Clinical investigation plan (in accordance with ISO14155)

An open-label, prospective, comparative human participant study to evaluate the clinically acceptable dressing presence and conformability properties of a prototype multilayer foam dressing in comparison to ALLEVYN◊ LIFE and another established medical device.

Author: Dr. Clare Vladimirskij

1 TITLE PAGE

Clinical investigation plan (in accordance with ISO14155)

Version: V4.0

An open-label, prospective, comparative human participant study to evaluate the clinically acceptable dressing presence and conformability properties of a prototype multilayer foam dressing in comparison to ALLEVYN◊ LIFE and another established medical device.

Short title	Human participant study of a prototype multilayer foam dressing on intact skin.	
EUDAMED number	CIV-24-02-046076	
Investigational medical devices (IMD) / comparators	**IMD:**	Prototype dressing
	Comparator_1:	Product name: [redacted]
		Generic pseudonym: Marketed dressing 1
	Comparator_2:	Product name: [redacted]
		Generic pseudonym: Marketed dressing 2
Intended purpose	Management of acute and chronic wounds.	
Design of the clinical investigation	Prospective, Open-Label, Comparative, Interventional Study	
Phase of development	Pre-market clinical evaluation	
Planned period of the clinical investigation	First participant in: JAN2025	Last participant out: APR2025
Sponsor	Smith & Nephew Medical Ltd. PO Box 81, 101 Hessle Road, Hull HU3 2BN, United Kingdom Phone: +44 (0) 1482 222 200, Fax: +44(0)1482 222 211	
Sponsor code:	HVS2313	
CRO	SGS proderm GmbH, Kiebitzweg 2, 22869 Schenefeld/Hamburg, Germany	
Principal investigator	Dr. med. K. Deuble-Bente, SGS proderm GmbH, Kiebitzweg 2, 22869 Schenefeld/Hamburg, Germany Phone: +49 40-839358-262, Fax: +49 40-839358-39	
SGS proderm study-no.	24.0062-99	

The clinical investigation will be performed in accordance with this document and the international standard ISO14155:2020 "Clinical investigation of medical devices for human subjects — Good clinical practice" was taken into account during the planning of this clinical investigation.

Summary of the revision history

Date	Version	Summary of changes	Author/ Updated by
16FEB2024	1.0	Initial version	Dr. Clare Vladimirskij
19APR2024	2.0	1. EUDAMED number was added (title page). 2. The references to the legislation which were no longer in force (MPG, MPSV, MEDDEV Guidelines) were updated / removed (sections 8.6., 15.1, and 16.2) 3. A statement that a device deficiency, which could have led to serious adverse events in the absence of appropriate measures or intervention or under less favourable circumstances, will be reported immediately to the BfArM as an individual report on the SAE reporting form from Germany, was added to section 18.8.2 and referenced to in section 18.8.5 . 4. [redacted] 5. Amended the days on which the subjective and objective dressing assessments were carried out (Table 2.1, sections 10.4.7, 10.4.15.6 and 10.4.15.7) to reflect that of the synopsis. 6. Updated section 6.1 reflect the Class IIB status. 7. Amended publication statement in section 21.1.	Dr. Clare Vladimirskij
13JUN2024	3.0	1. Added section on Information from the sponsor at the end of a clinical investigation or in the event of a temporary halt or early termination (section 20). 2. Changed typo ("lower" to "upper" confidence interval) in synopsis and section 11.3.1. 3. Justification for the 15% non-inferiority threshold added to section 9.3 and referenced to further in sections 11.2.1 and 11.3.1. 4. Updated the Biological Evaluation Report reference from BER015 to BER017 in sections 6.1, 7.1 and 8.6. 5. Updated the VT Risk Assessment reference from Feb2024 to v2_Jun2024 in sections 6.1, 7.1 and 8.6. 6. Added the rationale for the use of clinically acceptable dressing presence as the evaluation parameter for the primary endpoint (section 7.4). 7. Added comment that the assessments on percentage border lift, pad lift, pad integrity and adhesive offset will be based on the "counting grids method" to give an objective percentage score. (section 2, section 10.4.15) and a description of the grid counting method is given in section 10.4.10. 8. Added details of the pass criteria for clinically acceptable dressing presence to section 2 and section 11.2.1. 9. Updated the sponsor approvers (GCMA representatives).	Dr. Clare Vladimirskij
23SEP2024	V4.0	1. Removed 'clinically' from CADP (entire document apart from the title). 2. Removed pad lift and tracking to the pad from the	Dr. Clare Vladimirskij

		CADP and updated the details of the pass criteria. 3. Removed tracking to pad from objective assessment. 4. Added a definition of pad exposure to the description of primary endpoint in the Criteria for evaluation (statistics) section of the synopsis and section 11.2.1. 5. Updated the signature page (section 1.3) 6. Ordered bibliography alphabetically. 7. Completed footnote 9 about objective assessments (section 2.1). 8. Changed IMD name to Prototype dressing throughout. 9. Added generic pseudonym for comparators and changed this throughout. 10. Updated the planned period for the clinical investigation and the study duration (title page and synopsis, section 10.1.1, 10.3.2). 11. [redacted] 12. Added the abbreviation PD to section 4.1. 13. An explanation about determining non-inferiority based on confidence intervals and the non-inferiority limit was added to the synopsis (statistical methods) and section 11.3. 14. Updated the device description in section 6.1 to align with latest IB version, including the product design changes to the super-absorbent layer and release handles. 15. Updated the VT Risk Assessment reference from v2 Jun2024 to v3_Aug2024 in sections 6.1, 7.1, 8.3 and 8.6. 16. Updated the Biological Evaluation Report reference from BER017 to BER018 and added BES108 in sections 6.1, 7.1,8.3 and 8.6. 17. Added further detail to the rationale for the 15% non-inferiority margin (synopsis and section 9.3). 18. Updated the Figure 10.3 caption. 19. Harmonized section 11 to be aligned with comparable project (Sponsor study code: HVS2312; EUDAMED number: CIV-24-03-046336). 20. Updated section 12.3.3 to remove reference to 25 year retention period and make it compliant with current regulations for the product type. 21. Corrected RA to competent authority in section 14.1. 22. Removed repetitive mention of the dressing sizes (all outside of the IMD/comparator descriptions).	

1.1 Sponsor details

Name	Smith & Nephew Medical Ltd.
Phone no.:	+44(0)1482 222 200
Fax no.:	+44(0)1482 222 211
Email:	info@smith-nephew.com

1.2 Contact details of the investigation sites and external organizations

Name	Company / Institution	Administrative function related to the clinical investigation	Phone / Fax / Email
Dr. med. Kirstin Deuble-Bente	SGS proderm GmbH	Principal Investigator	Phone +49 40-839358-262 Fax +49 40-839358-39 Email KBente@proderm.de
David Ruwe	SGS proderm GmbH	Project Manager	Phone +49 40 839 358-323 Fax +49 40-839 358-39 Email DRuwe@proderm.de
Dr. Clare Vladimirskij	SGS proderm GmbH	Medical Writer	Phone +49 40 839 358-259 Fax +49 40-839 358-39 Email CVladimirskij@proderm.de
Elena Rehm	SGS proderm GmbH	Lead Data Management	Phone +49 40 839 358-954 Fax +49 40-839 358-39 Email Erehm@proderm.de
Eric Bibiza-Freiwald	SGS proderm GmbH	Lead Statistics	Phone +49 40-839 358-950 Fax +49 40-839 358-39 Email EBibiza@proderm.de

1.3 Signature page(s)

1.3.1 Approval statement of Smith & Nephew Medical Ltd.

The following persons have reviewed and approved this clinical investigation plan:

For Smith & Nephew Medical Ltd.

Rachel Jahnke
VP, Global Clinical Research Operations

Smith & Nephew
150 Minuteman Rd
Andover MA 01810
United States

Phone: +1520 989 4866

signature
Signed by:
Signer Name: Rachel Jahnke
Signing Reason: I approve this document
Signing Time: 25-Sep-2024 | 15:39:50 BST
98517B5EF45A456CBE7102BF1B8CCDA5

Karlie Morgan
Director of Clinical Study Management

7000 W. William Cannon Dr.
Austin Texas 78735
United States of America

Phone: +1 512 895 1257

signature
Signed by:
Karlie Morgan
Signer Name: Karlie Morgan
Signing Reason: I approve this document
Signing Time: 24-Sep-2024 | 15:35:57 BST
F420CE2095794AFD8CD1DC3D32055809

Kolja Boese
Senior Director, Global Medical Affairs

Smith & Nephew
Friesenweg 30
Hamburg 22763
Germany

Phone: +49 40879 744200

signature
Signed by:
Signer Name: Kolja Boese
Signing Reason: I approve this document
Signing Time: 24-Sep-2024 | 09:55:23 BST
DA5DDA49254C426E99365721E0A21315

Jaideep Banerjee
Director, Global Clinical Strategy & MSL

Smith & Nephew
150 Minuteman Rd
Andover MA 01810
United States

Phone: +1 614 558 6700

signature
Signed by:
Signer Name: Jaideep Banerjee
Signing Reason: I approve this document
Signing Time: 25-Sep-2024 | 13:09:39 BST
8167B6F2D41442A1BF94B6986205BB3C

Jay Jantz
Director of Global Biostatistics & Data Sciences

Smith & Nephew
150 Minuteman Rd
Andover MA 01810
United States

Phone: +1 978-749-1000

signature
Signed by:
Jay Jantz
Signer Name: Jay Jantz
Signing Reason: I approve this document
Signing Time: 23-Sep-2024 | 17:19:25 BST
B7D37248838E4CACAE11E7E55198A88D

Samuel Greenhalgh
Regulatory Affairs Director

Smith & Nephew
GBU Office
Hull, Yorkshire HU3 2BN
United Kingdom

Phone: +44 7818 550700

signature
Signed by:
sam greenhalgh
Signer Name: sam greenhalgh
Signing Reason: I approve this document
Signing Time: 24-Sep-2024 | 14:47:47 BST
1C73ED93193D48889F66F071859C80BC

Michael Howarth
Clinical Study Manager

Smith & Nephew
GBU Office
Hull, Yorkshire HU3 2BN
United Kingdom

Phone: +44 1482 673176

signature
Signed by:
Michael Howarth
Signer Name: Michael Howarth
Signing Reason: I approve this document
Signing Time: 24-Sep-2024 | 10:32:23 BST
6A0D1CAE89294A9AA17DE3C3B2061255

1.3.2 Approval statement of SGS proderm

The following persons have approved this clinical investigation plan:

Eric Bibiza-Freiwald
Lead Statistician

SGS proderm GmbH
Kiebitzweg 2
D-22869 Schenefeld
Tel: +49 40-839 358-950
Fax: +49 40-839 358-39

signature

Signiert von:
Eric Bibiza-Freiwald
Name des Unterzeichners: Eric Bibiza-Freiwald
Signiergrund: Ich habe dieses Dokument geprüft
Signierzeit: 24-Sep-2024 | 00:19:10 PDT
E00DEC46A3B24545B2C556D9F38DB375

1.3.3 Principal investigator statement

I have read this protocol and agree to conduct this clinical investigation in accordance with the regulations laid down in this clinical investigation plan, in the currently valid revision of the Declaration of Helsinki and in the International Standard ISO 14155 "Clinical investigation of medical devices for human patients — Good clinical practice" and applicable national laws and regulations.

Changes to this clinical investigation plan require written agreement of both investigator and sponsor. Changes may also be subject to additional submission and approval by the ethics committee and regulatory authorities.

Dr. Kirstin Deuble-Bente
Principal Investigator

SGS proderm GmbH
Kiebitzweg 2
D-22869 Schenefeld
Tel: +49 40 839358 262
Fax: +49 40 839358 39

signature

Signiert von:
Kirstin Deuble-Bente
Name des Unterzeichners: Kirstin Deuble-Bente
Signiergrund: Ich habe dieses Dokument geprüft
Signierzeit: 24-Sep-2024 | 11:39:56 MESZ
074A923ECD6C4BBEB655817010A20B7F

2 SYNOPSIS

Title of the clinical investigation	An open-label, prospective, comparative human participant study to evaluate the clinically acceptable dressing presence and conformability properties of a prototype multilayer foam dressing in comparison to ALLEVYN◊ LIFE and another established medical device.
Short title	Human participant study of a prototype multilayer foam dressing on intact skin.
Principal/coordinating investigator	Dr. med. K. Deuble-Bente, SGS proderm GmbH, Kiebitzweg 2, 22869 Schenefeld/Hamburg, Germany Phone: +49 40-839358-262, Fax: +49 40-839358-39
Study location (CRO)	SGS proderm GmbH, Kiebitzweg 2, 22869 Schenefeld
Period of the clinical investigation (planned)	First participant in: JAN2025 Last participant out: APR2025
References	**Obagi Z, et al.** Principles of Wound Dressings: A Review. Surg. Technol. Int. 2019;35:50-57. **Black J. et al.**, World Union of Wound Healing Societies (WUWHS) Consensus Document. Role of dressings in pressure ulcer prevention. Wounds International, 2016 **Rippon M. et al.**, Waring M., Bielfeldt S. An evaluation of properties related to wear time of four dressings during a five-day period. Wounds UK, 2015; 11(1):45-54 **Rossington A. et al.**, Clinical performance and positive impact on patient wellbeing of [redacted]. Wounds UK. 2013; 9(4): 91-95. **Forni C, et al.** Effectiveness of a multi-layer silicone-adhesive polyurethane foam dressing as prevention for sacral pressure ulcers in at-risk in-patients: Randomized controlled trial. Int. J. Nurs. Stud. 2022;127:104172.
Introduction	
Background	Wound dressings are integral to effective wound management, promoting healing and shielding the wound from infection (Obagi, 2019). Additionally, dressings can also be used on intact skin as part of a pressure injury prevention protocol in at-risk individuals. (Black, 2016). In order to be effective, the dressing must stay in place for an appropriate length of time. Factors influencing wear time are related to the patient, the wound and the properties of the dressing itself (Rippon, 2015). These properties determine the comfort during wear which in turn influences premature dressing removal. This study compares a Prototype dressing (IMD) with two established dressings (comparators) for a robust comparison of properties affecting wear time. Adverse events (AEs) like skin sensitization, blistering, contact dermatitis, maceration and pain on removal, are rare for such dressings, with a low incidence observed in the comparators, suggesting a similar risk profile for the Prototype dressing (Rossington, 2013; Forni, 2022).

Purpose of the clinical investigation	To evaluate the Prototype dressing on healthy, intact skin to assess dressing retention and other dressing performance parameters.
Objectives	
Primary objectives	To demonstrate non-inferiority of the Prototype dressing to Marketed dressing 1 and Marketed dressing 2 with regards to acceptable dressing presence in human participants on the thighs and shins at day 7.
Secondary objectives	To generate data to support: • 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
Population of the clinical investigation	
Number of participants (planned)	120 healthy participants are planned to be randomized for this study so that at least 105 participants are expected to complete the study.
Description of participants	Participants in general good health with intact skin (i.e. without indication for treatment with wound dressings) who will be recruited according to the in- and exclusion criteria.
Inclusion criteria	1. Participant is capable of providing informed consent 2. Participant is willing and able to make all required study visits 3. Aged 18-70 years at the time of signing the informed consent* 4. Participant must be in good health, as determined by the Investigator, based on medical evaluation, including medical history and skin application site assessment (healthy intact skin at or near any of the dressing application sites) 5. Participant is willing not to use cosmetic or medicinal lotions, creams, ointments and anything else which may interfere with dressing adhesion at dressing application sites for the duration of the study from 24 hours before dressing application on Day 0. 6. Participant is willing to have excess hair removed from the dressing application sites 7. Participant is willing to avoid immersing the dressings in water (no swimming or bathing) for the duration of the study *at least 10% of participants are aged >55 years
Exclusion criteria	1. Female participant who is pregnant, or lactating. 2. Participant has a known sensitivity to any of the study products, materials or ancillary product or components. 3. Known skin sensitivity or allergies to adhesives, skin wipes, soap, surgical first-aid dressings, natural rubber or rubber latex, etc. 4. Participants with a current active skin disease (e.g., eczema, psoriasis, or severe dermatoporosis), sunburn or skin peeling at the dressing application sites. 5. Participants with a medical condition which may interfere with their perception of pain (such as diabetes, small-fibre neuropathy, allodynia, hyperalgesia etc.). 6. Heavy smokers (e.g. >20 cigarettes (~1 pack) a day over the last 10 years) whose pain perception may have been affected through

	smoking. 7. Participants with any skin features near any of the dressing application sites that could be identifiable/may interfere with skin assessments (e.g. tattoos/distinctive markings or scars/keloids). 8. Participants diagnosed with hyperhidrosis or who self-report their normal sweating level to be severe as determined by the Sweating Severity Self-Assessment (SSSA) at screening (e.g. mild, moderate, severe). 9. Participants not willing to refrain from the use of pain relief medication on assessment days (1, 3 and 7) and in the case of certain medications, 24 hours before assessments. 10. Participants unwilling to refrain from activities which may directly affect the dressing, dressing application sites or assessments (such as undergoing planned scanning procedures, e.g., X-ray, magnetic resonance imaging (MRI) and computed tomography (CT) scanning; exposure to airport scanners or devices emitting radio waves; exposure to atypical conditions of pressure, humidity and temperature; immersing the dressing in water e.g. bathing / swimming / cleaning the dressing application sites; using a sauna; undertaking strenuous physical activity like aerobics, running, cycling, heavy labor etc.; using lotions/creams/ointments etc. at the dressing application sites; excessively exposing the dressing application sites to the sun (e.g. sunbathing for >1 hour); wearing tightly fitting clothes which could affect the dressings. 11. Individuals who have participated in a clinical study in the last 7 days, using the same dressing application sites. 12. Participants with poor compliance and / or poor willingness to co-operate. 13. Individuals who should not participate in the clinical investigation for any other reason (including the taking of certain medications) as judged by the Investigator. 14. Individuals who are inmates in psychiatric wards, prison or state institutions, or any individuals otherwise regarded as vulnerable (as per ISO 14155 Section 3.55). 15. Employees of the investigation sites directly involved in this clinical investigation or employees of the sponsor's company.
Investigational medical device(s)	
For this investigation, the sizes of the square dressings (Prototype dressing and Marketed dressing 2) will be the same, or the equivalent size for Marketed dressing 1, which has a different pad size and border width due to its quadrilobe shape.	
Investigational medical devices	**Name:** Prototype dressing **Materials/ingredients:** Five-layer foam dressing [redacted]. [redacted] Size: 10cm x 10 cm. **Intended purpose:** management of acute and chronic wounds. **Mode of application/use:** topical application. **Frequency of application/use:** single use
Comparators	**Name:** Marketed dressing 1 **Materials/ingredients:** Five-layer foam dressing [redacted]

	[redacted]. Size: 12.9×12.9cm. **Intended purpose:** management of acute and chronic wounds. **Mode of application/use:** topical application. **Frequency of application/use:** single use
	Name: Marketed dressing 2 **Materials/ingredients:** Five-layer foam dressing [redacted] Size: 10cm x 10 cm. **Intended purpose:** management of acute and chronic wounds. **Mode of application/use:** topical application. **Frequency of application/use:** single use
Allocation of the investigational medical devices	Three different dressings (the Prototype dressing and comparators) will be randomized over four locations. Participants will be allocated to one of two groups, with the dressing randomized to either the left or right thigh/shin in a 1:1 ratio. Both the group allocation and the side allocation are carried out using a randomization process. • Group 1: Prototype dressing and Marketed dressing 1 on the shins. Prototype dressing and Marketed dressing 2 on the thighs. • Group 2: Prototype dressing and Marketed dressing 1 on the thighs. Prototype dressing and Marketed dressing 2 on the shins.
Methodology	
Design of the clinical investigation	Prospective, open-label, comparative, interventional study with intra-individual comparison.
Schedule of the clinical investigation per participant:	Duration of the clinical investigation assessment period: 7 days. Duration of the clinical investigation including the screening period: maximum 2 weeks. The participants will attend 5 site visits: Day -7 to Day 0: one screening visit* Day 0: application of the dressings and 1st round of assessments Day 1: 2nd round of assessments Day 3: 3rd round of assessments Day 7: 4th round of assessments and removal of dressings * Screening can be completed on Day 0, or at a separate visit up to 7 days prior to Day 0.
Procedure(s)	<u>Informed consent</u> Potential participants may only be enrolled in the clinical investigation after providing written informed consent at the site. <u>Hair removal (24-48 hours before dressing application)</u> Hair should be removed 24 hours prior to dressing application using electric clippers/trimmers. Should the participant regularly wet shave the dressing application sites, they may prepare the site using the wet shave technique at most 48 hours prior to dressing application; otherwise participants will be instructed to only use electric clippers. The

	application site will be checked that it is free from hair at screening or, if screening occurred >24 hours before dressing application, again on Day 0. If the participant does not usually wet shave and does not have access to a pair of electric clippers/trimmers, the participant will undergo hair removal with electric clippers/trimmers at the study site at Day 0. The dressing application sites will be checked during the physical examination of the skin condition before dressing application on Day 0 and any shaving related injury at the application test site will be noted and the participant regarded as a screening failure and excluded from the study. <u>Dressing application (on Day 0)</u> Dressings will be applied by the investigator or trained site personnel as in accordance with the respective IFUs on Day 0. Thigh and shin dressings will be applied with participants standing up. Before dressing application, the dressing application site will be cleaned by trained site personnel with a saline wipe followed by air drying before dressing application on Day 0. <u>Dressing removal (on day 7)</u> The investigator or trained site personnel will remove the dressing as in accordance with the respective IFUs following the same standard procedure: Lift one corner and slowly peel back until completely removed; and following the same order of removal for each participant, e.g. (i) right thigh, (ii) left thigh, (iii) right shin, (iv) left shin. There will be a 10 min interval between the removal of each dressing to allow for any residual pain to subside. <u>Photography (on days 0, 1, 3 and 7)</u> Photographs will be taken by the investigator or trained site personnel 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). • after the dressing assessments on Day 1. • after the dressing assessments on Day 3. • before the dressing removal (any day that dressing requires removal).
Assessment(s)	<u>Physical examination of the skin condition at application test (at screening and on Day 0)</u> An assessment of current skin disease (e.g., eczema, psoriasis), sunburn or skin peeling at the dressing application sites will be performed by the investigator (or suitably medically qualified site personnel) at the Screening Visit and on Day 0 (if the two visits do not coincide). This is performed in order to establish eligibility. <u>Sweating Severity Self-Assessment (SSSA) (at screening)</u> During the screening visit, the participants will assess their normal level of sweating according to the ordinal scale: mild, moderate, severe. <u>Dressing quality control (QC) check (on Day 0)</u> Prior to dressing application the dressing should be checked by the investigator or trained site personnel to ensure: (i) packaging is intact;

(ii) dressings are not damaged; (iii) there are no visual contaminants.

Dressing application assessment (on Day 0)
The investigator or trained site personnel will assess the following:

[redacted]

Objective dressing assessment (on days 1, 3 and 7)
The investigator or trained site personnel will assess the following:

i) **Dressing presence**: is the dressing in place? : binary answer "yes" / "no". If "no" then the reason for premature removal or detachment will be recorded.
ii) **Acceptable dressing presence**: for dressings in place, do the dressings meet the definition of "acceptable dressing presence"?: binary answer "yes" / "no".
The definition of acceptable dressing presence criteria in this healthy participant study is: dressings present with no border lift reaching the pad and no pad exposure. This is a is a binary pass / fail assessment based on passing all three of the following criteria:
    1. Is the dressing missing? (pass = "no", fail = "yes")
    2. Is there border lift reaching the pad? (pass = "no", fail = "yes")
    3. Is the pad exposed*? (pass = "no", fail = "yes")

*Pad exposure is the lifting of the pad, or any other compromise that breaches the dressing seal (including tears to the top-film).

If dressings do not meet the acceptable dressing presence criteria, the reasons why (e.g., border lift, pad exposure) will be documented.

iii) **Border lift**: what is the percentage border lift?: according to the following ordinal scale "0% (no lift)", "1-25%", "26%-50%", "51%-75%", "76-100%", or "dressing missing". Based on the "counting grids method" to give an objective percentage score.
iv) **Pad lift**: what is the percentage pad lift?: according to the following ordinal scale "0% (no lift)", "1-25%", "26%-50%", "51%-75%", "76-100%", or "dressing missing". Based on the "counting grids method" to give an objective percentage score. Should any dressing demonstrate >=50% pad lift, it will be removed and Dressing Removal Assessments will be conducted.
v) **Pad integrity**: Are there any changes in pad integrity (e.g., bunching/folding/ridges)? according to the following ordinal scale "0% (no change)", "1-25%", "26%-50%", "51%-75%", "76-100%", or "dressing missing". Based on the "counting grids method" to give an objective percentage score.
vi) Did the dressing require removal today? (Days 1 and 3): "yes", "no" or "dressing missing". If "yes" then the reason for removal should be recorded.

Subjective Dressing Assessment (on Days 1, 3 and 7)
The participant will be asked to assess the following:

i) **Dressing comfort**: was the dressing comfortable during wear?:

"yes", "no" or "dressing missing".

ii) **Itching**: was the dressing itching during wear: according to the ordinal scale: "none", "mild/intermittent", "mild/persistent", "moderate", "severe", "dressing missing". The levels of itching corresponding to "mild/persistent", "moderate", "severe" would be classed as adverse events.

Extent of dressing exposure to water (on Days 1, 3 and 7)

[redacted]

Activity Assessment (on Days 1, 3 and 7)

The participant will be asked to assess the duration and level of their physical activity since their last study appointment. Specifically, using the ordinal scale: "0 minutes", "<1 hour", "1-6 hours", ">6 hours"; participants will be asked to report the duration of: (i) kneeling/crouching on the floor with legs beneath them (e.g., playing with children, reaching into a low cupboard, reaching for low laying files at work); (ii) mild activity (e.g., walking, light housework such as dusting/washing dishes, serving customers behind a counter); (iii) moderate activity (e.g., gardening, housework such as scrubbing floors/washing windows, carrying light loads at work); (iv) strenuous activity (e.g., aerobics, running, cycling, heavy labor). Each specific strenuous activity will be recorded in the electronic case report form.

Subjective dressing removal assessment (on Day 7)

Immediately following removal of the dressing, the participant will be asked to assess the following:

[redacted]

Objective dressing removal assessment (on Day 7)

The investigator or trained site personnel will assess the following:

i) **Skin erythema:** what was the extent of skin erythema 5 minutes after removal?: according to the ordinal scale: "no reddening", "mild reddening (slight pink)", "moderate reddening (red)", "severe reddening (beet red)". The latter two categories of skin erythema ("moderate reddening" or "severe reddening") would be classed as adverse events.

ii) **Blistering:** was there any sign of blistering 5 minutes after dressing removal?: binary "yes" or "no". Any blistering would be classed as an adverse event.

[redacted]

	[redacted] vi) **Skin occlusion**: what was the extent of skin occlusion after dressing removal?: according to the ordinal scale: "none", "clammy skin", "noticeable moisture", "whitening of skin", "skin breakdown". The latter two categories of skin occlusion ("skin whitening" or "skin breakdown") would be classed as adverse events. vii) **Skin stripping**: was there any visible signs of skin stripping after dressing removal?: binary "yes" or "no". Any occurrence of visible skin stripping would be classed as an adverse event. Investigator Dressing Quality Assessment (on Day 7) The investigator or trained site personnel will be asked to rank the 3 dressings in order of their quality or state that there was no difference. This assessment will record the general perception of dressing quality irrespective of location. Participant Dressing Quality Assessment (on Day 7) The participant will be asked to rank the 3 dressings in order of their quality or state that there was no difference. This assessment will record the general perception of dressing quality irrespective of location. Early Termination Assessment 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: • objective dressing assessment • subjective dressing assessment • activity assessment - After removal of the dressing the following should be performed: • subjective dressing removal assessment • objective dressing removal assessment • investigator dressing quality assessment • participant dressing quality assessment - If no dressings remain at the ET visit then only the two dressing quality assessments will be performed.
Safety assessment(s)	Skin assessment: Days 0, 1, 3 and 7. The condition of the skin in terms of any skin-related adverse events (AEs) and device deficiencies (DDs), e.g., blistering, erythema, swelling, rash, sensitivity to adhesive, skin stripping, skin occlusion or itching will be assessed by the investigator or suitably medically qualified site personnel. AE or DD reporting The participant can report an AE or DD at any point during the investigation.

	Changes in concomitant therapies This will be documented at each participant's visit at the investigational site.
Follow-up period	No general follow-up is planned.
Sample size calculation	The sample size is based on separate non-inferiority tests for Prototype dressing vs Marketed dressing 1 and Prototype dressing vs Marketed dressing 2 regardless of dressing location. 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 vs Marketed dressing 1 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 participants 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 1 – Prototype dressing), is lower than the non-inferiority threshold of 15% (%C - %IMD < 15%, were %IMD and %C denotes the proportion of devices with acceptable dressing presence for IMD and comparator). The same assumptions as above apply to the Prototype dressing vs Marketed dressing 2 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 study. The sample size was calculated using nQuery + nTerim 3.0 **Rationale for the 15% non-inferiority margin** The selection of a 15% non-inferiority margin is grounded in established statistical and clinical considerations for non-inferiority trials. This margin is deemed appropriate based on the guidance provided by Chow and Song (2016), who discuss the selection of non-inferiority margins in the context of active control (non-inferiority) trials. The paper indicates that, in the absence of a commonly accepted specific margin, a non-inferiority margin within the range of 10-15% of the baseline effect size (e.g., the percentage of comparator dressings with acceptable presence) is frequently utilized. Therefore, the choice of a 15% non-inferiority margin is both scientifically and clinically sound, ensuring that the results of the investigation will be meaningful and interpretable within the context of existing therapeutic standards. Furthermore, this is in compliance with US FDA advice on having a non-inferiority margin or equivalence limit of ±15% in non-inferiority or equivalence trials, where there is an expected response/success rate of 80–90% (see page 3 and Table 2 of Chow and Song (2016)). Wear time and clinical performance of multilayer foam dressings in clinical practice varies according to the quality of the dressing, the status of the wound (depth, area and exudate level/flow), the patient (age, skin elasticity, comorbidities, mobility, etc.) and the site of application to the body (performance is best on arms and legs compared with highly

	mobile jointed areas, such as the knees or elbows). Both comparator dressings in this study are market leaders with clinically proven high performance, which is unlikely to be surpassed; therefore, a non-inferiority study design is appropriate to validate the performance of a novel multilayer foam dressing.
Criteria for evaluation (statistics)	
	Primary endpoint • Non-inferiority comparison of the Prototype dressing vs Marketed dressing 1 in terms of the acceptable presence* of dressings at day 7 on thighs and shins. • Non-inferiority comparison of the Prototype dressing vs Marketed dressing 2 in terms of the acceptable presence* of dressings at day 7 on thighs and shins. *defined as dressings present, with no border lift reaching the pad, no pad exposure (where pad exposure is the lifting of the pad, or any other compromise that breaches the dressing seal (including tears to the top-film)). The parameter "acceptable dressing presence" is a binary pass / fail assessment based on passing all three of the following criteria: 1. Is the dressing missing? (pass = "no", fail = "yes") 2. Is there border lift reaching the pad? (pass = "no", fail = "yes") 3. Is the pad lifted or exposed? (pass = "no", fail = "yes") **Secondary endpoints** Non-inferiority comparison of the Prototype dressing vs the comparators in terms of: • Acceptable dressing presence (thigh and shins) 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. [redacted]

	
Safety	Descriptive presentation of the Prototype dressing vs the comparators in terms of: • 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.
Statistical Methods	
	The primary analysis is performed separately for the two primary endpoints, which represent the two IMDs: • Prototype dressing vs Marketed dressing 1 on thighs and shins. • Prototype dressing vs Marketed dressing 2 on thighs and shins. The primary endpoint is analyzed using a comparison of Newcombe's score method calculated confidence intervals against the non-inferiority threshold. Non-inferiority is subsequently demonstrated if the upper end of the 97.5% confidence interval is less than the non-inferiority threshold of 15%. As two primary endpoints are tested, the analysis is performed with a type I error of alpha=2.5%, so that the family wise error rate can be fixed at 5%. The analysis will not account the two groups used for randomisation or the dressing application site location. Consequently, all IMD data points are used in the statistical comparison against both comparators, which means that the IMD has twice the number of data points in the analysis. The primary analysis is planned as a non-inferiority test, using a non-inferiority threshold of 15% (%C - %IMD < 15%, where %IMD and %C denotes the proportion of devices with acceptable dressing presence for IMD and comparator). The testing of the secondary endpoints is planned as a non-inferiority analysis. The inferential analysis of the secondary endpoints is based on their scale properties. The corresponding analyses with specific non-inferiority thresholds are specified in writing in the statistical analysis plan before randomization of the first participant. The analysis of primary and secondary endpoints will be split into two separate hierarchies:

1. Prototype dressing vs Marketed dressing 1.
2. Prototype dressing vs Marketed dressing 2.

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

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 alpha = 2.5% significance level. This means that the alpha level is maintained to correct for multiple comparisons. The type I error of alpha = 2.5% results from the two primary endpoints and the Bonferroni adjustment required as a result

The order of each hierarchy will be defined as:

Hierarchy 1: Prototype dressing compared with Marketed dressing 1

Order	Endpoint
1	Acceptable dressing presence* (thigh and shin) at day 7 (Primary endpoint)
2	Acceptable dressing presence* (thigh and shin) 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.	

Hierarchy 2: Prototype dressing compared with Marketed dressing 2.

Order	Endpoint
1	Acceptable dressing presence* (thigh and shin) at day 7 (Primary endpoint)
2	Acceptable dressing presence* (thigh and shin) 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.

2.1 Schedule of the clinical investigation

Table 2.1 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	X	X
Objective dressing assessment[9]			X	X	X
Subjective dressing assessment (dressing comfort, itching)			X	X	X
[redacted]			X	X	X
Activity assessment[10]			X	X	X
Photographs (of dressing in place and, if required, of any AE [redacted])[11]		X	X	X	X
Dressing removal					X
Subjective dressing removal assessment (pain intensity)					X
Objective dressing removal assessment[12]					X
Investigator assessment of dressing quality					X
Participant assessment of dressing quality					X
Adverse event assessment including AEs, ADEs, SADEs, SAEs, device deficiencies		X	X	X	X[13]
Concomitant medication/therapy and	X	X	X	X	X

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]
changes thereof					
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 ≥ 5days 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. Thigh and shin dressings will be applied with participants standing up.
8. Includes assessment of the following parameters: [redacted]
9. Includes assessment of the following parameters: acceptable dressing presence, dressing presence, border lift, pad lift, pad integrity and if the dressing required removal..
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. Photographs of dressings in place and, if required, of any AE/adhesive offset will be taken at the following time points:
    - after the initial dressing application by the investigator (Day 0).
    - after the dressing assessments on Day 1.
    - after the dressing assessments on Day 3.
    - before the dressing removal (any day that dressing requires removal).
12. [redacted]
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:
    - objective dressing assessment
    - subjective dressing assessment
    - activity assessment

    After removal of the dressing the following should be performed:
    subjective dressing removal assessment
    - objective dressing removal assessment
    - investigator dressing quality assessment
    - participant dressing quality assessment

    If no dressings remain at the ET visit then only the two dressing quality assessments will be performed.

3 TABLE OF CONTENTS

3.1 List of in text tables

3.2 List of in text figures

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

4.1 Abbreviations

Abbreviation[1]	Definition
ADE(s)	Adverse Device Effect
AE(s)	Adverse Event(s)
BER	Biological Evaluation Report
BES	Biological Evaluation Statement
BfArM	Bundesamt für Arzneimittel und Medizinprodukte (Federal Office for Drugs and Medical Devices)
BRC	Blinded Review Committee
CDM	Clinical Data Management
CIP	Clinical Investigational Plan
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
DD	Device Deficiency
DMIDS	Deutsches Medizinprodukte-Informations- und Datenbanksystem (German Medical Devices Information and Database System)
DMP	Data Monitoring Committee
DMP	Data Management Plan
DRKS	Deutsches Register Klinische Studien (German Register of Clinical Studies)
eCRF	Electronic CRF
EDC	Electronic Data Capture System
FAS	Full Analysis Set
GCP	Good Clinical Practice
h	Hour
IEC	Independent Ethics Committee
IFU	Instructions for Use
IMD	Investigational Medical Device
IMDRF	International Medical Device Regulators Forum
IRB	Institutional Review Board
LDPE	Low Density Polyethylene
MedDRA	Medical Dictionary for Regulatory Activities

[1] Above mentioned abbreviations may but need not necessarily occur in this document.

Abbreviation[1]	Definition
min	Minute
MDCG	Medical Device Coordination Group
MPDG	Medical Device Law Implementation Act (*Medizinprodukterecht-Durchführungsgesetz)*
PD	Protocol Deviation
PP	Per Protocol Population
RA	Risk Analysis
SADE(s)	Serious Adverse Device Effect
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SDV	Source Data Verification
SEC	Self-Evident Correction
SOP	Standard Operating Procedure
SP	Safety Population
SSSA	Sweating Severity Self-Assessment
VAS	Visual Analog Scale
UADE	Unanticipated Adverse Device Effect
WMA	World Medical Association

4.2 Definition of terms

Term	Definition
Comparator	Medical device, therapy (e.g. active treatment, normal clinical practice), placebo or no treatment, used in the control group in a clinical investigation.
Compliance	Adherence to all clinical investigation-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.
Clinical investigation	Systematic investigation in one or more human participants to assess clinical performance, effectiveness, or safety of a medical device. The term "clinical investigation" is used synonymously with "investigation" in this document. Additionally, the terms "investigation" and "study" also used synonymously in this document.
Designee	A person/role with the appropriate training and qualifications to whom a task has been delegated without relinquishing responsibility of the specified person/role.
Start date of the clinical investigation	The date of the first participant's first visit.
End date of the clinical	The date of the last participant's last visit.

investigation	
Investigator's Brochure	A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the clinical investigation of the investigational product(s) in human participants.
Investigational (medical) device/investigational device (IMD)	Medical device being assessed for clinical performance, effectiveness, or safety in a clinical investigation. Note 1: This includes medical devices already on the market that are being evaluated for new intended uses, new populations, new materials or design changes. Note 2: This includes medical devices already on the market that are being evaluated within their intended use in a post-market clinical investigation (interventional or non-interventional). Note 3: For the purpose of this document, the terms "investigational medical device" and "investigational device" are used interchangeably.
Non-important protocol deviation (PD)	Non-important protocol deviations are defined as deviations that do not adversely affect the risk/benefit ratio of the investigation, the rights, safety, or welfare of the participants or others, the quality or integrity of data or the integrity of the investigation. For example, an isolated occurrence (noncompliance) of an out of-window visit for a non-pivotal measurement would be considered as a non-important PD.
Important protocol deviation (PD)	Important protocol deviations are liable to strongly impact the quality of the data, increase risks/benefit ratio of the investigation, substantially decrease the treatment benefit or mislead the interpretation of the investigation results, in particular for the analysis of the primary objective. For example, several occurrences (misconduct) of an out of-window visit for a pivotal measurement affecting the primary endpoint of the investigation would be considered as an important PD.
Regulatory authorities	Governmental bodies having the power to regulate, including authorities that review submitted clinical data and those that conduct inspections.
Screened participant	Participant who has signed an informed consent form.
Participant	An individual who participates in a clinical trial, either as the recipient of the investigational product(s) or of a comparator.
Test products	Both investigational and comparator product. Any substance or preparation intended to be placed in contact with the various external parts of the human body or with the teeth and the mucous membranes of the oral cavity.

4.3 Trademark information

Trademark	Company
[redacted]	Smith & Nephew Medical Ltd. [redacted]

5 INTRODUCTION

Wound dressings are integral to effective wound management, playing a crucial role in creating an environment which promotes healing and shields the wound from infection and external contaminants (Obagi, 2019). In addition, dressings can also be used on intact skin as part of a pressure injury prevention protocol. This practice is essential in helping prevent pressure injuries in individuals who are at risk, providing an additional layer of protection against potential skin damage and pressure ulcer formation (Black, 2016 and Heasler, 2019).

In order to be an effective wound dressing, the dressing must stay in place for an appropriate length of time as frequent removal of the dressing could cause trauma to the wound bed and irritation to surrounding skin (Rippon, 2012) as well as increasing the risk of infection and delaying the healing process (Bowler, 1999, Solowiei, 2012 and McGuiness, 2004).

Factors influencing the wear time of a dressing are related to the patient (i.e. the mobility of the patient and the frequency and extent of bathing), the wound (i.e. location, size, amount of exudate, surrounding skin condition and extent of infection) and the properties of the dressing itself (i.e. dressing adhesion, adhesive skin compatibility, exudate containment capacity, dressing conformability) (Rippon, 2015). Additionally, these properties will determine the comfort during wear which in turn will determine the extent to which the patient interferes with the dressing increasing the risk of premature dressing removal.

In this study one Prototype dressing (IMD) will be compared with two established marketed silicone foam dressings (comparators) at two anatomical locations for a robust comparison of the properties which influence wear time. Though very rare, reported AEs related to this type of dressing include: skin sensitization (including erythema, pruritus and skin rash), blistering, contact dermatitis, pain on removal and maceration. However, the incidence of these AEs with the comparators has been found to be low and therefore is also expected to be low for the Prototype dressing (Rossington, 2013; Beeckman, 2021; Forni, 2018; Forni, 2022).

6 IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

6.1 Summary

The Prototype dressing with its intended clinical use in treatment of acute and chronic wounds is a Class IIb medical device (EU Medical Device Regulation 2017/745 Annex VIII).

Figure 6.1 The dressing structure of the Prototype dressing.

Top Film

The breathable top film is both waterproof and acts as a bacterial barrier. The top film also allows controlled moisture evaporation, and thus facilitates a moist wound healing environment.

Masking Layer

The investigational device contains a polyurethane masking layer to help reduce the visual impact of absorbed exudate within the dressing.

Fluid Locking Layer

[redacted] The conformable design enables the dressing to be worn over challenging areas of the body which undergo a higher range of mobility. The dressing is designed to stay in place over the intended wear time, including during patient movement.

Absorbent [redacted] Foam

[redacted] The [redacted] foam helps to maintain a moist wound healing environment by absorbing exudate, but not drying out the wound.

[redacted] **Skin Adhesive Contact Layer (Wound Contact Layer)**

[redacted] The perforated WCL is a gentle yet enduring adhesive layer, maintaining retention for the wear time of the dressing, and allowing fluid to pass from the wound bed to the absorbent pad. [redacted]

Removable Plastic Protector (Release Handles)

There is removable protective material on the WCL. This protects the adhesive surface during transport, storage and initial handling before use. It also facilitates the handling of the dressing prior to application. Compared to the current Marketed dressing 1 range, the handles in the investigational device have been changed to be compatible with the modified silicone adhesive and have the addition of a coloured branded strip for product recognition and a visual anchor for application training/guidance. Immediately prior to the device's application to the skin, the protectors are to be removed.

Risk evaluations have been undertaken, indicating no unacceptable risks for any of the materials comprising the Prototype dressing or comparators (Risk Assessment RA_VT_HVS2313_v3_Aug2024; Biological Evaluation Report/BER BER018; Biological Evaluation Statement BES108).

Further details on the investigational device(s) and comparator(s) are provided in Section 10.2.

6.2 Details concerning the manufacturer of the investigational device

The legal manufacturer of the Prototype dressing and the comparator Marketed dressing 1 is Smith & Nephew Medical Limited, 101 Hessle Road, Hull, HU3 2BN UK, who is also the sponsor of the study.

The materials used in the manufacture of the investigational device are either manufactured by 3rd party suppliers (approved by Smith & Nephew to design and manufacture materials for medical devices) or manufactured by Smith & Nephew in the United Kingdom.

The assembly of the investigation devices will be manufactured by pilot process at the above address. During the manufacture process, 100% inspection will be performed on the dressings to ensure the investigational device is representative and equivalent to final product. Representative manufactured samples will be tested against the device specification for release of the investigational device for use in the clinical study.

The legal manufacturer or the comparator Marketed dressing 2 is [redacted]

6.3 Intended purpose of the investigational device in the investigation

To evaluate the Prototype dressing on healthy, intact skin to assess dressing retention and other dressing performance parameters.

6.4 Population and indications for which the investigational device is intended

The target population for the Prototype dressing (once CE marked) is patients with chronic or acute wounds.

6.5 Description of the investigational devices and comparators

The following investigational devices and comparators will be tested in this clinical investigation:

Investigational device 1	Prototype dressing
Materials/ingredients:	Five-layer foam dressing [redacted] Size: 10cm x 10 cm.
Intended purpose/use:	management of acute and chronic wounds.
Mode of application:	topical application.
Storage conditions:	Dry conditions; room temperature, not above 25 °C, 77 °F.
Manufacturer:	Smith & Nephew Medical Limited

Comparator 1	Marketed dressing 1
Materials/ingredients:	Five-layer foam dressing [redacted] Size: 12.9×12.9cm.
Intended purpose/use:	management of acute and chronic wounds.
Mode of application:	topical application.
Storage Conditions:	Dry conditions; room temperature, not above 25 °C, 77 °F.
Manufacturer:	Smith & Nephew Medical Limited

Comparator 2	Marketed dressing 2
Materials/ingredients:	[redacted] Size: 10cm x 10 cm.
Intended purpose/use:	management of acute and chronic wounds.
Mode of application:	topical application.
Storage Conditions:	Dry conditions; room temperature, below 35°C (95°F).

Manufacturer:	Mölnlycke Health Care AB

Composition and certificates of analysis for the test products will be provided by the Sponsor for the self-produced products and will be supplied with the study samples. The Sponsor ensures identity and for the self-produced products, additionally stability, strength, purity, composition and other characteristics that appropriately define the investigational device.

6.5.1 Justification for choice of comparator

Marketed dressing 1 and Marketed dressing 2 are also silicone foam wound dressings with similar functions as the Prototype dressing and are also designed for extended wear times (up to 7 days). In addition, as both comparators are high performing products in the market, they provide a rigorous benchmark for comparisons.

6.5.2 Number of investigational devices to be used together with a justification

One Prototype dressing or comparator will be applied individually to each test site with one device per test site. Each participant will receive four devices in total, two Prototype dressings and one of each comparator. Participants will receive the Prototype dressing and one of the comparators; one dressing at each test site on the thighs and at each test site on the shins (randomized left or right for more details see section 11.3.5.1).

6.6 Traceability of the investigational device during and after the clinical investigation

The Prototype dressing and comparators will be labelled in accordance with current regulation. Each Prototype dressing / comparator will be labeled individually so that traceability is assured.

For further details, please refer to Section 15.

6.7 Training and experience needed for use of the investigational device

The Prototype dressing will be applied by personnel trained in the application of dressings. Prior to participant recruitment, the Investigator and any other staff member involved in the study will be trained on the requirements of the protocol including application, assessments (i.e. judging clinical acceptable dressing presence as well as percentage scoring of applicable parameters according to the grid counting method, for details see section 10.4.10) and removal of the dressings (the Prototype dressing and comparators according to the respective IFUs). Training will be documented per local processes.

6.8 Description of specific medical or surgical procedures involved in the use of the investigational device

Not applicable.

6.9 References to the IB and IFU

For details regarding the investigational medical device, refer to the IB (IB/Avenger/001) and Section 6.5. The IFU is included in the IB.

7 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

7.1 Evaluation of pre-clinical data to date

Pre-clinical data have shown that the Prototype dressing as well as the comparators Marketed dressing 1 and Marketed dressing 2 are safe medical devices with no remaining unacceptable risks concerning the chosen ingredients (Biological Evaluation Report Reference (BER): BER018, Biological Evaluation Statement BES108, Risk Assessment RA_VT_HVS2313_v3_Aug2024)).

7.2 Evaluation of clinical data to date

Although there is no pre-existing clinical data for the Prototype dressing, its design and functionality are closely related to the comparator Marketed dressing 1, for which substantial clinical data exists (for details of the full literature review, pre-clinical, clinical, safety data and a risk analysis refer to the IB). As the differences between the Prototype dressing and this comparator are very small, the fact that the comparator is very well tolerated implies that the Prototype dressing would also be very well tolerated.

7.3 Clinical development stage

The investigational medical device is in the pre-market stage.

7.4 Rationale for the design of the clinical investigation

In this interventional pre-market clinical investigation, the Prototype dressing will be used on healthy intact skin and will evaluate the non-inferiority of the Prototype dressing with regard to parameters influencing the wear time of the Prototype dressing in comparison to the two high performing comparators already on the market. Intra-individual comparison will ensure consistency of the variable participant dependent factors which could affect the endpoints of this study.

The choice of the evaluation parameter of "acceptable dressing presence" for the primary endpoint was based on a comprehensive assessment of its relevance and accuracy in reflecting the clinical performance of wound dressings. While quantitative measures such as percentage adherence at specific time points provide valuable data, they often fail to capture critical nuances in clinical performance. For example, a dressing that maintains high adherence may still be clinically unacceptable if the pad is exposed or compromised, increasing the risk of infection.

By utilizing the proportion of dressings with 'acceptable dressing presence' as the primary endpoint, a holistic evaluation of dressing efficacy is ensured as the assessment encompasses both the quantitative measure of adherence (i.e., whether the dressing is present at the assessment) as well as key qualitative factors that directly impact patient outcomes. The investigator reviews the dressing across three specific criteria: presence, border lift reaching the pad and pad exposure. If any of these criteria indicate a compromised pad, the dressing is deemed unacceptable. This approach ensures a more precise evaluation of whether the dressing maintains its protective function over the wear period.

Furthermore, additional quantitative assessments for secondary endpoints, such as percentage border lift, pad lift, pad integrity, and adhesive offset, are conducted using counting grids. These tools provide objective percentage scores and reduce inter-assessor variability, ensuring consistent and accurate measurements. The site team will receive thorough training on the use of these grids prior to the study's commencement, further enhancing the reliability of the evaluations.

8 BENEFITS AND RISKS OF THE INVESTIGATIONAL DEVICE, CLINICAL PROCEDURE AND CLINICAL INVESTIGATION

8.1 Anticipated clinical benefits and intended use

As the participants will have no wounds there is no anticipated clinical benefit to the participants.

8.2 Anticipated adverse device effects

In this study, in- and exclusion criteria have been defined in order to avoid identified potential risks of adverse reactions.

Depending on individual sensitivity, the removal of the dressings may be perceived as unpleasant. Sensitive individuals may experience a brief reddening of the skin after dressing removal.

The investigational device may in some scenarios contribute to maceration, skin irritation or skin sensitization, due to the presence of a medical silicone skin adhesive. These anticipated adverse events have been addressed through the Risk Analysis activities carried out on this device and found acceptable (for details see the IB).

8.3 Risks associated with participation in the clinical investigation

The investigational devices are considered safe for the intended use, however adverse skin reactions to the dressing adhesive or materials can occur in rare cases. Therefore, participants with known sensitivity reaction to the materials of the dressings applied in this study or allergies to adhesives, skin wipes, soap, surgical first-aid dressings, natural rubber or rubber latex will be excluded to participate in this study for safety reasons. This has been captured as post mitigation evidence in the risk assessment carried out on the investigational devices (see details in IB). All residual risks, which are described as potential side effects as well as the existing precautions that exist for similar device Marketed dressing 1, will be explained to the participants and are outlined in the RA (RA_VT_HVS2313_v3_Aug2024), BER (BER018) and BES (BES108).

8.4 Possible interactions with concomitant medical treatments

There are no contra-indications for the investigational device. Precautions for use of the investigational device are the same as to those for existing Marketed dressing 1 except for the precautions related to a wound being present under the dressing. For full list of the precautions for the IMD, refer to the IB.

8.5 Steps to be taken to control or mitigate the risks

In this study in- and exclusion criteria have been defined in order to avoid identified potential risks of adverse reactions through sensitivity to the dressing adhesive or materials. The Risk Assessment also documents this as post-mitigation evidence carried out on the investigational devices.

8.6 Rationale for benefit-risk ratio

The Prototype dressing and comparators are safe medical devices with no remaining unacceptable risks concerning their comprising materials. The rate of side effects in this study is expected to be low. Side effects may occur only in participants who are hypersensitive to any of the materials which comprise the dressings (i.e. the dressing adhesive). Participants, who have a known intolerance reaction against one of the materials, will be excluded from participation in the study. Additionally, participants with allergies to adhesives, skin wipes, soap, surgical first-aid dressings, natural rubber or rubber latex will be excluded to participate in this study for safety reasons.

None of the procedures which the participants will undergo in this study are invasive. Upon dressing removal there may be discomfort / pain, but this is anticipated to be of low / mild intensity and only transient.

The planned study has no clinical benefit for the participating participants as they will be in good health with no wounds. The participants are informed about this during the informed consent process and in the information sheet. Risks associated with the conduct of the study and the study devices are considered to be low.

The investigational device has been evaluated to ensure that its performance and safety profile are appropriate for its intended use in the clinical study (see Risk Assessment Ref. RA_VT_HVS2313_v3_Aug2024). The biocompatibility of the investigational device has been evaluated according to ISO 10993-1 and is concluded to be safe for its intended use in the clinical study (see Biological Evaluation Report/BER BER018 and Biological Evaluation Statement BES108).

Based on characteristics identified and actions taken, the individual and overall residual risk posed by the investigational devices are considered acceptable and that the investigational device is considered safe for its intended use in this study (use on intact skin).

The clinical study will be conducted in accordance with the declaration of Helsinki, DIN EN ISO 14155, Regulation (EU) 2017/745 (MDR), the Medizinprodukterecht-Durchführungsgesetz (MPDG), and MDCG guidelines.

9 OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION

9.1 Purpose of the clinical investigation and claims to be verified

To evaluate the Prototype dressing on healthy, intact skin to assess dressing retention and other dressing performance parameters.

9.2 Objectives and hypotheses

The objectives of this study are to demonstrate non-inferiority of the Prototype dressing in comparison to Marketed dressing 1 and Marketed dressing 2.

9.2.1 Primary objectives

To demonstrate non-inferiority of the Prototype dressing to Marketed dressing 1 and Marketed dressing 2 with regards to acceptable dressing presence in human participants on the thighs and shins at day 7.

9.2.2 Secondary objectives

To generate data to support:

- 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

9.2.3 Primary and secondary hypotheses

Primary hypothesis

The study design implements a non-inferiority hypothesis, aiming to demonstrate that the Prototype dressing (IMD) is not significantly worse than the established comparators in terms of performance and safety. A value of 15% is assumed as the non-inferiority threshold at this point. The choice of the 15% threshold is justified in section 9.3.

The primary hypothesis is that the difference between the IMD and the two comparators terms of the proportion of acceptable dressing presence at day 7 is less than 15%.

$$H_0: \%C - \%IMD \geq 15\%$$

$$H_A: \%C - \%IMD < 15\%$$

Where %IMD and %C denotes the proportion of devices with acceptable dressing presence for IMD and comparator.

9.3 Scientific justification and clinical relevance for effect sizes

The study design tests a regular inequality hypothesis.

The effect sizes used for the number of cases correspond to the data of the respective preliminary studies.

Rationale for the 15% non-Inferiority margin

The selection of a 15% non-inferiority margin is grounded in established statistical and clinical considerations for non-inferiority trials. This margin is deemed appropriate based on the guidance provided by Chow and Song (2016), who discuss the selection of non-inferiority margins in the context of active control (non-inferiority) trials. The paper indicates that, in the absence of a commonly accepted specific margin, a non-inferiority margin within the range of 10-15% of the baseline effect size (e.g., the percentage of comparator dressings with acceptable presence) is frequently utilized. Therefore, the choice of a 15% non-inferiority margin is both scientifically and clinically sound, ensuring that the results of the investigation will be meaningful and interpretable within the context of existing therapeutic standards. Furthermore, this is in compliance with US FDA advice on having a non-inferiority margin or equivalence limit of ±15% in non-inferiority or equivalence trials, where there is an expected response/success rate of 80–90% (see page 3 and Table 2 of Chow and Song (2016)).

Wear time and clinical performance of multilayer foam dressings in clinical practice varies according to the quality of the dressing, the status of the wound (depth, area and exudate level/flow), the patient (age, skin elasticity, comorbidities, mobility, etc.) and the site of application to the body (performance is best on arms and legs compared with highly mobile jointed areas, such as the knees or elbows). Both comparator dressings in this study are market leaders with clinically proven high performance, which is unlikely to be surpassed; therefore, a non-inferiority study design is appropriate to validate the performance of a novel multilayer foam dressing.

10 DESIGN OF THE CLINICAL INVESTIGATION

10.1 General description

This is a Prospective, open-label, comparative, interventional study with intra individual comparison of a new wound dressing (the Prototype dressing) with two established wound dressings Marketed dressing 1 and Marketed dressing 2 on healthy intact skin.

The investigational medical device and comparators will be administered according to the respective IFUs.

Participants will be screened (at Visit 1) and eligible participants will be enrolled on to the study and invited to Visit 2 (Day 0) where, if not on the same day as the Screening visit, eligibility will be checked again (including a pregnancy test for female participants of childbearing potential, where screening was ≥ 5 days before Day 0 and physical skin assessment to ensure skin is healthy, intact and hair free) before the Prototype dressing and comparators will be applied by the investigator to the right/left thigh and the right/left shin of the participant according to the randomization plan. Four dressings will be applied to each participant.

Immediately following dressing application the investigator will assess the following: (i) ease of application; (ii) the adhesive offset on the dressing handles; (iii) skin assessment of the skin surrounding the dressing (i.e. signs of irritation: blistering, erythema, swelling); and the participant will assess the dressing comfort and any signs of irritation (i.e. pruritus and pain). In addition, photographs of the dressing, any adhesive offset and/or AE, will be taken at this stage.

Participants will present to the site for assessment visits on days 1, 3 and 7 according to the schedule of the clinical investigation in section 2.1.

Any participants who experience a SAE or SADE related to the dressings (Prototype dressing or comparators) will be instructed to contact the study site and schedule an early termination visit where the dressings will be removed and final assessments performed.

A detailed schedule of the clinical investigation is presented in Table 2.1

The schematic course of the clinical investigation is presented in Figure 10.1

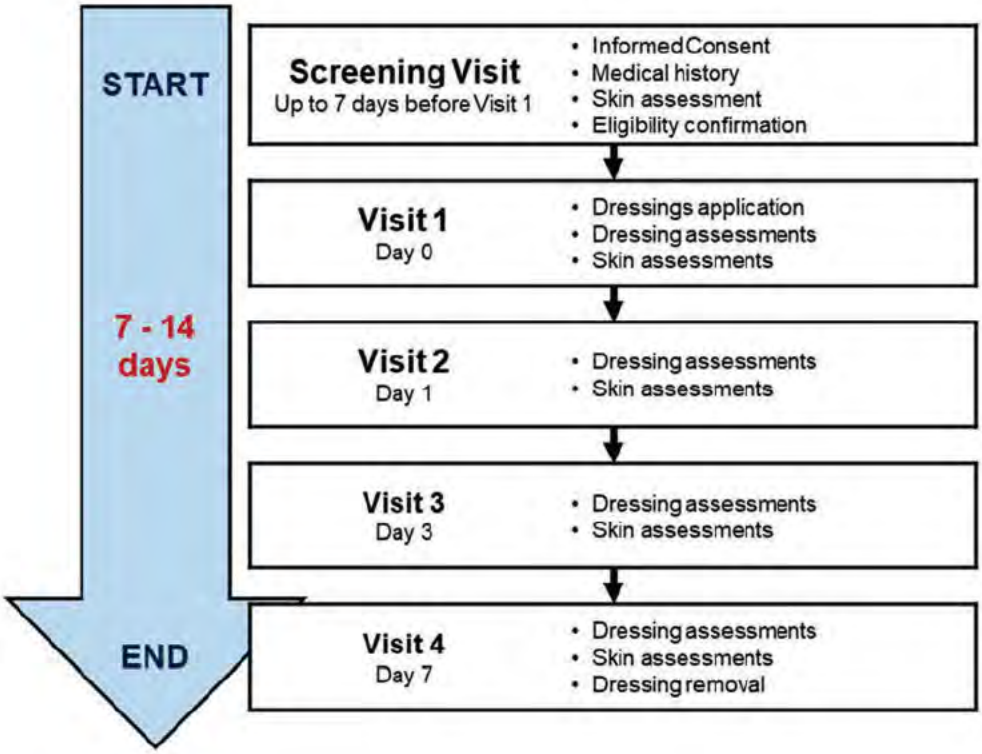


Figure 10.1 The course of the clinical investigation.

10.1.1 Timelines

The estimated timelines are presented below:

First participant in	JAN2025
Last participant out	APR2025
Total study duration	10-14 weeks
Observational period per participant	Up to 14 days

10.1.2 Primary and secondary endpoints

For definitions of endpoints and hypotheses of the clinical investigation please refer to section 11.2.

10.1.3 Control group(s)

As the study follows an intra individual design, each participant will serve as their own control with the comparator device.

10.1.4 Measures to minimize or avoid bias

This study will be performed as an open-label clinical investigation. The application site side (i.e. right or left thigh or shin) will be randomized (see also section 11.3.5 for details on methods of randomization). For factors which may compromise the outcome or interpretation of the results and methods to address them see section 10.4.10.

10.1.5 Methods and timing for assessing, recording and analyzing variables

A detailed description of methods and timing for assessing and recording of the variables is given in section 10.4.1 and 10.4.15. For analysis of the variables please refer to section 11.2.

10.1.6 Equipment for data assessment and monitoring

Not applicable.

10.1.7 Procedures for the replacement of participants

There will be no replacement of enrolled participants if they drop-out during the course of the investigation.

10.1.8 Investigation sites

This clinical investigation will be conducted at one investigation site in Germany: SGS proderm GmbH, Kiebitzweg 2, 22869 Schenefeld.

10.1.9 Definition of completion of the clinical investigation

The end of the clinical investigation is defined as the last visit of the last participant.

10.2 Investigational device(s) and comparator(s)

A detailed description of the investigational device is provided in Section 6.5.

10.2.1 Exposure to the investigational device or comparator(s)

Each participant will receive four devices in total, two Prototype dressings and one of each comparator. Participants will receive the Prototype dressing and one of the comparators at each dressing test site on the thighs and at each test site on the shins (randomized left or right, see section 11.3.5.1 for more details). Dressings will be applied to the designated application site on Day 0 and will remain in place until removed on Day 7 (or before, if premature removal/detachment should have occurred).

10.2.2 List of any other medical device or medication to be used during the clinical investigation

Other medical devices or medications, which are used by the participant on a regular or irregular basis during this investigation, will be documented as concomitant therapy or changes in concomitant therapy.
Restrictions during the clinical investigation are specified in section 10.3.6

10.3 Participants – population of the clinical investigation

Only healthy participants will be recruited for this clinical investigation (see section 10.3.3 for the inclusion criteria).

10.3.1 Sample size

Taking into account an approximate lost to follow up rate of 10%, 120 healthy participants are planned to be enrolled onto this study so that at least 105 participants are expected to complete the study. For further details about sample size considerations please refer to section 11.3.1.

10.3.2 Estimated time needed to select this number

The enrollment period is planned to start in JANUARY 2025. Approximately 8 weeks are estimated to recruit all participants.

10.3.3 Inclusion criteria for participant selection

Only participants meeting all the following inclusion criteria will be considered for enrollment into the study:

1. Participant is capable of providing informed consent
2. Participant is willing and able to make all required study visits
3. Aged 18-70 years at the time of signing the informed consent*
4. Participant must be in good health, as determined by the Investigator, based on medical evaluation, including medical history and skin application site assessment (healthy intact skin at or near any of the dressing application sites)
5. Participant is willing not to use cosmetic or medicinal lotions, creams, ointments and anything else which may interfere with dressing adhesion at dressing application sites for the duration of the study from 24 hours before dressing application on Day 0.
6. Participant is willing to have excess hair removed from the dressing application sites
7. Participant is willing to avoid immersing the dressings in water (no swimming or bathing) for the duration of the study

*at least 10% of participants are aged >55 years

10.3.4 Exclusion criteria for participant selection

1. Female participant who is pregnant, or lactating.
2. Participant has a known sensitivity to any of the study products, materials or ancillary product or components.
3. Known skin sensitivity or allergies to adhesives, skin wipes, soap, surgical first-aid dressings, natural rubber or rubber latex, etc.
4. Participants with a current active skin disease (e.g., eczema, psoriasis, or severe dermatoporosis), sunburn or skin peeling at the dressing application sites.
5. Participants with a medical condition which may interfere with their perception of pain (such as diabetes, small-fibre neuropathy, allodynia, hyperalgesia etc.).
6. Heavy smokers (e.g. >20 cigarettes (~1 pack) a day over the last 10 years) whose pain perception may have been affected through smoking.
7. Participants with any skin features near any of the dressing application sites that could be identifiable/may interfere with skin assessments (e.g. tattoos/distinctive markings or scars/keloids).
8. Participants diagnosed with hyperhidrosis or who self-report their normal sweating level to be severe as determined by the Sweating Severity Self-Assessment (SSSA) at screening (e.g. mild, moderate, severe).
9. Participants not willing to refrain from the use of pain relief medication on assessment days (1, 3 and 7) and in the case of certain medications, 24 hours before assessments.
10. Participants unwilling to refrain from activities which may directly affect the dressing, dressing application sites or assessments (such as undergoing planned scanning procedures, e.g., X-ray,

magnetic resonance imaging (MRI) and computed tomography (CT) scanning; exposure to airport scanners or devices emitting radio waves; exposure to atypical conditions of pressure, humidity and temperature; immersing the dressing in water e.g. bathing / swimming / cleaning the dressing application sites; using a sauna; undertaking strenuous physical activity like aerobics, running, cycling, heavy labor etc.; using lotions/creams/ointments etc. at the dressing application sites; excessively exposing the dressing application sites to the sun (e.g. sunbathing for >1 hour); wearing tightly fitting clothes which could affect the dressings.

11. Individuals who have participated in a clinical study in the last 7 days, using the same dressing application sites.
12. Participants with poor compliance and / or poor willingness to co-operate.
13. Individuals who should not participate in the clinical investigation for any other reason (including the taking of certain medications) as judged by the Investigator.
14. Individuals who are inmates in psychiatric wards, prison or state institutions, or any individuals otherwise regarded as vulnerable (as per ISO 14155 Section 3.55).
15. Employees of the investigation sites directly involved in this clinical investigation or employees of the sponsor's company

10.3.5 Prior and concomitant therapy

Any treatment that is not listed in the exclusion criteria will be allowed at the discretion of the investigator.

All concomitant medication and changes thereof will be documented in the eCRF (trade name, indication, dosage, unit, frequency, start and end of the intake, topical therapy in the test area(s)).

All diseases which occur during the study period are to be treated without respect to the study. The disease and the treatment will be documented in the eCRF.

10.3.6 Restrictions during the clinical investigation

During the course of the investigation the participants should refrain from activities which may directly affect the dressing, dressing application sites or assessments (such as undergoing planned scanning procedures, e.g., X-ray, magnetic resonance imaging (MRI) and computed tomography (CT) scanning; exposure to airport scanners or devices emitting radio waves; exposure to atypical conditions of pressure, humidity and temperature; immersing the dressing in water e.g. bathing / swimming / cleaning the dressing application sites; using a sauna; undertaking strenuous physical activity like aerobics, running, cycling, heavy labor etc.; using lotions/creams/ointments etc. at the dressing application sites; excessively exposing the dressing application sites to the sun (e.g. sunbathing for >1 hour); wearing tightly fitting clothes which could affect the dressings.

Additionally, participants should refrain from the use of pain relief medication on assessment days (1, 3 and 7) and in the case of certain medications, 24 hours before assessments.

A list of any other medical device or medication to be used during the clinical investigation, which are not subject to evaluation in the clinical investigation, is provided in section 10.2.2.

10.3.7 Criteria and procedures for participant withdrawal/discontinuation or lost to follow-up

The participation of a participant will be terminated by the investigator SGS proderm if medical or other reasons occur that conflicts with the conduct of the study or the safety of the participant, or if the participant refuses to continue, i.e. withdraws her / his consent.

The investigator can withdraw participants from the study at any time for any of the following reasons:

- Non-compliance in major aspects of the study.
- The participant is suspected or known not to comply with inclusion or exclusion criteria.
- The participant is suspected or known not to comply with the clinical investigational plan directives (e.g. use of prohibited medication, non-attendance at study assessments).

- The participant requires treatment with any medication known or suspected to interfere with the investigational product or comparators.

Other withdrawal criteria for this study are:

- Withdrawal of informed consent.
- Pregnancy.
- Medical reasons which do not allow the participant to come to scheduled visits (e.g. adverse events, clinically relevant surgery, clinically relevant intercurrent illness etc.).
- Any other condition which in the opinion of the Investigator no longer justifies or permits a safe participation of the participant.

Participants who are withdrawn from the study due to AEs will be treated according to standard clinical therapies and will be followed up until the AE is resolved or a stable condition is reached.

In the case that all four dressings become detached before the end of the study, the affected participant will contact the site and schedule an early termination visit. While any of the dressings are still attached, the participant will continue with the study until the study end on Day 7.

The participant may discontinue the study at any time without any penalty or loss of benefits according to the Declaration of Helsinki.

The reason for early termination should be documented and in the case the reason for early termination was not withdrawal of consent, the final assessments which are scheduled to be performed on Day 7 should be performed on the day of early termination for safety reasons (see Early termination assessments described in section 10.4.15.18).

Lost to follow-up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and if the investigation site is not able to get in contact with the participant after 3 attempts of phone contact.

If a participant fails to return to the study site for a required visit, before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant. These contact attempts should be documented in the participant's' medical record. Should the participant continue to be unreachable, they will be considered to have withdrawn from the investigation with a primary reason of lost to follow-up.

Participants who are lost-to follow-up or are prematurely discontinued after use of the IMD will not be replaced (see section 10.1.7).

10.3.8 Point of enrollment

Point of enrollment is the time point after which the participant has signed the informed consent, inclusion/exclusion criteria have been checked and the participant is considered to be eligible for the clinical investigation.

10.3.9 Point of randomization

The point of randomization is the time point at which the application sites have been randomly assigned for each dressing. This will occur at the site visit on Day 0 according to order of appearance at this visit.

10.3.10 Relationship of investigation population to target population

The target population for the marketed dressings Marketed dressing 1 and Marketed dressing 2 comprises patients with acute and chronic wounds or those at risk of developing pressure ulcers. However, for the purposes of this investigation, healthy participants without wounds will be recruited.

10.3.11 Information on vulnerable, pregnant, and breastfeeding population

Not applicable.

10.4 Procedures and assessments

10.4.1 Informed consent

Potential participants may only be enrolled in the clinical investigation after providing written informed consent at the site as described in section 17.

10.4.2 Hair removal from dressing application site

Hair should be removed 24 hours prior to dressing application using electric clippers/trimmers. Should the participant regularly wet shave the dressing application sites, they may prepare the site using the wet shave technique at most 48 hours prior to dressing application; otherwise participants will be instructed to only use electric clippers. The application site will be checked that it is free from hair at screening or, if screening occurred >24 hours before dressing application, again on Day 0. If the participant does not usually wet shave and does not have access to a pair of electric clippers/trimmers, the participant will undergo hair removal with electric clippers/trimmers at the study site at Day 0.

The dressing application sites will be checked during the physical examination of the skin condition before dressing application on Day 0 and any shaving related injury at the application test site will be noted and the participant regarded as a screening failure and excluded from the study.

10.4.3 Dressing quality control (QC) check

Prior to dressing application the dressing should be checked by the investigator or trained site personnel to ensure: (i) packaging is intact; (ii) dressings are not damaged; (iii) there are no visual contaminants.

10.4.4 Dressing application

Dressings will be applied by the investigator or trained site personnel as in accordance with the respective IFUs on Day 0. Thigh and shin dressings will be applied with participants standing up. Before dressing application, the dressing application site will be cleaned by trained site personnel with a saline wipe followed by air drying before dressing application on Day 0.

10.4.5 Dressing removal

The investigator or trained site personnel will remove the dressing as in accordance with the respective IFUs following the same standard procedure: Lift one corner and slowly peel back until completely removed; and following the same order of removal for each participant, e.g. (i) right thigh, (ii) left thigh, (iii) right shin, (iv) left shin. There will be a 10 min interval between the removal of each dressing to allow for any residual pain to subside.

10.4.6 Photography

Photographs will be taken by the investigator or trained site personnel 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).
- after the dressing assessments on Day 1.
- after the dressing assessments on Day 3.
- before the dressing removal (any day that dressing requires removal).

One image will be taken per test area and assessment time.

The photography will be performed using the following equipment:

- EOS 5D Mark III (Canon): The digital camera is used for standardized, computer-controlled photography of the test area, combined with appropriate flashes and lenses to obtain high quality

and reproducible images. Photography will use calibrated colors so that further assessment can be performed at a later phase.

- The MacIS XXL (Macroscopic Imaging System XXL) is a specifically designed handheld system for standardized photography and enables high reproducibility. The tailor-made setup is equipped with a Canon EOS 5D Mark III camera, a 35 mm macro lens, a ring flash as well as a CFK case which also functions as distance holder to enable reproducible images with defined magnification. The captured test area is 17 cm in diameter. For color consistency, white balancing and color calibration is performed using the X-Rite ColorChecker® target so that further assessment can be performed at a later phase.

Only the pseudonymized images can be used by the Sponsor for internal company purposes of the Sponsor. A corresponding informed consent will be signed by the participants.

10.4.7 Course of the clinical investigation

120 male/female participants meeting the inclusion criteria and not presenting any of the exclusion criteria (see Section 10.3.3 and 10.3.4) will be enrolled into the study so that 105 are expected to finish the study.

On Day 0 of the study: The Prototype dressing and the two comparators will be applied to either the right/left thigh or shin depending on the randomization scheme.

Before the start of the study the participants will be instructed NOT to:

i) apply any leave on cosmetics (e.g. creams, lotions, oily cleansing products) to the legs starting from 24 hours prior to the start of the study on Day 0 until the end of the study.

Before the start of the study the participants who normally wet shave or have access to electric clippers/trimmers will be instructed to:

i) remove hair from the test site as described in section 10.4.2. (Otherwise, hair will be removed at the study site at Day 0).

During the course of the study the participants will abide by the restrictions outlined in section 10.3.6.

The following activities or examinations will be performed:

Screening phase (Day -7 to Day -1)

- Informed consent form.
- Inclusion/ exclusion criteria will be checked.
- Documentation of demography and medical history
- Prior medication and treatment.
- Sweating Severity Self-Assessment (SSSA)
- Physical examination of the skin condition focused on the dressing application sites (thigh and shin: assessment of current skin disease (e.g., eczema, psoriasis), sunburn or skin peeling at the dressing application sites).
- Assessment of the presence of hair at dressing application sites and where necessary removal of hair with hair clippers at the study site.
- Pregnancy test for all female participants of childbearing potential.

Day 0

- Inclusion/ exclusion criteria will be checked to re-confirm eligibility (if the screening visit was not on the same day as Day 0).
- Pregnancy test (if the screening visit was more than 5 days before Day 0).
- Documentation of AEs.

- Documentation of changes in concomitant medication.
- Participant to be asked if application site has been cleaned, hair removed and is free from lotions etc.
- Physical examination of the skin condition focused on the dressing application sites (thigh and shin: assessment of current skin disease (e.g., eczema, psoriasis), sunburn or skin peeling at the dressing application sites). (If the screening visit was not on the same day).
- Randomization.
- Dressing QC check.
- Application of the dressings to the designated randomized application sites (see section 11.3.5.1 for details concerning the randomization).
- Dressing application assessments.
- Skin assessment (skin condition at application sites).
- Photographs of the dressings.

Day 1

- Documentation of AEs.
- Documentation of changes in concomitant medication.
- Skin assessment (skin condition at application sites).
- Objective dressing assessment.
- Subjective dressing assessment.
- [redacted]
- Activity assessment
- Photographs of the dressings

Day 2

No visit to the site.[2]

Day 3

- Documentation of AEs.
- Documentation of changes in concomitant medication.
- Skin assessment.
- Objective dressing assessment.
- Subjective dressing assessment.
- [redacted]
- Activity assessment.
- Photographs of the dressings.

Day 4

No visit to the site.[2]

Day 5

No visit to the site.[2]

Day 6

No visit to the site.[2]

Final Visit (Day 7)

- Documentation of AEs.

[2] In the case of premature dressing detachment, the participant will be instructed to contact the site and report the date and circumstances of the dressing detachment and if there is any skin related AE, as well as the application test site where the dressing in question was located. The participant will be instructed to bring the detached dressing to their next site visit.

- Documentation of changes in concomitant medication.
- Skin assessment.
- Objective dressing assessment.
- Subjective dressing assessment.
- [redacted]
- Activity assessment.
- Photographs of the dressings.
- Removal of the dressings.
- Subjective dressing removal assessment.
- Objective dressing removal assessment.
- Documentation of AEs after dressing removal.
- Investigator assessment of dressing quality.
- Participant assessment of dressing quality.

10.4.8 Treatment compliance

Since the application and removal of the dressings will be performed and documented by the investigator or trained site personnel, the compliance of the participants will be ensured.

10.4.9 Activities performed by sponsor representatives

Not applicable.

10.4.10 Factors that may compromise the outcome or the interpretation of results and methods to address them

For consistent objective evaluation trained study personnel will align their assessment as it cannot be assured that the assessment is performed by the same evaluator at all visits. Training will be provided on assessing acceptable dressing presence to ensure standardization. Moreover, when assessing the percentage border lift, pad lift, pad integrity [redacted]; the assessor will be trained in the use of "counting grids" to give a more objective percentage score for each parameter as well as mitigate any potential inter-assessor variability. An example guide for the square dressings is shown in Figure 10.2.

[redacted]

[redacted]

[redacted]

[redacted]

Further factors that may compromise the outcome or interpretation of the results include baseline characteristics and concomitant therapies / diseases. To minimize the influence of these factors, appropriate subject eligibility criteria (section 10.3.3 and 10.3.4) and restrictions (see 10.3.6) are applied. Furthermore, the study design includes intra individual comparison which effectively accounts for inter-participant variability ensuring consistency across participants.

Additionally, the order of removal of the dressings could influence the intensity of pain experienced by the participant. As the dressings are randomly assigned to the four different application sites, keeping the order of removal the same will ensure that each dressing is removed first, second, third and fourth an equal number of times across participants. Furthermore a standardized removal technique (as per the IFU) will be used to ensure consistency for all dressings and all participants and moreover, including a time interval of 10 ±2 min between the removal of each dressing, which will allow for any residual pain from the previous removal to subside before the next dressing is removed.

10.4.11 Follow-up period during the clinical investigation

A follow-up period is reflected by the study period of 7 days, which is regarded sufficient to demonstrate the performance and safety of the Prototype dressings.

10.4.12 Provision of additional care for participants after completion of the clinical investigation

Since only healthy participants will be enrolled in this study, additional care after study termination is not foreseen.

10.4.13 Follow-up period after completion of the clinical investigation

Not applicable.

10.4.14 Final disposition and potential future use of samples

Not applicable.

10.4.15 Variables assessed in the clinical investigation

10.4.15.1 Demographic data

The following demographic data will be recorded at the screening visit:

- Age (in years)
- Sex
- Height (cm)
- Weight (kg)

10.4.15.2 Medical history

Previous and concomitant diseases, surgical history and allergies relevant for the clinical investigation during the last 12 weeks will be recorded at the screening visit. For each condition, diagnosis, or surgical procedure, the start date and stop date will be recorded (it will also be recorded if the condition or diagnosis is ongoing).

Prior therapies used up to 12 weeks before the start of the clinical investigation and all concomitant therapies will be recorded at the screening visit (including; trade name, reason, start and end of intake, dosage and route of administration).

10.4.15.3 Sweating Severity Self-Assessment (SSSA)

During the screening visit, the participants will assess their normal level of sweating according to the ordinal scale: mild, moderate, severe.

10.4.15.4 Physical examination of the skin condition

An assessment of current skin disease (e.g., eczema, psoriasis), sunburn or skin peeling at the dressing application sites will be performed by the investigator (or suitably medically qualified site personnel) at the Screening Visit and on Day 0 (if the two visits do not coincide). This is performed in order to establish eligibility.

10.4.15.5 Assessment of dressing application (Day 0)

[redacted]

10.4.15.6 Objective assessment of the dressings (Days 1, 3 and 7)

The investigator or trained site personnel will assess the following:

i) **Dressing presence**: is the dressing in place? : binary answer "yes" / "no". If "no" then the reason for premature removal or detachment will be recorded.

ii) **Acceptable dressing presence**: for dressings in place, do the dressings meet the definition of "acceptable dressing presence"?: binary answer "yes" / "no".
The definition of acceptable dressing presence criteria in this healthy participant study is: dressings present with no border lift reaching the pad and no pad exposure. This is a is a binary pass / fail assessment based on passing all three of the following criteria:
   1. Is the dressing missing? (pass = "no", fail = "yes")
   2. Is there border lift reaching the pad? (pass = "no", fail = "yes")

3. Is the pad exposed*? (pass = "no", fail = "yes")

*Pad exposure is the lifting of the pad, or any other compromise that breaches the dressing seal (including tears to the top-film).

If dressings do not meet the acceptable dressing presence criteria, the reasons why (e.g., border lift, pad exposure) will be documented.

iii) **Border lift**: what is the percentage border lift?: according to the following ordinal scale "0% (no lift)", "1-25%", "26%-50%", "51%-75%", "76-100%", or "dressing missing". Based on the "counting grids method" to give an objective percentage score.

iv) **Pad lift**: what is the percentage pad lift?: according to the following ordinal scale "0% (no lift)", "1-25%", "26%-50%", "51%-75%", "76-100%", or "dressing missing". Based on the "counting grids method" to give an objective percentage score. Should any dressing demonstrate >=50% pad lift, it will be removed and Dressing Removal Assessments will be conducted.

v) **Pad integrity**: Are there any changes in pad integrity (e.g., bunching/folding/ridges)? according to the following ordinal scale "0% (no change)", "1-25%", "26%-50%", "51%-75%", "76-100%", or "dressing missing". Based on the "counting grids method" to give an objective percentage score.

vi) Did the dressing require removal today? (Days 1 and 3): "yes", "no" or "dressing missing".

10.4.15.7 Subjective assessment of the dressings (Days 1, 3 and 7)

The participant will be asked to assess the following:

i) **Dressing comfort**: was the dressing comfortable during wear?: "yes", "no" or "dressing missing".

ii) **Itching**: was the dressing itching during wear: according to the ordinal scale: "none", "mild/intermittent", "mild/persistent", "moderate", "severe", "dressing missing". The levels of itching corresponding to "mild/persistent", "moderate", "severe" would be classed as adverse events.

[redacted]

10.4.15.9 Assessment of level of activity (Days 1, 3 and 7)

The participant will be asked to assess the duration and level of their physical activity since their last study appointment. Specifically, using the ordinal scale: "0 minutes", "<1 hour", "1-6 hours", ">6 hours"; participants will be asked to report the duration of: (i) kneeling/crouching on the floor with legs beneath them (e.g., playing with children, reaching into a low cupboard, reaching for low laying files at work); (ii) mild activity (e.g., walking, light housework such as dusting/washing dishes, serving customers behind a counter); (iii) moderate activity (e.g., gardening, housework such as scrubbing floors/washing windows, carrying light loads at work); (iv) strenuous activity (e.g., aerobics, running, cycling, heavy labor). Each specific strenuous activity will be recorded in the electronic case report form.

10.4.15.10 Assessment of skin condition (Days 0, 1, 3 and 7)

The condition of the skin in terms of any skin-related adverse events (AEs) and device deficiencies (DDs), e.g., blistering, erythema, swelling, rash, sensitivity to adhesive, skin stripping, skin occlusion or itching will be assessed by the investigator or suitably medically qualified site personnel.

10.4.15.11 Subjective assessment of dressing removal (Day 7)

Immediately following removal of the dressing, the participant will be asked to assess the following:

[redacted]

10.4.15.12 Objective assessment of dressing removal (Day 7)

The investigator or trained site personnel will assess the following:

i) **Skin erythema:** what was the extent of skin erythema 5 minutes after removal?: according to the ordinal scale: "no reddening", "mild reddening (slight pink)", "moderate reddening (red)", "severe reddening (beet red)". The latter two categories of skin erythema ("moderate reddening" or "severe reddening") would be classed as adverse events.
ii) **Blistering:** was there any sign of blistering 5 minutes after dressing removal?: binary "yes" or "no". Any blistering would be classed as an adverse event.

[redacted]

vi) Skin occlusion: what was the extent of skin occlusion after dressing removal?: according to the ordinal scale: "none", "clammy skin", "noticeable moisture", "whitening of skin", "skin breakdown". The latter two categories of skin occlusion ("skin whitening" or "skin breakdown") would be classed as adverse events.
vii) Skin stripping: was there any visible signs of skin stripping after dressing removal?: binary "yes" or "no". Any occurrence of visible skin stripping would be classed as an adverse event.

10.4.15.13 Investigator Dressing Quality Assessment (Day 7)

The investigator or trained site personnel will be asked to rank the 3 dressings in order of their quality or state that there was no difference. This assessment will record the general perception of dressing quality irrespective of location.

10.4.15.14 Participant Dressing Quality Assessment (Day 7)

The participant will be asked to rank the 3 dressings in order of their quality or state that there was no difference. This assessment will record the general perception of dressing quality irrespective of location.

10.4.15.15 Adverse events

Participants will be asked about adverse events at all visits following enrollment into the study (Days 0, 1, 3 and 7).

10.4.15.16 Changes in concomitant medications/treatments

Participants will be asked about any changes in their concomitant medications/treatments at all visits following enrollment into the study (Days 0, 1, 3 and 7).

10.4.15.17 Pregnancy test

All female participants of childbearing potential will be tested for pregnancy at the screening visit of the study using a urine test. If the screening visit is not on Day 0 and took place 5 or more days before Day 0, then a second pregnancy test will be performed on Day 0.

10.4.15.18 Early Termination Assessment

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:

- objective dressing assessment
- subjective dressing assessment
- activity assessment

After removal of the dressing the following should be performed:

- subjective dressing removal assessment
- objective dressing removal assessment
- investigator dressing quality assessment
- participant dressing quality assessment

If no dressings remain at the ET visit then only the two dressing quality assessments will be performed.

10.5 Monitoring plan

10.5.1 General outline

The purpose of monitoring during the clinical investigation is to verify that the rights and well-being of participants are protected, that the reported study data are accurate, complete, and verifiable from source documents and that the conduct of the study is in compliance with the current approved clinical investigational plan / amendment(s), with Good Clinical Practice (GCP), and with the applicable laws and/or regulations.

The Investigator and his/her staff will be expected to co-operate with the clinical research department of the Sponsor or a designee and to be available during monitoring visits to answer questions and to provide any missing information.

10.5.2 Source data verification

Source data verification (SDV) is an essential element to ensure accuracy and credibility of the data and conclusions derived from clinical investigations. Monitoring personnel will be granted access to all source data relevant to the study and the participants that take part in the study. During monitoring visits reported data will be reviewed to verify that they are accurate, complete and verifiable from source documents (e.g., participant files, recordings from automated instruments, tracings (e.g. ECG), laboratory notes).

For source data verification at least the following information must be included in the participants' files:

- Name.
- Date of birth.
- Weight and height.
- Medical history.
- Concomitant medication.
- SAEs, AEs, UADEs, ADEs.
- Date of signature of informed consent.

Further source documents are the participant identification list and the Screening/ Enrollment-Log. Other source documents will be listed in the Source Document Identification Form. More details will be provided in the Monitoring Plan and Guidelines.

Participating participants must have given their written consent for the access to source documents by the monitor.

10.6 Audits and inspections

Audits and/ or inspections may be carried out by the Sponsor or an external auditor authorized by the Sponsor or by authorities. After an adequate announcement all documents pertinent to the clinical study must be made available for such an audit.

Participating participants must have given their written consent for the access to source documents by the auditor.

11 STATISTICAL DESIGN AND ANALYSIS

11.1 Analysis population

The blind review committee decides on the assignment of the participants to the PP, the FAS or the Safety Population (SP), before closure 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').

11.2 Endpoints and hypotheses of the clinical investigation

The statistical analysis is specified in detail in the statistical analysis plan (SAP) which is prepared before the meeting of the blind review committee (BRC). If the content of the SAP deviates from the proceeding as described in the clinical investigational plan, this is documented in the SAP, together with reasons and consequences.

If the necessary change between CIP and SAP is classified as a substantial modification, the corresponding changes are sent to the competent authorities and ethics committees for evaluation before implementation.

Substantial modifications are those changes that might have an impact on the safety, health or rights of the trial participants or on the robustness/reliability of the clinical data generated by the clinical trial.

11.2.1 Primary endpoint

The primary objective of the study is to demonstrate non-inferiority of the Prototype dressing with regard to acceptable dressing presence at day 7.

The primary endpoint is the proportion of acceptable dressing presence at day 7 for the Prototype dressing and will be tested via a comparison of proportion of acceptable dressing presence at day 7 of: (i) Prototype dressing vs Marketed dressing 1; and (ii) Prototype dressing vs Marketed dressing 2 at day 7.

The parameter "acceptable dressing presence" is a binary pass / fail assessment based on passing all three of the following criteria:

1. Is the dressing missing? (pass = "no", fail = "yes")
2. Is there border lift reaching the pad? (pass = "no", fail = "yes")
3. Is the pad exposed*? (pass = "no", fail = "yes")

* Pad exposure is the lifting of the pad, or any other compromise that breaches the dressing seal (including tears to the top-film).

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

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

$$H_A: \%C - \%IMD < 15\%$$

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 choice of the 15% non-inferiority threshold is justified in section 9.3.

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.

11.2.2 Secondary endpoints

To generate supportive data, the following endpoints are examined in the PP population:

- 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

The secondary endpoints therefore comprise the inferential and/or descriptive analysis of the following performance and descriptive evaluation of all safety parameters for the Prototype dressing vs the comparators, i.e. (i) Prototype dressing vs Marketed dressing 1; and (ii) Prototype dressing vs Marketed dressing 2.

<u>Performance assessments based on PP population:</u>

- Non-inferiority comparison of the Prototype dressing to the comparators for following parameters:
  - Acceptable dressing presence (thigh and shin) 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.

<u>Safety assessments based on SP population:</u>

- Descriptive presentation for following parameters:
  - 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.
  - Other Adverse Events

[redacted]

11.3 Statistical analysis methods

The primary endpoint is analyzed using a comparison of Newcombe's score method calculated confidence intervals against the non-inferiority threshold. Non-inferiority is subsequently demonstrated if the upper end of the 97.5% confidence interval (based on %C - %IMD in chapter 11.2.1) is less than the non-inferiority threshold of 15%.

The analysis will combine dressing application site locations, which are allocated based on randomisation into group 1 and group 2 (see 11.3.4). Consequently, all IMD data points are used in the statistical comparison against both comparators, which means that the IMD has twice the number of data points in the analysis. The statistical comparison of the Prototype dressing is performed separately for each comparator. 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% (Bonferroni-adjusted type I error).

The primary analysis is planned as a non-inferiority analysis with a non-inferiority-threshold of 15%.

The testing of the secondary endpoints is planned as a non-inferiority analysis. The inferential analysis of the secondary endpoints is based on their scale properties. The corresponding analyses with specific non-inferiority thresholds are specified in writing in the statistical analysis plan before randomization of the first participant.

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. The inferential analysis of the explorative endpoints is based on their scale properties. The corresponding analyses are specified in writing in the statistical analysis plan before randomization of the first participant.

The primary analysis is based on the FAS population, with a downstream sensitivity analysis repeating the primary analysis in the PP population.

All endpoints:

- Descriptive presentation of N, mean, standard deviation, median, minimum, maximum and 95% confidence limits will be given for raw data and differences to baseline of continuous data.
- Descriptive presentation of N, mean, standard deviation, median, minimum and maximum will be given for categorical data. Further evaluations will be summarized in tables by counts and percentage of scores.

More details about statistical analysis will be described in the Statistical Analysis Plan (SAP).

11.3.1 Sample size calculation

The sample size is based on separate non-inferiority tests for Prototype dressing vs Marketed dressing 1 and Prototype dressing vs Marketed dressing 2 regardless of dressing location. 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 vs Marketed dressing 1 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 1 – Prototype dressing), is lower than the non-inferiority threshold of 15% (%C - %IMD < 15%, were %IMD and %C denotes the proportion of devices with acceptable dressing presence for IMD and comparator). The choice of the 15% threshold is justified in section 9.3.

The same assumptions as above apply to the Prototype dressing vs Marketed dressing 2 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

11.3.2 Level of significance, power of the primary endpoint(s) and statistical testing strategy

The sample size calculation is performed at a power of 80% with alpha = 2.5%.

The two primary analyses are adjusted for multiple testing according to Bonferroni, so that the family wise error rate is fixed at 5%.

11.3.3 Rationale for the number of procedures

Not applicable.

11.3.4 Interim analysis

Not applicable.

11.3.5 Management of bias and potential confounding factors

Within the investigation, attempts will be made to minimize bias within the clinical investigation.

All documents specifying the statistical analysis in detail are finalized before the subjects are included in the investigation to avoid possible data-driven influence.

11.3.5.1 Method of randomization

Three different dressings (the Prototype dressing and comparators) will be randomized over four locations.

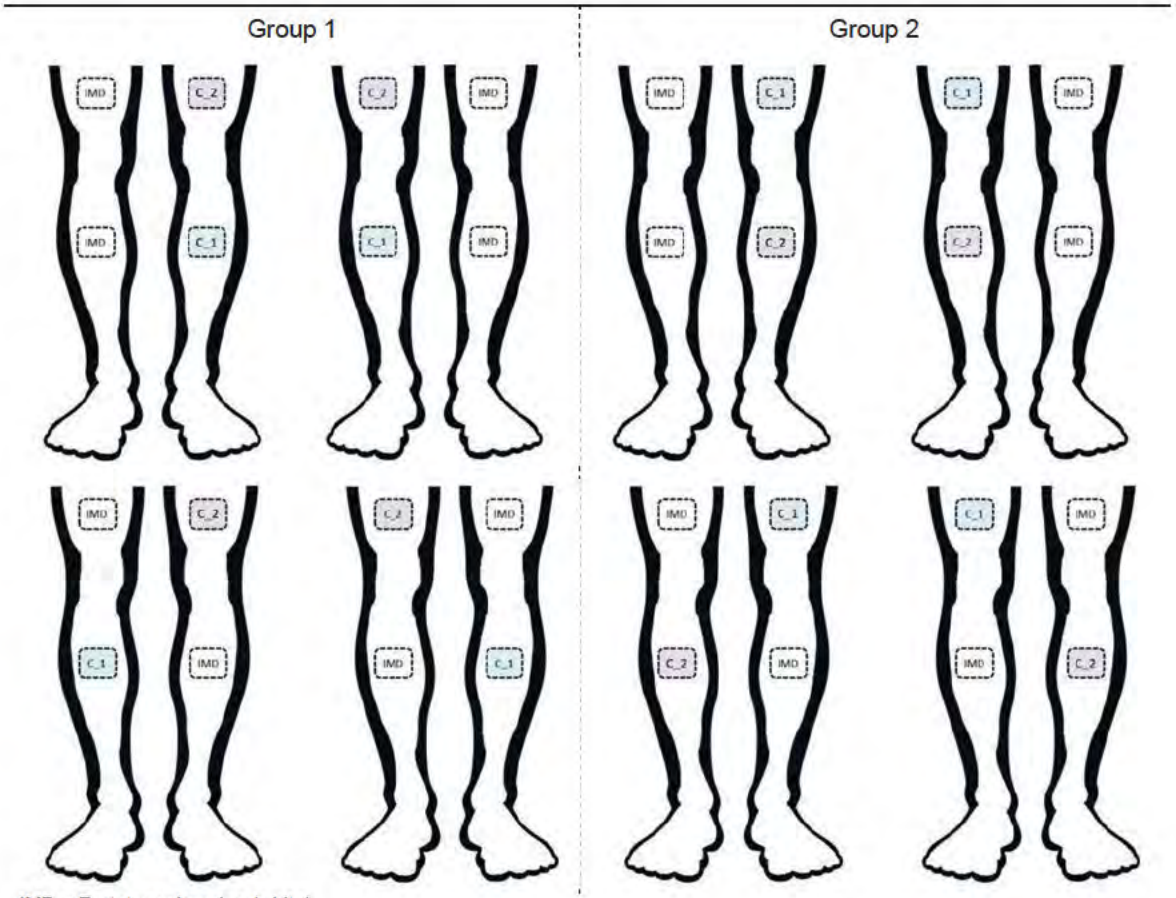
Participants will be allocated to one of two groups, with the dressing randomized to either the left or right thigh/shin in a 1:1 ratio.

Both the group allocation and the side allocation are carried out using a randomization process.

- Group 1: Prototype dressing and Marketed dressing 1 on the shins. Prototype dressing and Marketed dressing 2 on the thighs.
- Group 2: Prototype dressing and Marketed dressing 1 on the thighs. Prototype dressing and Marketed dressing 2 on the shins.

Both the group allocation and the side allocation 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.



IMD = Prototype dressing (white).
C_1 = Marketed dressing 1 (blue).
C_2 = Marketed dressing 2 (purple).

Figure 11.1 Device allocation between the application sites.

11.3.5.2 Blinding
Not applicable.

11.3.5.3 Potential confounding factors
Not applicable.

11.3.6 Multiplicity control and adjustment of error probabilities

The statistical comparison of the Prototype dressing (IMD) is performed separately for each comparator. 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 vs Marketed dressing 1
ii) Prototype dressing vs Marketed dressing 2

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 compared with Marketed dressing 1.

Order	Endpoint
1	Acceptable dressing presence* (thigh and shin) at day 7 (Primary endpoint)
2	Acceptable dressing presence* (thigh and shin) 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 compared with Marketed dressing 2.

Order	Endpoint
1	Acceptable dressing presence* (thigh and shin) at day 7 (Primary endpoint)
2	Acceptable dressing presence* (thigh and shin) 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.

11.3.7 Specification of subgroups for analysis

Not applicable.

11.3.8 Handling of missing, unused and spurious data including drop-outs and withdrawals

No replacement of outliers will be performed and the consequences of all clinical investigational plan violations are discussed during the meeting of the BRC.

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 acceptable dressing presence, 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 products 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.

11.3.9 Exploratory analysis and sensitivity analysis

The primary FAS analysis is performed again as part of a sensitivity analysis in the PP population It is examined whether there are clinically relevant differences between the results of the confirmatory FAS analysis and the non-confirmatory PP analysis or whether the results are consistent with each other.

The clinical relevance of the diversity of the results is defined and described by a clinical expert.

As an indication of clinically relevant differences in results between the populations, a statistical test for differences between the results is performed. If the results differ from the type I error of $\alpha = 0.05$, a significantly different result is assumed.

Possible differences are discussed in the discussion of the clinical investigation report.

Subsequent analyses requested by the sponsor after the finalized SAP are placed in a separate section of the report and are always referred to as unplanned analyses.

Furthermore, these unplanned analyses are only evaluated explanatively in each case.

11.3.10 Procedures for reporting deviation(s) in the statistical analysis between CIP, SAP and CIR

The statistical approach of the trial is pre-defined in this CIP, and expanded detail will be provided in the SAP.

Any changes to the statistical methodology after finalization of the CIP that would affect the safety, health, or rights of the trial participants or may alter the robustness/reliability of the clinical data generated by the clinical trial will be classified as a substantial deviation. Any substantial deviation must be reviewed and approved by competent authorities and ethics committees prior to implementation.

The same approach will apply to any changes in statistical analysis from finalization of the SAP and the final CIR. Finally, any change(s) in statistical analysis between the CIP, SAP, and CIR will reported in the CIR.

11.3.11 Procedures for reporting errors in statistical programming

If an error is detected in the statistical analysis during the internal control process (due to an error in the statistical programs, the statistical programming does not correspond to the required analyses of SAP), it is corrected immediately.

Should a methodological relevant deviation from the analysis plan (due to an error in the statistical programs, the statistical programming does not correspond to the required analyses of SAP) remain unnoticed in the internal control process and become apparent at a later time point, the following persons are informed immediately so that further action can be coordinated:

- Statistician
- Project manager
- Sponsor
- Principal investigator

However, the errors in the statistical programming are always corrected by the responsible statisticians so that the statistical programming meets the requirements of SAP.

11.3.12 Handling of potential imbalance of the numbers of participants across investigation sites

Not applicable.

11.3.13 Strategy for pooling data

Not applicable.

12 DATA MANAGEMENT

SGS proderm's medical data management will start with developing the CRF and will end with the database lock and transfer of the study data to the trial statistician and sponsor. Scope of tasks and handling of the study data is established in a data management plan (DMP). The clinical data manager is responsible for the creation of the DMP which will be approved by the sponsor.

The time schedule for the data management activities and cycle times are defined in the overall project plan and data management project log.

12.1 Methods for data entry and collection

All data of each participant generated according to the clinical investigational plan must be recorded into the case report form (CRF). For this study the CRO provides an electronic CRF (eCRF) which will be designed according to the clinical investigational plan and approved by the Sponsor.

It is the responsibility of the investigator that all required data are recorded in the eCRF in accordance with the clinical investigational plan and in consistence with the participant file. The investigator is responsible for the accuracy, completeness and legibility of the data recorded in the eCRF and in all required reports. The eCRF has to be signed and dated by the investigator. The investigator should maintain a list of personnel authorized to enter data into the eCRF.

There are two types of data in this study:

1. Directly entered data (single data entry into the eCRF, from source data as specified below).
2. Directly entered data with eCRF as source.

For the directly entered data the eCRF is the source data document. Besides the documentation in the eCRF the following data are additionally documented as source data in a participant file: date of birth, visit dates, date of entry into the study, weight, height, medical history, concomitant medication, AEs, SAEs, pregnancy information, illnesses, surgeries and allergies as well as documentation relating to the physical examination at screening and Day 0. Additional source data are the participants' identification list and the screening/enrollment log as well as the documentation relating to eligibility assessments using the inclusion and exclusion criteria. For the external data the digitally generated files of each measurement device-software are considered as source data.

12.1.1 Electronic CRFs (eCRF)

The database software for creation of the eCRF is secuTrial® (interActive Systems, version 6.5.1.5 or higher). All investigation data will be entered directly into the eCRF. The electronic data capture system (EDC) secuTrial® includes automated edit checks for data entry verification and electronic signatures as well as electronic queries and audit trail function.

All data, results and other findings are documented in an eCRF which contains programmed edit checks to prevent incorrect data entries. SGS proderm's data management is responsible for the design of the EDC study database and its functionality. Details for data validation for all entries are described in the data management plan (DMP).

The management of the eCRF includes the following procedures:

- Documentation of data in the eCRFs by the investigator or authorized staff.
- Electronic signing of eCRFs by the investigator where appropriate.
- Check of eCRF-documentation by the CRA during each visit; any further questions later on have to be clarified by the CRA using query function in secuTrial®.
- Release of eCRFs by the CRA after each visit indicated by the SDV icon.

- Queries are raised by the CDM via electronic query forms and sent to the Principal Investigator (PI) for clarification via the EDC system if not self-evident.
- Electronic signature of the eCRF by the PI.
- After closure of the complete database, data are transferred to the trial statistician and copies of the eCRFs as participant files are sent to the sponsor. At the end of the study the sponsor will receive the archived database with the study data and the metadata (e.g. audit trail, queries).

12.1.2 External Data

Not applicable.

12.1.3 Paper CRFs

Not applicable.

12.2 Database management and quality assurance

During the course of the clinical investigation, data will be reviewed by the assigned clinical CRO-personnel for accuracy and completeness. The level of source data verification, data checks, and monitoring visit intervals will be specified in a separate document, the monitoring plan. These monitoring activities will ensure:

- that the investigation is conducted in accordance with the CIP, relevant guidelines and other applicable governmental regulations;
- adequate protection of the rights and safety of the informed participants involved in the investigation by thoroughly providing accurate and complete data;
- the quality and integrity of the data.

Corrections and/or any necessary additions to the data will be requested automatically by programmed edit checks and, if required, queries for discrepant data will be generated by the CRA or the data manager.

Designated investigation personnel are expected to respond to data queries in a timely manner and ensure that the corrections / changes and additions to the data are made, as reflected in the participants' source documentation to ensure that the database is reflecting complete and accurate data.

All queries for the eCRF will be raised electronically within the EDC. This systematic validation will ensure that a clean and consistent database is provided for the statistical analysis.

The latest version of IMDRF classification will be used for coding diagnoses and adverse events

12.2.1 Clinical investigational plan deviations

Clinical investigational plan deviations will be documented in the PD log by the CRA. At the end of the study the data manager will list all outlined clinical investigational plan deviations for each included participant to be discussed in the meeting of the DRC.

12.3 Procedures for verification, validation, and securing of electronic clinical data systems

Specifically, timely, and reliable processes for recording data and rectifying errors and omissions, medical coding uniformity, and reconciliation, if applicable, are necessary to ensure delivery of a quality database and the achievement of the clinical investigation objectives through the implementation of the planned analysis.

12.3.1 Maintaining and protecting participant privacy

All information and data sent to the sponsor, and its authorized representatives, concerning participants or their participation in this investigation will be considered confidential. All data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the investigation participant, i.e. the data collected for the investigation are not linked to a participant's name or other identifying information, but a participant code ("Screening no."). This ensures that the personal data can no longer be assigned to the person and are, thus, pseudonymized. Only the investigator maintains and archives a decryption list that links the participant code to the actual participant (participant identification list).

Decryption will be necessary for quality assurance of the data, i.e. source data verification and potentially auditing by non-site staff: monitoring by the sponsor or a sponsor-delegate, or inspection by a regulatory body. Like site staff, non-site staff are bound to treat participant's personal information as strictly confidential. Review of source data that discloses a participant's identity and personal information can only take place onsite and only under the conditions described by law, i.e. in accordance with the provisions of the General Data Protection Regulation ("GDPR" EU 2016/679), the relevant national data protection legislation(s). That means participants can only participate in the clinical investigation if they agree to their data being processed for the use in this clinical investigation in the described manner and their source data being reviewed by sponsor and regulatory delegates.

This agreement will be part of the participant information and consent process and only data of participants with a valid signed informed consent form (ICF) may be collected, processed and reviewed by non-site staff. In this information, participants are also informed about where their data is being stored/processed (data security level of ex-EU countries needs to be explained, as applicable), to whom they can report privacy breeches and that in case they withdraw their consent, only data not needed for the investigation can be deleted.

12.3.2 Database lock and storage

Upon completion of the investigation and once the database is declared complete and accurate, the database will be locked and data will be transferred from CDM to the statistician for data analysis.

A DMP is set up to define rules and processes for data cleaning as well as data base lock.

12.3.3 Data retention and retention period

After closure of a participant's EDC-documentation, participant files are exported from the eCRF application. The sponsor will receive, after signing the final study report, the complete archived database that will include all study and meta data (audit trial, queries, etc.). The sponsor will archive the archived database and all provided exports for the data retention period. Audit trail information, including queries, will be included. The retention period of corresponding documents will comply with current regulations. For archiving purposes, the investigator will be supplied with an electronic copy of the eCRFs for all screened participants at the investigational site.

The investigator must make arrangements to retain the essential study documents, including the CRF-transcript, source documents and investigator site file for the required retention period after the end of the investigation or cancellation of the investigation. The investigator should take measures to prevent accidental or premature destruction of records. Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Participant (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator/institution notifies the sponsor if the archival arrangements change (e.g. relocation or transfer of ownership).

The investigator site file is not to be destroyed without the sponsor's approval.

12.4 Other aspects of clinical quality assurance

Not applicable.

12.5 Information regarding the Data Monitoring Committee

Not applicable.

12.6 Clinical investigation report

After the completion of the clinical investigation, a detailed report will be written according to ISO14155. The report includes statistical analyses and an appraisal of the results from a medical viewpoint. The correctness of the content will be confirmed by the signature of the Principal Investigator and the person responsible for writing the report.

Any publications of the results by the CRO or Principal Investigator, either in part or in total (articles in journals or newspapers oral presentation, etc.) require the written permission of the Sponsor.

13 AMENDMENTS TO THE CIP

Any major changes to the clinical investigational plan, after finalization, will be documented as amendments. Amendments will be numbered sequentially beginning with the number 1.0 (e.g., Clinical investigational plan Version 2.0, Amendment 1, 03FEB19). Amendments require approval by the Sponsor, the Project Manager and the Investigator. After approval, the amendment will be submitted and approved by the applicable IRB/EC(s) and/or regulatory authorities

Minor changes, which do not affect the participants health, the study preparations or only formal changes can be documented as notes to clinical investigational plan or notes to study and will be numbered as described above. They will be signed by the Sponsor, the Project Manager and the Investigator. Approval by the regulatory authorities is not necessary.

14 DEVIATIONS FROM THE CLINICAL INVESTIGATION PLAN

The Investigator may not deviate from the clinical investigational plan, except when necessary to eliminate imminent hazards to the participant or when the change(s) involve only logistical or administrative aspects of the study (see ISO 14155). Any deviation may result in the participant having to be withdrawn from the study and rendering that participant non-evaluable.

14.1 Statement specifying that the investigators are not allowed to deviate from the CIP

The investigator agrees in writing to conduct the investigation in accordance with this CIP. An investigator must not intentionally deviate from this CIP without first receiving approval in writing from the sponsor and EC (if required), except when necessary to eliminate apparent immediate health hazards to a participant or when the change(s) involve only logistical or administrative aspects of the study (see ISO 14155).

Investigators may not modify this CIP without obtaining written concurrence of the sponsor and the EC and competent authority when required.

14.2 Procedures for recording, reporting, and analyzing CIP deviations

Unintentional deviations from the CIP may still happen. Any deviation from this CIP (also referred to as protocol deviation, PD) will be documented, explained and reported to the sponsor in a timely manner regardless of whether medically justifiable or taken to protect the patient in an emergency. Details for reporting and analyzing of CIP deviations are specified in the investigation specific PD plan. Investigators will also adhere to procedures for reporting investigation deviations to their EC in accordance with their specific EC reporting policies and procedures. At the end of the investigation, all CIP deviations will be discussed in the meeting of the DRC and categorized (non-important / important).

All deviations from the CIP will be documented in the final clinical investigation report.

14.3 Corrective and preventive actions and principal investigator disqualification criteria

CIP deviations will be evaluated during monitoring visits. Individual event corrective and preventive actions (CAPA) will be recommended at that time.

In case of critical and/or repeated and/or intentional CIP deviations, despite agreed CAPA(s), the sponsor may decide to terminate the clinical investigation / disqualify the PI on this site. Disqualification criteria may be, but are not limited to: failure to adequately train the patients on the device, or any deviation that endanger a patients' well-being and/or the overall aim of the clinical investigation.

15 DEVICE ACCOUNTABILITY

SGS proderm will be responsible for storage and distribution of the test products (investigational device and comparator). Responsibility for the device accountability rests with the Investigator. The Investigator may assign some of the Investigator's duties for device accountability to an appropriately trained designee. The products will be used in accordance with this clinical investigational plan. SGS proderm will document the receipt, usage and return of any unused test products. The removed used dressings will be disposed of via clinical waste at the study site.

The devices will be inspected upon receipt to check that the integrity of the pouches, cartons and cases had been maintained and that there are no contaminants on the investigational devices.

Upon the completion or termination of the study unused test products will be returned to the Sponsor.

15.1 Packaging and labeling

The investigational devices and the comparators will be used in their original packages labeled with "nur für klinische Prüfungen" (English: for clinical trials only). All packaging and labeling operations are performed according to applicable legal requirements.

15.2 Access and storage of device(s)

Prototype dressings and comparators must be stored in a secure and restricted area under the conditions specified on the label and remain in the original container. The Prototype dressing and comparators must be used only in the clinical investigation and according to the CIP.

15.3 Record keeping and disposal of the device(s)

The sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigation sites until return or disposal.

The sponsor shall have instructions in place and make packaging materials available, if applicable, for the safe return or disposal of investigational devices. In the case that a device is removed / detaches on a non-visit day, the participant is instructed to return the said device to the study site at the next scheduled visit for disposal.

The principal investigator or an authorized designee shall keep records documenting the following:

a) name(s) of person(s) who received, used, returned, or disposed of the device;

b) the date of receipt, identification, and quantity of each investigational device (batch number/serial number or unique code);

c) the expiry date, if applicable;

d) the date or dates of use;

e) participant identification;

f) date on which the investigational device was returned/explanted from participant, if applicable;

g) the date of return of unused, expired, or malfunctioning investigational devices, if applicable;

h) the date and documentation of disposal of the investigational devices as per instructions of the sponsor, if applicable.

16 STATEMENTS OF COMPLIANCE

16.1 Ethical conduct of the study

The study is conducted in accordance with the ethical principles that have their origins in the current version of the Declaration of Helsinki (last revised at the 64th WMA Assembly in Fortaleza, 2013).

16.2 Compliance with international standards and regional or national regulations

This clinical investigation will be conducted according to the international standard for clinical investigations of medical devices for human participants. This includes the guideline for GCP (latest version: GCP E6 revision 2) (15), and the international standard of the DIN EN ISO 14155.

This clinical investigation will also be conducted according to the applicable national laws and regulatory requirements.

The European General Data Protection Regulation (GDPR) will be followed and consent to data processing will be obtained from all study participants prior to the study. Particularly, person-identifying documents will remain at the study site and will not be submitted to the sponsor. All study data to be submitted to the sponsor will be pseudonymized, including photographs, and the sponsor will store all study data in a restricted place with limited access for at least twenty years after study termination. The personnel of the study site will ensured that sponsors staff do not get in contact with person-identifying data during the study conduct. In case sponsors staff do get knowledge of personal data of the participants they will be instructed not to use this information further. Participants will wear participants' badges for unambiguous assignment with screening numbers only (no names). Participant identification list will be kept separately, in order to not be disclosed to sponsor staff present on-site.

It will abide by the Medical Device Regulation (MDR, Regulation (EU) 2017/745), the German Medical Device Law Implementation Act (Medizinprodukterecht-Durchführungsgesetz, MPDG) and ISO 14155, and takes into account SGS proderm's Standard Operating Procedures (SOPs). Additionally, the investigation is guided by the relevant Medical Device Coordination Group (MDCG) guidelines, which provide further clarity and guidance on the application of the MDR principles and requirements.

16.3 Independent Ethics Committee (IEC) or Institutional Review Board (IRB) and BfArM

SGS proderm will submit the relevant study-specific documents (clinical investigational plan, participant consent form etc.) to the internet-based entry system of DIMDI ("Deutsches Institut für Medizinische Dokumentation und Information"). The Ethics Committee and the Competent Authority (BfArM) will be automatically informed, will progress the applications and release them in the DIMDI-database.

Before initiating the study, the Sponsor will have received written and dated full approval from the responsible IEC for the clinical investigational plan, clinical investigational plan amendment(s) and participant consent form as well as participant recruiting procedures and advertisement and any other appropriate document related to the study. Furthermore the approval of BfArM must be available prior to start of the clinical study. Copies of the approval documents will immediately be sent to the Sponsor.

16.4 Insurance for participants

The Sponsor indemnifies the Investigator for proven research-related injuries for all participants who have given their consent to their participation in the clinical study. From the beginning of the study until its termination each participant is insured against any health impairment occurring as a result of the

participation in the study in accordance with the laws and regulations of the country in which the study is performed.

Insurance is filed for the participants covering a minimum amount of 500.000 Euro per participant in the event of a claim.

The participants are informed about the existence of this insurance and the resulting obligations. The insurance conditions will be handed out to the participants.

16.5 Financing of the clinical investigation

The financial aspects of the clinical investigation are covered by the clinical investigation contract(s) between the sponsor and the CRO, and if applicable, other investigators. The(se) contract(s) must be signed before the beginning of the clinical investigation.

17 INFORMED CONSENT PROCESS

Participant's consent will be obtained and documented according to the applicable regulatory requirements and will adhere to GCP and to the ethical principles that have their origin in the principles of the Declaration of Helsinki (last revised at the 64th WMA Assembly in Fortaleza, 2013).

Prior to obtaining consent, information is given in a language and at a level of complexity understandable to the participant in both oral and written form by the Investigator.

Prior to participation in the study, the written consent form is signed and personally dated by the participant, and by the Investigator. The participant receives a copy of the signed and dated consent form.

The consent form will be updated or amended whenever new information becomes available that may be relevant to the participant.

The informed consent process must be performed by the investigator and must:

- include all aspects of the clinical investigation that are relevant to the participant's decision to participate throughout the clinical investigation, as outlined in ISO 14155:2020;
- avoid any coercion or undue improper influence on, or inducement of, the participant to participate;
- not waive or appear to waive the participant's legal rights;
- use native non-technical language that is understandable to the participant;
- provide ample time for the participant to read and understand the informed consent form and to consider participation in the clinical investigation;
- include personally dated signatures of the participant and the principal investigator or an authorized designate;
- provide the participant with a copy of the signed and dated informed consent form and any other written information.

The process of obtaining informed consent must be documented in the participant source documents.

If new information becomes available that can significantly affect a participants' future health and medical care, that information shall be provided to the affected participant(s) in writing. If applicable, all affected participants shall be asked to confirm their continued informed consent in writing.

The participant or their legally acceptable representative, however, is free to withdraw consent at any time and for any reason, whether expressed or not.

18 ADVERSE EVENTS, ADVERSE DEVICE EFFECTS, AND DEVICE DEFICIENCIES

18.1 Definitions of adverse events and adverse device effects

18.1.1 Adverse event (AE)

An adverse event is defined as any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in participants, users or other persons, in the context of a clinical investigation, whether or not related to the investigational medical device and whether anticipated or unanticipated.

This definition includes events occurring in the context of a clinical investigation related to the investigational device, the comparator or the procedures involved.

For users or other persons this definition is restricted to events related to the investigational medical devices or comparators.

18.1.2 Adverse device effect (ADE)

An adverse device effect is defined as any adverse event related to the use of an investigational medical device or comparator, if it is a medical device.

This definition includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device as well as any event resulting from a usage error or intentional misuse of the investigational medical device.

18.1.2.1 Unanticipated adverse device effect (UADE)

Any adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment.

18.1.2.2 Adverse device effects of special interest

In addition to all findings of skin related ADEs which are discovered during the skin assessments during the course of the study, the following will be considered ADEs of special interest:

i) Subjectively assessed itching which is rated as "mild/persistent", "moderate", "severe".
ii) Objectively assessed skin occlusion falling in to either of the categories "skin whitening" or "skin breakdown".
iii) Objectively assessed occurrence of visible skin stripping.
iv) Objectively assessed skin erythema falling in to either of the categories "moderate reddening" or "severe reddening".
v) Objectively assessed blistering.
vi) Subjectively assessed pain intensity of either "moderate" or "severe".

18.2 Definitions of serious adverse events and serious adverse device effects

18.2.1 Serious adverse event (SAE)

A serious adverse event (SAE) is defined as any adverse event that leads to any of the following:

- death
- serious deterioration in the health of the participant, users, or other persons as defined by one or more of the following:
  (1) life-threatening illness or injury
  (2) permanent impairment of a body structure or a body function
  (3) hospitalization or prolongation of patient hospitalization

(4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
(5) chronic disease

- foetal distress, foetal death or a congenital physical or mental impairment or birth defect

Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

18.2.2 Serious adverse device effect (SADE)

A serious adverse device effect (SADE) is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

This includes device deficiencies that might lead to a serious adverse event if

a) suitable action is not been taken or
b) intervention is not been made or
c) if circumstances are less fortunate.

These are handled under the SAE reporting system.

18.3 Definition of device deficiencies

A device deficiency is defined as any inadequacy in the identity, quality, durability, reliability, usability, safety or performance of an investigational device or comparator, including malfunctions, use errors or inadequacy in information supplied by the manufacturer (including labelling).

18.4 List of non-reportable adverse events

Not applicable

18.5 List of anticipated adverse events/ adverse device effects

Not applicable.

18.6 Classification and relationship of the AE to the investigational device/ procedure

18.6.1 Severity

The severity of an adverse event is classified as:

Mild: Signs and symptoms, which can be easily tolerated. Symptoms can be ignored and disappear when the participant is distracted.

Moderate: Cause discomfort and interfere with normal functioning but are tolerable. They cannot be ignored and do not disappear when the participant is distracted.

Severe: Affect usual daily activity, incapacitating the participant to follow his/her daily activities.

The definitions above are difficult to apply for some data (e.g. laboratory values). Here, the Investigator should use their own judgment.

18.6.2 Relationship to investigational device

The sponsor and investigator will use the following definitions to assess the relationship of the AEs/SAEs to the application of the investigational device:

- Not related
- Possible
- Probable

- Causal relationship
- (Not applicable)

Not related	1. Relationship to the device, comparator or procedures can be excluded when: • The event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device; • The (S)AE does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible • The discontinuation of medical device application or the reduction of the level of activation/exposure – when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the (S)AE • The event involves a body-site or an organ that cannot be affected by the device or procedure • The (S)AE can be attributed to another cause (e.g. an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment or other risk factors) • The event does not depend on a false result given by the investigational device used for diagnosis, when applicable In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of devise/procedures and the (S)AE.
Possible	The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
Probable	The relationship with the use of the investigational device or comparator, or the relationship with the procedures, seems relevant and/or the event cannot be reasonably explained by another cause.
Causal Relationship	The (S)AE is associated with the investigational device, comparator or with procedures beyond reasonable doubt when: • The event is a known side effect of the product category the device belongs to or of similar devices and procedures • The event has a temporal relationship with investigational device/application or procedures • The event involves a body-site or organ that: o The investigational device or procedures are applied to o The investigational device or procedures have an effect on • The (S)AE follows a known response pattern to the medical device (if the response pattern is previously known) • The discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the (S)AE (when clinically feasible) • Other possible causes (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been

	adequately ruled out • Harm to the participants is due to error in use • The event depends on a false result given by the investigational device used for diagnosis, when applicable In order to establish the relatedness, not all criteria listed above might be met at the same time, depending on the type of device/procedures and the(S)AE.
Not applicable	The relationship to the device or comparator when the (S)AE occurred before the administration of the Prototype dressing.

18.6.3 Relationship to investigational procedure

The sponsor and investigator will use the following definitions to assess the relationship of the AEs/SAEs to the investigational procedure:

- Not related
- Possible
- Probable
- Causal relationship
- Not applicable

See table in Section 18.6.2 for detailed definitions of the categories listed above.

18.7 Categories of action taken and outcome

The actions and outcomes following the occurrence of an AE will be assessed as follows:

- Action taken with study treatment:
  - Medical device removed.
  - Unknown.
  - Not applicable.

- Other action taken:
  - None.
  - Non-drug therapy.
  - Other action taken.
  - Concomitant medication altered.

The outcome of each AE will be assessed as follows:

- Not recovered/not resolved.
- Recovered/resolved.
- Recovered/resolved with sequelae.
- Recovering/resolving.
- Fatal.
- Unknown.

18.8 Adverse event reporting

18.8.1 Adverse events

Reporting of AEs will start after the patient has signed the informed consent. At each visit during the clinical investigation patients will be asked using a non-leading question about AEs. All AEs will be documented by the investigator in the source data.

All adverse events will be reported using the eCRF (Adverse Event form). Information contains start- and stop-dates, action taken, outcome, assessments of severity, seriousness and relationship to the Prototype dressing, comparators and related procedures. In case an AE affects a treatment area, this location must be specified.

In general AEs / SAEs must be followed up until the events have subsided, returned to baseline, or, in case of permanent impairment, until the condition has stabilized. All details of follow up must be documented in the patient's medical record. Until patient's end of study visit, corresponding information should be documented in eCRF as well. AEs persisting at the end of study visit should be documented with the current status as "not recovered/not resolved" or "recovering/resolving" (outcome) in the eCRF.

If an AE is ongoing at end of study visit, it should be determined from a medical point of view whether follow-up is necessary or not. The decision should be documented in the eCRF.

In addition, all SAEs should continue to be followed and documented in the eCRF even after the patient's participation in the clinical investigation is over, if considered necessary by investigator and / or sponsor. For SAEs which have stabilized and from which the patient cannot be expected to recover during the clinical investigation or the safety follow-up periods, e.g. chronic or stabilized conditions, the final outcome at the investigator's discretion should be reported as 'recovering/resolving' or 'not recovered/not resolved'.

In addition, a statement detailing why the patient cannot be expected to recover during the clinical investigation, e.g. that the SAE has stabilized or is chronic, should be added to the narrative description of the SAE on the SAE form.

18.8.2 Immediate reporting of adverse events

All AEs which the Investigator classifies as serious by the above definitions disregarding causality must be reported to the Sponsor immediately after acknowledgement (within 24 hours).

The initial report must include the following:

- SAE Form describing the immediately reportable AE.
- SAE Form (including study number, participant screening and randomization number, age, gender, Investigator's name, address, and telephone number).

The initial report must be faxed or emailed to the following:

Name:	Dr. Nibler & Partner
Phone No.:	+49 89 56823726
Fax No.:	+49 700 3784723389 (+49 700 DRUGSAFETY)
Email:	SAE@drugsafety.de

Further following documentation is to be forwarded by fax or email to the same persons as described above and includes (for immediately reportable AEs only):

- Updated SAE forms and updated participant narratives which must be sent when further information becomes available using the above described route of transmission.
- A final SAE form and participant narrative which must be provided by the Investigator after final assessment of the SAE.

Other documents must be submitted upon request (e.g. histology findings, case report forms). All documents must be blinded with respect to a participant's name.

The sponsor keeps a detailed documentation of all (S)AEs reported by the investigator.

The sponsor is responsible for immediately reporting any SAE that has a causal relationship with the investigational medical device, the comparator or the investigation procedure or where such causal relationship is reasonably possible and any device deficiency that might have led to a SAE if appropriate actions had not been taken, intervention had not occurred or circumstances had been less fortunate to the higher national competent authority. These device deficiencies, which could have led to serious adverse events if appropriate actions had not been taken, intervention had not occurred or circumstances had been less fortunate, will be reported immediately to the BfArM as an individual report on the SAE reporting form from Germany. Details for reporting can be found in the safety management plan.

18.8.3 Non-immediate (segmental) reporting of all other AEs

All other AEs not fulfilling the criteria of "immediate" reporting must be recorded on the AE form of the CRF. This AE information will be collected and included in the final report.

Before the databases for safety data (SAEs) of Smith & Nephew Medical Ltd. and SGS proderm as well are closed, data reconciliation has to be carried out and documented. Details will be described in the Data Management Plan.

18.8.4 Reporting of AEs of special interest

In addition to the standard AE reporting, all AEs of special interest as well as all device related AEs will be reviewed by the sponsor during regular AE report updates.

18.8.5 Reporting of device deficiencies

Device deficiencies must be documented and reported by the investigator from Day 0 until Day 7 (end of study) on the appropriate form including an assessment if this deficiency might have led to a SADE. Device deficiencies must be reported to the sponsor contact (see 18.8.2) within 24 hours after acknowledgement using the contact data.

The sponsor will be responsible for reporting device deficiencies to ECs and regulatory authority according to national and local requirements. For requirements in Germany, see 18.8.2 for immediate reporting of device deficiencies that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

18.8.6 Reporting of pregnancies

Each pregnancy that started during the clinical investigation must be reported by the investigator to the sponsor within 24 hours of learning of its occurrence. Pregnancies and pregnancy follow-up will be reported on a Pregnancy Monitoring Form.

Pregnancy follow-up will describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, the presence or absence of any congenital abnormalities, birth defects, maternal or newborn complications and their relation to the investigational device.

18.8.7 Forms used for reporting

For AE and SAE reporting, forms of SGS proderm will be used. These forms will be included in the eCRF.

19 VULNERABLE POPULATION

Not applicable.

20 END, SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

20.1 Definition of the end of the clinical investigation

The end of the clinical investigation is deemed to coincide with the last visit of the last subject.

20.2 Stopping criteria and arrangements

The clinical investigation can be prematurely terminated or suspended by the Sponsor. Reasons for discontinuation may include, but are not limited to the following:

- Re-assessing the risks and benefits of the study.
- The incidence of adverse events constitutes a potential health hazard.
- New scientific data on the investigational product do not justify a continuation of the clinical study.
- Serious and/or persistent non-adherence to the clinical investigational plan, GCP and/or applicable regulatory requirements by an Investigator/Institution.
- Participant enrollment is unsatisfactory.
- Number of drop-outs is so that a statistical relevant analysis of the data is not ensured.
- IEC/regulatory authority decision to terminate or suspend approval for the investigation or Investigator.

20.3 Breaking the blinding/masking code

Not applicable.

20.4 Requirements for participant follow-up and continued care

Not applicable.

20.5 Information from the sponsor at the end of a clinical investigation or in the event of a temporary halt or early termination

In accordance with Article 77 of the Medical Device Regulation (MDR, Regulation (EU) 2017/745), the sponsor will adhere to the following obligations regarding provision of information at the end or in the event of a temporary halt or early termination of the investigation:

20.5.1 Notification of the end of an investigation, temporary halt or early termination

The sponsor shall notify the member state concerned of the end of the clinical investigation within 15 days of the end of the clinical investigation. If the sponsor temporarily halts or terminates a clinical investigation early, the sponsor shall inform the member state concerned within 15 days, providing a justification. If the temporary halt or early termination is due to safety grounds, the sponsor must inform the member state concerned within 24 hours.

20.5.2 Submission of clinical investigation report

Irrespective of the outcome of the clinical investigation, the sponsor shall submit a clinical investigation report and a summary presented in terms easily understandable to the intended user to the member state concerned within one year of the end of the clinical investigation, or within three months of early termination or temporary halt. The summary and the clinical investigation report shall adhere to guidelines issued by the Commission regarding their content and structure.

21 PUBLICATION POLICY

Any publication of the results, either in part or in total (articles in journals or newspapers, oral presentation, etc.) will require the agreement of the Principal Investigator and the Sponsor.

21.1 Statement that the clinical investigation will be registered in a publicly accessible database

The sponsor will register the study in a publicly accessible database and the results will be made available within that database.

21.2 Statement indicating that the results of the clinical investigation will be made publicly available

Upon completion of the investigation, the CRO is tasked with the preparation of the clinical investigation report on behalf of the sponsor. This report, or parts of it, must be submitted to the relevant authorities or ECs if applicable. The results will be entered in a publicly accessible database after completion of the clinical investigation.

21.3 Conditions and timeframes for publication

Investigators may publish results generated from this clinical investigation, but not without prior agreement with, and review by, the sponsor, as detailed in the clinical study agreement between sponsor and CRO/investigator.

22 BIBLIOGRAPHY

Beeckman D. Silicone adhesive multilayer foam dressings as adjuvant prophylactic therapy to prevent hospital-acquired pressure ulcers: a pragmatic noncommercial multicentre randomized open-label parallel-group medical device trial. British Journal of Dermatology. 2021; 185 (1): 52–61.

Black J. et al., World Union of Wound Healing Societies (WUWHS) Consensus Document. Role of dressings in pressure ulcer prevention. Wounds International, 2016.

Bowler PG, Jones SA, Davies BJ, Coyle E. Infection control properties of some wound dressings. J Wound Care. 1999; 8(10): 499–502.

Chow SC, Song F. On Selection of Margin in Non-Inferiority Trials. J Biom Biostat. 2016; 7(3): 301

Forni C, Gazineo D, Allegrini E, et al. Effectiveness of a multi-layer silicone-adhesive polyurethane foam dressing as prevention for sacral pressure ulcers in at-risk in-patients: Randomized controlled trial. *Int J Nurs Stud*. 2022;127:104172.

Forni C. D'Alessandro F, Gallerani P, et al. Effectiveness of using a new polyurethane foam multi-layer dressing in the sacral area to prevent the onset of pressure ulcer in the elderly with hip fractures: A pragmatic randomised controlled trial. Int Wound J. 2018;15(3):383-390.

Heasler E. et al., European Pressure Ulcer Advisory Panel (EPUAP), National Pressure Injury Advisory Panel (NPIAP) and Pan Pacific Pressure Injury Alliance (PPPIA). Prevention and Treatment of Pressure Ulcers/Injuries: Quick Reference Guide. 2019.

ISO14155: 2011 Clinical investigation of medical devices for human subjects- Good clinical practice

McGuiness W, Vella E, Harrison D. Influence of dressing changes on wound temperature. J Wound Care. 2004; 13(9): 383–5.

Obagi Z, Damiani G, Grada A, Falanga V. Principles of Wound Dressings: A Review. Surg Technol Int. 2019;35:50-57.

Rippon M, Davies P, White R. Taking the trauma out of wound care: the importance of undisturbed healing. J Wound Care. 2012; 21(8): 359–68.

Rippon M., Waring M., Bielfeldt S. An evaluation of properties related to wear time of four dressings during a five-day period. Wounds UK, 2015; 11(1):45-54.

Rossington A., Clinical performance and positive impact on patient wellbeing of [redacted] Wounds UK. 2013; 9(4): 91-95.

Solowiej K, Upton D. Painful dressing changes for chronic wounds: assessment and management. Br J Nurs. 2012; 21(20): 20–5.

DocuSign

Certificate Of Completion

Envelope Id: D779DA1C4C22402BADBC5A60C0B8736B
Status: Completed
Subject: Complete with Docusign: 24.0062_Avenger_CIP_V4.0_23SEP2024_CLEAN Unsigned.pdf
Source Envelope:
Document Pages: 87
Signatures: 9
Certificate Pages: 7
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Enabled
Time Zone: (UTC) Dublin, Edinburgh, Lisbon, London

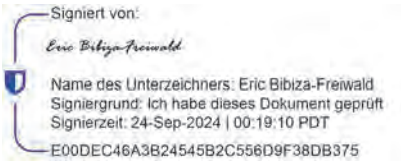
Envelope Originator:
Michael Howarth
TJ Smith & Nephew Limited
101 Hessle Road
Hull, Hull HU3 2BN
Michael.Howarth@smith-nephew.com
IP Address: 216.222.214.6

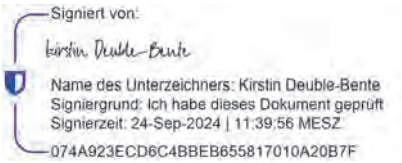
Record Tracking

Status: Original
23-Sep-2024 | 13:43

Holder: Michael Howarth
Michael.Howarth@smith-nephew.com

Location: DocuSign

Signer Events	Signature	Timestamp
Eric Bibiza-Freiwald EBibiza@proderm.de 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 geprüft	Sent: 23-Sep-2024 | 13:50 Viewed: 24-Sep-2024 | 08:18 Signed: 24-Sep-2024 | 08:19
Electronic Record and Signature Disclosure: Accepted: 24-Sep-2024 | 08:18 ID: 6d2699da-5094-4a58-980d-bb669ce57abb		
Jaideep Banerjee Jaideep.Banerjee@smith-nephew.com Senior Manager, MSl and clinical Strategies Smith & Nephew Security Level: Email, Account Authentication (Required)	 Signature Adoption: Uploaded Signature Image Signature ID: 8167B6F2-D414-42A1-BF94-B6986205BB3C Using IP Address: 73.249.194.229 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 23-Sep-2024 | 13:50 Resent: 25-Sep-2024 | 13:04 Viewed: 25-Sep-2024 | 13:08 Signed: 25-Sep-2024 | 13:10
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)	 Signature Adoption: Pre-selected Style Signature ID: B7D37248-838E-4CAC-AE11-E7E55198A88D Using IP Address: 216.222.208.4 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 23-Sep-2024 | 13:50 Viewed: 23-Sep-2024 | 17:18 Signed: 23-Sep-2024 | 17:19
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
Karlie Morgan Karlie.morgan@smith-nephew.com Director Clinical Study Management Smith & Nephew Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: F420CE20-9579-4AFD-8CD1-DC3D32055809 Using IP Address: 75.13.82.41 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 23-Sep-2024 | 13:50 Viewed: 24-Sep-2024 | 15:34 Signed: 24-Sep-2024 | 15:35
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
Kirstin Deuble-Bente KBente@proderm.de Dr. Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 074A923E-CD6C-4BBE-B655-817010A20B7F Using IP Address: 89.246.251.118 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): Ich habe dieses Dokument geprüft	Sent: 23-Sep-2024 | 13:50 Viewed: 24-Sep-2024 | 10:39 Signed: 24-Sep-2024 | 10:40
Electronic Record and Signature Disclosure: Accepted: 24-Sep-2024 | 10:39 ID: 29500117-3a7e-4aec-bd11-2fa639648aeb		

Signer Events	Signature	Timestamp
Kolja Boese Kolja.Boese@smith-nephew.com Sr. Medical Director Smith & Nephew Security Level: Email, Account Authentication (Required)	 Signature Adoption: Drawn on Device Signature ID: DA5DDA49-254C-426E-9936-5721E0A21315 Using IP Address: 216.222.214.6 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 23-Sep-2024 | 13:50 Viewed: 24-Sep-2024 | 09:54 Signed: 24-Sep-2024 | 09:55
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
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: 23-Sep-2024 | 13:50 Viewed: 24-Sep-2024 | 10:31 Signed: 24-Sep-2024 | 10:32
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
Rachel Jahnke Rachel.Jahnke@smith-nephew.com VP, Global Clinical Research Operations Smith+Nephew Security Level: Email, Account Authentication (Required)	 Signature Adoption: Drawn on Device Signature ID: 98517B5E-F45A-456C-BE71-02BF1B8CCDA5 Using IP Address: 75.104.93.231 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 23-Sep-2024 | 13:50 Resent: 25-Sep-2024 | 13:04 Viewed: 25-Sep-2024 | 15:02 Signed: 25-Sep-2024 | 15:39
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
sam greenhalgh Sam.Greenhalgh@smith-nephew.com Regulatory Affairs Director Smith & Nephew Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 1C73ED93-193D-4888-9F66-F071859C80BC Using IP Address: 208.127.123.112 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 23-Sep-2024 | 13:50 Viewed: 24-Sep-2024 | 14:47 Signed: 24-Sep-2024 | 14:47
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
David Ruwe druwe@proderm.de Security Level: Email, Account Authentication (Required) **Electronic Record and Signature Disclosure:** Not Offered via DocuSign	COPIED	Sent: 23-Sep-2024 | 13:50
Sophie Berry Sophie.Berry@smith-nephew.com Smith & Nephew Security Level: Email, Account Authentication (Required) **Electronic Record and Signature Disclosure:** Not Offered via DocuSign	COPIED	Sent: 23-Sep-2024 | 13:50 Viewed: 25-Sep-2024 | 16:01

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	23-Sep-2024 | 13:50
Certified Delivered	Security Checked	24-Sep-2024 | 14:47
Signing Complete	Security Checked	24-Sep-2024 | 14:47
Completed	Security Checked	25-Sep-2024 | 15:39

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, Smith Nephew - Sub (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact Smith Nephew - Sub:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: joshua.cohen@smith-nephew.com

To advise Smith Nephew - Sub of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at joshua.cohen@smith-nephew.com and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from Smith Nephew - Sub

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to joshua.cohen@smith-nephew.com and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with Smith Nephew - Sub

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to joshua.cohen@smith-nephew.com and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify Smith Nephew - Sub as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by Smith Nephew - Sub during the course of your relationship with Smith Nephew - Sub.