

**Clinical investigation plan**

Sponsor: Smith + Nephew

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**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 prototype non-medicated multilayer foam dressings compared to established medical devices.**

Author: Dr. Clare Vladimirkij

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**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 prototype non-medicated multilayer foam dressings compared to established medical devices.**

<b>Short title</b>	Human participant study of prototype non-medicated multilayer foam dressings on intact skin.		
<b>EUDAMED number</b>	CIV-24-03-046336		
<b>Investigational medical devices (IMD) / comparators</b>	<b>IMD_1:</b>	Prototype dressing (rectangle)	
	<b>IMD_2</b>	Prototype dressing (square)	
	<b>Comparator_1:</b>	Product name:	
		Generic pseudonym:	Marketed dressing (rectangle)
	<b>Comparator_2:</b>	Product name:	
		Generic pseudonym:	Marketed dressing (square)
<b>Intended purpose</b>	Management of acute and chronic wounds.		
<b>Design of the clinical investigation</b>	Prospective, Open-Label, Comparative, Interventional Study		
<b>Phase of development</b>	Pre-market clinical evaluation		
<b>Planned period of the clinical investigation</b>	First participant in:		Last participant out:
	OCT2024		JAN2025
<b>Sponsor</b>	Smith & Nephew Medical Ltd.		
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<b>Sponsor code:</b>	HVS2312		
<b>CRO</b>	SGS proderm GmbH, Kiebitzweg 2, 22869 Schenefeld/Hamburg, Germany.		
<b>Principal investigator</b>	Dr. med. K. Deuble-Bente,		
	SGS proderm GmbH, Kiebitzweg 2, 22869 Schenefeld/Hamburg, Germany .		
	Phone: +49 40-839358-262, Fax: +49 40-839358-39		
<b>SGS proderm study-no.</b>	24.0061-99		

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.

*(Confidentiality statement: The contents of this document are confidential. Unauthorized use, disclosure or reproduction is strictly prohibited. It is understood that the information will be disclosed to the Investigator's staff, applicable independent ethics committee(s) / institutional review board(s), regulatory authorities, and clinical investigation subjects to obtain informed consent without prior written approval.)*

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## Summary of the revision history

Date	Version	Summary of changes	Author/ Updated by
04MAR2024	V1.0	Initial version	N/A
22MAY2024	V2.0	<ol style="list-style-type: none"> <li>1. EUDAMED number was added (title page).</li> <li>2. The references to the legislation which were no longer in force (MPG, MPSV, MEDDEV Guidelines) were updated / removed (updated sections 8.6., 15.1, and 16.2)</li> <li>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.</li> <li>4. Amended the days on which the subjective and objective dressing assessments were carried out (Table 2.1, sections 10.4.8, 10.4.16.6 and 10.4.16.7) to reflect that of the synopsis.</li> <li>5. Updated section 6.1 reflect the Class IIB investigational device status, as well as the Class III future, marketed device status.</li> <li>6. Amended publication statement in section 21.1.</li> <li>7. Corrected DMIDS instead of DIMDI</li> <li>8. Corrected typo ("lower" to "upper" confidence interval) in synopsis and section 11.3.1</li> <li>9. Added detail relating to the description of the devices to section 6.1.</li> <li>10. Added details of information reporting obligations at study end to section 20.</li> <li>11. Corrected typo in abbreviation "DMP" to "DMC" (section 4.1).</li> </ol>	Dr. Clare Vladimirskij
28AUG2024	V3.0	<ol style="list-style-type: none"> <li>1. Changed IMD names (Prototype dressing (rectangle) and (square) (throughout document).</li> <li>2. Added Generic pseudonym for comparators to title page.</li> <li>3. Updated the planned period for the clinical investigation (title page and synopsis, section 10.1.1, 10.3.2).</li> <li>4. Updated signature page (section 1.3).</li> <li>5. Removed "clinically" from CADP over entire document (but NOT the title).</li> <li>6. Added comment that the assessments on percentage border lift, pad lift, pad integrity and [REDACTED] will be based on the "counting grids method" to give an objective percentage score (synopsis (assessments), sections 6.7 and 10.4.15) and a description of the grid counting method is given in section 10.4.11.</li> <li>7. Added details of the pass criteria for acceptable dressing presence to section 2 and section 11.2.1.</li> </ol>	Dr. Clare Vladimirskij

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		<ol style="list-style-type: none"> <li>8. A definition of pad exposure was added to the description of primary endpoint in the Criteria for evaluation (statistics) section of the synopsis and section 11.2.1.</li> <li>9. Removed tracking to pad from acceptable dressing presence and also the objective assessment (synopsis, section 7.4, 10.4.8).</li> <li>10. [REDACTED]</li> <li>11. Justification for the 15% non-inferiority threshold added to the synopsis (sample size calculation), section 9.3 and referenced to further in sections 11.2.1 and 11.3.1.</li> <li>12. 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.</li> <li>13. Completed footnote 9 about objective assessments (section 2.1).</li> <li>14. Added the abbreviation PD to section 4.1.</li> <li>15. Included the Biological evaluation statement reference in section 6.1 and 7.1.</li> <li>16. Added the rationale including references for the use of clinically acceptable dressing presence as the evaluation parameter for the primary endpoint (section 7.4).</li> <li>17. Added additional references to section 7.4.</li> <li>18. Added reference to Biological evaluation statement Ref.BES106 to section 8.3, 8.6.</li> <li>19. Updated study duration (section 10.1.1).</li> <li>20. Added a footnote concerning premature dressing detachment (section 10.4.8).</li> <li>21. Added a definition of substantial modification in terms of modification of the SAP from that planned in the CIP was added to section 11.2.</li> <li>22. Added a description of the sensitivity analysis to section 11.2.1 and 11.3.9.</li> <li>23. Added the missing sections: Rationale for the number of procedures; Potential confounding factors (sections 11.3.3 and 11.3.5.3 respectively).</li> <li>24. Added explanation of LOCF to section 11.3.8.</li> <li>25. Added section Procedures for reporting deviations in the statistical analysis between CIP, SAP and CIR; Procedures for reporting errors in statistical programming (sections 11.3.10 and 11.3.11).</li> <li>26. Up dated section 12.3.3 to remove reference to 25 year retention period and make it compliant with current regulations for the product type.</li> <li>27. Corrected RA to competent authority in section 14.1.</li> <li>28. Capitalized Prototype throughout where referring to IMD1/2.</li> <li>29. Added additional references to section 22 and the references were organized alphabetically.</li> </ol>	
26NOV2024	V4.0	<ol style="list-style-type: none"> <li>1. The sample size was increased from 120 to 135 participants (synopsis, sections 10.3.1, 10.4.8 and 11.3.1).</li> <li>2. In the sample size calculation the % discordant pairs was increased by 3% to 28% as a conservative estimate to account for potential lot to lot variability between the prototype and marketed dressing (synopsis and section 11.3.1).</li> <li>3. The number of participants expected to complete was</li> </ol>	Dr. Clare Vladimirskij



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		increased from 105 to 120 (synopsis, sections 10.3.1, 10.4.8 and 11.3.1).. 4. The Camera equipment suitability for the two types of dressing is indicated (section 10.4.7). 5. Detailed the rationale for the CIP amendments (section 13)	
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**1.1 Sponsor details**

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**1.2 Contact details of the investigation sites and external organizations**

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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.

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Signed by:  
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**1.3.2 Approval statement of SGS proderm**

The following persons have approved this clinical investigation plan:

Eric Bibiza-Freiwald  
*Lead Statistician*

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signature

Signiert von:  
*Eric Bibiza-Freiwald*

Name des Unterzeichners: Eric Bibiza-Freiwald  
Signiergrund: Ich genehmige dieses Dokument  
Signierzeit: 27-Nov-2024 | 01:31:49 PST  
E00DEC46A3B24545B2C556D9F38DB375

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**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*

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.....  
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Signiergrund: Ich habe dieses Dokument geprüft  
Signierzeit: 02-Dec-2024 | 10:32:27 MEZ  
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**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 prototype non-medicated multilayer foam dressings compared to established medical devices.
Short title	Human participant study of prototype non-medicated multilayer foam dressings 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: OCT2024 Last participant out: JAN2025
References	<p><b>Obagi Z, et al.</b> Principles of Wound Dressings: A Review. Surg. Technol. Int. 2019;35:50-57.</p> <p><b>Rippon M. et al.,</b> 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</p> <p><b>Rossington A. et al.,</b> Clinical performance and positive impact on patient wellbeing of [REDACTED]. Wounds UK. 2013; 9(4): 91-95.</p> <p><b>Forni C, et al.</b> 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.</p> <p><b>White R.</b> Evidence for atraumatic soft silicone wound dressing use. Wounds UK. 2005;1(3):104-109.</p>
<b>Introduction</b>	
Background	<p>Wound dressings are integral to effective wound management, promoting healing and shielding the wound from infection (Obagi, 2019). 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.</p> <p>This study will assess two prototype multilayer, non-medicated foam dressings (IMDs), each representing non-medicated versions of next-generation dressings derived from existing CE-marked medical devices. Both IMDs will be evaluated against a corresponding, established dressing (comparator) with a similar intended use profile and shape, 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 both the comparators and the existing CE marked devices on which the design of the non-medicated IMDs were based, suggesting</p>

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	a similar risk profile for the IMDs (Rossington, 2013; Forni, 2022; White 2005).
Purpose of the clinical investigation	To evaluate prototype non-medicated multilayer foam dressings on healthy, intact skin to assess dressing retention and other dressing performance parameters.
<b>Objectives</b>	
Primary objectives	<p>To demonstrate non-inferiority of the prototype non-medicated multilayer foam dressings (rectangle and square variants) with regards to acceptable dressing presence in human participants at day 7 in the following two comparison pairs:</p> <ol style="list-style-type: none"> <li>1. Prototype dressing (rectangle) vs Marketed dressing (rectangle) on the knee.</li> <li>2. Prototype dressing (square) vs Marketed dressing (square) on the thigh.</li> </ol>
Secondary objectives	<p>To generate data to support both primary objectives:</p> <ul style="list-style-type: none"> <li>• retention claims for up to 7 days</li> <li>• dressing presence claims for up to 7 days</li> <li>• pad integrity claims for up to 7 days</li> <li>• pad lift claims for up to 7 days</li> <li>• border lift claims for up to 7 days</li> <li>• comfort during wear claims for up to 7 days and at dressing removal</li> <li>• retention claims during joint mobilization including following a physiotherapy session</li> </ul>
<b>Population of the clinical investigation</b>	
Number of participants (planned)	135 healthy participants are planned to be randomized for this study so that at least 120 participants are expected to complete the study.
Description of participants	Participants in general good health with intact skin (i.e. <u>without</u> indication for treatment with wound dressings) who will be recruited according to the in- and exclusion criteria.
Inclusion criteria	<ol style="list-style-type: none"> <li>1. Participant is capable of providing informed consent</li> <li>2. Participant is willing and able to make all required study visits</li> <li>3. Aged 22-70 years at the time of signing the informed consent*</li> <li>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)</li> <li>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.</li> <li>6. Participant is willing to have excess hair removed from the dressing application sites</li> <li>7. Participant is willing to avoid immersing the dressings in water (no swimming or bathing) for the duration of the study</li> </ol> <p>*at least 10% of participants are aged &gt;55 years</p>
Exclusion criteria	<ol style="list-style-type: none"> <li>1. Female participant who is pregnant, or lactating.</li> <li>2. Participant has a known sensitivity to any of the study products, materials or ancillary product or components.</li> </ol>

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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 and with respect to the physiotherapy session) 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)

Prototype non-medicated multilayer foam dressing (rectangle and square variants)

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Investigational medical devices	<p><b>Name:</b> Prototype dressing (rectangle)</p> <p><b>Materials/ingredients:</b> Four-layer foam dressing [REDACTED]</p> <p><b>Size:</b> 30cm x 10cm</p> <p><b>Intended purpose:</b> management of acute and chronic wounds.</p> <p><b>Mode of application/use:</b> topical application.</p> <p><b>Frequency of application/use:</b> single use</p> <hr/> <p><b>Name:</b> Prototype dressing (square)</p> <p><b>Materials/ingredients:</b> Four-layer foam dressing [REDACTED]</p> <p><b>Size:</b> 7.5cm x 7.5cm.</p> <p><b>Intended purpose:</b> management of acute and chronic wounds.</p> <p><b>Mode of application/use:</b> topical application.</p> <p><b>Frequency of application/use:</b> single use</p>
Comparators	<p><b>Name:</b> Marketed dressing (rectangle)</p> <p><b>Materials/ingredients:</b> Five-layer foam dressing [REDACTED]</p> <p><b>Size:</b> 30cm x 10cm</p> <p><b>Intended purpose:</b> management of acute wounds, such as surgical wounds, cuts and abrasions.</p> <p><b>Mode of application/use:</b> topical application.</p> <p><b>Frequency of application/use:</b> single use</p> <hr/> <p><b>Name:</b> Marketed dressing (square)</p> <p><b>Materials/ingredients:</b> Five-layer foam dressing [REDACTED]</p> <p><b>Size:</b> 7.5cm x 7.5cm.</p> <p><b>Intended purpose:</b> management of acute and chronic wounds.</p> <p><b>Mode of application/use:</b> topical application.</p> <p><b>Frequency of application/use:</b> single use</p>
Allocation of the investigational medical devices	<p>Four different dressings (two IMDs and two comparators) will be investigated, with each participant receiving one of each of the two IMDs and one of each of the two comparators. The dressings will be divided into two groups of IMD vs comparator comparison pairs, i.e. (i) Prototype dressing (rectangle) vs Marketed dressing (rectangle); and (ii) Prototype dressing (square) vs Marketed dressing (square). Comparison pair (i) will be applied to the knees (one dressing per knee) and comparison pair (ii) will be applied to the thighs (one dressing per thigh). Each dressing of the comparison pair will be randomised to either the right or left knee / thigh in a 1:1 ratio.</p>
<b>Methodology</b>	
Design of the clinical investigation	Prospective, open-label, comparative, interventional study with intra-individual comparison.



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Schedule of the clinical investigation per participant:	<p>Duration of the clinical investigation assessment period: 7 days.</p> <p>Duration of the clinical investigation including the screening period: maximum 2 weeks.</p> <p>The participants will attend 5 site visits:</p> <p>Day -7 to Day 0: one screening visit*</p> <p>Day 0: application of the dressings and 1<sup>st</sup> round of assessments</p> <p>Day 1: 2<sup>nd</sup> round of assessments</p> <p>Day 3: 3<sup>rd</sup> round of assessments</p> <p>Day 7: 4<sup>th</sup> round of assessments and removal of dressings</p> <p>* Screening can be completed on Day 0, or at a separate visit up to 7 days prior to Day 0.</p>
Procedure(s)	<p><u>Informed consent</u></p> <p>Potential participants may only be enrolled in the clinical investigation after providing written informed consent at the site.</p> <p><u>Hair removal (24-48 hours before dressing application)</u></p> <p>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 &gt;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.</p> <p>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.</p> <p><u>Dressing application (on Day 0)</u></p> <p>Dressings will be applied by the investigator or trained site personnel as in accordance with the respective IFUs on Day 0. Dressings will be applied to each knee whilst the knee is bent at an approx. 30-degree angle (as determined using a goniometer). The thigh dressings will be applied at zero degrees with the legs extended flat. 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.</p> <p><u>Physiotherapy session (on Day 1)</u></p> <p>Will include 4 basic exercises, with 5 repetitions per leg: (i) lying on back and bending / straightening leg; (ii) lifting leg from chair sitting position; (iii) bending and extending knee from chair/bedside sitting position; (iv) bending knee back from standing position.</p>

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(i)	(ii)	(iii)	(iv)


**Dressing removal (on Day 7)**

The investigator or trained site personnel will remove the dressings as in accordance with the IFU of the prototype dressings, i.e. 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 knee, (iv) left knee. There will be a 10 min interval between the removal of each dressing to allow for any residual pain to subside.

**Photography (on Days 0, 1, 3 and 7)**

Following dressing application, the investigator or trained site personnel will take photographs of all dressing locations, with the leg positioned to achieve the same angle used for dressing application (i.e. knees bent at 30 degree angle or at 0 degrees). Photographs will be taken of dressings in place and, if required, of any AE/adhesive offset at the following time points for documentation purposes:

- after the initial dressing application by the investigator (Day 0).
- before and after the physiotherapy session on Day 1.
- after the dressing assessments on Day 3.
- before the dressing removal (any day that dressing requires removal).

<b>Assessment(s)</b>	<p><b><u>Physical examination of the skin condition at application test site (at screening and on Day 0)</u></b></p> <p>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.</p> <p><b><u>Sweating Severity Self-Assessment (SSSA) (at screening)</u></b></p> <p>During the screening visit, the participants will assess their normal level of sweating according to the ordinal scale: mild, moderate, severe.</p> <p><b><u>Dressing quality control (QC) check (on Day 0)</u></b></p> <p>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.</p> <p><b><u>Dressing application assessment (on Day 0)</u></b></p> <p>The investigator or trained site personnel will assess the following:</p> <p>i) </p>
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Dressing application assessments will be performed with the leg placed in the same position as adopted for the application of the dressings (the angle of the knee determined by goniometer: 30 degrees for knee dressings and 0 degrees for thigh dressings).

**Objective dressing assessment (on Days 1\*, 3 and 7)**

\*to be performed both before and after the physiotherapy session on Day 1.

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 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". Should any dressing demonstrate  $\geq 50\%$  pad lift, it will be removed and Dressing Removal Assessments will be conducted. Based on the "counting grids method" to give an objective percentage score.
- 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".

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- 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.

\*to be performed both before and after the physiotherapy session on Day 1.

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:

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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.

- iii)

- iv)

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	<p>[REDACTED]</p> <p>v) [REDACTED]</p> <p>vi) <b>Skin occlusion:</b> 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.</p> <p>vii) <b>Skin stripping:</b> 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.</p> <p><u>Early Termination Assessment</u></p> <p>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 <u>not</u> withdrawal of consent, the following assessments should be performed:</p> <ul style="list-style-type: none"><li>- If dressings still need to be removed then the following should be performed before removal:<ul style="list-style-type: none"><li>• subjective dressing assessment</li><li>• objective dressing assessment</li><li>• activity assessment</li></ul></li><li>- After removal of the dressing the following should be performed:<ul style="list-style-type: none"><li>• subjective dressing removal assessment</li><li>• objective dressing removal assessment</li></ul></li></ul>
Safety assessment(s)	<p><u>Skin assessment: Days 0, 1*, 3 and 7.</u></p> <p>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.</p> <p>*to be performed before the physiotherapy session on Day 1.</p> <p><u>AE or DD reporting</u></p> <p>The participant can report an AE or DD at any point during the investigation.</p> <p><u>Changes in concomitant therapies</u></p> <p>This will be documented at each participant's visit at the investigational site.</p>
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 (rectangle) vs Marketed dressing (rectangle) and Prototype dressing (square) vs Marketed dressing (square) regardless of dressing location (i.e. right or left application site). The alpha level used in the non-inferiority tests will therefore be adjusted to 2.5% for each product comparison.

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The assumptions for the Prototype dressing (rectangle) vs Marketed dressing (rectangle) comparison are that of no difference between the products in acceptable dressing presence by day 7. Also assumed is 28% discordant pairs and the proportion of participants where both dressings are acceptable is at least 60%. Using these conservative assumptions, a sample size of 120 evaluable participants is required to ensure 80% power using Newcombe's score method to show that the upper confidence limit of the 2-sided 97.5% confidence interval, for the difference in proportion of acceptable presence (Marketed dressing (rectangle) – Prototype dressing (rectangle)), is lower than the non-inferiority threshold of 15% ( $\%C - \%IMD < 15\%$ , where  $\%IMD$  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 (square) vs Marketed dressing (square) comparison and so the same sample size is acceptable, as these products will all be applied to the same participants then 120 total evaluable participants would be sufficient for the aims of both comparisons.

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

The sample size was calculated using nQuery 9.3.0.

**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  $\pm 15\%$  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). The comparator dressing in this study is a market leader 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.









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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 which are based on the two primary endpoints that represent the two IMDs. In order to control the alpha level for multiple comparisons a hierarchical testing method will be used within each hierarchy.

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 with the Bonferroni adjustment for multiple comparisons required as a result.

The order of each hierarchy will be defined as:

Hierarchy 1: Prototype dressing (rectangle) vs Marketed dressing (rectangle), on the knees

Order	Endpoint
1	Acceptable dressing presence* (knee) at day 7 (Primary endpoint)
2	Acceptable dressing presence* (knee) at days 1 and 3
3	Presence of dressings at days 1, 3 and 7
4	Pad integrity at days 1, 3 and 7
5	Percentage pad lift at days 1, 3 and 7
6	Percentage border lift at days 1, 3 and 7
7	Dressing comfort at days 1, 3 and 7

\*defined as dressings present, with no border lift reaching the pad and no pad lift or pad exposure.

Hierarchy 2: Prototype dressing (square) vs Marketed dressing (square), on the thighs

Order	Endpoint
1	Acceptable dressing presence* (thigh) at day 7 (Primary endpoint)
2	Acceptable dressing presence* (thigh) at days 1 and 3
3	Presence of dressings at days 1, 3 and 7
4	Pad integrity at days 1, 3 and 7
5	Percentage pad lift at days 1, 3 and 7
6	Percentage border lift at days 1, 3 and 7
7	Dressing comfort at days 1, 3 and 7

\*defined as dressings present, with no border lift reaching the pad and no pad exposure.

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

1. Non-inferiority of the primary endpoint

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**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.


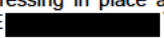
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## 2.1 Schedule of the clinical investigation

Table 2.1 Schedule of the clinical investigation

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

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Schedule of events	Pre-treatment data (screening) <sup>1</sup> max. 7 days before Day 0	Day 0 assessment	Day 1 assessment <sup>2</sup>	Day 3 assessment <sup>2</sup>	Day 7 (or early termination <sup>14</sup> ) assessment <sup>2</sup>
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  $\pm 2$  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  $\geq 5$  days before Day 0.
5. An assessment of current skin disease (e.g., eczema, psoriasis), sunburn or skin peeling at the dressing application sites will be performed at the Screening Visit. An additional skin assessment will be performed on Day 0 if there are separate visits for Screening and Day 0.
6. Up to 24 hours prior to dressing application. Hair should be removed 24 hours prior to dressing application using electric clippers. Should the participant regularly wet shave the dressing application sites, they may prepare the site using the wet shave technique (up to 48 hours prior to dressing application), otherwise participants will be instructed to only use electric clippers. If the participant does not have electric clippers, the hair will be removed at the study site on Day 0 following a standard procedure.
7. Dressings will be applied by the investigator or trained site personnel according to the application procedure as described in the IB/IFU. Dressings will be applied to each knee whilst the knee is bent at a 30-degree angle. The thigh dressings will be applied at zero degrees with the legs extended flat.
8. Includes assessment of the following parameters: [REDACTED]
9. Includes assessment of the following parameters: dressing presence, acceptable dressing presence, border lift, pad lift, pad integrity and if dressing removal was required.
10. The participant will be asked what the level of activity they have undertaken since last visit (e.g. crouching/kneeling, mild, moderate, strenuous).
11. Following dressing application, the investigator or trained site personnel will take photographs of all dressing locations, with the leg positioned to achieve the same angle used for dressing application (i.e. knees bent at 30 degree angle for knee dressings and 0 degrees for thigh dressings). Photographs will be taken of dressings in place and, if required, of any AE/adhesive offset at the following time points for documentation purposes:
  - after the initial dressing application by the investigator (Day 0).
  - before and after the physiotherapy session on Day 1.
  - after the dressing assessments on Day 3.
  - before the dressing removal (any day that dressing requires removal).
12. [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:
  - subjective dressing assessment
  - objective dressing assessment
  - activity assessment
 After removal of the dressing the following should be performed:
  - subjective dressing removal assessment
  - objective dressing removal assessment
15. To be performed before the physiotherapy session.
16. To be performed before and after the physiotherapy session.
17. To be performed after the physiotherapy session.

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**4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS****4.1 Abbreviations**

<b>Abbreviation<sup>1</sup></b>	<b>Definition</b>
ADE(s)	Adverse Device Effect
AE(s)	Adverse Event(s)
BER	Biological Evaluation Report
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)
DMC	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
IB	Investigator's Brochure
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

<sup>1</sup> Above mentioned abbreviations may but need not necessarily occur in this document.

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Abbreviation <sup>1</sup>	Definition
min	Minute
MPDG	Medical Device Law Implementation Act ( <i>Medizinprodukterecht-Durchführungsgesetz</i> )
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 investigation	The date of the last participant's last visit.





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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)	<p>Medical device being assessed for clinical performance, effectiveness, or safety in a clinical investigation.</p> <p><u>Note 1:</u> This includes medical devices already on the market that are being evaluated for new intended uses, new populations, new materials or design changes.</p> <p><u>Note 2:</u> 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).</p> <p><u>Note 3:</u> For the purpose of this document, the terms "investigational medical device" and "investigational device" are used interchangeably.</p>
Non-important protocol deviation (PD)	<p>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.</p> <p>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.</p>
Important protocol deviation (PD)	<p>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.</p> <p>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.</p>
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
	Smith & Nephew Medical Ltd.
	

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## 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, some dressings have been specifically developed to help prevent infection or manage infected wounds by incorporating antimicrobials.

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 McGuinness, 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.

The investigational devices are a modified product derived from the current CE marked [REDACTED] dressings. The first device is a rectangle shaped variant, while the second is square. Both IMDs will be evaluated against a corresponding, established dressing (comparator) with a similar intended use profile and shape, for a robust comparison of properties affecting 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 and the existing CE marked devices, on which the design of the non-medicated IMDs were based, has been found to be low and therefore is also expected to be low for the IMDs (Rossington, 2013; Forni, 2022; White, 2005).

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# 6 IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

## 6.1 Summary

The prototype non-medicated multilayer foam dressings (rectangle and square variants) with the intended clinical use in treatment of acute and chronic wounds, are Class IIb medical devices (EU Medical Device Regulation 2017/745 Annex VIII).

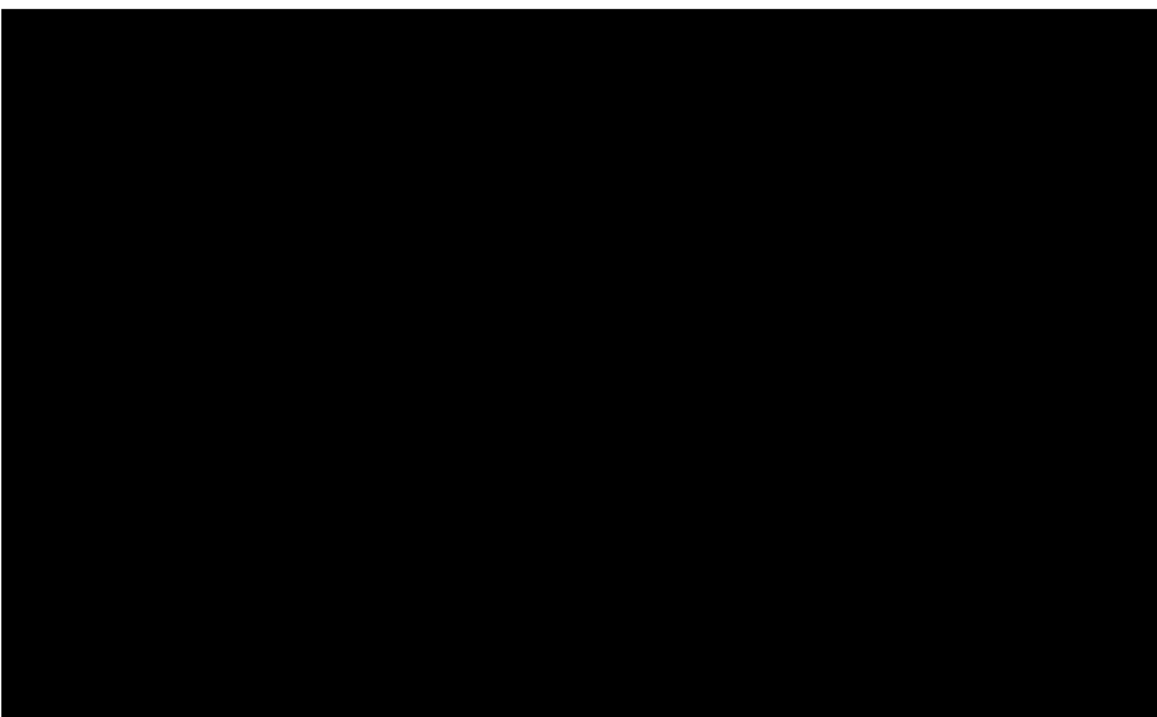
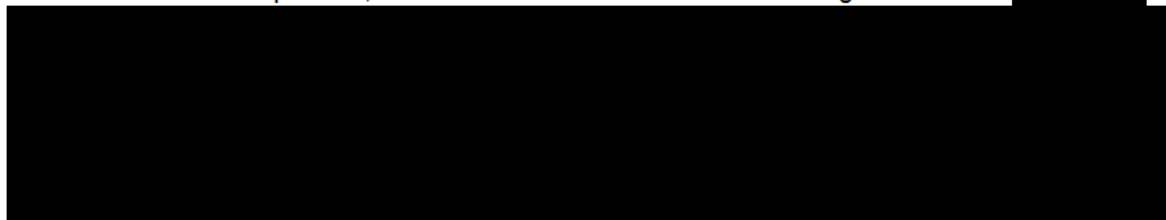


Figure 6.1 The dressing structure of the Prototype multilayer (non-medicated) foam dressing.

### 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.



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**Fluid Locking Layer**

[REDACTED] conformable design enables the dressing to be worn over challenging areas of the body which undergo a high range of mobility, such as the knee. The dressing is designed to stay in place over the intended wear time, including during patient movement such as that required by post-surgery physiotherapy exercises.

**Absorbent [REDACTED] Foam**

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

The future device as marketed will have [REDACTED] but in all other respects will be identical to the investigational product.

**[REDACTED] Adhesive Contact Layer (Wound Contact Layer)**

[REDACTED] wound contact layer (WCL) [REDACTED] WCL is a gentle yet enduring adhesive layer, maintaining retention for the wear time of the dressing d a l o i n f i d t o a s s f r m t h o u b d o e a s r b n p d [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. 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 IMDs or comparators (Risk Assessment RA\_VT\_HVS2312\_Feb2024; Biological Evaluation Report/BER BER014; Biological Evaluation Statement/BES BES106).

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 IMD dressings (Prototype non-medicated multilayer foam dressings (rectangle and square variants)) 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 approved 3rd party suppliers or manufactured by Smith & Nephew in the United Kingdom.

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The materials used in the manufacture of the investigational devices are Smith & Nephew factory-approved materials positively released on conformance to specification. The [REDACTED]

The assembly of the investigational 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 visually acceptable and free from contaminants. Manufactured samples will be tested against the device specification for release of the investigational device for use in the volunteer study.

The legal manufacturer for the comparators Marketed dressing (rectangle) and Marketed dressing (square) is [REDACTED].

6.3 Intended purpose of the investigational device in the investigation

To evaluate the non-medicated versions of two next-generation multilayer foam dressings 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 new [REDACTED] layer foam dressing (once marketed) includes patients who require management of chronic or acute wounds, or wounds at risk of infection. In this study a prototype non-medicated [REDACTED] version of the dressing will be evaluated in comparison with the focus on parameters influencing dressing retention.

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 (rectangle)
Materials/ingredients:	Four-layer foam dressing [REDACTED]
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

Investigational device 2	Prototype dressing (square)
Materials/ingredients:	Four-layer foam dressing [REDACTED]
Intended purpose/use:	management of acute and chronic wounds.
Mode of application:	topical application.
Storage conditions:	Dry conditions; room temperature, not above 25





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	°C, 77 °F.
Manufacturer:	Smith & Nephew Medical Limited

Comparator 1	Marketed dressing (rectangle)
Materials/ingredients:	Five-layer foam dressing [redacted]
Intended purpose/use:	management of acute wounds, such as surgical wounds, cuts and abrasions.
Mode of application:	topical application.
Storage Conditions:	Dry conditions; room temperature, not above 25 °C, 77 °F.
Manufacturer:	[redacted]

Comparator 2	Marketed dressing (square)
Materials/ingredients:	Five-layer foam dressing [redacted] cotton, viscose, polyester and polyolefin
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:	[redacted]

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

[redacted]

Marketed dressing (rectangle) and Marketed dressing (square) are [redacted] foam wound dressings with similar intended functions as the two IMDs under investigation 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.

Marketed dressing (rectangle) is intended for use post-operatively and thus is a suitable comparator for Prototype dressing (rectangle). Whereas Marketed dressing (square) is intended for management of both acute and chronic wounds and thus is a suitable comparator Prototype dressing (square).

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

Each participant will receive four devices in total, one Prototype dressing (rectangle) (IMD\_1), one Prototype dressing (square) (IMD\_2), one Marketed dressing (rectangle) (Comparator\_1) and one Marketed dressing (square) (Comparator\_2). IMD\_1 will be compared with Comparator\_1 on the knees, whereas IMD\_2 will be compared with Comparator\_2 on the thighs. The respective IMD and comparator comparison pairs will be randomized to the left or right dressing application sites, for more details see section 11.3.4.1.

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

The IMDs and comparators will be labelled in accordance with current regulation. Each IMD/comparator will be labelled 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 IMDs (and comparators) 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 acceptable dressing presence as well as percentage scoring of applicable parameters according to the grid counting method, for details see section 10.4.11) and removal of the dressings (the IMDs 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 IMDs, refer to the IB (IB/Emerald/001) and Section 6.5. The IFUs are included in the IB.

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## **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 IMDs: prototype non-medicated multilayer foam dressing (rectangle and square variants), as well as the comparators: Marketed dressing (rectangle) and Marketed dressing (square); are safe medical devices with no remaining unacceptable risks concerning the chosen ingredients (Biological Evaluation Report BER014, Risk Assessment RA\_VT\_HVS2312\_Feb2024, Biological Evaluation Statement BES106).

### **7.2 Evaluation of clinical data to date**

Although there is no pre-existing clinical data for the two IMDs, their design and functionality are closely related to other established CE marked dressing of the [REDACTED] range, 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 two IMDs and the established CE marked [REDACTED] dressings are small, the fact that these established dressings are very well tolerated implies that the IMDs would also be very well tolerated. The comparators Marketed dressing (rectangle) and Marketed dressing (square) are established CE marked medical devices themselves, both with a proven safety profile showing good tolerability and minimal adverse reactions (refer to the IB for details of the comparator safety profile evaluation).

### **7.3 Clinical development stage**

The IMDs are in the pre-market stage.

### **7.4 Rationale for the design of the clinical investigation**

In this interventional pre-market clinical investigation of IMD non-inferiority vs comparator, with regard to parameters influencing the wear time on healthy intact skin, each of the two IMDs will be compared to its own high-performing comparator currently available 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 (Gefen 2024, Santamaria 2023, WUWHS 2019).

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.

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## **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 devices 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 these devices 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 devices of the [REDACTED] range, will be explained to the participants and are outlined in the Risk Assessment Ref. RA\_VT\_HVS2312\_Feb2024, BER Ref. BER014, and BES Ref. BES106.

The study schedule includes a physiotherapy session and the exclusion criteria (see exclusion criteria number 13, in section 10.3.4) will be applied in order to exclude participants with underlying conditions which could mean that they are at a higher risk of injury by taking part.

### **8.4 Possible interactions with concomitant medical treatments**

There are no contra-indications for the investigational devices. Precautions for use of the investigational devices are the same as to those for existing dressings of the [REDACTED] range, 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 IMDs 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



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adhesives, skin wipes, soap, surgical first-aid dressings, natural rubber or rubber latex will be excluded from participating 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 devices have been evaluated to ensure that their performance and safety profile are appropriate for the intended use (intact skin) in the clinical study (see Risk Assessment RA\_VT\_HVS2312\_Feb2024). The biocompatibility of the investigational devices has been evaluated according to ISO 10993-1 and is concluded to be safe for their intended use in the clinical study (see Biological Evaluation Report BER014; Biological Evaluation Statement BES106).

Based on characteristics identified and actions taken, the individual and overall residual risk posed by the investigational devices is considered acceptable and that the investigational devices are considered safe for their 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 Medizinprodukte-Durchführungsgesetz (MPDG), and MDCG guidelines.



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## **9 OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION**

### **9.1 Purpose of the clinical investigation and claims to be verified**

To evaluate prototype non-medicated multilayer foam dressings 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 (rectangle) in comparison to Marketed dressing (rectangle) and the non-inferiority of Prototype dressing (square) in comparison to Marketed dressing (square).

#### **9.2.1 Primary objectives**

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

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

#### **9.2.2 Secondary objectives**

To generate data to support both primary objectives:

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

#### **9.2.3 Primary and secondary hypotheses**

##### Primary hypothesis

The study design implements a non-inferiority hypothesis, aiming to demonstrate that the respective IMD is not significantly worse than the established comparator in terms of performance and safety (according to the comparison groupings described in section 9.2.1). A value of 15% is assumed as the non-inferiority threshold. The choice of the 15% threshold is justified in section 9.3.

The primary hypothesis is that the difference between the respective IMD and comparator 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.

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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  $\pm 15\%$  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). The comparator dressing in this study is a market leader 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.

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## 10 DESIGN OF THE CLINICAL INVESTIGATION

### 10.1 General description

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

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  $\geq 5$  days before Day 0, and physical skin assessment to ensure skin is healthy, intact and hair free) before the IMDs and comparators will be applied by the investigator to the right/left knee (rectangle dressings) and the right/left thigh (square dressings) 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: (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 (IMDs 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.

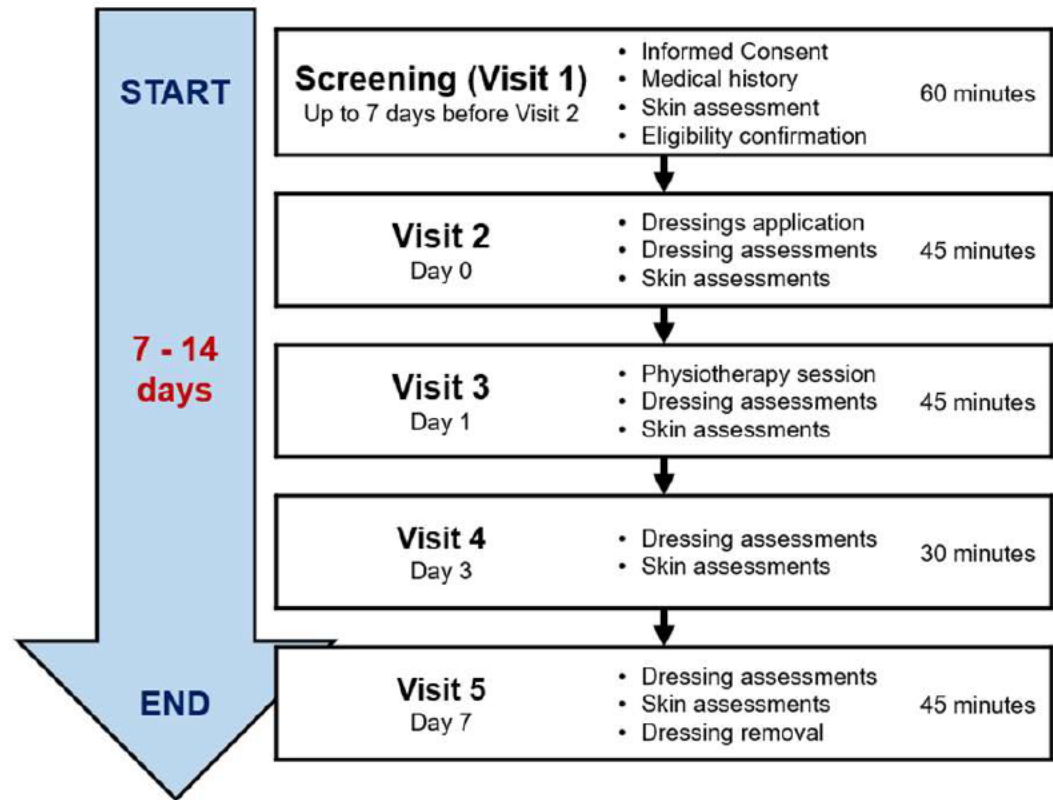


Figure 10.1 The course of the clinical investigation

#### 10.1.1 Timelines

The estimated timelines are presented below:

First participant in	OCT2024
Last participant out	JAN2025
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 knee for the rectangle dressings (comparison grouping 1) and right or left thigh for the square

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dressings (comparison grouping 2) will be randomized (see also section 11.3.4 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 10.4.11.

**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 10.4.16. 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, one of each IMD and one of each comparator. Participants will receive the Prototype dressing (rectangle) and the Marketed dressing (rectangle) at each dressing test site on the knees and the Prototype dressing (square) and Marketed dressing (square) at each test site on the thighs (randomized left or right, see section 11.3.4.1 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.



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**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%, 135 healthy participants are planned to be enrolled onto this study so that at least 120 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 enrolment period is planned to start in OCTOBER 2024. 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 enrolment 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 22-70 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,

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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 and with respect to the physiotherapy session) 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).

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- 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 10.4.16.16).

**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 enrolment**

Point of enrolment 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 new [REDACTED] multilayer foam dressing (once marketed) includes patients who require management of chronic or acute wounds, or wounds at risk of infection. In this study a prototype non-medicated [REDACTED] multilayer foam version of these dressings will be evaluated on intact skin with the focus on parameters influencing dressing retention.



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**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.

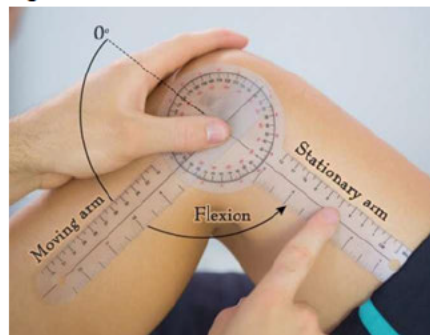
**10.4.3 Dressing quality control (QC) check**

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. Dressings will be applied to each knee whilst the knee is bent at an approx. 30-degree angle (as determined using a goniometer). The thigh dressings will be applied at zero degrees with the legs extended flat. 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.

Figure 10.2 illustrates how the angle of the knee will be defined.



**Figure 10.2** The knee angle for dressing application





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**10.4.5 Physiotherapy session**

Will include 4 basic exercises per leg: (i) lying on back and bending /straightening leg; (ii) lifting leg from chair sitting position; (iii) bending and extending knee from chair/bedside sitting position; (iv) bending knee back from standing position. The participant instructions for the exercises are detailed in Figure 10.3.

	i) Lying on your back, bend and straighten your right leg by slowly sliding your foot up until your knee is bent at a 90-degree angle, hold for 5 seconds and then relax. Repeat 5 times for the right leg.
	ii) Sit in a chair with both feet on the ground. Make sure your thigh is supported. Pull up your toes on your right foot, tighten your thigh muscle and straighten your knee. Hold for 5 seconds, then return the foot to resting position flat on the ground. Repeat 5 times for the right leg.
	iii) While sitting at bedside or in a chair with your thigh supported, start with both feet flat on the floor. Then, slowly bend your right knee back as far as you can until your toe still rests on the floor and hold for 5 seconds. From your toe lightly resting on the floor, slowly extend your knee and straighten the leg fully and hold for 5 seconds. Repeat bending and extending the knee 5 times for your right leg.
	iv) In standing, slowly bend your right knee to lift your heel towards your bottom until it is at a 90-degree angle. Hold for 5 seconds. Slowly relax until the toe is slightly resting on the ground. Repeat 5 times for the right leg.
<ul style="list-style-type: none"> <li>Repeat all exercises for the left leg.</li> </ul>	

**Figure 10.3 Physiotherapy session****10.4.6 Dressing removal**

The investigator or trained site personnel will remove the dressings as in accordance with the IFU of the prototype dressings, i.e. 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 knee, (iv) left knee. There will be a 10 min interval between the removal of each dressing to allow for any residual pain to subside.

**10.4.7 Photography**

Following dressing application, the investigator or trained site personnel will take photographs of all dressing locations, with the leg positioned to achieve the same angle used for dressing application (i.e. knees bent at 30 degree angle or at 0 degrees). Photographs will be taken of dressings in place and, if required, of any AE/adhesive offset at the following time points for documentation purposes:

- after the initial dressing application by the investigator (Day 0).
- before and after the physiotherapy session on Day 1.
- after the dressing assessments on Day 3.
- before the dressing removal (any day that dressing requires removal).

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

The photography will be performed using the following equipment:



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- 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. This system is suitable for the square dressings.
- The HiRIS (High Resolution Imaging System) is a specifically designed setup used for standardized photography with high reproducibility. The tailor-made setup is equipped with a Canon EOS 5D camera, a Canon 85mm Macro Lens and standardized illumination (with a Canon Speedlite 600EX, Round Flash(TM) Ring diffuser). 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. This system is suitable for the rectangle dressings.

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.

**10.4.8 Course of the clinical investigation**

135 male and 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 120 are expected to finish the study.

On Day 0 of the study: The Prototype dressing (rectangle) and respective comparator will be applied to either right/left knee and the Prototype dressing (square) and respective comparator will be applied to either the right/left thigh 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)

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- Physical examination of the skin condition focused on the dressing application sites (thigh and knee): 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 knee): 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 11.3.4.1 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.
- 
- Activity assessment
- Photographs of the dressings
- Physiotherapy session
- Objective dressing assessment.
- Subjective dressing assessment.
- Photographs of the dressings

### Day 3

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

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### Day 4

No visit to the site.<sup>2</sup>

### Day 5

No visit to the site.<sup>2</sup>

### Day 6

No visit to the site.<sup>2</sup>

### Final Visit (Day 7)

- 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.
- Removal of the dressings.
- Subjective dressing removal assessment.
- Objective dressing removal assessment.
- Documentation of AEs after dressing removal.

#### 10.4.9 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.

#### 10.4.10 Activities performed by sponsor representatives

Not applicable.

#### 10.4.11 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 10.4.

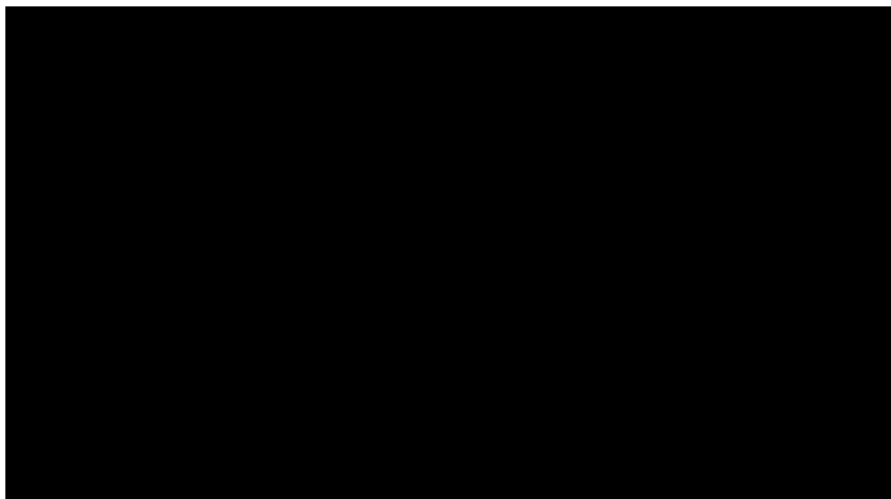
<sup>2</sup> In the case of premature dressing detachment, the participant will be instructed to contact the site and report the date and circumstances of the dressing detachment and if there is any skin related AE, as well as the application test site where the dressing in question was located. The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

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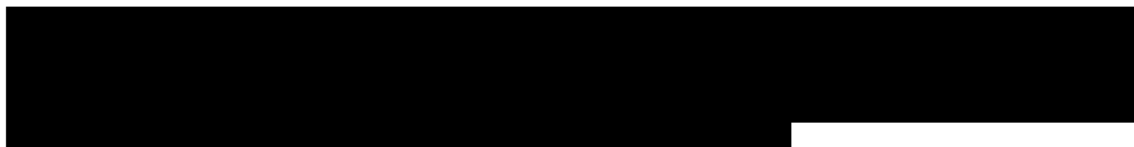
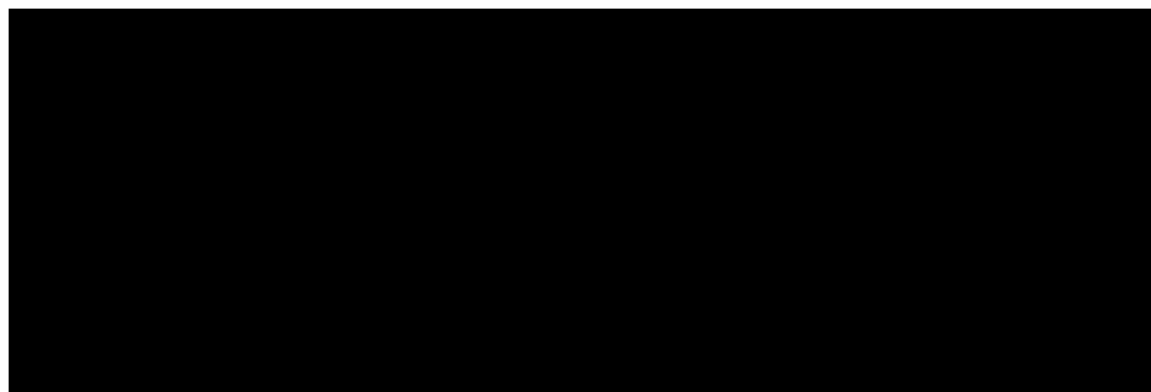
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**Figure 10.4 The grid counting method, example guide for a square dressing**



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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  $10 \pm 2$  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.

**10.4.12 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 IMDs and is in line with the maximum permitted wear time of the dressings.

**10.4.13 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.

**10.4.14 Follow-up period after completion of the clinical investigation**

Not applicable.

**10.4.15 Final disposition and potential future use of samples**

Not applicable.

**10.4.16 Variables assessed in the clinical investigation****10.4.16.1 Demographic data**

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

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

**10.4.16.2 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).

**10.4.16.3 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.

**10.4.16.4 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.



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**10.4.16.5 Assessment of dressing application (Day 0)**

Dressing application assessments will be performed with the leg placed in the same position as adopted for the application of the dressings (the angle of the knee determined by goniometer: 30 degrees for knee dressings and 0 degrees for thigh dressings).

**10.4.16.6 Objective assessment of the dressings (Days 1\*, 3 and 7)**

\*to be performed both before and after the physiotherapy session on Day 1.

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 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". Should any dressing demonstrate  $\geq 50\%$  pad lift, it will be removed and Dressing Removal Assessments will be conducted. Based on the "counting grids method" to give an objective percentage score.
- 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.

**10.4.16.7 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.

\*to be performed both before and after the physiotherapy session on Day 1.



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**10.4.16.9 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.

**10.4.16.10 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.

\*to be performed before the physiotherapy session on Day 1.

**10.4.16.11 Subjective assessment of dressing removal (Day 7)**


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

- 

**10.4.16.12 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.

- iii) 

- 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.

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**10.4.16.13 Adverse events**

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

**10.4.16.14 Changes in concomitant medications/treatments**

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

**10.4.16.15 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.

**10.4.16.16 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:

- subjective dressing assessment
- objective dressing assessment
- activity assessment

After removal of the dressing the following should be performed:

- subjective dressing removal assessment
- objective dressing removal assessment

## **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.

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- 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.

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## 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

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

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

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

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).

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

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

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

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
- retention claims during joint mobilization including following a physiotherapy session

The secondary endpoints therefore comprise the inferential and/or descriptive analysis of the following performance and descriptive evaluation of all safety parameters for the respective IMD vs comparator pairs, i.e. (i) Prototype dressing (rectangle) vs Marketed dressing (rectangle); and (ii) Prototype dressing (square) vs Marketed dressing (square).

Performance assessments based on PP population:

- Non-inferiority comparison of the IMD to its respective comparator for following parameters:
  - Acceptable dressing presence (thigh and knee) at days 1 and 3
  - Presence of dressings at days 1, 3 and 7.
  - Pad integrity at days 1, 3 and 7.
  - Percentage pad lift at days 1, 3 and 7.
  - Percentage border lift at days 1, 3 and 7.
  - Dressing comfort at days 1, 3 and 7.

Safety assessments based on SP population:

- 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]

[REDACTED]

[REDACTED]



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[REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[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 not take into account the dressing application site (left or right – see 11.3.4.1).

The statistical comparison of both IMDs against their respective comparators is performed separately. 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.

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

The assumptions for the Prototype dressing (rectangle) vs Marketed dressing (rectangle) comparison are that of no difference between the products in acceptable dressing presence by day 7. Also assumed is 28% discordant pairs and the proportion of subjects where both dressings are acceptable is at least 60%. Using these assumptions, a sample size of 120 evaluable participants is required to ensure 80% power using Newcombe's score method to show that the upper confidence limit of the 2-sided 97.5% confidence interval, for the difference in proportion of acceptable presence (Marketed dressing (rectangle) – Prototype dressing (rectangle)), is lower than the non-inferiority threshold of 15% ( $\%C - \%IMD < 15\%$ , where  $\%IMD$  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 (square) vs Marketed dressing (square) comparison and so the same sample size is acceptable, as these products will all be applied to the same participants then 120 total evaluable participants would be sufficient for the aims of both comparisons.

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

The sample size was calculated using nQuery 9.3.0.

**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.

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### 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.

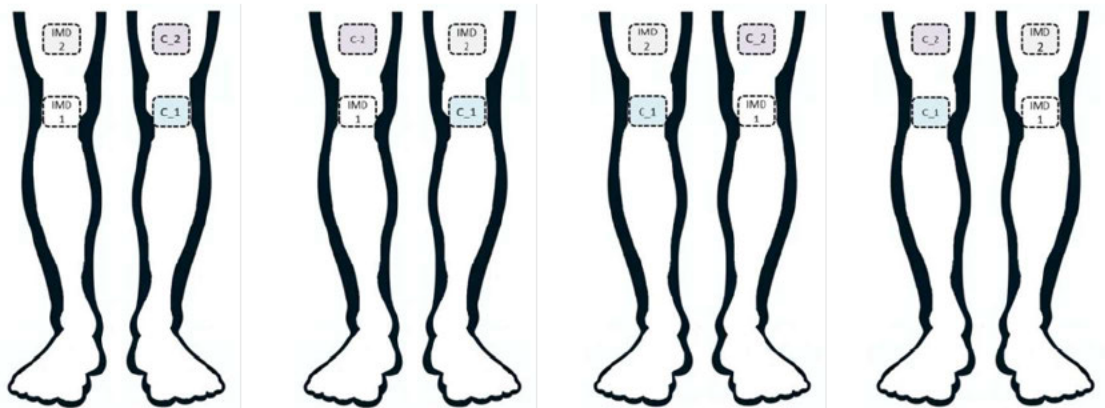
All documents specifying the statistical analysis in detail are finalized before the subjects are included in the investigation to avoid possible data-driven influence.

#### 11.3.5.1 Method of randomization

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

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

Randomization is performed using SAS Software 9.4 or higher.



IMD 1 = Prototype dressing (rectangle) (white).

IMD 2 = Prototype dressing (square) (grey)

C\_1 = Marketed dressing (rectangle) (blue).

C\_2 = Marketed dressing (square) (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.

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**11.3.6 Multiplicity control and adjustment of error probabilities**

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

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

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

The analysis will be split into two separate hierarchies:

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

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

The order of each hierarchy will be defined as:

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

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

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

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

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

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

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

This test sequence is carried out separately in each hierarchy.



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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 be reported in the CIR.



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**11.3.11 Procedures for reporting errors in statistical programming**

If an error is detected in the statistical programming 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.

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## 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.

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- 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.

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**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 breaches 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 trail, 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 the 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.

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### **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.



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**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.

Amendment	Changes made	Rationale
Amendment_1_to CIP V3.0_28AUG2024	1. The sample size was increased from 120 to 135 participants.	An additional sponsor-internal product test suggested the possibility of slightly different values for the paired performance between Prototype and Marketed dressings according to different manufacturing lots of each. The changed assumptions were taken into account from a conservative point of view as a 3% increase in discordant pairs in the current protocol and led to a slight increase in the required participants-to-complete and therefore also in the final sample size.  The changed assumptions are set out in section 11.3.1.
	2. The number of participants expected to complete was increased from 105 to 120.	
	3. The Camera equipment suitability for the two types of dressing is indicated.	During a dry run the site figured out that the camera system mentioned in the CIP (MacIS XXL) is not adequate to take a picture of the full rectangle dressings because they are too large (30 x 10 cm). For the square dressings the camera system is suitable. Therefore, they will use another camera system HiRIS (with Canon5DMkIII, 85mm makro lens, flash & ringlight diffuser) for the photography of the rectangle dressings.

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## **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.

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## 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 labelled with "nur für klinische Prüfungen" (English: for clinical trials only) in accordance with applicable legal requirements. All packaging and labelling operations are performed according to applicable legal requirements.

### 15.2 Access and storage of device(s)

IMDs 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 IMDs 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.

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## **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 ensure that sponsors staff did 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 (Medizinprodukte-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 BfArM, DMIDS ("Deutsches Medizinprodukte-Informations- und Datenbanksystem"). The Ethics Committee and the Competent Authority (BfArM) will be automatically informed, will progress the applications and release them DMIDS.

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.

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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.



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## 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.

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## **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

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- (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 taken or
- b) intervention is not 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

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- Probable
- Causal relationship
- (Not applicable)

Not related	<p>1. Relationship to the device, comparator or procedures can be excluded when:</p> <ul style="list-style-type: none"> <li>• The event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device;</li> <li>• 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</li> <li>• 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</li> <li>• The event involves a body-site or an organ that cannot be affected by the device or procedure</li> <li>• 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)</li> <li>• The event does not depend on a false result given by the investigational device used for diagnosis, when applicable</li> </ul> <p>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 device/procedures and the (S)AE.</p>
Possible	<p>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.</p>
Probable	<p>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.</p>
Causal Relationship	<p>The (S)AE is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:</p> <ul style="list-style-type: none"> <li>• The event is a known side effect of the product category the device belongs to or of similar devices and procedures</li> <li>• The event has a temporal relationship with investigational device/application or procedures</li> <li>• The event involves a body-site or organ that: <ul style="list-style-type: none"> <li>○ The investigational device or procedures are applied to</li> <li>○ The investigational device or procedures have an effect on</li> </ul> </li> <li>• The (S)AE follows a known response pattern to the medical device (if the response pattern is previously known)</li> <li>• 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)</li> <li>• Other possible causes (e.g. an underlying or concurrent illness/clinical</li> </ul>

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	<p>condition or/and an effect of another device, drug or treatment) have been adequately ruled out</p> <ul style="list-style-type: none"> <li>• Harm to the participants is due to error in use</li> <li>• The event depends on a false result given by the investigational device used for diagnosis, when applicable</li> </ul> <p>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.</p>
Not applicable	The relationship to the device or comparator when the (S)AE occurred before the administration of the IMD or comparator.

**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 (e.g. AEs related to use of the IMD such as dressing application / removal, rather than a study procedure such as the Day 1 physiotherapy session):

- 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.
  - None.
  - 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.



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**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 IMDs or 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**

The Sponsor will receive notification per email when any new AE is reported and in addition 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:

<b>Name:</b>	Dr. Nibler & Partner
<b>Phone No.:</b>	+49 89 56823726
<b>Fax No.:</b>	+49 700 3784723389 (+49 700 DRUGSAFETY)
<b>Email:</b>	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.

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- 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 serious adverse event. 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.

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## **19 VULNERABLE POPULATION**

Not applicable.

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## 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 enrolment 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.

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## **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.



## Clinical investigation plan

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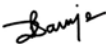
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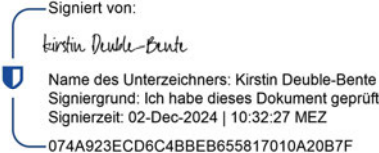
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