AMENDMENT No. 1 to SAP

Nature of Amendment	Changes in statistical analysis plan version V1
Necessary due to	Changes to the clinical investigation plan (V3 to V4)
Title of Study	An open-label, prospective, comparative human participant study to evaluate the clinically acceptable dressing presence and conformability properties of prototype non-medicated multilayer foam dressings compared to established medical devices.
Sponsor	Smith & Nephew Medical Ltd PO Box 81, 101 Hessle Road, Hull HU3 2BN United Kingdom
Sponsor code.	5025003
SGS proderm Study-No.	HVS2312
EUDAMED -No.	CIV-24-03-046336
Description of Amendment(s)	Changes are shown with underlined words
Page 11, chapter 7: Populations of clinical investigation	It is estimated that 120 evaluable participants randomized to the treatments will be needed to achieve the primary objective. Approximately 150 participants will be screened, expecting a screening failure rate of around 20%. This single-center investigation will be conducted at a clinical research facility located in Germany.
Changed as follows	It is estimated that 135 evaluable participants randomized to the treatments will be needed to achieve the primary objective. Approximately 160 participants will be screened, expecting a screening failure rate of around 20%. This single-center investigation will be conducted at a clinical research facility located in Germany.

[redacted]

[redacted]

Page 32, chapter 12.6:

Sample size and statistical power

The sample size is based on separate non-inferiority tests for (i) Prototype dressing (rectangle) vs Marketed dressing (rectangle); and (ii) Prototype dressing (square) vs Marketed dressing (square), regardless of dressing location, i.e. right or left dressing application site). The alpha level used in the non-inferiority tests will therefore be adjusted to 2.5% for each product comparison.

The assumptions for the Prototype dressing (rectangle) vs Marketed dressing (rectangle) comparison are that of no difference between the products in acceptable dressing presence by day 7. Also assumed is 25% discordant pairs and the proportion of subjects where both dressings are acceptable is at least 60%. Using these assumptions, a sample size of 105 evaluable participants is required to ensure 80% power using Newcombe's score method to show that the upper confidence limit of the 2-sided 97.5% confidence interval, for the difference in proportion of acceptable presence (Marketed dressing (rectangle) – Prototype dressing (rectangle)), is lower than the non-

	inferiority threshold of 15% (%C - %IMD < 15%-point, where %IMD and %C denotes the proportion of devices with acceptable dressing presence for IMD and comparator). The choice of the 15%-point threshold is justified in section 9.3. The same assumptions as above apply to the Prototype dressing (square) vs Marketed dressing (square) comparison and so the same sample size is acceptable, as these products will all be applied to the same participants then 105 total evaluable participants would be sufficient for the aims of both comparisons. Accounting for an approximate 10% lost to follow up rate, 120 participants will be recruited into this clinical study. The sample size was calculated using nQuery + nTerim 3.0 The sample size calculation was provided by sponsor.
Changed as follows	The sample size is based on separate non-inferiority tests for (i) Prototype dressing (rectangle) vs Marketed dressing (rectangle); and (ii) Prototype dressing (square) vs Marketed dressing (square), regardless of dressing location, i.e. right or left dressing application site). The alpha level used in the non-inferiority tests will therefore be adjusted to 2.5% for each product comparison. The assumptions for the Prototype dressing (rectangle) vs Marketed dressing (rectangle) comparison are that of no difference between the products in acceptable dressing presence by day 7. Also assumed is 28% discordant pairs and the proportion of subjects where both dressings are acceptable is at least 60%. Using these conservative assumptions, a sample size of 120 evaluable participants is required to ensure 80% power using Newcombe's score method to show that the upper confidence limit of the 2-sided 97.5% confidence interval, for the difference in proportion of acceptable presence (Marketed dressing (rectangle) – Prototype dressing (rectangle)), is lower than the non-inferiority threshold of 15% (%C - %IMD < 15%-point, where %IMD and %C denotes the proportion of devices with acceptable dressing presence for IMD and comparator). The choice of the 15%-point threshold is justified in section 9.3. The same assumptions as above apply to the Prototype dressing (square) vs Marketed dressing (square) comparison and so the same sample size is acceptable, as these products will all be applied to the same participants then 120 total evaluable participants would be sufficient for the aims of both comparisons. Accounting for an approximate 10% lost to follow up rate, 135 participants will be recruited into this clinical study. The sample size was calculated using nQuery + nTerim 9.3.0 The sample size calculation was provided by sponsor.

Page 33, chapter 12.7: Randomisation	The following aspects are considered for the generation of the randomization list: • Patients will be assigned a 3-digit randomization number from 001 to 120 (based on the 120 planned participants) • One single blinded randomization list for the whole study will be prepared • The randomization list will be uploaded to Trial Master File in a pre-specified format.
Changed as follows	The following aspects are considered for the generation of the

randomization list:

- Patients will be assigned a 3-digit randomization number from 001 to 135 (based on the 135 planned participants)
- One single blinded randomization list for the whole study will be prepared
- The randomization list will be uploaded to Trial Master File in a pre-specified format.

Page 39-42, chapter 18: Overview

[Interpretation of table]
Method of explorative superiority analysis for

- Acceptable dressing presence (page 40)
- Presence of dressings (page 40)
- Dressing comfort (page 41)
- Ease of application/removal (page 42)

was defined as “McNemar” test.

Changed as follows

[Interpretation of table]
Method of explorative superiority analysis for

- Acceptable dressing presence (page 40)
- Presence of dressings (page 40)
- Dressing comfort (page 41)
- Ease of application/removal (page 42)

was defined as “Mixed logistic regression” test.

Reason/Justification for Change:

Sample Size:

Across 2023-2024 there have been 11 Smith & Nephew internal volunteer studies (VS) conducted on prototype wound dressings related to the devices used in the HVS2312 VT (CIV-24-03-046336), whereby the 11 VS were completely independent and detached from the HVS2312 VT. These ethically-approved internal VS include a small number of healthy volunteers and provide confidence for important research and development questions. The purpose of the latest internal VS performed in October 2024, was to gain confidence in batch variability versus dressing presence. The data gathered in October was reviewed alongside previous VS data to further inform the statistical assumptions for the HVS2312 VT.

As described in the protocol (CIP section 13), analysis of the internal VS data suggested the possibility of slightly different values for the paired performance between prototype and marketed dressings according to different manufacturing lots of each. The changed assumptions were considered from a conservative point of view as a 3% increase in discordant pairs in the current HVS2312 VT (CIV-24-03-046336) protocol and led to a slight increase in the required participants-to-complete and therefore also in the final sample size.

Change of Analysis method:

The change of analysis method for the exploratory endpoint was made

because mixed logistic regression is a more advanced method that makes better use of the information in the data.

Impact of the Changes on the Scientific Validity

☒ This amendment has no impact on the scientific validity or outcome of this study.

Justification:

The marginal increase in discordant pairs has no effect on the scientific validity of the study.

The change in the analysis method only affects the exploratory endpoints and therefore has no effect on the confirmatory statements.

❑ This amendment impacts the study in the following manner

Classification of the Changes for Substantiality

☒ At least one of the changes in this amendment is a substantial change.

☐ All changes of this amendment are non-substantial.

Justification:

Increasing the sample size affects the safety of the participants, as this means that more participants are exposed to the procedure. Furthermore, the increased sample size is used to be able to demonstrate a weaker effect (compared to the initial planning) with the same power, which consequently affects the robustness of the data.

Consequently, the change must be approved by the competent authorities, which was done with the decision of Dr. Anatoli Astvatsatourov (Federal Institute for Drugs and Medical Devices [BfArM]; file number 94.1.02-5660-15200) dated December 12, 2024.

Amendment approved:

Dated signature

Jay Jantz
Director of Global Biostatistics & Data Sciences
Smith & Nephew

Dated signature

David Ruwe
Project Manager
SGS proderm

Dated signature

Eric Bibiza-Freiwald
Project Statistician
SGS proderm

Statistical analysis plan

Title: An open-label, prospective, comparative human participant study to evaluate the clinically acceptable dressing presence and conformability properties of prototype non-medicated multilayer foam dressings compared to established medical devices.

Protocol Version: V4.0, 26NOV2024

Statistical Analysis Plan
Author: Simayi Yusufu, PhD

Sponsor: Smith & Nephew Medical Ltd
PO Box 81, 101 Hessle Road, Hull HU3 2BN
United Kingdom

Sponsor code: HVS2312
EUDAMED number: CIV-24-03-046336

CRO: SGS proderm GmbH
Kiebitzweg 2
22869 Schenefeld/Hamburg
Germany

SGS proderm Study No.: 24.0061-99

Statistical Analysis Plan
Date and Version: 13JAN2025 – Final V2.0

Approval Signature Page

With my dated signature, I declare my approval to the procedures described in this document.

Document approved by	Dated signature
Eric Bibiza, M.Sc. Project statistician SGS proderm GmbH	Signiert von Eric Bibiza Eric Bibiza Ich genehmige dieses Dokument 14 January 2025 | 9:54:03 PM MEZ E00DEC46A3B24545B2C556D9F38DB375
Simayi Yusufu, PhD 2nd statistician and author SGS proderm GmbH	Signed by Simayi Yusufu Simayi Yusufu I am the author of this document 15 January 2025 | 7:53:10 AM CET 06024348F39B4BF6890215A8974354E1
David Ruwe, M.Sc Project manager SGS proderm GmbH	Signed by David Ruwe David Ruwe I approve this document 15 January 2025 | 6:58:53 AM CET 50F53FD888534C4094FA85474FF9C4FD
Michael Howarth, M.Sc. Clinical Study Manager Smith & Nephew	Signed by Michael Howarth Michael Howarth I approve this document 15 January 2025 | 3:58:16 PM CET 6A0D1CAE89294A9AA17DE3C3B2061255
Jay Jantz, PhD Director of Global Biostatistics & Data Sciences Smith & Nephew	Signed by Jay Jantz Jay Jantz I approve this document 15 January 2025 | 11:27:00 PM CET B7D37248838E4CACAE11E7E55198A88D

Version control of statistical analysis plan after final version.

Version	Date	Reason for change / request / changed by
Final V1.0	24OCT2024	-
Final V2.0	13JAN2025	- The sample size was adjusted by a protocol amendment. This adjustment will now be transferred to SAP. - In addition, an analysis method for the exploratory endpoints is being optimized. A detailed and comprehensive list of all changes can be found in amendment no.1.

Note: After the final version, changes are documented as an amendment to the SAP.

Table of contents

1 List of abbreviations

Abbreviation	Description
ADE	Adverse Device Event
ADR	Adverse Drug Reaction
AE	Adverse Event
CI	Confidence Interval
CRF	Case Report Form
CRO	Clinical Research Organization
CIP	Clinical Investigation Plan
DD	Device Deficiency
DRC	Data Review Committee
eCRF	Electronic Case Report Form
ET	Early Termination
FAS	Full Analysis Set
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International Conference Of Harmonisation
IFU	Instructions for Use
IMD	Investigational Medical Device
IMDRF	International Medical Device Regulators Forum
IP	Investigational Product
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MH	Medical History
PP	Per Protocol
PT	Preferred Term
SD	Standard Deviation
SADE	Serious Adverse Device Event
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAP	Statistical Analysis Plan
[redacted]	[redacted]
SOC	System Organ Class
SOP	Standard Operating Procedure
SP	Safety Population
SSSA	Sweating Severity Self-Assessment
TEAE	Treatment Emergent Adverse Events

2 Introduction

The statistical analysis plan (SAP) is a detailed technical extension to the clinical investigation plan (CIP) and follows the principles of the guidelines ICH - E9 and E9 - R1, ISO 14155:2020 and the relevant standard operating procedure (SOP) DMD_MED_1003_000 "Analysis in Medical Trials" of SGS proderm.

All statistical analyses mentioned in the SAP are performed by SGS proderm.

The SAP is based on the following documents:

- Clinical investigation plan "An open-label, prospective, comparative human participant study to evaluate the clinically acceptable dressing presence and conformability properties of prototype non-medicated multilayer foam dressings compared to established medical devices.", final version 3.0, dated 28AUG2024.
- Electronic and annotated case report form (CRF) work version 1.0 dated 30AUG2024.

3 Study design

The clinical investigation is designed as a prospective, open-label, comparative, interventional study with intra individual comparison of two prototype wound dressings (Prototype non-medicated multilayer foam dressing (rectangle and square variants) each against its own respective established wound dressing (either Marketed dressing (rectangle) or Marketed dressing (square) respectively) on healthy intact skin.

4 Study objectives

Primary objective

To demonstrate non-inferiority of the prototype non-medicated multilayer foam dressings (rectangle and square variants) with regards to acceptable dressing presence in human participants at day 7 in the following two comparison pairs:

- Prototype dressing (rectangle) vs Marketed dressing (rectangle) on the knee.
- Prototype dressing (square) vs Marketed dressing (square) on the thigh.

Secondary objectives

The secondary objectives of this investigation are created to generate support data for:

- retention claims for up to 7 days
- dressing presence claims for up to 7 days
- pad integrity claims for up to 7 days
- pad lift claims for up to 7 days
- border lift claims for up to 7 days
- comfort during wear claims for up to 7 days and at dressing removal
- retention claims during joint mobilization including following a physiotherapy session

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

Safety objectives

The safety objectives of this investigation are as follows:

- Descriptive analysis of adverse events
- Descriptive analysis of device deficiencies
- Changes in concomitant medication

5 Schedule of the clinical investigation

Schedule of events	Pre-treatment data (screening)[1] max. 7 days before Day 0	Day 0 assessment	Day 1 assessment[2]	Day 3 assessment[2]	Day 7 (or early termination[14]) assessment[2]
Informed consent	X				
Inclusion and exclusion criteria	X				
Re-check eligibility (in-/exclusion criteria)[3]		X			
Demography and medical history	X				
Pregnancy test (females only) [4]	X	X			
Prior medication/treatment	X				
Sweating Severity Self-Assessment (SSSA)	X				
Physical examination of the skin condition at dressing application site[5]	X	X			
Assessment of hair presence at dressing application site	X	X			
Hair removal at dressing application site	X[6]				
Randomization		X			
Dressing quality control check		X			
Dressing application[7]		X			
Dressing application assessment[8]		X			
Skin assessment		X	X[15]	X	X
Objective dressing assessment[9]			X[16]	X	X
Subjective dressing assessment (dressing comfort, itching)			X[16]	X	X
Extent of dressing exposure to water (including frequency of showers)			X	X	X
Activity assessment[10]			X	X	X
Photographs (of dressing in place and, if required, of any AE / adhesive offset)[11]		X	X[16]	X	X
Physiotherapy session			X		
Dressing removal					X
Subjective dressing removal assessment (pain intensity)					X
Objective dressing removal assessment[12]					X
Adverse event assessment including AEs, ADEs, SADEs, SAEs, device deficiencies		X	X[17]	X	X[13]
Concomitant medication/therapy and changes thereof.	X	X	X	X	X
Early termination assessment					X
End of study/exit					X

1. Screening may be completed at the same visit as Day 0 or at a separate visit up to 7 days before Day 0.
2. Visits on Days 1, 3 and 7 should occur within ± 2 hours of the original dressing application time on Day 0.
3. Eligibility will be rechecked on Day 0 if the screening visit was not performed on the same day.
4. An additional urine pregnancy test will be performed on Day 0 if there are separate visits for Screening and Day 0 and the screening visit was ≥ 5 days before Day 0.

5. An assessment of current skin disease (e.g., eczema, psoriasis), sunburn or skin peeling at the dressing application sites will be performed at the Screening Visit. An additional skin assessment will be performed on Day 0 if there are separate visits for Screening and Day 0.
6. Up to 24 hours prior to dressing application. Hair should be removed 24 hours prior to dressing application using electric clippers. Should the participant regularly wet shave the dressing application sites, they may prepare the site using the wet shave technique (up to 48 hours prior to dressing application), otherwise participants will be instructed to only use electric clippers. If the participant does not have electric clippers, the hair will be removed at the study site on Day 0 following a standard procedure.
7. Dressings will be applied by the investigator or trained site personnel according to the application procedure as described in the IB/IFU. Dressings will be applied to each knee whilst the knee is bent at a 30-degree angle. The thigh dressings will be applied at zero degrees with the legs extended flat.
8. Includes assessment of the following parameters: Adhesive offset on dressing handles and ease of application.
9. Includes assessment of the following parameters: dressing presence, acceptable dressing presence, border lift, pad lift, pad integrity and if dressing removal was required.
10. The participant will be asked what the level of activity they have undertaken since last visit (e.g. crouching/kneeling, mild, moderate, strenuous).
11. Following dressing application, the investigator or trained site personnel will take photographs of all dressing locations, with the leg positioned to achieve the same angle used for dressing application (i.e. knees bent at 30 degree angle for knee dressings and 0 degrees for thigh dressings). Photographs will be taken of dressings in place and, if required, of any AE/adhesive offset at the following time points for documentation purposes:
    - after the initial dressing application by the investigator (Day 0).
    - before and after the physiotherapy session on Day 1.
    - after the dressing assessments on Day 3.
    - before the dressing removal (any day that dressing requires removal).
12. Includes assessment of the following parameters: Ease of removal, adhesive offset on skin, [redacted] prototype dressings only), extent of skin occlusion, extent of erythema and skin stripping.
13. Recording of AEs to be done before and after dressing removal in order to record any unexpected AEs relating to dressing removal which would not be assessed in the objective/subjective dressing removal assessments.
14. Early termination: To be performed in the event of early termination at the early termination visit (ET), which would be timed to coincide with the next scheduled visit. The reason for early termination as well as any AEs that may have occurred should be recorded. Additionally, in the case the reason for early termination was not withdrawal of consent, the following assessments should be performed:

    If dressings still need to be removed then the following should be performed before removal:
    - subjective dressing assessment
    - objective dressing assessment
    - activity assessment

    After removal of the dressing the following should be performed:
    - subjective dressing removal assessment
    - objective dressing removal assessment
15. To be performed before the physiotherapy session.
16. To be performed before and after the physiotherapy session.
17. To be performed after the physiotherapy session.

6 Study centers

This is a single-centre study performed at

SGS proderm GmbH
Kiebitzweg 2
22869 Schenefeld /Hamburg
Germany

6.1 Identification-variable in multicenter study

Not applicable.

7 Populations of clinical investigation

It is estimated that 135 evaluable participants randomized to the treatments will be needed to achieve the primary objective. Approximately 160 participants will be screened, expecting a screening failure rate of around 20%.

This single-center investigation will be conducted at a clinical research facility located in Germany.

8 Analysis Datasets

The review committee decides on the assignment of the participants to the per protocol population (PP), the full analysis set (FAS) or the safety population (SP), before closure (hardlock) of the data base. The different populations are defined as follows.

- Safety population (SP) includes all participants who were included to the study and who received at least either one of the test products, regardless of the number of further assessments.
- FAS includes all participants of SP with at least one post baseline assessment.
- PP includes all participants of FAS who finished the study in accordance with the clinical investigational plan without major clinical investigational plan deviations.

As this study is an open label study, the data review committee (DRC) will only have access to the safety data as part of the decision-making process and will not have access to efficacy/performance data of the primary, secondary or explorative endpoints.

The cleaned data base – inclusive performance data – will be locked before it is transmitted to the study statistician ('closure of data base').

All analyses are carried out on the basis of the intention-to-treatment principle.

9 Target variables

The following variables are recorded in the final database and will be presented adequately in the final report.

9.1 Variables evaluated for efficacy

Objective dressing assessment for all four application sites separately

Primary target variable

- Does the dressing meet the definition of "acceptable dressing presence"? [yes/no]

Other target variable

Dressing presence

- Is the dressing in place? [yes/no]
- Specify the reason if "no" [free text]
- When was the dressing removed/missing? [dd.mm.yyyy]

Objective dressing assessment

- What is the percentage border lift? [0%/1-25%/26-50%/51-75%/76-100%/dressing missing]
- Is there border lift reaching the pad? [yes/no/dressing missing]
- What is the percentage pad lift? [0%/1-25%/26-50%/51-75%/76-100%/dressing missing]
- Is the pad exposed? [yes/no/dressing missing]
- Are there any changes in pad integrity? [0%/1-25%/26-50%/51-75%/76-100%/dressing missing]
- Did the dressing require removal today? [yes/no/dressing missing]
- Specify the reason if "yes" [free text]

Dressing application and assessment

Dressing quality control check

- Packaging of all dressings were intact [yes/no]
- No dressing was damaged [yes/no]
- There are no visual contaminants on any of the dressings [yes/no]
- Specification, if at least one of three questions was answered with no [free text]

Dressing application

- Were all dressings applied according to protocol? [yes/no]
- Specify the dressing, area and reason if not applied according to protocol [free text]

Adhesive offset on dressing handles for all four application sites separately

- Film/oil of silicone residue [none/minimal/slight/moderate/extensive]
- Clear visible bobbling [none/minimal/slight/moderate/extensive]
- Delamination from film [none/minimal/slight/moderate/extensive]
- Was the dressing easy to apply? [yes/no]
- Specify the reason if "no" [free text]

Assessment of skin condition

- How is the condition of the skin in terms of any skin-related adverse events (AEs) and device deficiencies (DDs) assess? [ok/not ok]
- Specify skin condition and application site if 'not ok' [free text]

Subjective dressing assessment, water exposure and activity assessment

Subjective dressing assessment

- Was the dressing comfortable during wear?
    - right thigh [yes/no/dressing missing]
    - right knee [yes/no/dressing missing]
    - left thigh [yes/no/dressing missing]
    - left knee [yes/no/dressing missing]

- Was the dressing itching during wear?
    - right thigh [None/ mild intermittent/mild persistent/moderate/ severe /dressing missing]
    - right knee [None/ mild intermittent/mild persistent/ moderate/severe /dressing missing]
    - left thigh [None/ mild intermittent/mild persistent/ moderate/ severe /dressing missing]
    - left knee [None/ mild intermittent/mild persistent/ moderate/ severe /dressing missing]

Extent of dressing exposure to water

- To what extent did their dressing get wet since the last assessment?
    - right thigh [not at all/splashed/showered/submerged/dressing missing]
    - right knee [not at all/splashed/showered/submerged/dressing missing]
    - left thigh [not at all/splashed/showered/submerged/dressing missing]
    - left knee [not at all/splashed/showered/submerged/dressing missing]

Activity Assessment (for all application sites)

- Kneeling/crouching on the floor with legs beneath them [0 min/<1 h/ 1-6 h/ >6 h]
- mild activity [0 min/<1 h/ 1-6 h/ >6 h]
- moderate activity [0 min/<1 h/ 1-6 h/ >6 h]

- strenuous activity [0 min/<1 h/ 1-6 h/ >6 h]
- Listing of every strenuous activity done by the participant [free text]

Photographs of the dressings

- Photographs of all four dressings done according to protocol? [yes/no]
- Reason and applicable dressing if "no" [free text]

Physiotherapy session

- Lying on back and bending/straightening leg performed according to protocol? [yes/no]
- Specify the reason and the application legs if "no" [free text]
- Lifting leg from chair sitting position performed according to protocol? [yes/no]
- Specify the reason and application legs if "no" [free text]
- Bending and extending knee from chair/bedside sitting position is performed according to protocol? [yes/no]
- Specify the reason and application legs if "no" [free text]
- Bending knee back from standing position is performed according to protocol? [yes/no]
- Specify the reason and application legs if "no" [free text]

Objective dressing assessment - After physiotherapy session

Dressing presence

- Is the dressing in place? [yes/no]
- Specify the reason if "no" [free text]
- When was the dressing removed/missing? [dd.mm.yyyy]

Objective dressing assessment

- What is the percentage border lift? [0%/1-25%/26-50%/51-75%/76-100%/dressing missing]
- Is there border lift reaching the pad? [yes/no/dressing missing]
- What is the percentage pad lift? [0%/1-25%/26-50%/51-75%/76-100%/dressing missing]
- Is the pad exposed? [yes/no/dressing missing]
- Are there any changes in pad integrity? [0%/1-25%/26-50%/51-75%/76-100%/dressing missing]
- Did the dressing require removal today? [yes/no/dressing missing]
- Specify the reason if "yes" [free text]

Acceptable dressing presence

- Does the dressing meet the definition of "acceptable dressing presence"? [yes/no]

Subjective dressing assessment - After physiotherapy session

- Was the dressing comfortable during wear?
    - right thigh [yes/no/dressing missing]
    - right knee [yes/no/dressing missing]
    - left thigh [yes/no/dressing missing]
    - left knee [yes/no/dressing missing]
- Was the dressing itching during wear?
    - right thigh [none/mild or intermittent/mild or persistent/ moderate/ severe /dressing missing]
    - right knee [none/mild or intermittent/mild or persistent/ moderate/ severe /dressing missing]
    - left thigh [none/mild or intermittent/mild or persistent/ moderate/ severe /dressing missing]
    - left knee [none/mild or intermittent/mild or persistent/ moderate/ severe /dressing missing]

Photographs of the dressings - After physiotherapy session

- Photographs of all four dressings done according to protocol? [yes/no]
- Reason and the application dressings if "no" [free text]

Subjective dressing removal and quality assessment for all four application sites separately

- How intense was the pain experienced on dressing removal? [Numerical rating scale with range from 0 to 9 by 1 with 0 as "no pain at all" / dressing missing]

Objective dressing removal

General information

- Were all dressings removed or missing? [yes/no]
- Specify the reason if "no" [free text]

Objective dressing removal assessment for all four application sites separately

- Dressing missing? [yes/no]
- Dressing removed / went missing on [dd.mm.yyyy]
- Extent of skin erythema 5 minutes after removal [no reddening/mild reddening(slight pink) /moderate reddening (red) / severe reddening (beet red)]
- Any sign of blistering 5 minutes after dressing removal [yes/no]
- Was the dressing easy to remove? [yes/no]
- Specify the reason if "no" [free text]
- What was the extent of adhesive offsetting on skin following dressing removal, for each of the following

- Film/oil of silicone residue [none/minimal/slight/moderate/extensive]
- Clear visible bobbling [none/minimal/slight/moderate/extensive]
- Delamination from film [none/minimal/slight/moderate/extensive]

- At the time of dressing removal, was there visible evidence of [redacted] [yes/no/NA]
- Extent of skin occlusion after dressing removal [none/clammy skin/noticeable moisture/whitening of skin/skin breakdown]
- Any visible signs of skin stripping after dressing removal [yes/no]

9.2 Variables evaluated for safety analysis

(Serious) Adverse Events

(Serious) Adverse events [(S)AEs] as reported spontaneously by the participant or observed by the Investigator, recorded in the course of the clinical investigation will be described individually. The following data will be compiled in the (e)CRF:

- Randomization number
- Screening number
- AE number
- Reported term [free text]
- Localization on body [free text]
- Age [years]
- Sex [male/female/diverse]

Relation to product and procedure

- Relation to investigational device [not related/possible/probable/causal relationship/not applicable]
- Relation to investigational procedure [not related/possible/probable/causal relationship/not applicable]
- Spreading in test field(s)? [yes/no]
  - right thigh [yes/no]
  - right knee [yes/no]
  - left thigh [yes/no]
  - left knee [yes/no]
- Is the AE of special interest? [yes/no]

Details

- Onset date unknown [yes/no]
- Onset date and time [dd.mm.yyyy hh:mm]
- Date when investigator was informed [dd.mm.yyyy]
- Pattern [single episode/continuous/intermittent/unknown]
- Time between application and onset [hh:mm:ss]
- Severity [Mild/Moderate/Severe]
- Action taken with study treatment [Medical device removed/none/unknown/not applicable]
- Other action taken [none/none drug therapy/ concomitant therapy altered/other action taken]
- Specify if other action [free text]

Seriousness

- Is event serious (SAR/SAE)? [yes/no]
- Specification
    - death [yes/no]
    - is life threatening illness or injury [yes/no]
    - permanent impairment of a body structure or a body function [yes/no]
    - hospitalization or prolongation of patient hospitalization [yes/no]
    - foetal distress, foetal death or a congenital physical or mental impairment or birth defect [yes/no]
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function [yes/no]
    - chronic disease [yes/no]

- Hospitalization and/or death (including primary cause) [free text]
- Admission date [dd.mm.yyyy]
- Discharge date [dd.mm.yyyy]
- Date of death [dd.mm.yyyy]

Outcome

- Outcome [not recovered or not resolved/recovering or resolving/recovered or resolved/ recovered with sequalae or resolved with sequalae/ fatal/unknown]
- End date [dd.mm.yyyy]
- Ongoing [yes/no/unknown, due to lost to follow-up]

Investigator

- Name of investigator [free text]

- Address [free text]
- Code [five digit number]
- City [free text]
- Telephone [fifteen digit number]
- Fax [fifteen digit number]
- Type of investigative site [hospital in-patient/hospital out-patient/general practitioner/specialist]

Standardized classification of adverse events

- IMDRF or MedDRA coding of (S)AEs

Device deficiency details

- Device deficiency identifier [DD01, DD02, …]
- Are there any device deficiencies? [yes/no]
- Date and time of device deficiency [dd.mm.yyyy – hh:mm]
- Please enter details for device deficiency [free text]
- Is this Device Deficiency associated with an AE? [yes/no]
- If yes, please enter the associated AE [XXX]
- For which area is this device deficiency being reported? [right thigh/right knee/left thigh/left knee]
- Which dressing type is the dressing in question? [Prototype multilayer foam dressing rectangle and square [redacted]
- Lot/batch number of device [free text]
- Reference number of device [free text]
- Could the device deficiency have led to a serious adverse event? [yes/no]

Pregnancy test

- Results of pregnancy test on participants of childbearing potential [positive/negative/not done]
- If pregnancy test was not performed, please clarify reason why [free text]
- Is the visit day 0 less than 5 days after screening? [yes/no]

Concomitant Therapies

Any change of concomitant therapy for participant during the course of the clinical study will be reported individually, the following data will be collected on the (e)CRF:

- Are there any concomitant medications currently being taken by the participant? [yes/no]
- Therapy number (CT01, CT02, …)
- Therapy/Medication (trade name)

- Indication (AE01, AE02, ...)
- Does the medication belong in one of the groups? [pain relief medication / other]
- Combination drug? [yes/no]
- Details for active ingredient
    - Dose
    - Unit of administration
    - Specification of other
- Details for second active ingredient (Only for combination drugs)
    - Dose
    - Unit of administration
    - Specification of other
- Dose form
- Frequency
- Specification of other 'Frequency' [free text]
- Route
- Specification of other 'Route' [free text]
- Topical therapy in test area(s) [yes/no]
- Right thigh [yes/no]
- Right knee [yes/no]
- Left thigh [yes/no]
- Left knee [yes/no]
- Start date [dd.mm.yyyy]
- End date [dd.mm.yyyy]
- Ongoing [yes/no]

9.3 Other variables

Other relevant variables include the following:

Inclusion and exclusion criteria

- Inclusion criteria met [yes/no/not applicable]
- Exclusion criteria met [yes/no/not applicable]

General questions

- Did the participant adhere to the rules since last visit? [yes/no]
- Specify if "no" [free text]
- New adverse event since last visit? [yes/no]
- Visit 7 or early termination? [Visit 7/early termination]

Demographic and baseline characteristics

Baseline characteristics and demographic information will be recorded. This will include:

- Sex [male/female/diverse]
- Age [years]
- Height [XYZ cm]
- Weight [XYZ.X kg]
- Is the participant of childbearing potential? [yes/no]

Sweating severity self-assessment (SSSA)

What is normal level of sweat according to the participant? [mild/moderate/severe]

Physical examination and hair removal

- Is the skin in the dressing applications sites healthy?
    - Right thigh [yes/no]
    - Right knee [yes/no]
    - Left thigh [yes/no]
    - Left knee [yes/no]
    - Specification if any "no" [free text]

Hair removal

- Are the applications sites cleaned, hair removed and free of lotions? [yes/no]
- Are there any shaving related injuries at the application sites? [yes/no]

Re-check of eligibility and randomization

- Date of randomization [dd.mm.yyyy]
- Are there any changes concerning in- and exclusion criteria since screening visit? [yes/no]
- Drop-down list of all in- and exclusion criteria for selection
- Assigned randomization number

Medical history

- Does the participant have any relevant medical or surgical history during the last year before screening? [yes/no]
- Medical history: Concomitant diagnosis and therapy

  Concomitant Diagnosis

  - Diagnosis number (MH01, MH02, …)
  - Diagnosis/Surgery [free text]
  - Start date [dd.mm.yyyy]
  - End date [dd.mm.yyyy]
  - Ongoing [yes/no]

- Was there any therapy/medication prior to study start that needs to be registered? [yes/no]

  Prior therapies

  - Therapy number (PT01, PT02, …)
  - Therapy/Medication (trade name)
  - Indication (MH01, MH02, ...)
  - Combination drug? [yes/no]
  - Details for active ingredient
    - Dose
    - Unit of administration
    - Specification of other
  - Details for second active ingredient (*Only for combination drugs)*
    - Dose
    - Unit of administration
    - Specification of other
  - Dose form
  - Frequency
  - Specification of other 'frequency' [free text]
  - Route
  - Specification of other [free text]
  - Topical therapy in test area(s) [yes/no]
    - Right thigh [yes/no]
    - Right knee [yes/no]
    - Left thigh [yes/no]

        - Left knee [yes/no]
    - Start date [dd.mm.yyyy]
    - End date [dd.mm.yyyy]
- Any concomitant therapy at present? [yes/no]

Standardized classification of medical history – concomitant diagnosis

- IMDRF or MedDRA coding of all collected medical history – concomitant diagnosis

Termination

- Date of last contact [dd.mm.yyyy]
- Check one primary reason to indicate end of study [screen failure/ completed/ drop out]
- Please specify screen failure [did not fulfill inclusion or exclusion criteria/met eligibility criteria but not needed/other]
- Specification of screen failure [free text]
- Please specify drop out [adverse event/lost to follow-up/pregnancy/withdrawal by participant/protocol deviation/other]
- Specification of drop out [free text]
- Who took the decision [Investigator/subject]
- Date of completion or discontinuation [dd.mm.yyyy]

Visit remarks

- Are there any remarks for the current visit? [yes/no]
- Remark [free text]

Additional remarks

- Are there any additional non-visit specific remarks? [yes/no]
- Remark [free text]

10 Data handling

10.1 Transfer of data

After doing the hard lock of the cleaned secuTrial® database, the clinical data management will transfer an export of all datasets to the responsible trial statistician. The trial statistician will get the information that the database is locked by receiving the database hard lock form for signature. Afterwards, the trial statistician will generate permanent SAS® master data sets on the server and file the corresponding code.

10.2 Unblinding

Not applicable, as this is an open label investigation.

For emergency unblinding

Not applicable, as this is an open label investigation.

10.3 Treatment of baseline values

The "Baseline" for this study is defined as "Day 0 assessment" as this is the day when the first application of the IMD takes place.

10.4 Categorizations

Not applicable

10.5 Calculation of derived variables

Not applicable

10.6 Treatment of missing values

In case of the occurrence of missing data, the following rules apply:

In the primary analysis, missing values are continued using a last observation carried forward imputation (LOCF) to ensure the intention-to-treat principle. To ensure comparability with other secondary results, the secondary and exploratory analyses, which are carried out with the dressings present, are also performed using LOCF-imputed values. LOCF imputation is considered appropriate in this case, as missing values are only expected to occur due to the absence of the participant at the time of assessment (forgotten appointment or dropout). Due to this fact, the absence of a single product is highly unlikely and a missing participant will always affect all dressings at the same time. As all IMDs would subsequently be imputed with the LOCF, the individual difference between the products from the last existing assessment day is retained, whereby no test product is favoured or disadvantaged. Consequently, the imputation does not improve any significance and can be classified as conservative.

10.7 Treatment of outliers

No replacement of outlying data values will be performed.

11 Statistical methods

11.1 Dichotomous and categorical variables

For all dichotomous and categorical variables, absolute and relative frequencies will be calculated if not stated otherwise.

For safety variables:

Two separate counting rules apply for AEs:

- Total number of AEs (possibly counting participants with several AEs more than once)
- Total and relative number of participants suffering from at least one AE

Frequencies of AEs will be summarized in tables overall and by terminology based on International Medical Device Regulators Forum (IMDRF) Coding including only adverse events with onset dates on or after baseline (treatment emergent adverse events [TEAEs]).

Two separate counting rules apply for concomitant therapies:

- Total number of concomitant therapies (possibly counting participants more than once)
- Total and relative number of participants having at least one concomitant therapies

Two separate counting rules apply for concomitant diagnoses:

- Total number of diagnoses/therapies (possibly counting participants more than once)
- Total and relative number of participants having at least one diagnose/therapies

11.2 Continuous and quasi-continuous variables

For all continuous and quasi-continuous variables the following sample characteristics will be calculated for descriptive presentation:

- count of participants evaluated (n)
- arithmetic mean (Mean)
- standard deviation (SD)
- median (Median)
- minimum (Min)
- maximum (Max)
- lower confidence interval limit (lower CI limit)
- upper confidence interval limit (upper CI limit).

11.3 Graphical presentations

The following plots will be presented:

- TBD after first sponsor review.

11.4 Statistical tests employed

The following methods are employed in this study:

- Newcombe's score method for calculation of confidence intervals for paired proportion difference
    - The actual statistical test is carried out by comparing the confidence intervals with the predefined threshold
- Wilcoxon signed-ranks test for paired data
- Paired t-test
- McNemar test for paired data

For primary endpoint (FAS analysis set):

The primary analysis is based on the two statistical non-inferiority comparisons of Prototype dressing (rectangle) vs Marketed dressing (rectangle) on the knee and Prototype dressing (square) vs Marketed dressing (square) on the thigh regardless of dressing location, whereby the primary binary-outcome variable is the "acceptable dressing presence".

Non-inferiority is tested using the classic approach of comparing a confidence interval with a predefined threshold. Based on the corresponding proportion values of the binary endpoint of both products, a proportion difference (statistically more precisely referred to as "risk difference") of both products is calculated. Given paired data structure, the confidence intervals of the proportion difference are calculated using the Newcombe's score method. Since the study has two primary endpoints, the 97.5% confidence intervals will be calculated due to a Bonferroni adjustment for multiple testing.

The primary test examines whether the upper 97.5% Newcombe confidence limit of the proportion difference is smaller than the non-inferiority threshold, which statistically results in the following non-inferiority comparison:

%C - %IMD < 15%,

where %IMD and %C denotes the proportion of devices with acceptable dressing presence for IMD and comparator. The non-inferiority threshold is given in percentage points.

The Newcomb confidence intervals required for the primary analysis are generated using the following syntax:

```
PROC FREQ DATA = TEST;
      TABLE TIME*PRODUCT / CHISQ RELRISK RISKDIFF(CL=NEWCOMBE) ALPHA=0.025;
RUN;
```

The primary analysis is carried out in the FAS collective. A sensitivity analysis is performed in the PP collective. The primary analysis is performed on the basis of the intention to treat principle.

For secondary endpoints (PP analysis set)

The secondary and safety endpoints are analysed according to the scale level of the dependent and independent variables. The analyses of the secondary endpoints are conducted in the PP collective and are based and performed on the basis of the intention to treat principle.

A descriptive presentation of all parameters used in the primary and secondary analysis is given.

- Non-inferiority comparison of acceptable dressing presence (thigh and knee) at days 1 and 3 between Prototype dressing (rectangle) vs Marketed dressing (rectangle) as well as Prototype dressing (square) vs Marketed dressing (square) separately.
    - Comparison of the lower confidence interval according to Newcomb with a non-inferiority threshold
    - Non-inferiority threshold: 15%-points based on proportion difference
- Non-inferiority comparison of presence of dressings at days 1, 3 and 7 between Prototype dressing (rectangle) vs Marketed dressing (rectangle) as well as Prototype dressing (square) vs Marketed dressing (square) separately.
    - Comparison of the lower confidence interval according to Newcomb with a non-inferiority threshold
    - Non-inferiority threshold: 15%-points based on proportion difference

- Non-inferiority comparison of pad integrity at days 1, 3 and 7 between Prototype dressing (rectangle) vs Marketed dressing (rectangle) as well as Prototype dressing (square) vs Marketed dressing (square) separately.
    - Comparison of the lower confidence interval according to Hodges–Lehmann for paired data with a non-inferiority threshold
    - Non-inferiority threshold: 15%-points based on the median difference, whereby the concrete threshold therefore corresponds to 15% of the range of the scale
- Non-inferiority comparison of percentage pad lift at days 1, 3 and 7 between Prototype dressing (rectangle) vs Marketed dressing (rectangle) as well as Prototype dressing (square) vs Marketed dressing (square) separately.
    - Comparison of the lower confidence interval according to Hodges–Lehmann for paired data with a non-inferiority threshold
    - Non-inferiority threshold: 15%-points based on the median difference, whereby the concrete threshold therefore corresponds to 15% of the range of the scale
- Non-inferiority comparison of percentage border lift at days 1, 3 and 7 between Prototype dressing (rectangle) vs Marketed dressing (rectangle) as well as Prototype dressing (square) vs Marketed dressing (square) separately.
    - Comparison of the lower confidence interval according to Hodges–Lehmann for paired data with a non-inferiority threshold
    - Non-inferiority threshold: 15%-points based on the median difference, whereby the concrete threshold therefore corresponds to 15% of the range of the scale
- Non-inferiority comparison of pressing comfort at days 1, 3 and 7 between Prototype dressing (rectangle) vs Marketed dressing (rectangle) as well as Prototype dressing (square) vs Marketed dressing (square) separately.
    - Comparison of the lower confidence interval according to Newcomb with a non-inferiority threshold
    - Non-inferiority threshold: 15%-points based on proportion difference

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For Safety Endpoints (SP)

- Descriptive analysis of adverse events (covering AEs, SAEs, ADEs), i.e. skin related AE's and Device Deficiencies e.g., blistering, erythema, sensitivity to adhesive, skin stripping, skin occlusion, pruritus and itching.
- Changes in concomitant medication.

12 Endpoints of clinical investigation

12.1 Statistical hypotheses for primary endpoint

Primary endpoints: To demonstrate non-inferiority of the prototype non-medicated multilayer foam dressings (rectangle and square variants) with regards to acceptable dressing presence in human participants at day 7 in the following two comparison pairs:

1. Prototype dressing (rectangle) vs Marketed dressing (rectangle) on the knee.

2. Prototype dressing (square) vs Marketed dressing (square) on the thigh.

The primary endpoint is the proportion of acceptable dressing presence at day 7 for Prototype non-medicated multilayer foam dressings (rectangle and square variants) and will be tested via a comparison of the proportion of acceptable dressing presence at day 7 of: (i) Prototype dressing (rectangle) vs Marketed dressing (rectangle); and (ii) Prototype dressing (square) vs Marketed dressing (square).

In this context the following Hypothesis will be tested on FAS population:

$$\mathbf{H_0}: \%C - \%IMD \geq 15\%$$

$$\mathbf{H_A}: \%C - \%IMD < 15\%$$

Where %IMD denotes the proportion of acceptable dressing presence for the investigational medical device and %C denotes the proportion acceptable dressing presence for the comparator. The non-inferiority threshold is given in percentage points.

As part of a sensitivity analysis, the statistical model of the primary analysis is reapplied on the PP population in a non-confirmatory manner to ensure the consistency of the results. The consistency check examines whether the results between the confirmatory FAS analysis and the non-confirmatory PP analysis show clinically relevant differences or postulate different results.

Only the confirmatory FAS analysis is used for the assessment of the primary endpoint. Possible differences to the non-confirmatory PP analysis are addressed accordingly in the discussion of the clinical investigational report.

12.2 Secondary and explorative endpoints

The secondary and safety endpoints are analyzed according to the scale level of the dependent and independent variables. No adjustment for multiple testing is made in the secondary analyses. The analyses of the secondary endpoints are conducted in the PP collective.

A descriptive presentation of all parameters used in the primary and secondary analysis is given.

Statistical testing	Non-inferiority comparison of the prototype non-medicated multilayer foam dressing to the comparators for following parameters: • Acceptable dressing presence (thigh and knee) at days 1 and 3 • Presence of dressings at days 1, 3 and 7. • Pad integrity at days 1, 3 and 7. • Percentage pad lift at days 1, 3 and 7. • Percentage border lift at days 1, 3 and 7. • Dressing comfort at days 1, 3 and 7. Non-inferiority comparison of the prototype non-medicated multilayer foam dressing vs the comparators in terms of: - Prototype dressing (rectangle) vs Marketed dressing (rectangle), on the knees - Prototype dressing (square) vs Marketed dressing (square), on the thighs

	in terms of: • Adhesive offset on dressing handles at time of application. • Adhesive offset on skin at time of removal. • Ease of application/removal. • Extent of dressing exposure to water during wear (ie, water-/shower-proofing). • Pain on removal. Superiority comparison of: - Prototype dressing (rectangle) vs Marketed dressing (rectangle), on the knees - Prototype dressing (square) vs Marketed dressing (square), on the thighs in terms of: • Acceptable dressing presence at days 1, 3 and 7. • Presence of dressings at days 1, 3 and 7. • Pad integrity at days 1, 3 and 7. • Percentage pad lift at days 1, 3 and 7. • Percentage border lift at days 1, 3 and 7. • Dressing comfort at days 1, 3 and 7. • Adhesive offset on dressing handles at time of application. • Adhesive offset on skin at time of removal. • Ease of application/removal. • Extent of dressing exposure to water during wear (i.e. water-/shower-proofing). • Pain on removal. •

Descriptive analysis	A descriptive analysis is performed for each of the primary, secondary and safety endpoints separately for each product.

97.5 % confidence intervals	The corresponding 97.5% confidence intervals are calculated and given for all primary, secondary and exploratory endpoints.

External Report	Not applicable

Sensitivity analysis	The primary analysis is carried out in the FAS collective. A sensitivity analysis, the primary is repeated in the PP collective. No sensitivity analyses are planned as part of the secondary analyses.

12.3 Considerations for non-inferiority and equivalence testing

The primary and all secondary endpoints will be tested in the first instance as part of a non-inferiority analysis.

The clinical experts specified that a negative deviation of less than 15% is considered clinically non-inferior.

Accordingly, the threshold for non-inferiority is set at 15%-point. This limit applies irrespective of the respective endpoint.

In the case of a risk difference, this value can be used directly. In the case of medians and mean values, the corresponding 15%-point limit must first be determined in relation to the range of scale.

12.4 Model Assumptions

Due to the study design, all data are available in paired form. Therefore, only statistical parameters and tests for paired data are used.

As non-parametric tests, the Newcomb confidence intervals, the McNemar test and the Wilcoxon signed-ranks test do not require any special model requirements apart from the respective scale level.

The pain intensity during removal was assessed using a 10-point Likert scale. This generates a quasi-metric scale level for which a normal distribution assumption applies. Due to the exploratory testing, no further testing of the normal distribution is carried out. Deviations in the variance homogeneity of both groups are compensated for by means of a Welch approximation in the t-test.

12.5 Multiplicity

The statistical comparison of the IMD vs comparator is performed separately for each comparison pair (i + ii). As two primary endpoints are therefore tested, the analysis is performed with a probability of error of 2.5%, so that the family wise error rate can be fixed at 5%.

In order to control the alpha level for multiple comparisons a hierarchical testing method will be used.

The testing of the secondary endpoints is designed as a non-inferiority test as well.

The analysis will be split into two separate hierarchies:

i) Prototype dressing (rectangle) vs Marketed dressing (rectangle)
ii) Prototype dressing (square) vs Marketed dressing (square)

In the hierarchical testing method, the next endpoint down on the list can only be tested if the previous endpoint successfully demonstrates non-inferiority at a 2.5% significance level. This means that the alpha level is maintained to correct for multiple comparisons.

The order of each hierarchy will be defined as:

Table 11.1 Hierarchy 1: Prototype dressing (rectangle) vs Marketed dressing (rectangle)

Order	Endpoint
1	Acceptable dressing presence* (knee) at day 7 (Primary endpoint)
2	Acceptable dressing presence* (knee) at days 1 and 3
3	Presence of dressings at days 1, 3 and 7
4	Pad integrity at days 1, 3 and 7
5	Percentage pad lift at days 1, 3 and 7
6	Percentage border lift at days 1, 3 and 7
7	Dressing comfort at days 1, 3 and 7
*defined as dressings present, with no border lift reaching the pad and no pad exposure.	

Table 11.2 Hierarchy 2: Prototype dressing (square) vs Marketed dressing (square)

Order	Endpoint
1	Acceptable dressing presence* (thigh) at day 7 (Primary endpoint)
2	Acceptable dressing presence* (thigh) at days 1 and 3
3	Presence of dressings at days 1, 3 and 7
4	Pad integrity at days 1, 3 and 7
5	Percentage pad lift at days 1, 3 and 7
6	Percentage border lift at days 1, 3 and 7
7	Dressing comfort at days 1, 3 and 7
*defined as dressings present, with no border lift reaching the pad and no pad exposure.	

The following test sequence is summarized in terms of the hierarchical test principle:

1. Non-inferiority of the primary endpoint
2. Non-inferiority of all secondary endpoints according to the order above

If a non-significant result occurs in this serial sequence, the respective test hierarchy is cancelled and all subsequent tests are no longer interpreted as confirmatory. However, the p-values are still presented for information purposes.

This test sequence is carried out separately in each hierarchy.

For all non-inferiority tests, if non-inferiority is achieved, then superiority will be tested within the explorative endpoints.

12.6 Sample size and statistical power

The sample size is based on separate non-inferiority tests for (i) Prototype dressing (rectangle) vs Marketed dressing (rectangle); and (ii) Prototype dressing (square) vs Marketed dressing (square), regardless of dressing location, i.e. right or left dressing application site). The alpha level used in the non-inferiority tests will therefore be adjusted to 2.5% for each product comparison.

The assumptions for the Prototype dressing (rectangle) vs Marketed dressing (rectangle) comparison are that of no difference between the products in acceptable dressing presence by day 7. Also assumed is 28% discordant pairs and the proportion of subjects where both dressings are acceptable is at least 60%. Using these conservative assumptions, a sample size of 120 evaluable participants is required to ensure 80% power using Newcombe's score method to show that the upper confidence limit of the 2-sided 97.5% confidence interval, for the difference in proportion of acceptable presence (Marketed dressing (rectangle) – Prototype dressing (rectangle)), is lower than the non-inferiority threshold of 15% (%C - %IMD < 15%-point, where %IMD and %C denotes the proportion of devices with acceptable dressing presence for IMD and comparator). The choice of the 15%-point threshold is justified in section 9.3.

The same assumptions as above apply to the Prototype dressing (square) vs Marketed dressing (square) comparison and so the same sample size is acceptable, as these products will all be applied to the same participants then 120 total evaluable participants would be sufficient for the aims of both comparisons.

Accounting for an approximate 10% lost to follow up rate, 135 participants will be recruited into this clinical study.

The sample size was calculated using nQuery + nTerim 9.3.0 The sample size calculation was provided by sponsor.

12.7 Randomisation

Four different dressings (two IMDs and two comparators) will be investigated, with each participant receiving one of each of the two IMDs and one of each of the two comparators. The dressings will be

divided into two groups of IMD vs comparator comparison pairs, i.e. (i) Prototype dressing (rectangle) vs Marketed dressing (rectangle); and (ii) Prototype dressing (square) vs Marketed dressing (square). Comparison pair (i) will be applied to the knees (one dressing per knee) and comparison pair (ii) will be applied to the thighs (one dressing per thigh). Each dressing of the comparison pair will be randomised to either the right or left knee / thigh in a 1:1 ratio.

The side allocations are carried out using a randomization process and the possible combinations thereof are illustrated in Figure 11.1.

Randomization is performed using SAS Software 9.4 or higher.

Description of the randomization process:

The following aspects are considered for the generation of the randomization list:

- Patients will be assigned a 3-digit randomization number from 001 to 135 (based on the 135 planned participants)
- One single blinded randomization list for the whole study will be prepared
- The randomization list will be uploaded to Trial Master File in a pre-specified format.

Randomization is carried out according to the guidelines of the site with the help of the randomization list. Here, the smallest previously unused randomization number is always assigned to the eligible participant.

12.8 Interim analyses

Not applicable.

12.9 Subgroup analyses

Not applicable.

12.10 Adjustment for covariates

Not applicable.

12.11 Confidence intervals

Confidence intervals (CI) for means are given where suitable. They are computed two-sided based on asymptotic normality at a confidence level of 95 % =100*(1- α) %, if not stated otherwise:

$$CI = \mu \pm c \frac{\sigma}{\sqrt{n}}$$

for μ = *Sample mean for the respective variable*

$c = t_{1-\frac{\alpha}{2};n-1}$ *Percentile of the t distribution*

σ = *Sample standard deviation for the respective variable*

n = Sample size

Confidence Intervals for Wilcoxon signed rank test are calculated according to Hodges-Lehmann. This is done according to the following method:

Let $[\lambda_*, \lambda^*]$ be the exact $100 \cdot (1-\alpha)\%$ confidence interval for the median difference. Let $M = \frac{N(N+1)}{2}$ and let $A_{[1]} \leq A_{[2]} \leq A_{[\ldots]} \leq A_{[M]}$ be the M averages, $\frac{(d_i+d_j)}{2}$ for all $i \leq j$, sorted in ascending order.
The lower confidence interval is formed by setting $\lambda_* = A_{[\ddot{t}]}$ where $[\ddot{t}] = 1 + \ddot{t}_*$ where $\ddot{t}_*$ rounds down t_* to the nearest integer.
The upper confidence interval is formed by setting $\lambda^* = A_{[\ddot{t}]}$ where $[\ddot{t}] = \ddot{t}^*$ where $\ddot{t}^*$ rounds up t^* to the nearest integer.

t_* is determined by finding a value for t_* so that the formula satisfies the following condition:

$$\Phi\left(\frac{t_* - \frac{N(N+1)}{4}}{\sqrt{\frac{N(N+1)(2N+1)}{24}}}\right) = \frac{\alpha}{2}$$

t^* is determined by finding a value for t^* so that the formula satisfies the following condition:

$$1 - \Phi\left(\frac{t^* - \frac{N(N+1)}{4}}{\sqrt{\frac{N(N+1)(2N+1)}{24}}}\right) = \frac{\alpha}{2}$$

Confidence Intervals for binomial proportion are calculated according to Wilson. This is done according to the following method: Wilson started with the normal approximation to the binomial:

$$Z_\alpha \approx \frac{(p - \hat{p})}{\sigma_n},$$

where $\hat{p}$ is the proportion of successes in a Bernoulli trial process and an estimator for p in the underlying Bernoulli distribution, and Z_α is the standard normal interval half-width corresponding to the desired confidence $1-\alpha$. The analytic formula for a binomial sample standard deviation is

$$\sigma_n = \sqrt{\frac{p(1-p)}{n}}.$$

Combining the two, and squaring out the radical, gives an equation that is quadratic in :

$$(p - \hat{p})^2 = \frac{Z_\alpha^2}{n} p(1-p) \quad \text{or} \quad p^2 - 2p\hat{p} + \hat{p}^2 = p\frac{Z_\alpha^2}{n}$$

Transforming the relation into a standard-form quadratic equation for p treating $\hat{p}$ and n as known values from the sample (see prior section), and using the value of Z_α that corresponds to the desired confidence $1-\alpha$ for the estimate of p gives this:

$$\left(1 + \frac{Z_\alpha^2}{n}\right) p^2 - \left(2\hat{p} + \frac{Z_\alpha^2}{n}\right) p + \hat{p}^2 = 0,$$

where all of the values bracketed by parentheses are known quantities. The solution for p estimates the upper and lower limits of the confidence interval for p. Hence the probability of success p is estimated by $\hat{p}$ and with $1-\alpha$ confidence bracketed in the interval

$$p \in_\alpha (w^-, w^+) = \frac{1}{1+z_\alpha^2/n}\left(\hat{p} + \frac{z_\alpha^2}{2n} \pm \frac{z_\alpha^2}{2n}\sqrt{4n\hat{p}(1-\hat{p}) + z_\alpha^2}\right),$$

where $\in_\alpha$ is an abbreviation for

$$\mathbf{P}\{p \in_\alpha (w^-, w^+)\} = 1 - \alpha.$$

Confidence Intervals for paired proportion difference are calculated according to Newcomb.

The following applies: $d = p_1 - p_2$, with $p_i = \frac{x_i}{n_i}$.

Where n_i is the total number of IMDs and x_i is the number of IMDs that fulfill the respective criteria, whereby p_i is the proportion value.

$$d_L = (\hat{p}_1 - \hat{p}_2) - \sqrt{(\hat{p}_1 - L_1)^2 + (U_2 - \hat{p}_2)^2}$$
$$d_U = (\hat{p}_1 - \hat{p}_2) + \sqrt{(U_1 - \hat{p}_1)^2 + (\hat{p}_2 - L_2)^2}$$

Here, U_i and L_i result according to the Wilson score confidence intervals.

$$L_i = \hat{p}_i \frac{z_{\alpha/2}^2}{2n_i} - \frac{z_{\alpha/2}\sqrt{\frac{\hat{p}_i(1-\hat{p}_i) + \frac{z_\alpha^2}{4n_i}}{n_i}}}{1 + \frac{z_{a/2}^2}{n_i}}, \qquad for\ i = 1,2$$

And

$$U_i = \hat{p}_i \frac{z_{\alpha/2}^2}{2n_i} - \frac{z_{\alpha/2}\sqrt{\frac{\hat{p}_i(1-\hat{p}_i) + \frac{z_\alpha^2}{4n_i}}{n_i}}}{1 + \frac{z_{a/2}^2}{n_i}}, \quad for\ i = 1,2$$

12.12 Conventions

Number of decimal places for raw data and calculated values are determined by an internal guideline. The presentation of target variables follows the SGS proderm style guide.

For frequency tables, only those categories for which there is at least one participant represented, will be included in the tables, except the intention is the direct visual comparison between categories.

13 Preparation and control of program code

All SAS® Code used for statistical analysis is in the responsibility of the trial statistician but may be delegated to a programmer. The statistical output programmed in SAS® version 9.4 is based on this SAP. All statistical analysis programs are subjected to a version control system so that changes in the program can be tracked. The output log files of SAS® are searched automatically for errors and these are written, if available, automatically into an additional file. The log and error file of the final analysis is saved.

Controlling of program codes and statistical outputs is done by a person responsible for quality control e.g., a 2nd statistician according to SOPs DMD_MED_1003_000 “Analysis in medical trials”.

The control follows a standardised scheme, which can be extended if necessary. The results of the control are saved in a separate Excel document signed.

The primary statistician implements the control's observations, documenting all actions taken.

All program codes and statistical outputs will be controlled based on a risk assessment. The recommended quality control strategy will be examined, and its appropriateness verified until release.

14 Formats

Statistical outputs will be presented in British English. Fonts point sizes of at least 8 will be used.

Data presented in listings and tables will be formatted as follows:

- alphanumeric data will be middle-justified
- numeric values and date values will be middle-justified
- column heading will be aligned center for alphanumeric data, for numeric values and date values
    - If local conditions make it necessary, the alignment of the headings may differ.

Units will be given in the column heading for numeric values where appropriate.

Any abbreviations in tables and figures will be explained in footnotes unless they are already specified in the abbreviation list of the report.

Values in the data listing will be presented as recorded in the (e)CRF, except technical variables. Technical variables are labeled with "tc_" in the variable name in the (e)CRF and may not be shown in the data listing.

Estimated means and standard deviations for continuous or quasi-continuous variables will be printed to one more decimal place than the individual value of measurement. Percentage values will be printed with one decimal place.

All p-values will be given with four digits to the right of the decimal point. In case a rounded value of p=0.0000 is computed by SAS®, 'p<0.0001' will be printed.

15 Changes from clinical investigational plan

No changes were made between the CIP and SAP.

16 Software utilized

Task	Software	Version
Sample Size Estimation	SAS® for Windows nQuery Advisor 5.0 or other	9.4 or higher
Statistical Analysis	SAS® for Windows	9.4 or higher
Clinical database	secuTrial®	6.5.1.5 or higher

Topline results

The topline results include:

- Allocation of participants in the respective study populations (SP, FAS, PP)

- Statistical analysis of the primary endpoint (FAS and PP)
- Selection of secondary and exploratory efficacy endpoint(s) to support the primary endpoint (FAS and PP)
    - Non-inferiority comparison of acceptable dressing presence (thigh and knees) at days 1 and 3 between Prototype dressing (rectangle) vs Marketed dressing (rectangle) as well as Prototype dressing (square) vs Marketed dressing (square) separately. (secondary)
    - Non-inferiority comparison of presence of dressings at days 1, 3 and 7 between Prototype dressing (rectangle) vs Marketed dressing (rectangle) as well as Prototype dressing (square) vs Marketed dressing (square) separately. (secondary)
    - Non-inferiority comparison of dressing comfort at days 1, 3 and 7 between Prototype dressing (rectangle) vs Marketed dressing (rectangle) as well as Prototype dressing (square) vs Marketed dressing (square) separately. (secondary)
    - [redacted]
    - [redacted]
    - [redacted]
- Counts and percentages of TE(S)AEs (SP)
- Description of events in conjunction with causality to the study, pattern, intensity and outcome of TE(S)AEs (SP)

17 References

ICH-Guideline Structure and Content of Clinical Study Reports (ICH E3, final signed off, 30 November 1995)

ICH-Guideline Guideline for Good Clinical Practice (ICH E6 (R2), final signed off, 14 Jun 2017)

ICH-Guideline Statistical Principles for Clinical Trials (ICH E9, final signed off, 5 February 1998)

ICH E9 (R1) Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (ICH E9 (R1), Date for coming into effect, 30 July 2020)

ISO 14155:2020: Clinical investigation of medical devices for human subjects — Good clinical practice (Third Edition; July 2020)

18 Overview

The summary of the statistical analysis scheme is presented in the following table:

Target variables	Population	Graphs	Statistical methods
Disposition of participants	**SP**	Flowchart	
Disposition of investigational products	**SP**	Flowchart	
Baseline characteristics	**SP**		
Age, Height, Weight	SP	--	Descriptive statistics 95 % confidence intervals
Gender	SP	--	Counts and percentages
Medical history	SP	--	
Physical examination of the skin condition	SP	--	Counts and percentages
Primary variable	**FAS*, PP****		
Acceptable dressing presence	FAS*, PP**	Bar chart with 97.5 % Confidence Intervals	Descriptive statistics 97.5 % Wilson confidence intervals of proportion 97.5% Newcomb confidence intervals of risk difference
Secondary variables	**PP**		
Acceptable dressing presence	PP	Bar chart with 97,5 % Confidence Intervals	Descriptive statistics 97.5 % Wilson confidence intervals of proportion 97.5% Newcomb confidence intervals of risk difference
Presence of dressings	PP	Bar chart with 97,5 % Confidence Intervals	Descriptive statistics 97.5 % Wilson confidence intervals of proportion 97.5% Newcomb confidence intervals of risk difference

Target variables	Population	Graphs	Statistical methods
Pad integrity	PP		Descriptive statistics Hodges–Lehmann-estimator and 97.5% confidence intervals
Percentage of pad lift	PP	Bar chart with 97,5 % Confidence Intervals	Descriptive statistics Hodges–Lehmann-estimator and 97.5% confidence intervals
Percentage of border lift	PP	Bar chart with 97,5 % Confidence Intervals	Descriptive statistics Hodges–Lehmann-estimator and 97.5% confidence intervals
Dressing comfort	PP	Bar chart with 97,5 % Confidence Intervals	Descriptive statistics 97.5 % Wilson confidence intervals of proportion 97.5% Newcomb confidence intervals of risk difference
Exploratory variable(s)	**PP**		
Acceptable dressing presence	PP	Bar chart with 95 % Confidence Intervals	Descriptive statistics 97.5 % Wilson confidence intervals of proportion Mixed logistic regression
Presence of dressings	PP		Descriptive statistics 97.5 % Wilson confidence intervals of proportion Mixed logistic regression

Target variables	Population	Graphs	Statistical methods
Pad integrity	PP		Descriptive statistics Hodges–Lehmann-estimator and 97.5% confidence intervals Wilcoxon signed-ranks test
Percentage of pad lift	PP		Descriptive statistics Hodges–Lehmann-estimator and 97.5% confidence intervals Wilcoxon signed-ranks test
Percentage of border lift	PP		Descriptive statistics Hodges–Lehmann-estimator and 97.5% confidence intervals Wilcoxon signed-ranks test
Dressing comfort	PP		Descriptive statistics 97.5 % Wilson confidence intervals of proportion Mixed logistic regression
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]		[redacted]

Target variables	Population	Graphs	Statistical methods
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]		[redacted]
Safety variables	**SP**		
Evaluation of tolerability of the investigational products	SP	--	Descriptive statistics 95 % confidence intervals
Number of participants with Treatment-Emergent Adverse Events (TEAEs)	SP	--	Counts and percentages

*: Confirmatory Hypothesis Testing

**: No Confirmatory Hypothesis Testing, part of secondary analysis

Additional tables and figures are acceptable for illustrative purposes. Additional statistical tests can be performed, if reasons are given in the final report. The corresponding p-values have to be interpreted purely descriptive in the context of an explorative data analysis.

Examples of crucial tables, listings and figures can be seen in Chapter 19.

19 Appendices

19.1 Mock listing

A complete listing of participants' raw data will be integrated in the final report. The layout will be according to the following mock listings:

Listing general data

Random No.	[Variable 1 NUMERIC]	[Variable 2 DATE]	[Variable …]	[Variable N ALPHANUMERIC]
1	[VALUE]	[VALUE]		[VALUE]
2	[VALUE]	[VALUE]		[VALUE]
...	...	...		...
n-1	[VALUE]	[VALUE]		[VALUE]
n	[VALUE]	[VALUE]		[VALUE]

Listing demographic data

Random No.	Participant ID	Screening Date	Age [years]
1	X	DDMMMYYYY	X
2	X	DDMMMYYYY	X
...	...	...	...
n-1	X	DDMMMYYYY	X
n	X	DDMMMYYYY	X

Listing efficacy/tolerability data (derandomized)

RandomNo.	Time	Product	Variable 1 [<unit>]	Variable 2 [<unit>]	Variable 3 [<unit>]	Variable 4 [<unit>]
1	[TIME 1]	[PRODUCT 1]	X	X	X	X
	[TIME…]	[PRODUCT 1]	X	X	X	X
	[TIME N]	[PRODUCT 1]	X	X	X	X
2	[TIME 1]	[PRODUCT N]	X	X	X	X
	[TIME…]	[PRODUCT N]	X	X	X	X
	[TIME N]	[PRODUCT N]	X	X	X	X

19.2 Mock tables

Tables of the following kind will be presented to illustrate the efficacy analysis in the final report of the study:

Mock table for descriptive statistics of (quasi)continuous variables - baseline characteristics

	Descriptive Statistics						95% CI	
	n	Mean	Standard Deviation	Minimum	Median	Maximum	Lower limit	Upper limit
<Variable [<unit>]>								
SP	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
FAS	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
PP	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX

Mock table for descriptive statistics of (quasi)continuous variables – baseline characteristics

	Descriptive Statistics						95% CI	
Visit	n	Mean	Standard Deviation	Minimum	Median	Maximum	Lower limit	Upper limit
<Variable [<unit>]> [[FAS/PP] (N = n)]								
IP 1	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
IP 2	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
IP 3	X	XXX.XX	XXX.XX	XXX.XX	XXX.XX	XXX.XX	XXX.XX	XXX.XX
<Variable [<unit>]> [[FAS/PP] (N = n)]								
IP 1	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
IP 2	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
IP 3	X	XXX.XX	XXX.XX	XXX.XX	XXX.XX	XXX.XX	XXX.XX	XXX.XX
<Variable [<unit>]> [[FAS/PP] (N = n)]								
IP 1	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
IP 2	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
IP 3	X	XXX.XX	XXX.XX	XXX.XX	XXX.XX	XXX.XX	XXX.XX	XXX.XX

Mock table of counts and percentages of categorical variables – baseline characteristics

	[Category 1]		[Category ...]		[Category N]		Total	
Visit	n	(%)	n	(%)	n	(%)	n	(%)
<Variable [<unit>]> [[FAS/PP] (N = n)]								
SP	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
FAS	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
PP	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
<Variable [<unit>]> [[FAS/PP] (N = n)]								
SP	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
FAS	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
PP	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
<Variable [<unit>]> [[FAS/PP] (N = n)]								
SP	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
FAS	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
PP	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)

Mock table of counts and percentages of categorical variables – baseline characteristics

	[Category 1]		[Category ...]		[Category N]		Total	
Visit	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
<Variable [<unit>]> [[FAS/PP] (N = n)]								
IP 1	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
IP 2	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
<Variable [<unit>]> [[FAS/PP] (N = n)]								
IP 1	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
IP 2	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
<Variable [<unit>]> [[FAS/PP] (N = n)]								
IP 1	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
IP 2	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)

Mock table for descriptive statistics of (quasi)continuous variables – efficacy variables

	Descriptive Statistics						[95;99]% CI	
Visit	**n**	**Mean**	**Standard Deviation**	**Minimum**	**Median**	**Maximum**	**Lower limit**	**Upper limit**
<Variable [<unit>]> [[FAS/PP] (N = n)] – IP 1								
Time 1	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
Time ...	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
Time N	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
<Variable [<unit>]> [[FAS/PP] (N = n)] – IP 2								
Time 1	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
Time ...	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
Time N	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX

Mock table for descriptive statistics of (quasi)continuous variables – difference to baseline

	Descriptive Statistics						[95;99]% CI	
Visit	**n**	**Mean**	**Standard Deviation**	**Minimum**	**Median**	**Maximum**	**Lower limit**	**Upper limit**
<Variable [<unit>]> [[FAS/PP] (N = n)] – IP 1								
Time 1	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
Time ...	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
Time N	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
<Variable [<unit>]> [[FAS/PP] (N = n)] – IP 2								
Time 1	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
Time ...	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX
Time N	X	XXX.XX	XXX.XX	XXX.X	XXX.X	XXX.X	XXX.XX	XXX.XX

Mock table of counts and percentages of scores for dichotomous and categorical variables

	[Score 1]		[Score ...]		[Score N]		Total	
Visit	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
<Variable [<unit>]> [[FAS/PP] (N = n)] – IP 1								
Time 1	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
Time ...	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
Time N	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
<Variable [<unit>]> [[FAS/PP] (N = n)] – IP 2								
Time 1	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
Time ...	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
Time N	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
<Variable [<unit>]> [[FAS/PP] (N = n)] – IP N								
Time 1	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
Time ...	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)
Time N	X	(X.X)	X	(X.X)	X	(X.X)	X	(X.X)

Mock table of counts and percentages of adverse events: preferred term, intensity.

		Mild				Moderate				Severe				Total				Total
Population	**PT**	**R0**	**R1**	**R2**	**R3**	**R0**	**R1**	**R2**	**R3**	**R0**	**R1**	**R2**	**R3**	**R0**	**R1**	**R2**	**R3**	**R0+R1+R2+R3**
	PT 1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	PT 2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

R0=none, R1=possible, R2=probable, R3=definitive

Mock table for results of Wilcoxon signed rank test for assessment time comparisons

		Results of Wilcoxon Signed Rank Test for Comparisons of Assessment Times on <Variable Name> [<unit>]						
Population	**Time**	**Comparison**	**n (Pairs)**	**n with < Product /TIME 1>- < Product/TIME 2> < 0**	**n with < PRODUCT/TIME 1>- < PRODUCT/TIME 2> > 0**	**Mean Difference**	**Median Difference**	**p-Value**
FAS (N = n)	<TIME X>	<TIME X> vs. <TIME Y>	X	X	X	XX.XX	XX.XX	X.XXXX
PP (N = n)	<TIME X>	< TIME X> vs. < TIME Y>	X	X	X	XX.XX	XX.XX	X.XXXX

Note on the result: **bold p-Value: significant (p ≤ 0.05)**

Mock table for descriptive statistics for risk difference

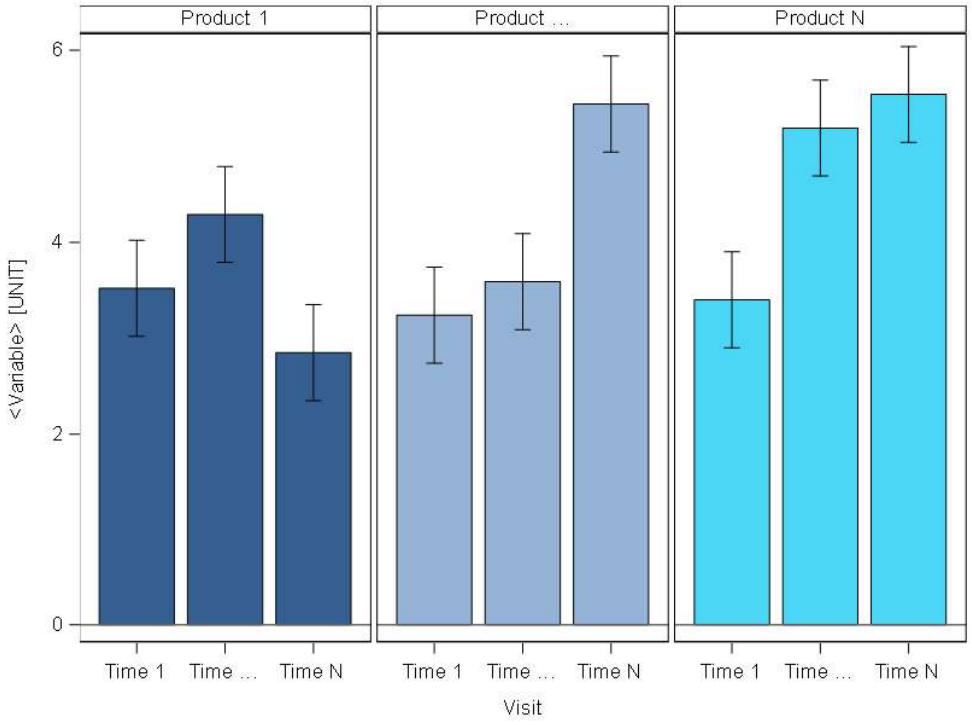
Descriptive statistics for risk difference (FAS or PP)			
Product	**Risk**	**97.5% Confidence interval**	
		Lower Limit	**Upper Limit**
PRD1	XX.XX	XX.XX	XX.XX
PRD1	XX.XX	XX.XX	XX.XX

Mock table for results of non-inferiority product comparison

Results of non-inferiority product comparison (FAS or PP)					
Risk Difference or Median Difference	**Non-Inferiority threshold in percent**	**Non-Inferiority threshold**	**97.5% Confidence interval**		**Non-inferiority accepted**
			Lower Limit	**Upper Limit**	
XX.XX	15%	XX.XX	XX.XX	XX.XX	**Yes**
Note on the result: **bold character: accepted**					

19.3 Mock graphs

Graphs of the following kind will be presented to illustrate the efficacy analysis in the final report of the study:



19.4 Tables planned

The following tables with the respective descriptive statistics to deliver the data basis for the results part of the report (Chapter 11 and 14) are planned:

14.1. Demographic, baseline *and compliance data for participants (if available) (SP)*

Table 14.1.1	Counts and percentages of participants per analysis set
Table 14.1.2	Counts and percentages of protocol deviations
Table 14.1.3	Counts and percentages of eligible participants
Table 14.1.4	Counts and percentages of screening failures
Table 14.1.5	Counts and percentages of premature terminations (if applicable)
Table 14.1.6	Descriptive statistics for demographics
Table 14.1.7	Counts and percentages of result of pregnancy test at screening
Table 14.1.8	Counts and percentages of skin condition screening
Table 14.1.9	Counts and percentages of medical history

14.2. Efficacy *Data*

14.2.1. Primary Variable

Table 14.2.1.1	Counts and percentages of acceptable dressing presence at visit 1, 3 and 7 for Prototype dressing (rectangle) vs Marketed dressing (rectangle) on the knee (FAS/PP)
Table 14.2.1.2	Descriptive statistics for relative risk of acceptable dressing presence for visit 7 for Prototype dressing (rectangle) vs Marketed dressing (rectangle) on the knee (FAS/PP)
Table 14.2.1.3	Results of non-inferiority product comparison at visit 7 for Prototype dressing (rectangle) vs Marketed dressing (rectangle) on the knee (FAS/PP)
Figure 14.2.1.1	Bar chart of acceptable dressing presence at visit 7 for Prototype dressing (rectangle) vs Marketed dressing (rectangle) on the knee (FAS/PP)

*: No confirmatory hypothesis testing on PP population

Table 14.2.1.4	Counts and percentages of acceptable dressing presence at visit 1, 3 and 7 for Prototype dressing (square) vs Marketed dressing (square) on the thigh (FAS/PP)
Table 14.2.1.5	Descriptive statistics for relative risk of acceptable dressing presence for visit 7 for Prototype dressing (square) vs Marketed dressing (square) on the thigh (FAS/PP)
Table 14.2.1.6	Results of non-inferiority product comparison at visit 7 for Prototype dressing (square) vs Marketed dressing (square) on the thigh (FAS/PP)
Figure 14.2.1.2	Bar chart of acceptable dressing presence at visit 7 for Prototype dressing (square) vs Marketed dressing (square) on the thigh (FAS/PP)

*: No confirmatory hypothesis testing on PP population

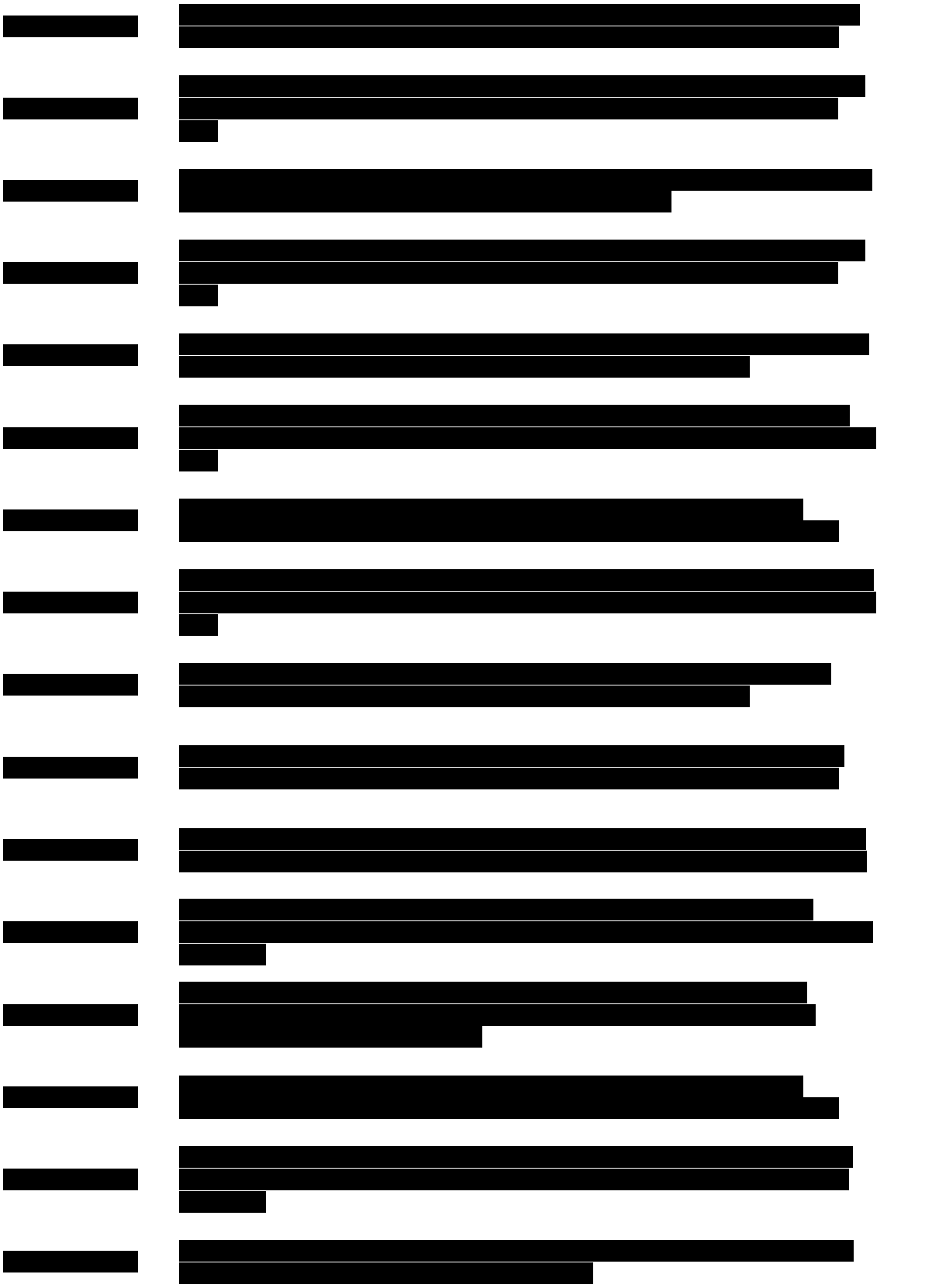
14.2.2 Secondary Variables (PP)

Prototype dressing (rectangle) vs Marketed dressing (rectangle) on the knee

Table 14.2.2.1	Counts and percentages of acceptable dressing presence at visit 1, 3 and 7 for Prototype dressing (rectangle) vs Marketed dressing (rectangle) on the knee (PP)
Table 14.2.2.2	Descriptive statistics for relative risk of acceptable dressing presence for visit 1, 3 and 7 for Prototype dressing (rectangle) vs Marketed dressing (rectangle) on the knee (PP)
Table 14.2.2.3	Results of non-inferiority product comparison for acceptable dressing presence at visit 1, 3 and 7 for Prototype dressing (rectangle) vs Marketed dressing (rectangle) on the knee (PP)
Table 14.2.2.4	Counts and percentages of dressing presence at visit 1, 3 and 7 for Prototype dressing (rectangle) vs Marketed dressing (rectangle) on the knee (PP)
Table 14.2.2.5	Descriptive statistics for relative risk of dressing presence for visit 1, 3 and 7 for Prototype dressing (rectangle) vs Marketed dressing (rectangle) on the knee (PP)
Table 14.2.2.6	Results of non-inferiority product comparison for dressing presence at visit 1, 3 and 7 for Prototype dressing (rectangle) vs Marketed dressing (rectangle) on the knee (PP)
Table 14.2.2.7	Counts and percentages of pad integrity at visit 1, 3 and 7 for Prototype dressing (rectangle) vs Marketed dressing (rectangle) on the knee (PP)
Table 14.2.2.8	Results of non-inferiority product comparison for pad integrity at visit 1, 3 and 7 for Prototype dressing (rectangle) vs Marketed dressing (rectangle) on the knee (PP)

[redacted]

[redacted]



14.3. Safety Data (SP)

14.3.1. Display of Adverse Events of participants

Table 14.3.2.1 Counts and percentages of AEs and participants with AEs

Table 14.3.2.2 Counts and percentages of TEAEs and participants with TEAEs

Table 14.3.2.3 Counts and percentages of TEAEs and participants with TEAEs by IMDRF terminology

Table 14.3.2.4 Counts and percentages of TEAEs: relationship to IP or procedure

Table 14.3.2.5 Counts and percentages of TEAEs: severity

Table 14.3.2.6 Counts and percentages of TEAEs: action taken

Table 14.3.2.7 Counts and percentages of TEAEs: outcome

Table 14.3.2.8 Counts and percentages of participant withdrawn due to TEAE

Table 14.3.2.9 Counts and percentages of TEAEs: serious adverse event

14.3.2. Display of deaths, other serious and significant adverse events (if applicable)

14.3.3. Narratives of deaths, other serious and certain other significant adverse events (if applicable)

14.3.4. Abnormal Laboratory Value Listing

Not applicable

19.5 Listings planned

All data collected within the scope of the clinical investigation are mapped within the listings. This includes collected raw data as well as derived data.

Technical variables (indicated by "tc_" in the variable name) are an exception here, as they only contain redundant information and can therefore be omitted without any loss of information.

Certificate Of Completion

Envelope Id: 5A20BF0B-AA9E-46D3-ACBB-3E7D9250EA91
Status: Completed
Subject: Mit Docusign abschließen: 24.0061_amendment_to_SAP_no1.pdf, 24.0061_SAP_V2.pdf
Source Envelope:
Document Pages: 65
Signatures: 8
Certificate Pages: 6
Initials: 0
AutoNav: Enabled
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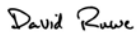
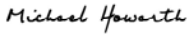
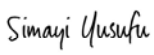
Location: DocuSign

Signer Events	Signature	Timestamp
David Ruwe DRuwe@proderm.de Head of Data Operations & Monitoring Medical proderm GmbH Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 50F53FD8-8853-4C40-94FA-65474FF9C4FD Using IP Address: 217.231.213.23 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document I approve this document	Sent: 1/14/2025 9:53:24 PM Viewed: 1/15/2025 6:58:25 AM Signed: 1/15/2025 6:59:05 AM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
Eric Bibiza ebibiza@proderm.de Statisician proderm GmbH Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: E00DEC46-A3B2-4545-B2C5-56D9F38DB375 Using IP Address: 89.246.251.118 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): Ich habe dieses Dokument verfasst Ich genehmige dieses Dokument	Sent: 1/14/2025 9:53:24 PM Viewed: 1/14/2025 9:53:48 PM Signed: 1/14/2025 9:54:13 PM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

Signer Events	Signature	Timestamp
Jay Jantz Jay.Jantz@smith-nephew.com Security Level: Email, Account Authentication (Required), Login with SSO	 Signature Adoption: Pre-selected Style Signature ID: B7D37248-838E-4CAC-AE11-E7E55198A88D Using IP Address: 216.222.219.1 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document I approve this document	Sent: 1/14/2025 9:53:25 PM Viewed: 1/15/2025 11:26:50 PM Signed: 1/15/2025 11:27:15 PM
Electronic Record and Signature Disclosure: Accepted: 1/15/2025 11:26:50 PM ID: 21ed4b9d-45b9-4fac-b706-5f9dd51dac3e		
Michael Howarth michael.howarth@smith-nephew.com Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 6A0D1CAE-8929-4A9A-A17D-E3C3B2061255 Using IP Address: 216.222.214.6 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 1/14/2025 9:53:27 PM Viewed: 1/15/2025 3:56:45 PM Signed: 1/15/2025 3:58:58 PM
Electronic Record and Signature Disclosure: Accepted: 1/15/2025 3:56:45 PM ID: 1746521f-b3dc-413c-926b-78cf55ef39e8		
Simayi Yusufu SYusufu@proderm.de Statisician SGS proderm Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 86024048-F39B-4BF6-8902-15A8974351E1 Using IP Address: 89.246.251.118 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 1/14/2025 9:53:26 PM Viewed: 1/15/2025 7:52:46 AM Signed: 1/15/2025 7:53:40 AM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	1/14/2025 9:53:27 PM
Certified Delivered	Security Checked	1/15/2025 7:52:46 AM
Signing Complete	Security Checked	1/15/2025 7:53:40 AM
Completed	Security Checked	1/15/2025 11:27:15 PM

Payment Events	Status	Timestamps

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