mHCS consists of 6 wound characteristics, evaluated as “poor” or “good”

- Each of the characteristics is graded on a 0 (no/good) or l (yes/poor) point scale. A total cosmetic score is derived by the addition of the scores.

- One product-related questionnaire for investigators (Section 15.5) will be completed for each site when the last randomized subject at the site completes the Month 1 visit (Section 7.1.2). This questionnaire will be completed at the Early Discontinuation visit if the visit is earlier than the Month 1 visit or if the questionnaire has not previously been completed.

    - This questionnaire consists of 8 yes/no questions and 1 opinion question that evaluate the investigator's experience with use of the adhesive (ie, instructions easy to understand, preparation of the syringe being easy and fast, glue hardening time).

- Subject-related questionnaire completed by investigators (Section 15.6) will be done at the Day 0, Month 1, and Early Discontinuation (if earlier than Month 1 or if the questionnaire has not previously been completed) visits and if there is premature removal of the adhesive (Section 7.1.2).

    - This questionnaire consists of 5 yes/no questions that assess the investigator's experience applying the adhesive (ie, easy to use, fast, without complications), a visual analog scale that rates usability of the product from 1 to 100, and 1 question that evaluates satisfaction with the adhesive. The questions are categorized into 3 sections, each section to be completed at different visits.

- A subject-completed questionnaire (Section 15.7) will be done at the Day 10, Month 1, and Early Discontinuation (if earlier than Month 1 or if the questionnaire has not previously been completed) visits (Section 7.1.2).

    - The questionnaire at the Day 10 visit consists of 5 yes/no questions that evaluate the subject's experience with the adhesive, 1 question that rates the effect of the closed wound on several daily activities (ie showering, getting dressed), 1 question that evaluates satisfaction with the wound closure, and visual analog scales which rate pain on a scale of 1 to 10.

    - The questionnaire at the Month 1 visit consists of 3 questions including a visual analog scale which rates pain on a scale of 1 to 10, and 2 questions relating to the subject's overall satisfaction with the wound closure.

Note: For children, parents or legal guardians may assist in the completion of the questionnaires.

9.3 Safety Assessments

- Adverse events.
- Wound infection incidence assessed at the Day 10, Month 1, and Month 3/Early Discontinuation study visits (diagnosed according to the Centers for Disease Control and Prevention [CDC] criteria for surgical site infection).
- Wound infection assessed on a binary scale ("1 - yes" or "0 - no") for the following criteria (total score):

- Presence of erythema
- Presence of edema
- Presence of pain at rest
- Presence of elevated temperature at target wound area

9.3.1 Safety Definitions

Adverse Event

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the IMD.

This includes events related to the IMD or the comparator. This includes events related to the procedures involved (any procedure in the clinical investigation plan). For users or other persons this is restricted to events related to the IMD.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of IMD, whether or not it is related to the IMD. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, or the significant worsening of the indication under investigation that is not recorded elsewhere in the eCRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

Adverse Device Effect

Adverse event related to the use of an IMD.

This includes any AE resulting from insufficiencies or inadequacies in the Instructions for Use, the deployment, the implantation, the installation, the operation, or any malfunction of the IMD. This includes any event that is a result of a use error or intentional misuse.

Device Deficiency

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling.

All DDs related to the identity, quality, durability, reliability, safety or performance of an IMD shall be documented throughout the clinical investigation and appropriately managed by the sponsor.

Device deficiencies that did not lead to an AE but could have led to a medical occurrence:

- If either suitable action had not been taken,
- If intervention had not been made, or
- If circumstances had been less fortunate, shall be reported to regulatory authorities and ethic committees, as required by the national regulations.

Serious Adverse Event

An SAE is any untoward medical occurrence or effect that:

- Led to death, or
- Led to serious deterioration in the health of the subject, that either resulted in:
  - a life-threatening illness or injury, or
  - a permanent impairment of a body structure or a body function, or
  - in-patient or prolonged hospitalization, or
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent, or
  - impairment to a body structure or a body function.
- Led to fetal distress, fetal death, or a congenital abnormality or birth defect.

This includes DDs that might have led to an SAE:

- if suitable action had not been taken, or
- if intervention had not been made, or
- if circumstances had been less fortunate.

These are handled under the SAE reporting system.

Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered an SAE. Important medical reactions that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

The term “life-threatening”, in the definition, refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it would have been more severe.

In addition, medical and scientific judgement is required to decide if prompt notification is required in situations other than those defined for SAEs above. This may include any event that the investigator regards as serious that did not strictly meet the criteria above but may have jeopardized the subject or required intervention to prevent one of the outcomes listed above, or that would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the investigational product.

Serious Adverse Device Effect

An adverse device effect (ADE) that has resulted in any of the consequences characteristic of an SAE.

Unanticipated Serious Adverse Device Effect

Serious ADE which by its nature, incidence, severity or outcome has not been identified in the current version of the MAR-CUTIS risk analysis report or Instructions for Use for Dermabond Advanced.

- Anticipated: an effect which by its nature, incidence, severity or outcome has been previously identified in applicable product information (risk analysis report, Instruction for use).

9.3.2 Safety Reporting

9.3.2.1 Documentation and Reporting of Adverse Events

Adverse events should be reported and documented in accordance with the procedures outlined below. All AEs occurring during the study must be documented on the relevant eCRF pages. The following data should be documented for each AE:

- Description of the symptom event
- Classification of 'serious' or 'not serious'
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action taken
- Causal relationship
- Outcome of event (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported])

The investigator will record all AEs from the time following the signature of informed consent/assent until the last visit of the subject or later in case of ongoing AEs.

It is the responsibility of the investigator to document all AEs that occur during the study. Adverse events may be directly observed, evident in laboratory or diagnostic results, reported spontaneously by the subject, or by questioning the subject at each study visit. Subjects should be questioned in a general way, without directly prompting about the occurrence of any specific symptoms (eg, "How have you been feeling since the last visit?"). Adverse events should be reported on the appropriate page of the eCRF.

9.3.2.2 Reporting of Serious Adverse Events

From the signature of informed consent/assent until the last visit of the subject, the investigator must notify Syneos Health of the following events immediately (within 24 hours of the investigator becoming aware of the event) regardless of their causality:

- Any SAE
- Any DD
- New findings/updates in relation to already reported events

Serious AEs occurring in or to subjects that are in the comparator arm of an investigation shall also be reported in accordance with the SAE reporting system.

This initial notification is the object of the SAE/DD form reported by e-mail or by fax (see Section 15.8). The investigator will be requested to supply as much detailed information regarding the event that is available at the time of the initial contact (examinations carried out, laboratory results, etc.).

The investigator is also required to submit follow-up reports as soon as possible, including additional information such as diagnosis, outcome, causality assessment, results of specific investigations, and any new significant information that has not been previously reported.

Copies of additional laboratory tests, consultation reports, post mortem reports, hospital case reports, autopsy reports, and other documents should be sent when requested and applicable.

Instances of death, congenital abnormality, or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the investigator at any time after cessation of study device administration and linked by the investigator to this study, should be reported to the study monitor. The sponsor and/or Syneos Health will promptly notify all relevant safety information to the competent authorities, central Ethics Committees and investigators according to the local, national specific, safety reporting requirements and timelines in compliance with the required deadlines, and in accordance with European Union medical device directives and medical device guidelines: MEDDEV 2.7/3 rev 3. The same notification process and reporting timelines will apply for all products involved in the study. This also applies to the reporting of any new safety information which may modify significantly the benefit risk ratio of an investigational product or which may lead to modification of the conditions of use of the investigational product.

Details of the procedures to be followed if a pregnancy occurs are provided in Section 7.3.4.

9.3.2.3 Follow-up of Adverse Events

All investigators should follow-up with subjects with AEs/ADEs/SAEs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the eCRF. If the AE extends beyond the end of the study, it will be followed until resolution although the study will proceed with close-out activities independently.

Subjects should be followed-up by the end of study visit (Month 3/Early Discontinuation), and any AEs/ADEs/SAEs/DDs that occur during this time should be reported according to the procedures outlined above.

For all SAEs, where important or relevant information is missing, active follow-up should be undertaken. The subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized or until the last study visit, whichever comes first. This information should be documented in the subject's medical records.

9.3.3 AE Assessments

9.3.3.1 Assessment of Severity

Each AE will be assigned a category by the investigator as follows:

Mild:	An AE that is easily tolerated by the subject, causes minimal discomfort and does not interfere with everyday activities.
Moderate:	An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.

Severe:	An AE that prevents normal everyday activities; treatment or other intervention usually needed.

The most severe manifestation will be used for the final AE characterization. It will be recorded as the same AE.

9.3.3.2 Assessment of Causality

Every effort will be made by the investigator to assess the relationship of the AE, if any, to the IMD. Causality should be assessed using the categories presented in the following table:

Unrelated:	Clinical event with an incompatible time relationship to IMD use, and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the IMD.
Unlikely:	Clinical event whose time relationship to IMD use makes a causal connection improbable, but that could plausibly be explained by underlying disease or other drugs or chemicals.
Possible:	Clinical event with a reasonable time relationship to IMD use, but that could also be explained by concurrent disease or other drugs or chemicals.
Probable:	Clinical event with a reasonable time relationship to IMD use, and is unlikely to be attributed to concurrent disease or other drugs or chemicals.
Very Likely/Certain:	Clinical event with plausible time relationship to IMD use, and that cannot be explained by concurrent disease or other drugs or chemicals.

9.3.3.3 Action Taken

For each AE, the investigator will describe the action taken with the IMD in the appropriate section of the eCRF, as follows:

- None
- Medication or therapy provided
- IMD removed
- Concomitant medication changed
- Other, specify.

9.3.3.4 Outcome

The outcome of an AE has to be classified as follows: unknown, recovered, not yet recovered, recovered with sequelae, death.

9.3.4 Pregnancy

Pregnancy by itself will not be considered an AE. Hospitalization for a normal delivery or elective abortion of a normal fetus will not be considered as an SAE. However, the occurrence of an adverse pregnancy outcome for the mother or child may constitute an AE or SAE. If pregnancy occurs during the study, the investigator must inform the sponsor.

9.3.5 Laboratory Assessments

Screening for pregnancy will be performed (urine β-HCG at baseline [Day 0] visit only).

9.3.6 Other Safety Assessments

Wound infection incidence, diagnosed according to the CDC criteria for surgical site infection, will be assessed by an investigator at the Day 10, Month 1, Month 3/Early Discontinuation, and any unscheduled study visits. In addition, the infection will be assessed on a binary scale ("1 - yes" or "0 - no") for the criteria below. A total score will be generated for each subject.

- Presence of erythema
- Presence of edema
- Presence of pain at rest
- Presence of elevated temperature

9.4 Data Safety Monitoring Board

Not applicable.

9.5 Appropriateness of Measurements

The efficacy and safety assessments planned for this study are widely used and generally recognized as reliable, accurate, and relevant to the disease condition.

10 STATISTICAL METHODS

10.1 Statistical and Analytical Plans

A detailed statistical analysis plan (SAP) will be created and finalized before first subject first visit. Protocol deviations will be defined at the beginning of the study and data will be checked on a regular basis (ICH E6 [R2] addendum).

A data review meeting will be convened to define the important protocol deviations. This will be held on clean data shortly before the database lock.

10.1.1 Datasets or Populations Analyzed

- The Enrolled Set includes all subjects who signed the informed consent form (ICF).
- The Allocated Set includes all subjects who are allocated to treatment.
- The Safety Analysis Set includes all subjects where the application of MAR-CUTIS or Dermabond Advanced has started. Subjects will be analyzed under the actual treatment received.

- The Full Analysis Set (FAS) includes all subjects randomized that were allocated to one of the 2 treatment groups and had at least 1 posttreatment assessment. Subjects from the FAS will be analyzed under the randomized treatment group.

- The Per Protocol Set (PPS) defines a subset of subjects in the FAS without any major protocol deviations affecting the primary endpoint. Subjects from the PPS will be analyzed under the randomized treatment group.

10.1.2 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized on the FAS population.

10.1.3 Efficacy Variables

Unless otherwise stated, efficacy analyses will be performed on the FAS population.

10.1.3.1 Definition and Analysis of Primary Efficacy Endpoint

10.1.3.1.1 Definition

The primary efficacy endpoint will be the total dehiscence rate until the Day 10 visit. Thus, if the wound is assessed as showing dehiscence at Day 1 or an unscheduled visit before Day 10 visit but showing "No" dehiscence at Day 10, dehiscence will be evaluated as "Yes" in the analysis.

The dehiscence rate will be defined as "Yes" if the wound shows dehiscence, or "No" if the wound remains closed.

10.1.3.1.2 Main Analysis

During this trial, it is expected that a subject will have only one incision/laceration treated with the IMD (=target wound). In case the subject has more than one incision/laceration, the target wound will be the one with the greatest length (ie, the longest) that meets the study entry criteria. If the length of 2 or more wounds is equal, the investigator can choose either of them to be the target wound. Dehiscence will be assessed only for the target wound; for the analysis of the primary efficacy endpoint, only the treated target wound can and will be analyzed.

To minimize any possible user bias in the dehiscence rates, sites will provide adequate training to all device users in cooperation with the sponsor.

Missing data will be handled as described in Section 10.1.5.

The primary null and alternative hypotheses to be tested in this trial is that treatment with MAR-CUTIS is noninferior to treatment with Dermabond at the margin of 8%, ie,

$$H_0: p\_M - p\_D \geq 0.08 \text{ versus } H_1: p\_M - p\_D < 0.08$$

where p_M is the dehiscence rate of subjects treated with MAR-CUTIS, and p_D is the dehiscence rate of subjects treated with Dermabond. Since the dehiscence rates for both treatments are influenced by several factors, the effect of these will be considered and estimated with a statistical model.

Maximum-Likelihood estimates will be obtained fitting a logistic regression model to the dehiscence rates using the 3 randomization factors skin type (types I to III/types IV to VI), age group (2-21/≥22 years) and type of wound (incision/laceration), as well as treatment (MAR-CUTIS/Dermabond Advanced) as explanatory variables.

The method of Farrington-Manning (FM; Farrington and Manning, 1990) will be applied to determine the variance estimator.

Noninferiority will be declared if the upper limit of the 90% confidence interval (computed using the FM method) of the risk difference (computed from Maximum-Likelihood estimates after fitting a logistic regression) MAR-CUTIS:Dermabond is less than 8% in the FAS.

If the logistic regression model as describe above does not converge due to a low number of subjects in one or more of the stratification factors, a back-up strategy for the analysis will be provided in the SAP.

The following sensitivity analyses for primary efficacy will be performed:

1) The primary efficacy analysis as described above will be repeated using the PPS.
2) An analysis will be performed by repeating the logistic regression model described in the primary efficacy main analysis, albeit considering the length of the incision/laceration in the logistic regression model instead of the type of wound. This analysis will be performed using the FAS.
3) The primary efficacy analysis will be repeated, albeit by considering all subjects with missing data for the primary efficacy analysis as experiencing "Yes" dehiscence (ie, the wound did not remain closed). This analysis will be performed using the FAS.
4) An additional sensitivity analysis will be performed using a Cochran-Mantel-Haenszel (CMH; Cochran, 1954; Mantel and Haenszel, 1959) test. The dehiscence rates MAR-CUTIS:Dermabond will be analyzed with the CMH test, stratified by skin type (types I to III ; types IV to VI), age group (pediatric with age between 2 to 21 years; adult with age ≥22 years), type of wound (incision; laceration) and treatment (MAR-CUTIS; Dermabond Advanced). This analysis will be performed using the FAS.
5) A final sensitivity analysis will be performed by repeating the logistic regression model described in the primary efficacy main analysis, albeit introducing additionally the effect of the center where the subject was treated (given by the center ID) in the logistic regression model. This analysis will be performed using the FAS, and will only be considered if the logistic regression model converges.

10.1.3.1.3 Supplementary Analyses

Supplemental analyses may be performed and will be described in the SAP.

10.1.3.2 Definition and Analysis of Secondary Efficacy Endpoints

Secondary efficacy endpoints, as described in Section 6 are:

- Comparison of the dehiscence rate between MAR-CUTIS and Dermabond Advanced at the Month 1 or Early Discontinuation visit.

- Score from POSAS recorded for the subject at Month 1 and Month 3/Early Discontinuation.
- Comparison of wound infection incidence assessed on a binary scale (‘1-yes’ or ‘0-no’) between both treatment groups. In addition, a total score will be calculated for each subject based on the wound infection assessed on the presence of erythema, edema, pain or elevated temperature (also assessed on a binary scale: “1-yes” or “0-no” for each characteristic).
- Score from POSAS recorded for the investigator at Month 1 and Month 3/Early Discontinuation. Assessments will be presented by subject treated.
- Score from mHCS recorded for the investigator at Day 10 and Month 1 or Early Discontinuation. Assessments will be presented by subject treated.
- Score from a questionnaire related to subject experience and satisfaction with the device at Day 10 and at Month 1 or Early Discontinuation.
- Scores from 2 investigator-completed questionnaires to evaluate overall satisfaction and ease of use with the device:
    - A product-related questionnaire to be completed for each center when the last randomized subject at the center completes the Month 1 visit or at Early Discontinuation. This assessment will be presented by center.
    - A subject-related questionnaire at Day 0 and Month 1 or Early Discontinuation. This assessment will be presented by subject treated.

Secondary efficacy endpoints will be summarized using descriptive statistics.

FAS will be used on all analyses.

10.1.3.3 Exploratory Analyses

Exploratory analysis of dehiscence rates based on individual subgroups (eg, by wound type, skin type, or age group) might be performed. More details of these analyses will be provided in the SAP.

10.1.4 Safety Variables

Safety endpoints, as described in Section 6 are:

- Adverse events classified by severity and relatedness to treatment.

Descriptive analysis of safety variables will be performed on the Safety Analysis Set. In addition, descriptive analyses will be conducted within the randomization strata. Further information on each analysis will be provided in the SAP.

10.1.5 Handling of Missing Data

For the primary endpoint main analysis on the FAS population, any missing data for the primary endpoint will be handled as outlined in the following:

- Subjects with a provided reason for not attending the Day 10 Visit related to problems with the wound closure will be counted as a failure (ie, the subject experiences a dehiscence)

- Subjects with a dehiscence experienced and recorded before the Day 10 Visit (Day 1 or unscheduled visit) will be counted as a failure (ie, the subject experiences a dehiscence)

- All other subjects (eg, lost to follow-up with no dehiscence before) will be counted as success (ie, the subject experiences no dehiscence up to Day 10 for the primary endpoint analysis), since it is expected that subjects with problems of wound closure will attend the Day 10 visit to see the investigator and assess the wound status, and given the very low expected rate of dehiscence

In any case, all efforts will be made to contact subjects not attending Day 10 visit to gain information about the reason for nonattendance and about potential dehiscence.

Further information on how to treat missing data for other variables will be given in the SAP.

10.2 Determination of Sample Size

Assuming a dehiscence rate of 3.05% for MAR-CUTIS and 0.85% for Dermabond Advanced, 189 subjects (2:1, 126 MAR-CUTIS versus 63 Dermabond Advanced) ensure a power of 85% to show noninferiority of MAR-CUTIS compared with Dermabond Advanced using a one-sided significance level of $\alpha = 0.05$ and a FM test given a noninferiority margin of 8%.

The assumed dehiscence rates of 3.05% and 0.85% were derived based on the assumption to have 15% of subjects in the trial with lacerations that have a dehiscence rate of 0.5% for MAR-CUTIS and 0% for Dermabond Advanced and 85% of subjects in the trial with incisions, with dehiscence rates of 3.5% for MAR-CUTIS and 1% for Dermabond Advanced.

Due to the lack of placebo information for ethical reasons, the assumed noninferiority margin of 8% is based on an average of dehiscence rates observed in previous studies, eg, Siddiqui DS et al 2013 (dehiscence between 2% to 13%), Muncie et al 2018 (dehiscence rates between 0.8% to 7.5%), and Eymann et al 2010 (dehiscence rates between 2% and 24%). The KF7021-04 trial tries to mimic a real-life general surgery population. As such, a rather heterogeneous population is anticipated to be entered into the trial. Depending on the surgical indication, quite different dehiscence rates might be observed. Noninferiority versus a placebo would not be ethical in the context of this trial, and thus a non-inferiority design versus an approved IMD (Dermabond) has been set conservatively. The noninferiority margin is further supported by the fact that the use of no wound closure method would result in an expected dehiscence rate of 100%; the use of a placebo method (eg, adding a substance similar to a glue without any effect on wound closure) would be expected to be similar to no treatment, so that a noninferiority margin of 8% represents a clear improvement versus placebo.

10.3 Protocol Deviations

Deviations from the protocol will be defined in advance and documented on an ongoing basis during conduct of the clinical study.

The investigator should not implement any deviation from, or changes of the protocol, without agreement by the sponsor and prior review and documented approval/favorable opinion from the Independent Ethics Committee or Institutional Review Board (IEC/IRB) of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects. The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

Protocol deviations will be assessed individually on whether they are important or non-important. A log will be maintained by Grünenthal of important protocol deviations.

11 QUALITY ASSURANCE AND QUALITY CONTROL

11.1 Audit and Inspection

Study centers and study documentation may be subject to Quality Assurance audit during the course of the study by the sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

11.2 Monitoring

Data for each subject will be recorded on an eCRF. Data collection must be completed for each subject/legal guardian who signs an ICF/assent form and is administered IMD.

In accordance with current Good Clinical Practice (GCP) and ICH guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable.

The investigator must permit the monitor, the IEC/IRB, the sponsor's internal auditors, and representatives from regulatory authorities direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the eCRFs.

11.3 Data Management and Coding

Syneos Health will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant standard operating procedures of the data management and biostatistics departments of Syneos Health.

Study centers will enter data directly into an electronic data capture system by completing the eCRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study center. Data to be recorded directly on the eCRF will be identified and the eCRF will be considered the source document. Any changes to the data entered into the electronic data capture system will be recorded in the audit trail and will be Food and Drug Administration CFR 21 Part 11 compliant.

Medical coding will use the most recent version of the Medical Dictionary for Regulatory Activities for concomitant diseases and AEs, and WHODrug for medications.

Missing or inconsistent data will be queried in writing to the investigator for clarification. Subsequent modifications to the database will be documented.

12 RECORDS AND SUPPLIES

12.1 Investigational Medical Device Accountability

Upon receipt of the IMD, the investigator (or deputy) will conduct an inventory of the supplies and verify that IMD supplies are received intact and in the correct amounts before completing a supplies receipt. The investigator will retain a copy of this receipt at the study center. The monitor may check the study supplies at each study center at any time during the study.

It is the responsibility of the study monitor to ensure that the investigator (or deputy) has correctly documented the amount of the IMD received, dispensed, and returned on the dispensing log that will be provided. A full IMD accountability log will be maintained at the study center at all times. The study monitor will arrange collection of unused IMD returned by the subject. The study monitor will also perform an inventory of IMD at the close-out visit to the study center. All discrepancies must be accounted for and documented.

12.2 Financing and Insurance

Financing and insurance of this study will be outlined in a separate agreement between Syneos Health and the sponsor.

13 ETHICS

13.1 Independent Ethics Committee or Institutional Review Board

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the subjects, and any other relevant study documentation will be submitted to the appropriate IEC/IRB. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the IMD is released to the investigator. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study such as amendments to the protocol, the ICF or other study documentation. The written approval of the IEC/IRB together with the approved ICF must be filed in the study files.

The investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The investigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

13.2 Regulatory Authorities

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

13.3 Ethical Conduct of the Study

The investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines, the applicable national and local laws and regulatory requirements, and International Standard ISO 14155:2011: Clinical investigation of medical devices for human subjects.

13.4 Informed Consent

The process of obtaining informed consent/assent must be in accordance with applicable regulatory requirement(s) and must adhere to GCP.

The investigator is responsible for ensuring that no subject undergoes any study-related examination or activity before that subject/legal guardian has given written informed consent/assent to participate in the study.

The investigator or designated personnel will inform the subject of the objectives, methods, anticipated benefits and potential risks and inconveniences of the study. The subject should be given every opportunity to ask for clarification of any points s/he does not understand and, if necessary, ask for more information. At the end of the interview, the subject will be given ample time to consider the study. Subjects will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the investigator in the investigator's study file. A signed and dated copy of the subject ICF will be provided to the subject or their authorized representative.

It should be emphasized that the subject may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the subject is otherwise entitled. Subjects/legal guardians who refuse to give or who withdraw written informed consent/assent should not be included or continue in the study.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, a new ICF will be approved by the IEC(s)/IRB(s) (and regulatory authorities, if required). The study subjects will be informed about this new information and reconsent/reassent will be obtained.

13.5 Subject Confidentiality

Monitors, auditors, and other authorized agents of the sponsor and/or its designee, the IEC(s)/IRB(s) approving this research, as well as that of any other applicable agency(ies) such as the European Medicines Agency, will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

13.6 Reporting and Publication, Including Archiving

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study (end of study defined as the date of the last visit of the last subject), all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. This file will be available for inspection by the sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the investigational product. It is the responsibility of the sponsor to inform the study center when these documents no longer need to be retained. The investigator must contact the sponsor before destroying any study-related documentation. In addition, all subject medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

The sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the investigator(s). Published data must not compromise the objectives of the study. Data from individual study centers in multi-center studies must not be published separately.

14 REFERENCES

Bruns TB, Simon HK, McLario DJ, Sullivan KM, Wood RJ, Anand KJ. Laceration repair using a tissue adhesive in a children's emergency department. Pediatrics. 1996;98(4 Pt 1):673-5.

Coover HW, Joyner FB, Shearer NH, Wicker TH. Chemistry and performance of cyanoacrylate adhesives. J Soc Plast Eng. 1959;15:413-7.

Dumville JC, et al. Tissue adhesives for closure of surgical incisions. Cochrane Database Syst Rev. 2014;(11):CD004287.

Eymann R, Kiefer M. Glue instead of stitches: a minor change of the operative technique with a serious impact on the shunt infection rate. Acta Neurochirurgica Suppl. 2010;106:87-9.

Farrington CP, Manning G. Test Statistics and Sample Size Formulae for Comparative Binomial Trials with Null Hypothesis of Non-zero Risk Difference or Non-unity Relative Risk. Stat Med. 1990;9(12):1447-54.

Farion K, et al. Tissue adhesives for traumatic lacerations in children and adults. Cochrane Database Syst Rev. 2002;(3):CD003326.

Houston S, Hodge JW Jr, Ousterhout DK, Leonhard F. The effect of α-cyanoacrylates on wound healing. J Biomed Mater Res 1969;3(2):281-9.

Muncie C, Herman R, Collier A, Berch B, Blewett C, and Sawaya D. Wound complications after chemo-port placement in children: Does closure technique matter? J Pediatr Surg. 2018;53(3):572-5.

Pocock SJ and Simon, R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics. 1975;31(1):103-15.

Quinn J, et al. A randomized, controlled trial comparing a tissue adhesive with suturing in the repair of pediatric facial lacerations. Ann Emerg Med. 1993;22(7):1130-5.

Quinn J, et al. A randomized trial comparing octylcyanoacrylate tissue adhesive and sutures in the management of lacerations. JAMA. 1997;277(19):1527-30.

Sajid MS, Siddiqui MR, Khan MA, Baig MK. Meta-analysis of skin adhesives versus sutures in closure of laparoscopic port-site wounds. Surg Endosc. 2009;23(6):1191-7.

Siddiqui DS, Lacuna EM, Chen HY, and Chauhan SP. Skin closure of pfannenstiel incision with dermabond, staples, or suture during cesarean delivery: experience of a single attending. Am J Perinatol. 2013;30(3):219-24.

Smith TO, Sexton D, Mann C, Donell S. Sutures versus staples for skin closure in orthopaedic surgery: meta-analysis. BMJ. 2010;340:c1199.

15 APPENDICES

15.1 Centers for Disease Control and Prevention Surgical Site Infection Criteria

Criterion	Surgical Site Infection (SSI)
	Superficial incisional SSI Must meet the following criteria:
	Date of event for infection occurs within 30 days after any NHSN operative procedure (where day 1 = the procedure date) **AND** involves only skin and subcutaneous tissue of the incision **AND** patient has at least ***one*** of the following: a. purulent drainage from the superficial incision. b. organisms identified from an aseptically-obtained specimen from the superficial incision or subcutaneous tissue by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment (for example, not Active Surveillance Culture/Testing (ASC/AST). c. superficial incision that is deliberately opened by a surgeon, attending physician** or other designee and culture or non-culture based testing is not performed. **AND** patient has at least one of the following signs or symptoms: pain or tenderness; localized swelling; erythema; or heat. d. diagnosis of a superficial incisional SSI by the surgeon or attending physician** or other designee. www.cdc.gov/nhsn/xls/icd10-pcs-pcm-nhsn-opc.xlsx www.cdc.gov/nhsn/xls/cpt-pcm-nhsn.xlsx ** The term attending physician for the purposes of application of the NHSN SSI criteria may be interpreted to mean the surgeon(s), infectious disease, other physician on the case, emergency physician or physician's designee (nurse practitioner or physician's assistant).

Comments	There are two specific types of superficial incisional SSIs: 1. Superficial Incisional Primary (SIP) – a superficial incisional SSI that is identified in the primary incision in a patient that has had an operation with one or more incisions (for example, C-section incision or chest incision for CBGB) 2. Superficial Incisional Secondary (SIS) – a superficial incisional SSI that is identified in the secondary incision in a patient that has had an operation with more than one incision (for example, donor site incision for CBGB)
Reporting Instructions for Superficial SSI	**The following do not qualify as criteria for meeting the NHSN definition of superficial SSI:** • Diagnosis/treatment of cellulitis (redness/warmth/swelling), by itself, does not meet criterion "d" for superficial incisional SSI. Conversely, an incision that is draining or that has organisms identified by culture or non-culture based testing is not considered a cellulitis. • A stitch abscess alone (minimal inflammation and discharge confined to the points of suture penetration). • A localized stab wound or pin site infection- Such an infection might be considered either a skin (SKIN) or soft tissue (ST) infection, depending on its depth, but not an SSI **Note:** A laparoscopic trocar site for an NHSN operative procedure is not considered a stab wound. • Circumcision is not an NHSN operative procedure. An infected circumcision site in newborns is classified as CIRC and is not an SSI • An infected burn wound is classified as BURN and is not an SSI.

	Deep incisional SSI Must meet the following criteria: The date of event for infection occurs within 30 or 90 days after the NHSN operative procedure (where day 1 = the procedure date) according to the list in Table 2 **AND** involves deep soft tissues of the incision (for example, fascial and muscle layers) **AND** patient has at least ***one*** of the following: a. purulent drainage from the deep incision. b. a deep incision that spontaneously dehisces, or is deliberately opened or aspirated by a surgeon, attending physician** or other designee **AND** organism is identified by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment (for example, not Active Surveillance Culture/Testing (ASC/AST) or culture or non-culture based microbiologic testing method is not performed **AND** patient has at least ***one*** of the following signs or symptoms: fever (>38°C); localized pain or tenderness. A culture or non-culture based test that has a negative finding does not meet this criterion. c. an abscess or other evidence of infection involving the deep incision that is detected on gross anatomical or histopathologic exam, or imaging test. ** The term attending physician for the purposes of application of the NHSN SSI criteria may be interpreted to mean the surgeon(s), infectious disease, other physician on the case, emergency physician or physician's designee (nurse practitioner or physician's assistant).
Comments	There are two specific types of deep incisional SSIs: 1. Deep Incisional Primary (DIP) – a deep incisional SSI that is identified in a primary incision in a patient that has had an operation with one or more incisions (for example, C-section incision or chest incision for CBGB) 2. Deep Incisional Secondary (DIS) – a deep incisional SSI that is identified in the secondary incision in a patient that has had an operation with more than one incision (for example, donor site incision for CBGB)

	Organ/Space SSI Must meet the following criteria: Date of event for infection occurs within 30 or 90 days after the NHSN operative procedure (where day 1 = the procedure date) according to the list in Table 2 **AND** infection involves any part of the body deeper than the fascial/muscle layers, that is opened or manipulated during the operative procedure **AND** patient has at least ***one*** of the following: a. purulent drainage from a drain that is placed into the organ/space (for example, closed suction drainage system, open drain, T-tube drain, CT guided drainage) b. organisms are identified from fluid or tissue in the organ/space by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment (for example, not Active Surveillance Culture/Testing (ASC/AST). c. an abscess or other evidence of infection involving the organ/space that is detected on gross anatomical or histopathologic exam, or imaging test evidence suggestive of infection. **AND** meets at least ***one*** criterion for a specific organ/space infection site listed in Table 3. These criteria are found in the Surveillance Definitions for Specific Types of Infections chapter.

Table 2. Surveillance Periods for SSI Following Selected NHSN Operative Procedure Categories. Day 1 = the date of the procedure.

30-day Surveillance			
Code	**Operative Procedure**	**Code**	**Operative Procedure**
AAA	Abdominal aortic aneurysm repair	LAM	Laminectomy
AMP	Limb amputation	LTP	Liver transplant
APPY	Appendix surgery	NECK	Neck surgery
AVSD	Shunt for dialysis	NEPH	Kidney surgery
BILI	Bile duct, liver or pancreatic surgery	OVRY	Ovarian surgery
CEA	Carotid endarterectomy	PRST	Prostate surgery
CHOL	Gallbladder surgery	REC	Rectal surgery
COLO	Colon surgery	SB	Small bowel surgery
CSEC	Cesarean section	SPLE	Spleen surgery
GAST	Gastric surgery	THOR	Thoracic surgery
HTP	Heart transplant	THYR	Thyroid and/or parathyroid surgery
HYST	Abdominal hysterectomy	VHYS	Vaginal hysterectomy
KTP	Kidney transplant	XLAP	Exploratory Laparotomy
90-day Surveillance			
Code	**Operative Procedure**		
BRST	Breast surgery		
CARD	Cardiac surgery		
CBGB	Coronary artery bypass graft with both chest and donor site incisions		
CBGC	Coronary artery bypass graft with chest incision only		
CRAN	Craniotomy		
FUSN	Spinal fusion		
FX	Open reduction of fracture		
HER	Herniorrhaphy		
HPRO	Hip prosthesis		
KPRO	Knee prosthesis		
PACE	Pacemaker surgery		
PVBY	Peripheral vascular bypass surgery		
VSHN	Ventricular shunt		

Note: Superficial incisional SSIs are only followed for a 30-day period for all procedure types.

Secondary incisional SSIs are only followed for a 30-day period regardless of the surveillance period for the primary site.

Table 3. Specific Sites of an Organ/Space SSI.

Code	Site	Code	Site
BONE	Osteomyelitis	MED	Mediastinitis
BRST	Breast abscess or mastitis	MEN	Meningitis or ventriculitis
CARD	Myocarditis or pericarditis	ORAL	Oral cavity (mouth, tongue, or gums)
DISC	Disc space	OREP	Other infections of the male or female reproductive tract
EAR	Ear, mastoid	PJI	Periprosthetic Joint Infection
EMET	Endometritis	SA	Spinal abscess without meningitis
ENDO	Endocarditis	SINU	Sinusitis
GIT	GI tract	UR	Upper respiratory tract
IAB	Intraabdominal, not specified	USI	Urinary System Infection
IC	Intracranial, brain abscess or dura	VASC	Arterial or venous infection
JNT	Joint or Bursa	VCUF	Vaginal cuff
LUNG	Other infections of the lower respiratory tract		

15.2 Dermabond Advanced Instructions for Use

ETHICON
DERMABOND ADVANCED
TOPICAL SKIN ADHESIVE

INSTRUCTIONS FOR USE

TOPICAL SKIN ADHESIVE
(2-Octyl Cyanoacrylate)

DESCRIPTION

DERMABOND ADVANCED™ Topical Skin Adhesive is a sterile, liquid topical skin adhesive containing a monomeric (2-octyl cyanoacrylate) formulation and the colorant D & C Violet #2. It is provided as a single-use applicator in a blister package. The pen style applicator is composed of a crushable ampoule contained within a plastic applicator. As it is applied to the skin, the liquid is syrup-like in viscosity and polymerizes within minutes. Studies have shown that following application, DERMABOND ADVANCED™ Adhesive acts as a barrier to prevent microbial penetration as long as the adhesive remains. See DIRECTIONS FOR USE.

INDICATIONS

DERMABOND ADVANCED™ Adhesive is intended for topical application only, to hold closed easily approximated skin edges of wounds from surgical incisions, including incisions from minimally invasive surgery, and simple, thoroughly cleansed, trauma-induced lacerations. DERMABOND ADVANCED™ Adhesive may be used in conjunction with, but not in place of, deep dermal stitches.

CONTRAINDICATIONS

- Do not use on any wound with evidence of active infection, gangrene, or wounds of decubitus etiology.
- Do not use on mucosal surfaces or across mucocutaneous junctions (e.g., oral cavity, lips), or on skin which may be regularly exposed to body fluids or with dense natural hair.
- Do not use on patients with a known hypersensitivity to cyanoacrylate or formaldehyde.

WARNINGS

- DERMABOND ADVANCED™ Adhesive is a fast setting adhesive capable of adhering to most body tissue and many other materials, such as surgical gloves and stainless steel. Inadvertent contact with any body tissue, and any surfaces or equipment that are not disposable or that cannot be readily cleaned with a solvent such as acetone should be avoided.
- Polymerization of DERMABOND ADVANCED™ Adhesive may be accelerated by water or fluids containing alcohol. DERMABOND ADVANCED™ Adhesive should not be applied to wet wounds.
- DERMABOND ADVANCED™ Adhesive should not be applied to the eye. If contact with the eye occurs, flush the eye copiously with saline or water. If residual adhesive remains, apply topical ophthalmic ointment to help loosen the bond and contact an ophthalmologist.
- When closing facial wounds near the eye with DERMABOND ADVANCED™ Adhesive, position the patient so that any runoff of adhesive is away from the eye. The eye should be closed and protected with gauze. Prophylactic placement of petroleum jelly around the eye, to act as a mechanical barrier or dam, can be effective in preventing inadvertent flow of adhesive into the eye. DERMABOND ADVANCED™ Adhesive will not adhere to skin pre-coated with petroleum jelly. Therefore, avoid using petroleum jelly on any skin area where DERMABOND ADVANCED™ Adhesive is intended to adhere.
- DERMABOND ADVANCED™ Adhesive should not be used below the skin because the polymerized material is not absorbed by tissue and can elicit a foreign body reaction. Avoid excessive pressure of the applicator tip against wound edges or surrounding skin. This can force the wound edges apart and allow adhesive into the wound. DERMABOND ADVANCED™ Adhesive should be applied with a light brushing motion of the applicator tip over easily approximated wound edges.
- DERMABOND ADVANCED™ Adhesive should not be used in areas of high skin tension or across areas in which tension may increase, such as knuckles, elbows, or knees, unless the joint will be immobilized during the skin healing period or unless skin tension has been removed by application of another wound closure device (e.g., sutures or skin staples) prior to application of DERMABOND ADVANCED™ Adhesive.
- As with all wounds, DERMABOND ADVANCED™ Adhesive treated wounds should be monitored for signs of infection. Wounds with signs of infection, such as erythema, edema, warmth, pain, and purulent exudate, should be evaluated and treated according to standard practice for infection.
- DERMABOND ADVANCED™ Adhesive should not be used on wound sites that will be subjected to repeated or prolonged moisture or friction.

- DERMABOND ADVANCED™ Adhesive should only be used after wounds have been thoroughly and adequately cleaned and debrided in accordance with standard surgical practice.
- DERMABOND ADVANCED™ Adhesive polymerizes through an exothermic reaction in which a small amount of heat is released sometimes resulting in a sensation of warmth. Applying DERMABOND ADVANCED™ Adhesive in one continuous layer onto a dry wound and allowing time for polymerization, will minimize the warm sensation.
- DERMABOND ADVANCED™ Adhesive is packaged for single patient use. Discard remaining opened material after each wound closure procedure.
- Do not resterilize DERMABOND ADVANCED™ Adhesive.
- Do not place DERMABOND ADVANCED™ Adhesive in a procedure pack/tray that will be sterilized prior to use. Exposure of DERMABOND ADVANCED™ Adhesive, to excessive heat (as in autoclaves or ethylene oxide sterilization) or radiation (such as gamma or electron beam) will increase its viscosity and may render the product unusable.

PRECAUTIONS

- Do not apply liquid or ointment medications or other substances to the wound after closure with DERMABOND ADVANCED™ Adhesive, as these substances can weaken the polymerized film and allow for skin edge separation. Prior to application, cleanse the application site thoroughly to remove any remaining topical medications/anesthetics.
- DERMABOND ADVANCED™ Adhesive, as a liquid, is syruplike in viscosity. To prevent inadvertent flow of liquid DERMABOND ADVANCED™ Adhesive to unintended areas, the wound should be maintained in a horizontal position, with DERMABOND ADVANCED™ Adhesive applied from above.
- DERMABOND ADVANCED™ Adhesive should be used immediately after crushing ampoule because the adhesive will polymerize in the applicator, rendering the device unusable.
- If unintended bonding of intact skin occurs, peel the adhesive from the skin, but do not pull the skin edges apart. Petroleum jelly or acetone may help loosen the bond. Other agents such as water, saline, or soap are not expected to immediately loosen the bond.

ADVERSE REACTIONS

- Reactions may occur in patients who are hypersensitive to cyanoacrylate or formaldehyde. See CONTRAINDICATIONS.
- Adverse reactions may be experienced following contact with the eye.

DIRECTIONS FOR USE

1. The application of DERMABOND ADVANCED™ Adhesive requires thorough wound cleansing. Follow standard surgical practice for wound preparation before application of DERMABOND ADVANCED™ Adhesive (i.e., anesthetize, irrigate, debride, assure hemostasis, and close deep layers making sure that the wound edges can be easily approximated).
2. Pat the wound dry with dry, sterile gauze to assure direct contact of the DERMABOND ADVANCED™ Adhesive to the skin. Moisture accelerates DERMABOND ADVANCED™ Adhesive's polymerization and may affect wound closure results.
3. To prevent inadvertent flow of liquid DERMABOND ADVANCED™ Adhesive to unintended areas of the body, the wound should be maintained in a horizontal position and the DERMABOND ADVANCED™ Adhesive should be applied from above the wound.
4. DERMABOND ADVANCED™ Adhesive should be used immediately after crushing the ampoule, since the liquid DERMABOND ADVANCED™ Adhesive will flow freely from the tip for only a few minutes.
5. Refer to the instructions on the package for crushing the ampoule and expressing the liquid adhesive. Remove the applicator from the blister package. Hold the applicator with the thumb and a finger, away from the patient to prevent any unintentional placement of the liquid DERMABOND ADVANCED™ Adhesive into the wound or on the patient. With the applicator tip pointing downward, apply pressure at the midpoint of the bulb to crush the ampoule. Gently squeeze the applicator sufficiently to moisten the internal filter with the liquid adhesive. Stop squeezing and allow the liquid DERMABOND ADVANCED™ Adhesive to draw back into the applicator.
6. Approximate the wound edges with gloved fingers or sterile forceps. Slowly apply the liquid DERMABOND ADVANCED™ Adhesive in one continuous layer to the surface of the approximated wound edges using a gentle brushing motion. Maintain manual approximation of the wound edges for approximately 60 seconds after the application. The width of the layer can be increased or decreased by adjusting the amount of pressure applied to the bulb during application. Full apposition strength is expected to be achieved within minutes after the adhesive is applied. Full polymerization is expected when the DERMABOND ADVANCED™ Adhesive layer is no longer sticky.
7. Do not apply liquid or ointment medications onto wounds closed with DERMABOND ADVANCED™ Adhesive because these substances can weaken the polymerized film, leading to skin edge separation.
8. Protective dry dressings such as gauze may be applied only after DERMABOND ADVANCED™ Adhesive film is completely polymerized: not tacky to the touch after a few minutes. Allow the DERMABOND ADVANCED™ Adhesive to fully polymerize before applying a bandage.

9. Patients should be instructed to not pick at the polymerized film of DERMABOND ADVANCED™ Adhesive. Picking at the film can disrupt its adhesion to the skin and cause skin edge separation.
10. Patients should be instructed that until the polymerized film of DERMABOND ADVANCED™ Adhesive has sloughed naturally (usually in 5–10 days), there should be only transient wetting of the treatment site. Patients may immediately shower or bathe the site gently as directed by their physician. The site should not be scrubbed, soaked, or exposed to prolonged wetness until after the film has sloughed naturally and the physician has determined that the wound is adequately healed. Patients should be instructed not to swim during this period.
11. If removal of DERMABOND ADVANCED™ Adhesive is necessary for any reason, carefully apply petroleum jelly or acetone to the DERMABOND ADVANCED™ Adhesive film to help loosen the bond. Peel off the film; do not pull the skin edges apart.

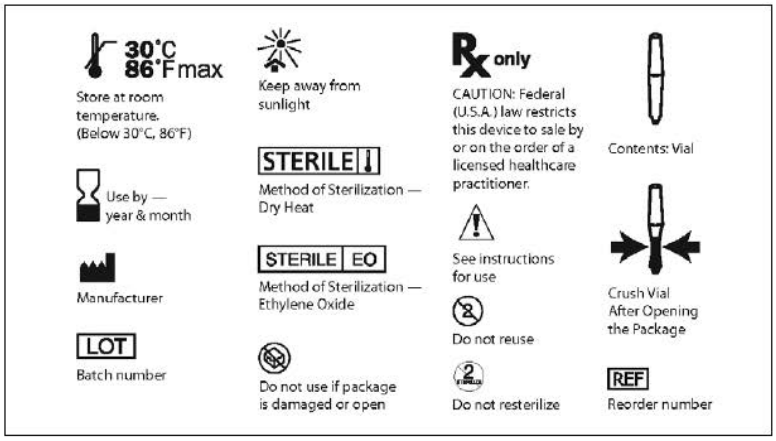
HOW SUPPLIED
DERMABOND ADVANCED™ Adhesive is supplied sterile, in a pre-filled, single-use applicator. The pen style applicator consists of a crushable ampoule contained within a plastic applicator. The applicator contains the liquid adhesive. The applicator is supplied in a blister package to maintain the sterility of the device until opened or damaged. DERMABOND ADVANCED™ Adhesive is available in boxes of 6 or 12 applicators.

STORAGE
Recommended storage conditions: below 30°C, 86°F, away from moisture, direct heat, and direct light. Do not use after expiry date.

STERILITY
DERMABOND ADVANCED™ Adhesive has been sterilized by dry heat and ethylene oxide gas. Do not resterilize. Do not use if package is opened or damaged. Discard any unused material following completion of each medical procedure.

STERILE SINGLE USE ONLY

REPORTING
Physicians should use the following toll-free number 1-800-255-2500 (valid in U.S.A. only), when reporting adverse reactions or potentially threatening complications involving DERMABOND ADVANCED™ Adhesive.



PM72434B
LAB0012189.2
STATUS: 03/2011

ETHICON, LLC
San Lorenzo, Puerto Rico 00754

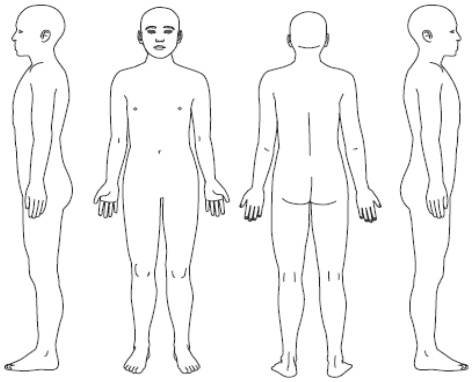
ETHICON™
DERMABOND ADVANCED™
TOPICAL SKIN ADHESIVE

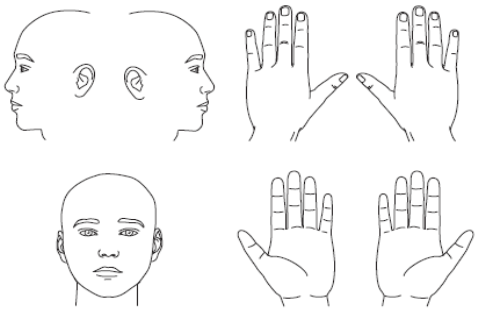
15.3 Patient and Observer Scar Assessment Scale

POSAS Patient scale

The Patient and Observer Scar Assessment Scale v2.0 / EN

Date of examination:	**Name of patient:**
Observer:	
Location:	**Date of birth:**
Research / study:	**Identification number:**





	1 = no, not at all									yes, very much = 10
	1	2	3	4	5	6	7	8	9	10
HAS THE SCAR BEEN PAINFUL THE PAST FEW WEEKS?	○	○	○	○	○	○	○	○	○	○
HAS THE SCAR BEEN ITCHING THE PAST FEW WEEKS?	○	○	○	○	○	○	○	○	○	○

	1 = no, as normal skin									yes, very different = 10
	1	2	3	4	5	6	7	8	9	10
IS THE SCAR COLOR DIFFERENT FROM THE COLOR OF YOUR NORMAL SKIN AT PRESENT?	○	○	○	○	○	○	○	○	○	○
IS THE STIFFNESS OF THE SCAR DIFFERENT FROM YOUR NORMAL SKIN AT PRESENT?	○	○	○	○	○	○	○	○	○	○
IS THE THICKNESS OF THE SCAR DIFFERENT FROM YOUR NORMAL SKIN AT PRESENT?	○	○	○	○	○	○	○	○	○	○
IS THE SCAR MORE IRREGULAR THAN YOUR NORMAL SKIN AT PRESENT?	○	○	○	○	○	○	○	○	○	○

	1 = as normal skin									very different = 10
	1	2	3	4	5	6	7	8	9	10
WHAT IS YOUR OVERALL OPINION OF THE SCAR COMPARED TO NORMAL SKIN?	○	○	○	○	○	○	○	○	○	○

POSAS Observer scale

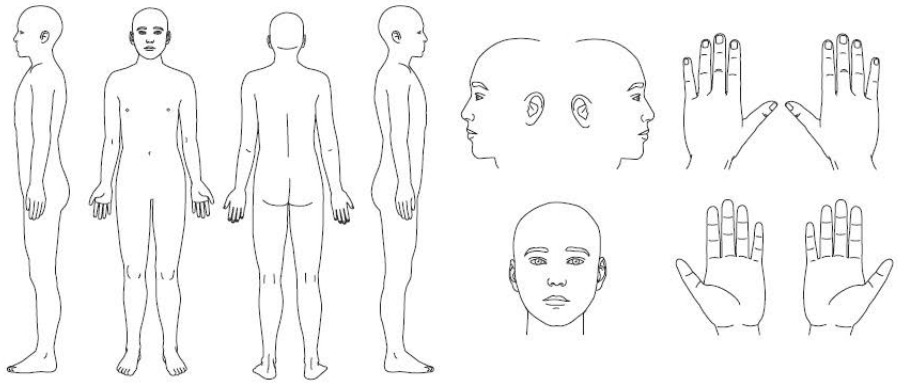
The Patient and Observer Scar Assessment Scale v2.0 / EN

Date of examination: **Name of patient:**

Observer:

Location: **Date of birth:**

Research / study: **Identification number:**



1 = normal skin worst scar imaginable = 10

PARAMETER	1	2	3	4	5	6	7	8	9	10	CATEGORY
VASCULARITY	○	○	○	○	○	○	○	○	○	○	PALE | PINK | RED | PURPLE | MIX
PIGMENTATION	○	○	○	○	○	○	○	○	○	○	HYPO | HYPER | MIX
THICKNESS	○	○	○	○	○	○	○	○	○	○	THICKER | THINNER
RELIEF	○	○	○	○	○	○	○	○	○	○	MORE | LESS | MIX
PLIABILITY	○	○	○	○	○	○	○	○	○	○	SUPPLE | STIFF | MIX
SURFACE AREA	○	○	○	○	○	○	○	○	○	○	EXPANSION | CONTRACTION | MIX
OVERALL OPINION	○	○	○	○	○	○	○	○	○	○	

Explanation

The observer scale of the POSAS consists of six items (vascularity, pigmentation, thickness, relief, pliability and surface area).
All items are scored on a scale ranging from 1 ('like normal skin') to 10 ('worst scar imaginable').
The sum of the six items results in a total score of the POSAS observer scale. Categories boxes are added for each item. Furthermore, an overall opinion is scored on a scale ranging from 1 to 10.
All parameters should preferably be compared to normal skin on a comparable anatomic location.

Explanatory notes on the items:

- **VASCULARITY** Presence of vessels in scar tissue assessed by the amount of redness, tested by the amount of blood return after blanching with a piece of Plexiglas
- **PIGMENTATION** Brownish coloration of the scar by pigment (melanin); apply Plexiglas to the skin with moderate pressure to eliminate the effect of vascularity
- **THICKNESS** Average distance between the subcutical-dermal border and the epidermal surface of the scar
- **RELIEF** The extent to which surface irregularities are present (preferably compared with adjacent normal skin)
- **PLIABILITY** Suppleness of the scar tested by wrinkling the scar between the thumb and index finger
- **SURFACE AREA** Surface area of the scar in relation to the original wound area

15.4 Modified Hollander Cosmesis Scale

Modified Hollander Cosmesis Scale (part of the "Wound registry")

Evaluation Characteristics	Yes (poor)	No (good)
Step-off borders	1	0
Contour irregularities	1	0
Wound margin separation	1	0
Edge inversion	1	0
Excessive inflammation	1	0
Overall appearance	1	0

15.5 Product-related Questionnaire for Investigators

Each investigator will complete this questionnaire after the assumed last randomized subject at the site has completed the Month 1 or Early Discontinuation (if earlier than Month 1) visit (one per site).

Date of completion: dd/mmm/YYYY

1)	The instructions for use were:	MAR-CUTIS		Dermabond	
	Clear and easy to understand for you	Yes	No	Yes	No
	Clear and easy to implement for subjects	Yes	No	Yes	No

if answered "No" for MAR-CUTIS, please explain the issue below:

if answered "No" for Dermabond, please explain the issue below:

2)	Package opening, assembly and preparation of the syringe was:	MAR-CUTIS		Dermabond	
	Easy	Yes	No	Yes	No
	Fast	Yes	No	Yes	No

if answered "No" for MAR-CUTIS, please explain the issue below:

if answered "No" for Dermabond, please explain the issue below:

3)	Preparation of the target wound area was easy?	MAR-CUTIS		Dermabond	
		Yes	No	Yes	No
		Yes	No	Yes	No

if answered "No" for MAR-CUTIS, please explain the reason below:

if answered "No" for Dermabond, please explain the reason below:

4)	Appropriate thickness of the strip was easy to assess?	MAR-CUTIS		Dermabond	
		Yes	No	Yes	No
		Yes	No	Yes	No

if answered "No" for MAR-CUTIS, please explain the issue below:

if answered "No" for Dermabond, please explain the issue below:

5)	Maintaining the target wound edges during application was easy:	MAR-CUTIS		Dermabond	
		Yes	No	Yes	No
		Yes	No	Yes	No

if answered "No" for MAR-CUTIS, please explain the issue below:

if answered "No" for Dermabond, please explain the issue below:

6)	Precision of application was satisfactory?	MAR-CUTIS		Dermabond	
		Yes	No	Yes	No
		Yes	No	Yes	No

if answered "No" for MAR-CUTIS, please explain the reason below:

if answered "No" for Dermabond, please explain the reason below:

7)	Time for the glue to harden was:	MAR-CUTIS	Dermabond
		Too quick	Too quick
		Too slow	Too slow
		Just right	Just right

If you have any comments, please provide below:

8)	Do you have previous experience with other topical skin adhesive?	yes	no

If answered “yes”,

	Was MAR-CUTIS easier to apply than the other topical skin adhesives?	yes	no
	Was Dermabond easier to apply than the other topical skin adhesives?	yes	no

9)	Overall, the use of the glue made wound closure more hassle-free for me than using sutures	MAR-CUTIS		Dermabond	
		Yes	No	Yes	No

if answered “no” for MAR-CUTIS, please explain the reason below:

if answered “no” for Dermabond, please explain the reason below:

15.6 Subject-related Questionnaire for Investigators

Subject-related Questionnaire for investigators

Please complete this questionnaire for each subject in the study at specified time points.

Section 1 (to be completed at Day 0)

1) Application of the glue strip

Easy	Yes	No
Fast	Yes	No
Without complications	Yes	No

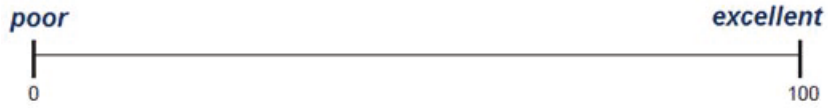
2) Overall, would you say that the use of the glue saved you time as compared with the use of sutures? Yes No

3) Overall, would you say that the use of the glue reduced effort? Yes No

Section 2 (to be completed at Month 1)

Practical experience

8) Please rate your impression on the usability of this product on a scale from 1 (poor = very difficult to use) to 100 (excellent = very easy to use)



9) With regards to this subject, my experience with MAR-CUTIS can be described as

Very satisfied
Satisfied
Dissatisfied
Very dissatisfied

10) Did you observe any pain or burning at time of application?

Yes
No

Section 3 (to be completed only in case of intentional premature removal of the adhesive)

1) Premature, intentional removal of glue strip was:

Painless for subject	Yes	No
Easy	Yes	No
Quick	Yes	No
Didn't cause any additional complications	Yes	No

if any answered "no", please explain the issue below:

Please explain which technique you used to remove the adhesive:

Please provide reason(s) for the removal:

15.7 Subject-completed Questionnaire

Questionnaire for Subjects

Your opinion is very important to us and will help us to improve the quality of the product. We therefore would like to ask you to complete the following questionnaire which assesses positives and negatives of the wound closing method that has been used. Your doctor should be able to provide any help needed to complete this questionnaire.

This questionnaire should take a few minutes to complete.

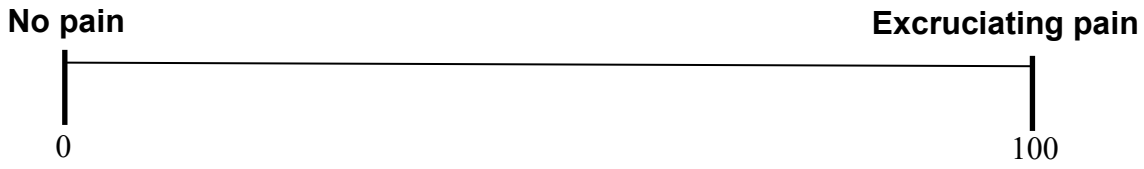
Thank you

Section 1 (to be completed at Day 10 visit)

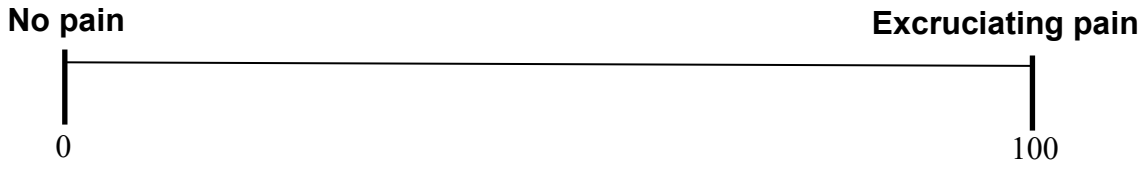
1. Wound pain

Please evaluate the pain you are **now** experiencing in the area of your wound by indicating on the 100-mm line scale below with "no pain" at the left end (0 mm) and "excruciating pain" at the right" end (100 mm).

My pain right now is:



Please evaluate the **average** pain you have experienced in the area of your wound within the last seven (7) days by indicating on the 100-mm line scale below with "no pain" at the left end (0 mm) and "excruciating pain" at the right end (100 mm).



Section 2 (to be completed at Day 10 visit)

2. Practical Experience/Ease of Use

1) You were given written instructions of how to take care of your wound after the surgery. Please answer the questions below by indicating 'yes' or 'no':

The instructions were easy to understand Yes No

The instructions were easy to implement Yes No

2) How did the wound affect your daily activities? Please complete the table below, based on what you experienced after your surgical procedure:

	Very inconvenient	***A little bit inconvenient***	***Neither positive, nor negative***	***Convenient***	***Very convenient***
Impact on your daily activities: During showering/washing					
When getting dressed and while wearing clothes					
During the day (moving, sitting, working)					
During the night (sleeping/lying in bed)					

3) How did you experience the application and changing of the wound dressing?

I did it myself Yes No

Easy/no problem Yes No

4) The glue strip of MAR-CUTIS is transparent when applied to the skin.

Did you find it useful? Yes No Not applicable (had Dermabond)

5) Please indicate how the wound closure felt on your skin:

Comfortable Yes No

Tight (tension at the wound) Yes No

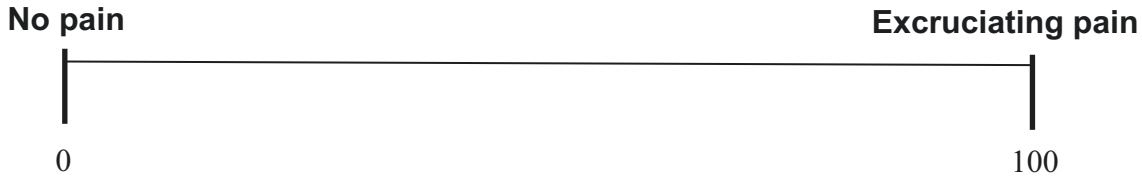
Itchy Yes No

Loose (as if falling off) Yes No

Section 3 (to be completed at 1 Month visit)

1. Wound pain

1) Please evaluate the pain you are **now** experiencing in the area of your wound by indicating on the 100-mm line scale below with "no pain" at the left end (0 mm) and "excruciating pain" at the right" end (100 mm)



2. Satisfaction/Preference

2) My overall experience with the wound closure is best described as

Very satisfied
Satisfied
Dissatisfied
Very dissatisfied

3) I would recommend this type of wound closure to a friend or relative

Yes No

15.8 Contact Information for Safety Reporting

The initial SAE notification report to be sent by e-mail or fax:

e-mail	[redacted]

Country	Fax number
France	[redacted]
Germany	[redacted]
Spain	[redacted]
United Kingdom	[redacted]

15.9 Investigator Signature Page

Protocol Title: A randomized, open-label, multi-center, controlled clinical study to compare MAR-CUTIS with Dermabond Advanced in closure of surgical incisions and lacerations ≤15cm

Protocol Number: KF7021-04

Confidentiality and Current Good Clinical Practice Compliance Statement

I, the undersigned, have reviewed this protocol (and amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), International Standard ISO 14155:2011: Clinical investigation of medical devices for human subjects, Good Clinical Practice, and Declaration of Helsinki.

Once the protocol has been approved by the IEC/IRB, I will not modify this protocol without obtaining prior approval of Grünenthal GmbH and of the IEC/IRB. I will submit the protocol amendments and/or any ICF modifications to Grünenthal GmbH and IEC/IRB, and approval will be obtained before any amendments are implemented.

I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all eCRFs, laboratory samples, or source documents forwarded to the sponsor. Clinical information may be reviewed by the sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

Information developed in this clinical study may be disclosed by Grünenthal GmbH, to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

_____ _____

Investigator Signature Date

_____

Printed Name

_____

Institution