NCT Number: NCT03688880

STATISTICAL ANALYSIS PLAN

Trial code:	KF7021-04
Title of trial:	A Randomized, Open-label, Multi-center, Controlled Clinical Study to Compare MAR-CUTIS with Dermabond Advanced in Closure of Surgical Incisions and Lacerations ≤15cm
{EudraCT number:}	Not applicable
Development phase:	Pivotal
Investigational medicinal product:	MAR-CUTIS topical tissue adhesive

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This document was approved according to the Syneos Health standard operating procedures.

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2 ABBREVIATIONS

Abbreviation	Explanation
ADE	Adverse Device Effect
AE	Adverse event
CDC	Center for Disease Control and Prevention
CI	Confidence interval
CIR	(Crude) Incidence rate
CMH	Cochran-Mantel-Haenszel
ED	Early Discontinuation
FAS	Full Analysis Set
FM	Farrington-Manning
ICTR	Integrated clinical trial report
IMD	Investigational medical device
N	Number of subjects in population
Max	Maximum
MLE	Maximum-Likelihood Estimate
MedDRA	Medical Dictionary for Regulatory Activities
mHCS	Modified Hollander Cosmesis Scale
Min	Minimum
Q1	First quartile
POSAS	Patient and Observer Scar Assessment Scale
PPS	Per Protocol Set
Q3	Third quartile
SAE	Serious adverse event
SAF	Safety Set
SAP	Statistical analysis plan
SAS	Statistical analysis software
SD	Standard deviation
TEAE	Treatment emergent adverse event
WHO-DD	World Health Organization Drug Dictionary

Système International d'Unités units are not included in this list.

3 INTRODUCTION

This statistical analysis plan (SAP) includes all definitions and analysis details for the analysis of the trial in accordance with the protocol dated 16 Jul 2018. The analysis will be performed by a contract research organization in accordance with this SAP.

4 TRIAL 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 (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 visit.
• To compare the incidence of AEs between MAR-CUTIS and Dermabond Advanced at additional study timepoints.	• 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.
• To compare the wound infection incidence between both treatment groups.	• Wound infection incidence assessed at the Day 10, Month 1, and Month 3 visits (diagnosed according to the Centers for Disease Control and Prevention [CDC] criteria for surgical site infection [See Protocol Section **Error! Reference source not found.** for more details]). • 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 medical practitioner 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. • Investigator completed Modified Hollander Cosmesis Scale (mHCS) done at the Day 10 and Month 1 visits.
• 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 at the Day 10 and Month 1 visits.
• To evaluate the medical practitioner 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 questionnaire for investigators completed at the Month 1 visit.

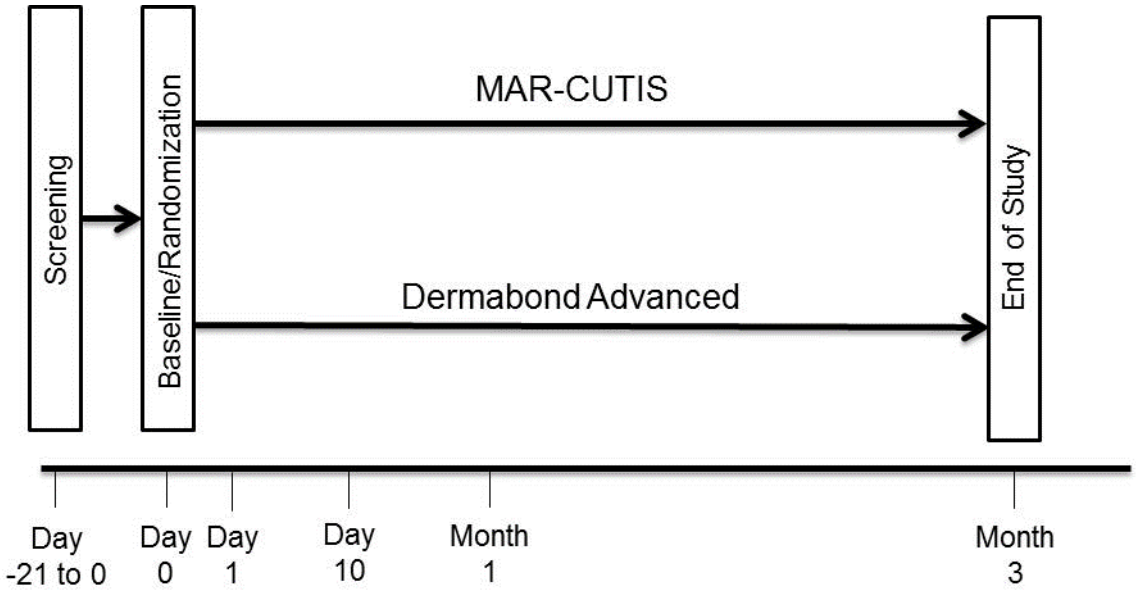
5 TRIAL DESIGN

5.1 Overall trial design and plan

Only a brief synopsis of the trial design is presented here; full details can be found in the trial protocol.

This is a randomized, open-label, multicenter, comparator-controlled clinical study to compare MAR-CUTIS with Dermabond Advanced in closure of surgical incisions 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 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 (D0) with wound evaluation occurring on Day 1 (D1), Day 10 (D10), Month 1, and Month 3. Training on the application of both devices will be provided. An overview of the study design is shown in Figure 1.

Figure 1: Study design



The Study Procedures are described in Protocol Section 7.1.2.

5.2 Sample size

Assuming a dehiscence rates of 3.05% for MAR-CUTIS and 0.85% for Dermabond Advanced, 189 subjects (2:1, 126 MAR-CUTIS vs 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.

The assumed noninferiority margin of 8% is based on an average of dehiscence rates observed in previous studies, e.g. 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).

5.3 Randomization

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 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 (i.e., wound type having more importance than the other two 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 treating physician 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 vs. types IV to VI)
- By age group (aged 2 to 21 years and ≥22 years)

Additionally, center will be considered as a further randomization factor as recommended by ICH E9.

6 OVERVIEW OF PLANNED ANALYSES

6.1 Final analysis

The final analysis will be performed after all subjects have completed the trial, and the data has been hard locked. The results of the final analysis will be the basis for the integrated clinical trial report (ICTR).

7 DOCUMENT AND CHANGE HISTORY

7.1 Changes in analysis compared to the trial protocol

Change from protocol	Rationale for change
Determination of Sample Size	The assumed dehiscence rates for the determination of sample size have been described more clearly. Moreover, the text has been revised, and further information about the choice of the assumed dehiscence rates and noninferiority margin were added. These changes will be implemented in the upcoming protocol amendment.
Randomization	Additional text was added in Section 5.3 to clarify the setting up of the dynamic allocation, and preparation of the subject before randomization.
Adding center as randomization factor	Although not specifically mentioned in the protocol, center has been added in the randomization process as recommended by ICH E9. This change will be implemented in the upcoming protocol amendment.
Per Protocol Set (PPS)	The PPS was added in Section 9.5 to perform a sensitivity analysis of the primary efficacy. This change will be implemented in the upcoming protocol amendment.

8 ANALYSIS CONVENTIONS

8.1 General principles

If two of the analysis sets as defined in the SAP coincide, presentations will only be prepared for one analysis set.

All presentations will be done by treatment group and overall, and by visit where applicable.

The data collected and derived in the trial will be presented in subject data listings sorted by subject number and treatment.

Data collected in this trial will be summarized according to their nature as follows:

- Continuous variables: number of non-missing observations, arithmetic mean, standard deviation (SD), minimum (Min) and maximum (Max) values, median, and first (Q1) and third (Q3) quartiles. If there are less than 5 observations, descriptive statistics will be presented based on the rules specified in Section 16.1.1.2.
- Categorical variables: absolute and relative frequencies. If not defined otherwise, the percentage denominator will be the number of subjects still in the trial (including missing values) at the respective time point in the analysis set. The category missing will only be displayed if missing values occur. Categories with a frequency of 0 will not be presented if not otherwise specified.

Medical terms (e.g., prior and concomitant diseases, adverse events) will be coded via Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or latest version before the database is locked. For the analysis, the primary System Organ Class (SOC) will be used. Medications will be coded according to World Health Organization Drug Dictionary (WHO-DD) version March 2018 or latest version before the database is locked.

Shells for summary tables, subject listings, and figures are described in a separate document, which is included as an Appendix to the SAP. Templates for each unique table, listing, and figure are provided. These provide only a draft indication of the content and appearance of the tables, listings, and figures, and the final output may vary in appearance from these templates.

All statistical analyses will be performed using SAS statistical software version 9.4 or higher (SAS Institute, Cary, NC).

Table 1 shows the use of analysis sets in different analyses as defined in Section 9.

Table 1: Use of analysis sets

	Enrolled Set	Allocated Set	SAF	FAS
Subject disposition	X	X		
Discontinuations			X	
Protocol deviations			X	
Demographics			X	X
Other baseline characteristics			X	X
Subject medical history			X	
Previous and concomitant medication			X	
Exposure			X	
Compliance			X	
Primary endpoint			X	X
Secondary endpoints				
Secondary efficacy endpoints			X	X
Wound infection			X	X
Adverse events	X		X	
Laboratory values			X	
Other safety assessments			X	

FAS = Full Analysis Set, SAF = Safety Analysis Set

8.2 Definitions

8.2.1 Definition of subgroups

For selected outcomes (specified in the following sections), descritptive statistics will be summarized for the following subgroups: type of wound (incision/laceration), skin type (Fitzpatrick skin types I to III/types IV to VI) and age group (pediatric 2 to <22 years/adult ≥22 years).

8.2.2 Further definitions

Baseline	Baseline is defined as the last observation (scheduled or unscheduled) before application of the IMD (i.e., D0), if not otherwise specified.

Investigational Medical Devices (IMD)	- MAR-CUTIS: a polyurethane-based skin adhesive, used for topical closure of incisions and surgical wounds replacing the last dermal suture line. - Dermabond Advanced: a topical skin adhesive used to hold closed easily approximated skin edges of wounds from surgical incisions, and simple, thoroughly cleansed, trauma-induced lacerations.
On-treatment-period	After the start of the application of the IMD (D0) until the end-of-treatment visit (Month 3).
Pre-treatment-period	Before the start of the application of the IMD, i.e. D-21 to D0.
Trial completers	Trial completers will complete the screening-presurgical examination visit (Day -21 to D0), the D0 visit, and at least the Month 3 follow-up visit.

9 SUBJECT POPULATIONS

9.1 Enrolled Set

The Enrolled Set includes all subjects who signed the informed consent form.

9.2 Allocated Set

The Allocated Set includes all subjects who are allocated to treatment. Presentation of the Allocated Set will be conducted according to the allocated treatment.

9.3 Safety Set

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.

9.4 Full Analysis Set

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 efficacy assessment. Subjects from the FAS will be analyzed under the randomized treatment group.

9.5 Per Protocol Set

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 DISPOSITION

10.1 Subject disposition

All presentations for subject disposition will be by treatment group and overall.

For describing the subject disposition, the following populations will be summarized overall and for the subgroups described in Section 8.2.1.

- Subjects enrolled (only overall).
- Subjects enrolled but not allocated and reason for non-allocation.
- Subjects allocated.
- Subjects allocated but not treated and the reasons for not being treated.
- SAF.
- FAS.
- Trial completers.
- Subjects allocated and discontinued from the trial.

For subjects enrolled but not allocated and for the reasons for not being allocated, the percentage denominator will be the number of enrolled subjects. For the reasons for not being treated for subjects allocated but not treated, the percentage denominator is the number of allocated but not treated. For all other calculations, the percentage denominator will be the number of allocated subjects.

In addition, an overview table will be prepared presenting the number of subjects enrolled, allocated, in the SAF, and in the FAS per country. Percentage calculation will be done in 2 ways:

- Denominator will be the number of all allocated subjects.
- Denominator will be the number of allocated subjects in the respective country.

Reasons for exclusion from the analysis populations will be summarized. The percentage denominator will be the number of subjects allocated.

10.2 Subject discontinuations

Discontinuations from the trial will be presented for the SAF overall.

Reasons for discontinuations from the trial will be presented for

- Subjects discontinued from the trial.
- Subjects discontinued from the trial for the subgroups described in Section 8.2.1.

Percentage denominator will be the number of subjects discontinuing in the respective group.

The details for “other reasons” will be listed and included in the subject discontinuation frequency table, if applicable.

10.3 Protocol deviations

Major protocol deviations will be presented overall and by center for the SAF. They will be grouped into categories as collected and summarized descriptively.

Major protocol deviations will be presented in a subject data listing.

11 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

No statistical tests for comparison of demographic and baseline data between treatment groups will be performed.

Subject demographics and baseline characteristics will be summarized descriptively by treatment group and overall. Subject demographics and other baseline characteristics will be descriptively summarized for the SAF and the FAS. An additional summary will be provided by country for the SAF and FAS. Subject demographics will also be presented for the enrolled set; presentation will be without treatment group but only for overall.

11.1 Subject demographics

Subject demographics are age [years], weight [kg], height [m], body mass index (BMI) [kg/m^2], sex, race, ethnicity and age group. All data will be reported as recorded in the e-CRF.

Age groups will be ≥2 years and <12 years, ≥12 years and <18 years, ≥18 years and <65 years, ≥65 years and <85 years, and ≥85 years. Additionally, as a separate block also the age groups pediatric ≥2 years and <22 years and adult ≥22 years will be presented.

11.2 Other baseline characteristics

The remaining other relevant baseline characteristics will be descriptively summarized:

Continous baseline characteristics are: length of target wound.

Categorical baseline characteristics are: Skin type, type of target wound, current smoking status, alcohol abuse and if the target wound required deep suturing.

11.3 Subject medical and surgical history

Diseases and surgical interventions are presented as “prior” or “concomitant” as documented by the investigator (i.e., “concomitant” will be documented as “Ongoing” in the e-CRF).

Medical and surgical history will be summarized and sorted alphabetically, separately for prior and concomitant, by SOC and Preferred Term (PT). The number of subjects will be displayed for each SOC and PT.

The target wound description (for incisions and lacerations) will be recorded in the e-CRF, summarized and listed.

11.4 Prior and concomitant medication

Prior and concomitant medication is collected in the e-CRF as per enrollment. For the analysis, the following algorithm will be used to define prior and concomitant medication:

- Prior is all medication stopped before the start of the application of the IMD, regardless of its start date.
- Concomitant is any medication not stopped before the start of the application of the IMD, regardless of its start date or medication started after the start of the application of the IMD.

Medication will be summarized and sorted alphabetically separately for prior and concomitant medication by Anatomical Therapeutic Chemical categories (Level 2: pharmacological or therapeutic subgroup and Level 3: chemical or therapeutic or pharmacological subgroup).

For each medication, the number of subjects will be displayed. In addition, for concomitant medication the number of subjects with medication taken while the glue remains attached (i.e., the glue is not detached nor intentionally removed) will be displayed in the same summary table.

Medication started after the the glue is detached or intentionally removed will be flagged in the subject data listing.

12 EXPOSURE AND COMPLIANCE

12.1 Exposure

Exposure to the IMD will be presented in days and summarized for each subject using the following formula:

Treatment exposure = date and time of glue detachment or removal – date and time of application of the IMD

For the formula above, the time of glue detachment or removal will be used only if it is recorded in the e-CRF (recorded for on-site assessments, but not recorded for the subject diary).

If no glue detachment or removal was applicable, the exposure will be calculated instead with the formula:

Treatment exposure = date of study completion or early withdrawal – date and time of application of the IMD

Treatment exposure will be reported in days rounding to one decimal place.

Treatment exposure will also be assessed using the following (as recorded in the e-CRF for IMD application and performance):

- Number of syringe(s) used for glue application
- Total volume used (mL)

12.2 Compliance

The IMD will only be applied on Day 0 by the medical practitioner. The type of IMD and , whether the IMD was applied to the target wound will be recorded in the e-CRF and summarized descriptively.

Additionally, a summary of the wound exposure to water will be presented including whether the wound was exposed and the number of days. This summary will be presented separately for subjects with or without early glue detachment or removal.

12.3 Device performance and deficiency

Detailed instructions and training on the application of MAR-CUTIS and Dermabond Advanced will be provided to each investigational center.

The performance of the IMD in each subject will be recorded in the e-CRF. Additionally, the device deficiency (due to e.g. malfunction or user error) and the early glue detachment of removal (as well as the reasons and timing) will be assessed. All data will be presented in subject listings.

For device performance, the following variables will be summarized descriptively: overall performance of the IMD, whether any AE/SAE occurred during application or since the last visit, and if the correction of adhesive was performed (and if done within the stipulated time).

For device deficiency, the following variables will be summarized descriptively: any deficiency occurred with the IMD during the application or at subsequent visits, type of deficiency, whether the deficiency lead to a serious deterioration of the subject's health, description of deficiency, and location where the incident occurred.

12.4 Premature and/or unintentional detachment of glue

The premature and/or unintentional detachment of the glue will be recorded in the e-CRF. All data will be listed. The following variables will be summarized descriptively: whether the glue was prematurely or unintionally detached and the surrounding condition at time of detachment.

13 EFFICACY ANALYSES

13.1 Primary endpoint

The primary efficacy endpoint is the total dehiscence rate of target incision/laceration assessed until the Day 10 visit. For this analysis, all evaluations of dehiscence until Day 10 (at Day 1, Day 10 or other unscheduled visits before Day 10) will be included in the analysis.

13.1.1 Main analysis

The primary efficacy analysis will be performed on the FAS population. All subjects should be treated under equal conditions at all centers and no center-specific variance effects are considered.

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 (i.e., 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.

In the context of the primary endpoint, dehiscence will be defined as "Yes" if the treated wound shows dehiscence until Day 10, or "No" if the wound remains closed. Thus, if the wound is assessed as showing dehiscence at Day 1 but showing no dehiscence at Day 10, dehiscence will be evaluated as "Yes" in the main analysis.

To minimize any possible user bias in the dehiscence rates, investigational centers will provide adequate training to all device users in cooperation with the sponsor. The evaluation of dehiscence, as well as the dehiscence classification and classification according to their grade will be recorded in the e-CRF.

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%, i.e.

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

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 (MLEs) 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 (pediatric with age between 2-21 years; adult with age ≥ 22 years), type of wound (incision; laceration) and treatment (MAR-CUTIS; Dermabond Advanced) as explanatory variables. The model will be estimated in SAS using proc logistic and the LSMEANS statement with the option OBSMARGINS, in order to specify a potentially different weighting scheme for the computation of the MLE coefficients across classification effects. The weighting scheme will be the same as in the analysis data set (default use of option OBSMARGIN).

The MLEs of the treatment effect obtained with the logistic regression will provide the logit estimates for both treatments, defined as:

$$\text{logit}_{\_M} = \log(p_{\_M} / (1 - p_{\_M}))$$

$$\text{logit}_{\_D} = \log(p_{\_D} / (1 - p_{\_D}))$$

for MAR-CUTIS and Dermabond, respectively. Thus, by transforming the MLEs to the linear scale, estimates of the Odds are given with:

$$\text{Odds}_{\_M} = p_{\_M} / 1 - p_{\_M}$$

$$\text{Odds}_{\_D} = p_{\_D} / 1 - p_{\_D}$$

for $p_{\_M}$ and $p_{\_D}$. Therefore, estimated event probabilities for $p_{\_M}$ and $p_{\_D}$, denoted by $p_{\_M}^*$ and $p_{\_D}^*$, can be obtained with:

$$p_{\_M}^* = \text{Odds}_{\_M} / (\text{Odds}_{\_M} + 1)$$

$$p_{\_D}^* = \text{Odds}_{\_D} / (\text{Odds}_{\_D} + 1).$$

After the event probabilities defined above are estimated by fitting the logistic regression model with the event of interest given by Dehiscence occurrence (i.e., if Dehiscence='Yes' then event=1), the inverse probabilities denoted by q_M^* and q_D^* can be obtained as:

$$q_M^* = 1 - p_M^*$$

$$q_D^* = 1 - p_D^*$$

for MAR-CUTIS and Dermabond, respectively. Using these four estimated probabilities, it is possible to construct a contingency table of the form:

	Dehiscence = No (0)	Dehiscence = Yes (1)
Treatment = Dermabond	$N_D \times q_D^*$	$N_D \times p_D^*$
Treatment = MAR-CUTIS	$N_M \times q_M^*$	$N_M \times p_M^*$

where $N_M$is the number of subjects treated with MAR-CUTIS, and $N_D$is the number of subjects treated with Dermabond.

Based on this contingency table, a comparison of the response rates of both treatments using the method of Farrington-Manning (FM; Farrington and Manning, 1990) will be performed. The FM estimate for the standard error, the p-value of the FM test regarding non-inferiority, and the two-sided 90% confidence interval (CI) for the difference in dehiscence rates will be obtained and reported.

Non-inferiority of MAR-CUTIS compared with Dermabond Advanced will be declared if the p-value of the FM test is significant at the level alpha=0.05 and the upper limit of the two-sided 90% CI is below the non-inferiority margin of 8%.

Subjects with problems of wound closure are expected to attend the Day 10 visit to see the investigator and assess the wound status. If the subject is unable to attend the Day 10 visit on-site, he/she will be contacted by phone to obtain the information to assess wound closure. For the primary endpoint main analysis on the FAS, any missing data will be imputed as follows:

- Subjects with a provided reason for not attending Day 10 visit related to problems with the wound closure will be counted as failure, i.e. the subject experiences a dehiscence (Dehiscence="Yes")

- Subjects with a dehiscence experienced and recorded before the Day 10 visit (Day 1 or unscheduled visit) will be counted as failure, i.e. the subject experiences a dehiscence (Dehiscence="Yes")

- All other subjects (e.g., lost to follow-up with no dehiscence before) will be counted as a success, i.e. the subject experiences no dehiscience up to Day 10 (Dehiscence="No"), since it is expected that subjecs with problems of wound closure would 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.Descriptive statistics of the evaluation, grading and classification of dehiscence as recorded in the e-CRF and following the imputation rule will be presented for overall and the sub-groups described in Section 8.2.1.

Convergence of model fit

Following Mallinckrodt et al. (2008) we prespecify a fixed sequence of measures to further increase stability of the model to ensure convergence of the primary analysis model. The following prespecified fixed sequence will be applied until a converging model is found:

1. Fit a logistic regression model to the dehiscence rates using the treatment, age group, and skin type and type of wound as explanatory variables

2. Fit a logistic regression model to the dehiscence rates using the treatment, age group, and type of wound as explanatory variables.

3. Fit a logistic regression model to the dehiscence rates using the treatment and type of wound as explanatory variables.

4. Fit a logistic regression model to the dehiscence rates using treatment as explanatory variable

The first converging model in this sequence will be the primary analysis model. This testing sequence is defined based on the expected clinical relevance of the respective explanatory variables. Moreover, this approach is consistent with the dynamic allocation algorithm implemented for the randomization (see Section 5.3 for more details).

13.1.2 Sensitivity analysis

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 subjects with missing data for the primary efficacy analysis as experiencing “Yes” dehiscence (i.e., the wound did not remain closed). This analysis will be performed using the FAS. Descriptive statistics of dehiscence assessment following this second imputation rule will be added to the dehiscence descriptive statistics summary described in Section 13.1.1.
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 2-21 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.

13.2 Secondary endpoints

The following secondary efficacy endpoints will be analyzed in the study:

1) Total dehiscence rate of target incision/laceration assessed at the Month 1 visit.
2) Subject completed POSAS done at the Month 1 and Month 3 visits.
3) Wound infection incidence between both treatment groups, with two analyses:
    3.1) Wound infection incidence assessed at the Day 10, Month 1, and Month 3 visits.
    3.2) Wound infection assessed on a binary scale
4) Evaluation of the medical practitioner satisfaction with the Device, with two analyses:
    4.1) Investigator completed POSAS done at the Month 1 and Month 3 visits.
    4.2) Investigator completed mHCS at Day 10 and Month 1 visits.
5) Evaluation of the subject comfort with the Device during and after treatment.
6) Evaluation of the medical practitioner overall satisfaction and ease of use with the Device during and after the closure of the target surgical incision/laceration.

All analyses for secondary endpoints will be performed on the FAS.

13.2.1 Total dehiscence rate at Month 1

The total dehiscence rate of target incision/laceration assessed at the Month 1 visit will be analyzed descriptively only by using the same descriptive statistics described in Section 13.1.1. For this analysis, all evaluations of dehiscence until Month 1 (at Day 1, Day 10, Month 1 or other unscheduled visits before Month 1) will be included in the analysis. Thus, if the wound is assesed as showing dehiscence at Day 1 or Day 10 but showing no dehiscence at subsequent visit(s), dehiscence will be evaluated as “Yes”.

13.2.2 Subject completed POSAS

The Patient and Observer Scar Assessment Scale (POSAS) is a questionnaire developed to assess scar quality which contains 6-item scales (observer and patient scale), both of which are scored on a 10-point rating scale. Moreover, each scale has an overall “opinion” to compare the pain and itching of the scar compared to normal skin (with a value of 1 indicating no pain and no itching, and a value of 10 indicating worst scar imaginable with pain and itching).

The subject completed POSAS will be recorded in the e-CRF at Month 1, Month 3 and the Early Discontinuation (ED) visit. For the analysis of this endpoint, descriptive statistics of each of the 6-item scales plus the overall "opinion" will be presented by visit.

13.2.3 Wound infection

Wound infection evaluation, diagnosed according to the CDC criteria for surgical site infection, will be assessed by a treating physician and recorded in the e-CRF.

13.2.3.1 Wound infection incidence at Day 10, Month 1 and Month 3

Wound infection incidence, evaluated through the presence of erythema, edema, pain at rest or elevated temperature, will be summarized with descriptive statistics at the Day 10, Month 1, and Month 3 study visits.

13.2.3.2 Wound infection evaluated with a binary scale

Wound infection will be additionally assessed at the same timepoints by calculating a Wound Infection Score utilizing a binary scale as follows:

Wound Infection Score = $I_{erythema} + I_{edema} + I_{pain\_rest} + I_{elevated\_temperature}$,

where the four indicator variables above are equal to 1 if the wound reported the presence of erythema, edema, pain at rest or elevated temperature, and equal to 0 if the presence of each category is not recorded or is missing. Thus, the Wound Infection Score will have a maximum value of 4, and a minimum value of 0.

Descriptive statistics of the Wound Infection Score will be presented by visit.

13.2.4 Evaluation of the medical practitioner satisfaction with the Device

The satisfaction of the medical practitioner with the cosmetic outcome after the closure of the target surgical incision/laceration will be evaluated with the two questionnaires described below.

13.2.4.1 Investigator completed POSAS

The investigator completed POSAS will be recorded in the e-CRF at Month 1 and Month 3. Similarly as for the subject completed POSAS described in Section 13.2.2, this questionnaire contains a 6-item scale and an overall "opinion" to compare the pain and itching of the scar after the closure of the surgical incision/laceration. Additionally, the investigator completed POSAS also contains a categorization of each parameter to describe further the state of the scar.

For the analysis of this endpoint, descriptive statistics of each of the 6-item scales, the categorization of each parameter and the overall "opinion" will be presented by visit.

13.2.4.2 Investigator completed mHCS

The investigator completed Modified Cosmesis Scale (mHCS) contains 6 wound characteristics measurements to describe the scar after wound closure. Each characteristic is graded on a 0 (no/good) or 1 (yes/poor) point scale. A total cosmetic score is derived by the addition of the six characteristic-scores. The mHCS will be analyzed as recorded in the e-CRF at Day 10 and Month 1.

For the analysis of this endpoint, descriptive statistics of each of the six characteristic-scores and the total cosmetic score will be presented by visit.

13.2.5 Subject comfort with the Device

A subject-completed questionnaire to evaluate the comfort with the Device during and after treatment will be done at the Day 10 and Month 1 visits, and recorded in the e-CRF.

The questionnaire for Day 10 contains two main blocks of questions:

- The first block examines the wound pain experienced at the area of the wound, and should be completed with a value between 0 and 100 to rate the wound pain.
- The second block consists of 5 yes/no questions that evaluate the subject's experience and ease of use with the Device.

The questionnaire for Month 1 also contains two main blocks of questions:

- Similarly as for the questionnaire at Day 10, the first block examines the wound pain experienced.
- The second block consists of 2 yes/no questions that evaluate the subject's satisfaction and preference with the use of the Device.

Descriptive statistics for each question of both questionnaires will be presented for the analysis of this endpoint.

The complaints with the the device recorded in the Subject e-diary will be listed.

13.2.6 Medical practitioner overall satisfaction and ease of use with the Device

For the evaluation of the overall satisfaction of the medical practitioner with the Device during and after the closure of the target surgical incision/laceration two questionnaires will be applied:

1) Product-related questionnaire for Investigators, to be completed for each center when the last randomized subject at the center completes the D10 visit. The same questionnaire will be completed for both MAR-CUTIS and Dermabond.

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

2) Subject-related questionnaire for Investigators, to be completed at the Day 0 and Month 1 visits, and recorded in the e-CRF.

   - The questionnaire for Day 0 consists of 5 yes/no questions that assess the investigator's experience applying the adhesive (i.e., easy to use, fast, without complications, time saving and reduced efforts).
   - The questionnaire for Month 1 consists of a visual analog scale that rates usability of the product from 1 to 100, and two questions that evaluate the experience with the adhesive and the pain or burning at the time of application. Moreover, it also contains additional questions to describe the event of a premature removal of the adhesive.

Descriptive statistics for each question of both questionnaires will be presented for the analysis of this endpoint.

13.3 Additional exploratory analysis

For secondary endpoints only, the following additional analysis will apply: if the assessment is performed at the ED visit, descriptive statsitics for the ED visit and the combined ED plus last planned assessment (at visit Month 1 or Month 3) will also be presented.

14 SAFETY ANALYSES

No statistical tests for comparison of safety data between treatment groups will be performed.

Safety data will be summarized descriptively by treatment group and overall.

All safety data will be presented for the SAF unless otherwise specified.

14.1 Adverse events

A treatment emergent adverse event (TEAE) is defined as any adverse event that, based on start date information, occurs in the on-treatment-period as defined in Section 8.2.2. This includes any events related to the procedures, the IMD, or the comparator.

A pre-treatment non-TEAE is an adverse event starting in the pre-treatment period as defined in Section 8.2.2.

A serious adverse event (SAE) is any untoward medical occurrence of teffect that:

- Led to death, or
- Led to serious deterioration in the health of the subject, or
- Led to fetal distress, fetal death, or a congenital abnormality or birth defect.

This includes device deficiencies that might have led to a SAE. More details on the definition of SAEs are available in Protocol Section 9.3.1.

If there are partial dates or times, an adverse event will be considered treatment emergent unless the information available will clearly exclude it. Further details can be found in Section 16.1.4.1.

Assignment of TEAEs to treatment will be based on the definition of the on-treatment-period given in Section 8.2.2, thus, TEAEs occurring during the on-treatment period are assigned to the respective treatment.

The causal relationship of TEAEs to IMD is categorized as follows:

Category	Assessment by investigator
Related	probable certain/very likely possible
Not related	unlikely unrelated

An Adverse Device Effect (ADE) is an AE related to the use of an IMD. This includes any AE resulting from insufficiencies or inadequacies in the instructions for use, deployment, implantation, installation, operation or any malfunction of the IMD. ADEs are a subset of TEAEs.

An ADE that results in any of the consequences characteristic of a SAE will be considered as a serious ADE.

Serious ADEs which by its nature, incidence, severity or outcome have not been identified in the current version of the MAR-CUTIS risk analysis report or Instructios for use for Dermabond Advance (see Protocol Section 15.2 for more details) will be considered as unanticipated ADEs. Anticipated ADAs are defined as events that have been previously identified in applicable product information.

The following overview tables will be generated by treatment group and overall.

1. Summary of the number and percentage of subjects with at least 1of the following events, and of summary of the number and percentage of TEAEs for:
    - TEAEs.
    - Serious TEAEs.
    - Non-serious TEAEs.
    - TEAEs leading to withdrawal from the trial.
    - ADEs.
    - Serious ADEs.
    - ADEs leading to withdrawal from the trial.
    - Anticipated/Unanticipated ADEs
    - TEAEs/ADEs with fatal outcome.

The percentage denominator will be the number of subjects by treatment group in the SAF, or the number of TEAEs, respectively.

14.1.1 Incidence, incidence rates and number of events

The incidence of an adverse event is defined as the number of subjects with occurrence of this adverse event during the period of interest.

The incidence rate (crude incidence rate [CIR]) of an adverse event is defined as the number of subjects with occurrence of this adverse event during the period of interest divided by the total number of subjects N in the respective group (e.g., treatment group).

The incidence, incidence rate, the number of events, and the percentage of events will be summarized by PT (sorted by decreasing incidence rate in the MAR-CUTIS treatment group) for:

- TEAEs.
- Serious TEAEs.
- Non-serious TEAEs.
- TEAEs leading to withdrawal from the trial.

- ADEs.
- Serious ADEs.
- ADEs leading to withdrawal from the trial.
- Anticipated/Unanticipated ADEs.

Percentages will be calculated related to the total number of subjects/events presented in the respective table e.g., for the presentation of PTs for serious TEAEs percentages will be related to the number of subjects with serious TEAE/the total number of serious TEAEs, respectively.

For serious TEAEs, percentages will additionally be presented related to the total number of all subjects/events, respectively.

All tables above will be presented only for incidence rates greater than or equal to 2% in any treatment group.

The incidence, incidence rate, the number of events and the percentage of events will be summarized by SOC and PT (sorted alphabetically) for each:

- TEAEs.
- Serious TEAEs
  - Fatal TEAEs.
- Non-serious TEAEs.
- TEAEs leading to withdrawal from the trial
- ADEs
- Serious ADEs
  - Fatal ADEs.
- ADEs leading to withdrawal from the trial.
- Anticipated/Unanticipated ADEs.

Percentages will be calculated related to the total number of subjects/events presented in the respective table e.g., for the presentation of SOC and PT for serious TEAEs percentages will be related to the number of subjects with serious TEAE/the total number of serious TEAEs, respectively.

For serious TEAEs, percentages will additionally be presented related to the total number of all subjects/events, respectively.

If more than 10% subjects are withdrawn from the trial due to TEAE, the incidence and the incidence rate of TEAEs leading to withdrawal from the trial will be summarized by SOC and PT.

For all enrolled subjects, the incidence, incidence rate, the number of events and the percentage of events (related to the total number of events) will be summarized by SOC and PT (sorted alphabetically) for each:

- Pre-treatment non-TEAEs.
- Serious pre-treatment non-TEAEs.

Presentation will only be overall and not per treatment.

The number and percentage of events will be summarized by SOC and PT (sorted alphabetically) for the following TEAE /ADEs descriptors. Presentation will be for TEAEs / ADEs only:

- Intensity: mild, moderate, severe.
- Outcome: recovered, not yet recovered, recovered with sequelae, death, unknown.
- Action taken with the IMD: none, medication or therapy provided, IMD removed, concomitant medication changed, other.

Denominator for percentage calculation will be the number of all TEAEs / ADEs for presentation of overall SOCs, and the number of TEAEs/ADEs per SOC or PT respectively, for the presentation per SOC or PT, respectively.

Measures of location and variation will be calculated for:

- Duration of TEAEs.
- Time to onset of TEAEs.

The following listings will be produced for all enrolled subjects:

- Deaths.
- Serious adverse events other than death.
- Adverse events leading to withdrawal from the trial.

14.2 Laboratory assessments

A urine β-HCG pregnancy test will be performed at baseline (D0 visit) only. Results will be listed.

14.3 Wound infection

The analysis of wound infection described in Section 13.2.3 will be repeated for the SAF.

15 REFERENCES

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16 APPENDIX

16.1 Data derivation and analysis rules

The purpose of this section is to give technical details for the implementation of the SAP.

16.1.1 General specifications

16.1.1.1 Percentages and decimal places

If not otherwise specified, the following rules are applied:

- Percentages are presented to 1 decimal point.
- Percentages equal to 0 or 100 are presented as such without a decimal point.
- For descriptive summary statistics, the same number of decimal places as in the raw data are presented when reporting minimum and maximum values, 1 more decimal place when reporting mean, median, quartiles and confidence interval and standard deviation.
- P-values are presented to 3 decimal points. P-values <0.001 will be reported as such.
- Ratios are presented to 3 decimal points.

The above described displaying rules must not be changed (e.g., rounding) for the integrated clinical trial report text and are used 1:1 in the body report as well.

16.1.1.2 Presentation of descriptive statistics

Calculation of mean: if not otherwise specified, the arithmetic mean is used.

Table 2: Presentation of descriptive statistics in clinical trials

Number of non-missing values	n	Missing n	Mean	SD	Min	Q1	Median	Q3	Max	{CI for mean}
0	+	+	-	-	-	-	-	-	-	-
1.2.3.4	+	+	+	-	+	-	+	-	+	-
≥5	+	+	+	+	+	+	+	+	+	+

+ summary statistic will be presented; - summary statistic will not be presented.

CI = confidence interval, Max = maximum, Min = minimum, n = number of values, Q1 = first quartile, Q3 = third quartile, SD = standard deviation

For all ordinary levels of categorical parameters including missing values, both the number and the corresponding percentage is displayed. If no missing values occur at any time point/visit, then the number of missing values can be omitted.

16.1.1.3 Presentation of differences and changes

For differences between MAR-CUTIS and Dermabond, MAR-CUTIS will constitute the minuend and Dermabond the subtrahend.

16.1.1.4 Trial day count

The day of baseline visit is defined as trial Day 0.

Calculate the trial day according to the following rules:

- If date < trial Day 0, then trial day in SDTM = Date – trial Day 0.
- If date ≥ trial Day 0, then trial day in SDTM = Date – trial Day 0 +1.

16.1.1.5 Presentation of units

If applicable, parameters will be displayed together with the used unit of measurement. The unit of measurement is enclosed in square brackets ([ ]).

16.1.1.6 Presentation of dates

Where applicable (e.g., in listings), dates will be displayed in ISO8601 format (example: 2014-09-29T12:16, see CDISC 2013). In case of incomplete dates, both the original value and the imputed value is displayed.

16.1.1.7 Handling of missing values

At each time point/visit, all subjects still in the trial (i.e., subjects who have not been withdrawn from the study) are reported. Missing values will be taken into account as missing in the analysis, unless specified differently (e.g., primary efficacy analysis). The number of observed values and the number of missing values must add up to the number of subjects in the trial at the respective time point/visit.

Unless otherwise specified in the SAP, missing values will not be imputed (with the sole exception of primary efficacy data, as discussed in Section 13.1.1). If missing values are imputed, the result of all imputation strategies and newly derived information must be stored in the ADaM data set.

Imputed values will be listed in the subject data listing and marked as imputed.

16.1.1.8 Visit windows

Recorded data will be analyzed in accordance to the respective visit and the Schedule of Assessments. Time window violations will not be considered.

If an assessments is scheduled at the ED visit, the ED visit will be analyzed together with the last assessment before ED (Month 1 or Month 3) to provide an estimate of the “last assessment”.

16.1.1.9 Conversion of time intervals

If a time interval was calculated in minutes, hours or days and needs to be converted into months or years, the following conversion factors will be used:

- 1 month = 30 days.
- 1 year = 365.25 days.

16.1.1.10 Mandatory tables without data

Recommended tables must be created. If no subject qualifies for the table, the header will be created and the table itself will be replaced by “No subject in this category”.

16.1.1.11 Unscheduled visits

Unscheduled visits are time points not planned in the protocol.

In listings, unscheduled visits will be listed as recorded. All visits will be ordered chronologically including the dates of unscheduled visits.

Unscheduled visits will be excluded from the per time point/visit presentation.

16.1.2 Disposition

16.1.2.1 Subject withdrawal

Reasons for subject withdrawal as specified in the End-of-trial page of the e-CRF will be used.

16.1.2.2 Protocol deviations

Protocol deviations are based on the analysis dataset ADDV. Major protocol deviations are retrieved from the respective SDTM dataset (SDTM.DV.DVCAT). No further protocol deviations are programmed in the analysis datasets for ADDV (if not otherwise specified in the SAP).

16.1.3 Demographics and other baseline characteristics

16.1.3.1 Subject demographics

Derivation of age

Age as derived in SDTM.DM.AGE will be used.

Derivation of BMI:

BMI is extracted from the SDTM.

Derivation of race:

If for race more than 1 entry per subject is documented, a category "multiple" will be created.

16.1.3.2 Prior and concomitant medication

Prior and concomitant medication is collected as of enrollment in the e-CRF and described like that in the trial protocol. For the analysis, the definition as described in the following is used.

The following rules are used to define the categories "prior" and "concomitant" medication.

Pre-requisite is a complete date of application of IMD.

Stop of medication		
Date	**Condition**	**Category**
Complete date is available	Stop date is earlier than date of the start of the application of IMD.	Prior
Missing month	Year of stop date is earlier than year of the start of the application of IMD.	Prior
Missing day	Month/year of stop date are earlier than month/year of the start of the application of IMD.	Prior
Otherwise		Concomitant

Medication ticked in the e-CRF as "ongoing" will be classified as concomitant.

16.1.4 Safety analysis

16.1.4.1 Adverse events

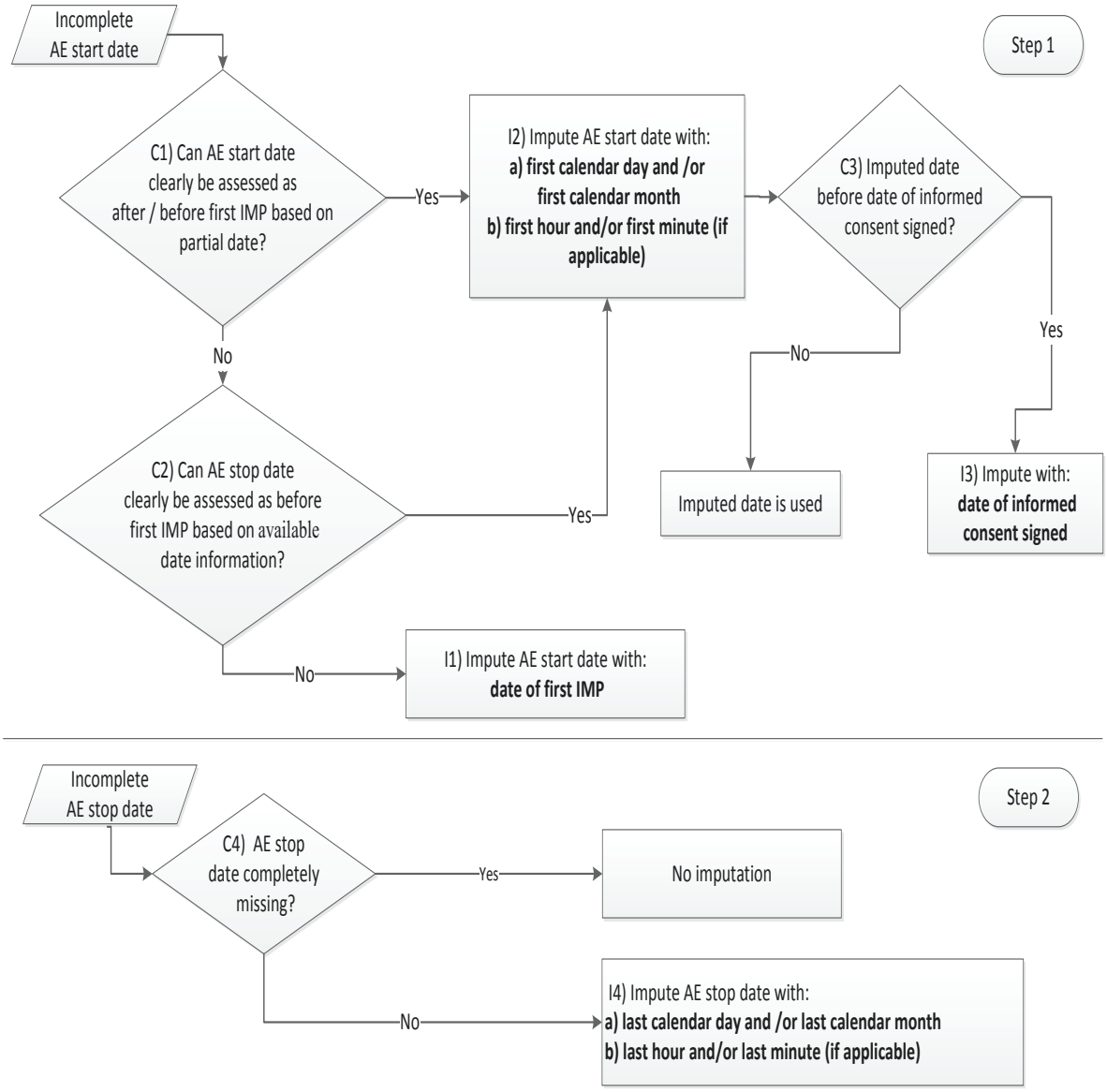
The result of all imputation strategies (e.g., incomplete start dates of adverse events and new derived information (e.g., treatment-emergent flag) must be stored in ADaM data set.

Handling of missing date information

The term missing date refers to a completely missing date or to an incomplete date where parts are not available.

The following imputation strategy is applied.

Missing start and end date will be imputed conservatively, i.e., missing values will be imputed in such a way that the duration of the adverse event is considered with the longest possible duration and such that, whenever the adverse event may potentially start after first IMD application, the adverse event will be handled as a TEAE.



I1-I4: imputation steps
C1-C4: checkpoints
AE = adverse event, IMP = investigational medicinal product

Figure 2: Graphical overview about the imputation strategy

Further explanations on the flow chart:

The different steps of the displayed imputation strategy must be completed from the first to the last step. All procedures in each step must be completed in the order given.

- Imputation:
  - I1: Impute with date of the start of the application of IMD
  - I2:
    a) Impute with first calendar day and/or first calendar month
    Imputation will be done based on the available partial information starting with month and then day. The respective first month and day will be chosen for imputation:

Missing date	**Imputed date**
2014-Mar	2014-Mar-*01*
2014	2014-*Jan-01*

  - I3: Impute with date of informed consent signed
  - I4:
    a) Impute with last calendar day and/or calendar last month
    Imputation will be done based on the available partial information starting with month and then day. The respective last month and day will be chosen for imputation:

Missing date	**Imputed data**
2014-Mar	2014-Mar-*31*
2014	2014-*Dec-31*

For February leap years must to be taken into account when calculating the last day in February.

1.1.

- Checkpoints
  - C1: The decision must be taken based on the available information (date) before imputation.
  - C2: Adverse event stop date before the start of the application of IMD

1.2. 1) The decision must be taken based on the available information (date) before imputation.

2) If the end date is completely missing (with or without the information that the adverse event was continuing), this will be considered as after the start of the application of IMD.

  - C3: The decision must be taken based on the available information (date) before imputation.
  - C4: The decision must be taken based on the available information (date) before imputation.

A replacement of missing year for adverse event start information is not foreseen. If needed, this will be considered on a case-by-case decision which must be documented together with the documentation of ADaM data sets.

Assessment of TEAEs

The assessment whether an adverse event is a TEAE will be done after replacement of missing date information.

Assignment adverse events to time periods

Assignment of adverse events to time periods will be done after replacement of missing date information.

List of deaths

Death will be identified by outcome of adverse event equals “Death”.

Time to onset of adverse events

Time to onset of adverse events will be calculated based on the start of the application of IMD based on the imputed value for adverse event start date.

Subject experiencing a non-serious treatment emergent adverse event

All subjects who had at least 1 non-serious TEAE will be taken into account regardless of the experience of a serious TEAE.

16.2 List of statistical output documentation

List of outputs:

Total dehiscence rate of target wound assessed until Day 10 (Full Analysis Set)

Total dehiscence rate of target wound assessed until Day 10 - considering wound length (Full Analysis Set)

Total dehiscence rate of target wound assessed until Day 10 - considering imputation of missing values as experiencing Dehiscence (Full Analysis Set)

Total dehiscence rate of target wound assessed until Day 10 - CMH test (Full Analysis Set)

Total dehiscence rate of target wound assessed until Day 10 - considering site effect (Full Analysis Set)