Clinical Investigation Plan

CP357

Investigation of the clinical performance of Biatain Fiber Ag on burns

May 2023 – January 2024

ClinicalTrials.gov ID: NCT05824026

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CHANGE LOG

VERSION NUMBER	ISSUED BY *(INITIALS)*	COMMENTS (MAJOR CHANGES SINCE LAST REVISION)
1.0	[redacted]	[redacted]
2.0	[redacted]	[redacted]
3.0	[redacted]	[redacted]

SYNOPSIS OF THE CLINICAL INVESTIGATION

Title and aim

Investigation of the clinical performance of Biatain Fiber Ag on burns.

The overall purpose of this investigation is to obtain clinical data supporting effectiveness of the final product to obtain the CE-mark.

Test product

The test product, Biatain Fiber Ag is a non-CE-marked gelling fiber wound dressing, containing silver. The product is intended for moist wound healing and exudate management of moderate to high exuding wounds. The product has a classification III, as it contains the active ingredient silver.

Intended use

Biatain Fiber Ag is **Primary** intended for moist wound healing and exudate management of moderate to high exuding wounds, including cavity wounds, that are infected or at risk of infection.

[redacted]

Objective

The primary objective is to evaluate the non-inferiority of Biatain Fiber Ag to similar products using percentage of wounds healed in partial thickness burns within 14 days.

Design of the investigation

The clinical investigation is a non-comparative, one-armed, open-labelled, multi-centre study.

The total study duration for the subject will be approximately two weeks, consisting of a two-week test period and 4 study visits (V0/V1, V2 and V3). V3 will also terminate the 2-week study period.

Expected duration of the clinical investigation

The expected duration of the clinical investigational period is approximately 14 days (+/-2 days).

Primary endpoint and Exploratory endpoints

Primary endpoint
Percentage of wounds healed within 14 days (≥ 95 % reepithelialisation)

[redacted]

Additional assessments

- Use of antibiotics and antiseptic since last visit

Population/subjects

The clinical investigation will be conducted in a total of 50 eligible subjects with a partial thickness burn wound that are infected or at risk of infection. To be included in the investigation, the subjects must comply with the criteria presented below.

Inclusion criteria	Exclusion criteria
1. Has signed informed consent	1. Is pregnant/breastfeeding
2. Is between 18-65 years old (both included)	2. Is currently receiving or has within the past 60 days received radio- and/or chemotherapy (low doses radio- and/or chemotherapy is allowed for other indications than cancer if assessed by investigator not to influence study wound area)
3. Is capable of following study procedure (assessed by investigator).	3. Known history of skin sensitivity to any components of the test dressings
4. Has a partial thickness burn wound	4. >72 hours from time of injury
5. Has a burn wound that is infected or at risk of infection (assessed by investigator)	5. Intake of antibiotics within one week before the start of the enrolment
6. The size of burn (including both study wound and non-study injuries) has a Total Body Surface Area (TBSA) less than 10% (assessed by investigator).	6. Use of chemical debridement
7. The wound should fit under a 20x30 cm dressing (600 cm2) or smaller	7. Participation in any other clinical studies that can compromise this study treatment (assessed by the investigator).
8. The shape and location of the wound should be suitable for photo capture (assessed by the investigator).	
9. Has a wound that has medium to high level of exudate (assessed by the investigator)	
10. Is suitable to use the test product for wound treatment (assessed by the investigator).	

LIST OF ABBREBIATIONS

ABBREVIATION	WRITTEN OUT	EXPLANATION
ADE	Adverse Device Effect	See section 18.2
AE	Adverse Event	See section 18.1
ASADE	Anticipated Serious Adverse Device Effect	See section 18.4.2
CA	Competent Authority	
CIP	Clinical Investigation Plan	
CRF	Case Report Form (paper or electronic)	Questionnaire to be used for data collection
CM	Clinical Manager	
DQF	Data Query Forms	A DQF is a query specifically used in clinical research. The DQF is the primary data query tool from the sponsor to clarify discrepancies and ask the investigator for clarification. The DQF is part of the data validation process in a clinical investigation.
DD	Device deficiency	
[redacted]	[redacted]	
EC	Ethics Committee	
IB	**Investigator's Brochure**	Compilation of the current clinical and non-clinical information on the investigational medical device(s,) relevant to the clinical investigation.
IFU	Instruction For Use	
ITT	Intention to Treat	
PI	Principal Investigator	Qualified person responsible for conducting the clinical investigation at an investigation site. If the clinical investigation is conducted by a team of individuals at an investigation site, the PI is the responsible leader of the team. Whether this is the responsibility of an individual or an institution can depend on national regulations.
PP	Per Protocol	
SADE	Serious Adverse Device Effect	See section 18.4.1
SAE	Serious Adverse Event	See section 18.4
USADE	Unanticipated Serious Adverse Device Effect	See section 18.4.3

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1. List of personnel involved in the Investigation

1.1. Sponsor representatives

COORDINATION SENIOR CLINICAL MANAGER	DIRECTOR OF CLINICAL OPERATIONS
[redacted]	[redacted]
CLINICAL MANAGER	**SENIOR SCIENTIFIC MANAGER**
[redacted]	[redacted]
SENIOR BIOSTATISTICIAN	**SENIOR PROJECT MANAGER**
[redacted]	[redacted]
PRINCIPAL DATA MANAGEMENT SPECIALIST	**CLINICAL STRATEGY PROJECT MANAGER**
[redacted]	[redacted]

In case of emergency, please contact coordinating Clinical Manager from the above list of Sponsor representatives.

1.2. Chief Investigator

CHIEF PRINCIPAL INVESTIGATOR
[redacted]

This clinical investigation involves up to 10 sites in United Kingdom (UK).

2. Rational/justification for conducting the clinical investigation

Gelling fibers are highly absorbent advanced wound dressings made to manage moderate to large amounts of exudate. They form a gel when in contact with the wound and thus conforms well to the wound bed. Gelling fibers are primary dressings and always require a secondary dressing to keep them in place.

The product features ensure absorption and exudate management while creating a moist wound healing environment for moist wound healing for a broad variety of acute and chronic wounds.

[redacted] The major roles for antimicrobial dressings (such as silver dressings) are to reduce the bioburden in acute or chronic wounds that are at risk of infection, infected or prevented from healing due to microorganisms. Furthermore, the dressings can provide an antimicrobial barrier for acute or chronic wounds at high risk of infection or re-infection.

[redacted] Biatain Fiber Ag is a class III device and clinical data on the actual product is required for the CE-mark.

Silver containing products has been on the market for decades and Silver containing gelling fibers similar to Biatain Fiber Ag has been on the marked for more than two decades. Biatain Fiber Ag is thus a well-known type of product and based on a well-established technology. The product is intended to be used by Health Care Professionals and the handling of the product is evaluated to be simple and well known as it is similar to other wound care dressings, and it is evaluated that most HCP would not require any extra training prior to the use of the product. It is therefore evaluated that the potential bias due to study inclusion is limited. A large portion of the clinical studies conducted and published previously on silver containing wound dressings is non-comparative. It is evaluated that it would not be ethical correct to perform a clinical study with a similar non-antimicrobial dressing and conducting a comparative study with a similar silver containing dressing as comparator would require a large amount of patients with no additional benefit for the patients included. The study design chosen has therefore been a non-comparative study, which has been evaluated to be sufficient, and the data obtained will be evaluated and compared to data on performance available on similar devices.

Several clinical investigations on silver containing gelling fibers have been published mainly in the chronic wound indication venous leg ulcers and the acute wound indication burns. The wound indication burns have therefore been chosen for the clinical study providing clinical data on an acute wound indication. The data obtained in the clinical investigation will in the Clinical Evaluation Report be evaluated and compared to the data available on similar devices to ensure the performance and safety profile for Biatain Fiber Ag is similar to other antimicrobial gelling fibers.

3. Objective of the clinical investigation

3.1. Primary Objective

The primary objective is to evaluate the non-inferiority of Biatain Fiber Ag to similar products using percentage of wounds healed in partial thickness burns within 14 days.

4. Investigational device

The investigational test product will be used according to intended use and indications during the investigation.

4.1. Description of investigational device

The investigational device, Biatain Fiber Ag is a non-CE-marked gelling fiber wound dressing, containing silver.

[redacted]

The product has a classification III, as it contains the active ingredient silver.

[redacted]

4.2. Manufacturing

Coloplast A/S, [redacted] is legal manufacturer of the medical device on the EU, UK and US market and has the overall responsibility for the design and documentation of the product. [redacted]

4.3. Identification and traceability of the investigational test product

The investigational test product will be identified as Biatain Fiber Ag and will in this investigation be available in size 20 x 30 cm. For smaller size wounds the dressing can be cut to fit the wound.

The investigational test product is labelled as per regulations and include "Exclusively for Clinical Investigational Use" on the label and accounted for through a master sponsor accountability log.

Upon Ethics Committee (EC) and Competent Authority (CA) approval, investigational test products will be shipped to the local Principal Investigator (PI), or delegate. Additionally, all investigational test products will be accounted for and documented on a site accountability log. All unused products will be returned to Coloplast at the completion of the investigation.

4.4. Intended use of the device in the clinical investigation

Biatain Fiber Ag is **Primary** intended for moist wound healing and exudate management of moderate to high exuding wounds, including cavity wounds, that are infected or at risk of infection.

[redacted]

See instruction for use (IFU) in Appendix 1.

4.5. Intended population for the device

Biatain Fiber Ag is intended to a wide range of moderate- to highly exudating wounds. This includes acute wounds such a donor sites, traumatic wounds, post-operative wounds, partial thickness wounds; and chronic wounds such as arterial- and venous ulcers, diabetic ulcers, pressure ulcers (stage II- IV), and exudate absorption in oncology wounds.

In this clinical investigation the intended population is subjects with **partial thickness burns**, that are infected or at risk of infection.

4.6. Handling of the investigational device

The handling of Biatain Fiber Ag is described in detail in the IFU, which is included in the box containing the test product. Storage conditions is also stated in the IFU.

Wear time

The dressing should be replaced when wound care practice indicates that a change is needed, or when it has reached its maximum absorption capacity, but no more than 7 days.

The test product can be covered by a moisture-retentive secondary dressing appropriate to the clinical condition of the wound and volume of exudate.

Removal

If removing the dressing is difficult, the dressing should be fully saturated with sterile saline or water and removed slowly.

All PI´s and delegates will receive training by sponsor and/or PI in handling and correct use of the investigational test product.

For further details regarding Biatain Fiber Ag, please refer to the IFU in Appendix 1.

4.7. Total number of devices intended for the clinical investigation

The subjects will be included for 2 weeks of investigation. On average, it is expected that subjects will require 1-4 dressing changes/week. Therefore, each subject is expected to use a maximum of 8 products during their participation. Additionally, an extra buffer will be produced and in total 1000 dressings.

5. Design of the clinical investigation

5.1. General

The clinical investigation is a non-comparative, one-armed, open-labelled, multi-centre study. The study is planned to be conducted in UK.

The total study duration for the subject will be approximately two weeks, consisting of a two-week test period and 4 study visits (V0/V1, V2 and V3)

In total 50 subjects will be included in the investigation. Eligible subjects are invited to a Screening Visit (V0). Screening visit (V0) and Baseline visit (V1) can be combined and performed on the same day. If subject wishes to reconsider his/her participation at V0, the subjects must be given at least 24 hours to consider their participation. V0 can be done remotely.

At V0 the subject will be informed about the investigation, where the PI or delegate will give a detailed information about the requirements, the content and what it involves participating in the investigation. See section 6.2 for recruitment.

Informed Consent will be signed at the Baseline Visit (V1) and obtained before any study-related activities are initiated. Informed consent must be signed within 72 hours from burn injury.

Subjects will use the investigational test product in a 2-week test period (+/- 2 days) and have a scheduled visit once per week, visit 2 (V2) and visit 3 (V3). V3 will also terminate the 2-week study period unless a situation occurs where a subject terminates earlier than expected.

Withdrawn subjects must be encouraged to complete the Termination visit V3, regardless of the reason for withdrawal.

If dressing change is needed due to a clinical need between the weekly scheduled study site visits, additional visits can be performed. See section 7.2 for Dressing changes between study site visits.

If visits are needed due to circumstances related to a specific issue, an unscheduled visit can be performed. See section 7.3 for Unscheduled visits.

If the wound is evaluated by PI or delegate to be healed before or at the termination visit V3 subjects will be terminated according to termination – Wound healed. See section 7.4 Wound healed.

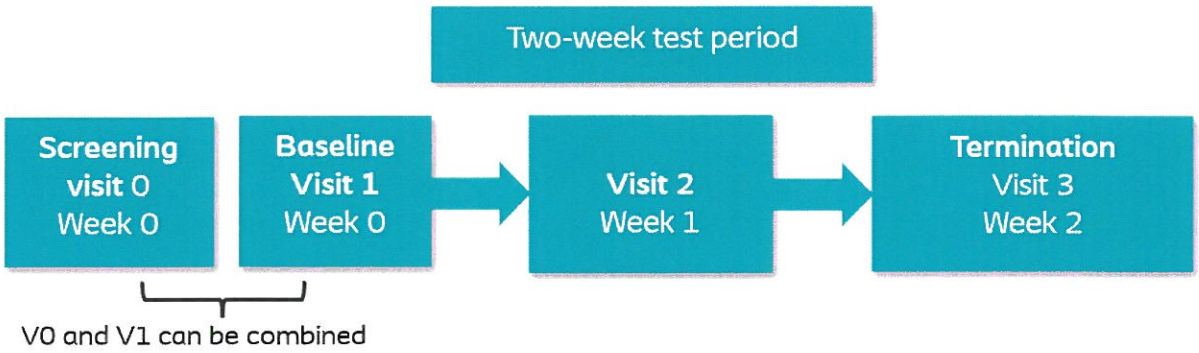
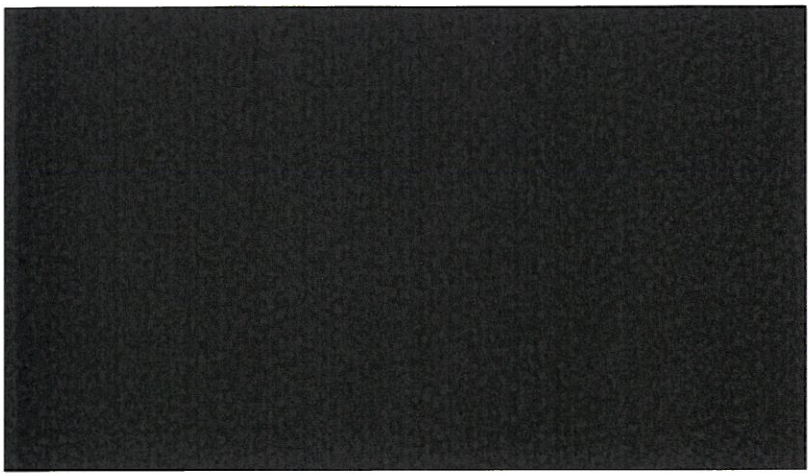


Figure 1: Study design CP357

5.2. Primary endpoint

Percentage of wounds healed within 14 days (≥ 95 % reepithelialisation)



Additional assessments

- Use of antibiotics and antiseptic since last visit

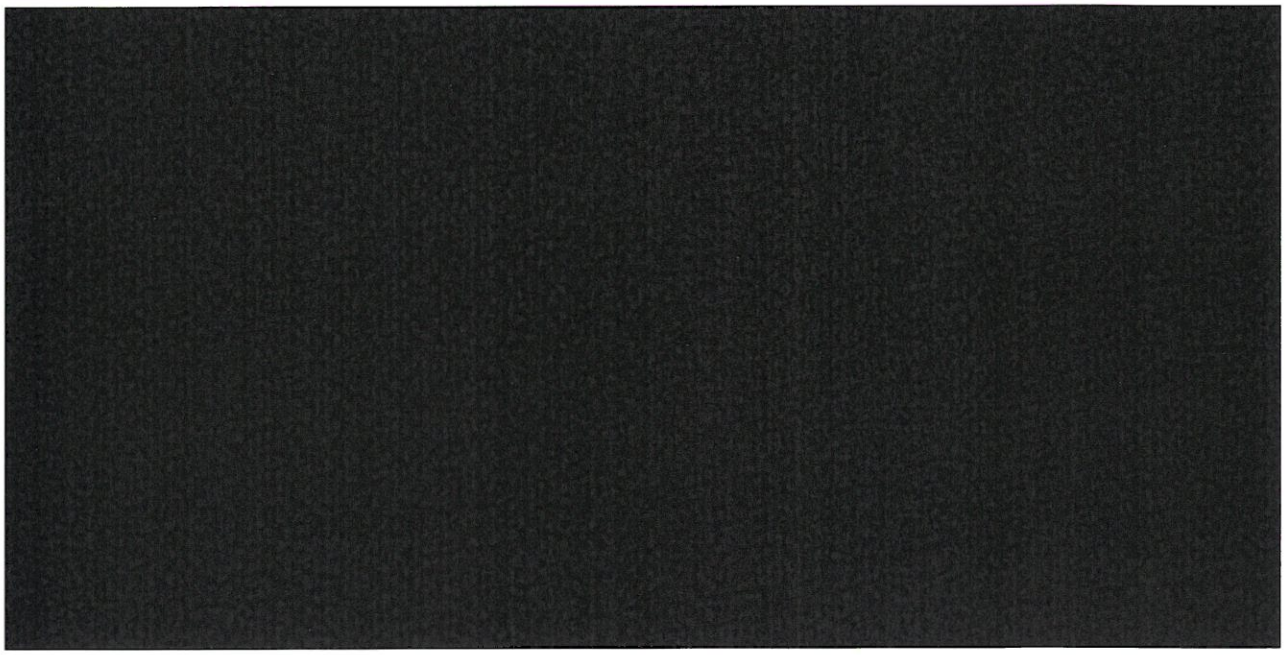
Safety assessments

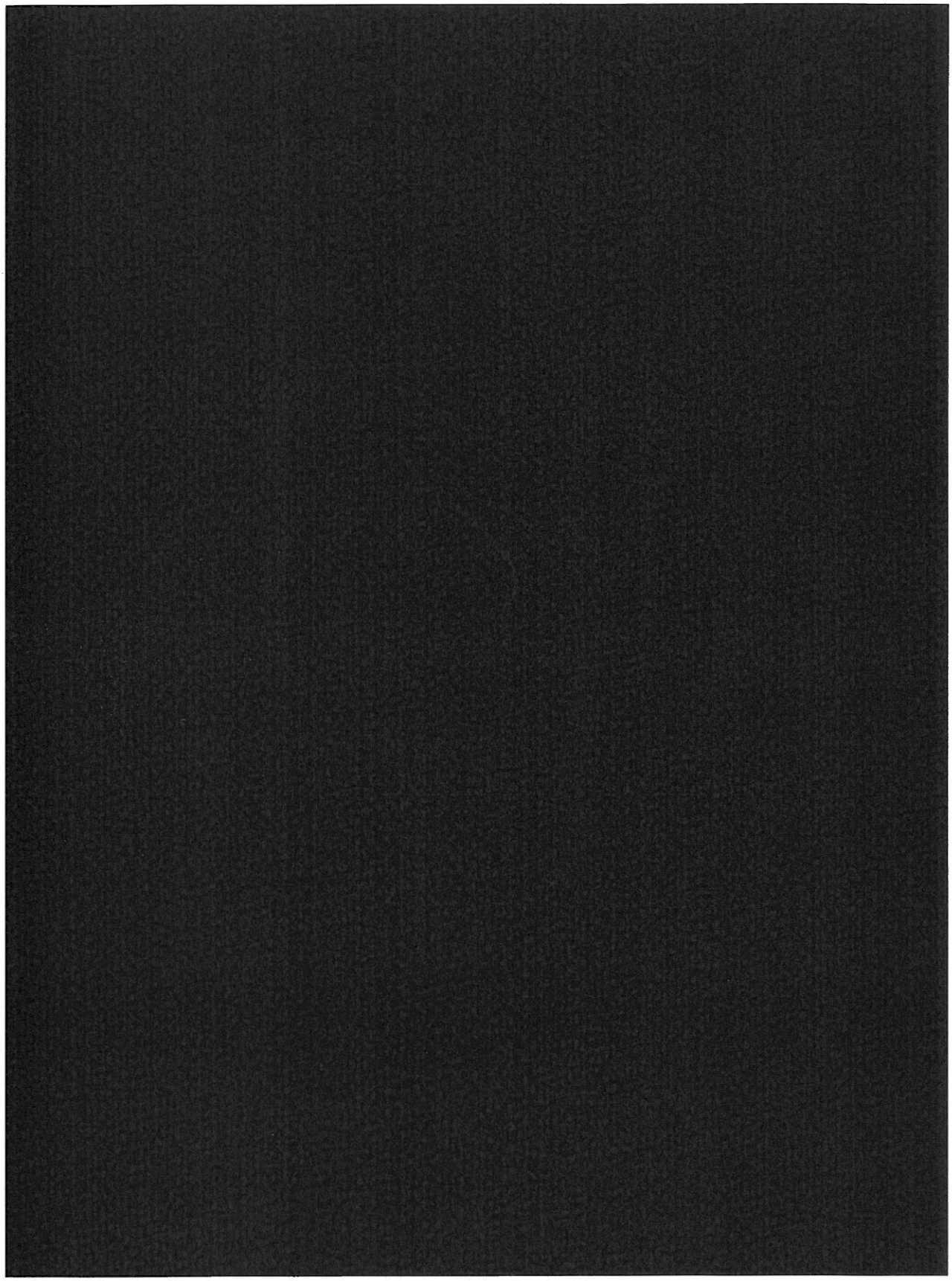
- Adverse events
- Device deficiencies

5.4. Rationale for selection and measurement of endpoints

The **Primary endpoint** percentage of wounds healed within 14 days has been selected for this investigation.

The endpoint is used to evaluate clinical performance in terms of percentage of wounds achieving healing within 14 days (+/- 2 days). Complete healing is defined as ≥ 95% reepithelisation.





[redacted]

Additional assessment

Use of antibiotics and antiseptics

Use of antibiotics and antiseptic will be evaluated to justify any antimicrobial effect observed is due to the test product and not the antibiotic or antiseptics.

Subject will be instructed to document on the sheet for dressing change if any use of antiseptics in the study wound between the scheduled visits, or if they don´t know. If subject has used antibiotic or antiseptic, the reason for use and type used will be registered by the PI or delegate at V2 or V3.

Safety assessments

Adverse events and device deficiencies

Will be collected to ensure safety of the intervention during the investigation

5.5. Demography and potential compromising factors

The following baseline data will be collected and reported at the baseline visit by the PI or delegate.

- Age (years)
- Weight (kg)
- Height (cm)
- Gender (male/female)
- Nutritional status (well-nourished, malnourished)
- Mobility status (good mobility, bad mobility)
- Smoking (yes/no)
- Alcohol (Units/week)
- Comorbidities (That can affect wound healing (diabetes, venous insufficiency, peripheral arterial disease, cardiopulmonary conditions, immune deficiencies, dementia, other) or none as deemed relevant by investigator)
- Relevant concomitant medication that can impact wound healing (NSAID, Glucocorticoid steroids and chemotherapeutic drug)
- Use of antiseptics in study wound within the last week and reason for use

Wound description

- Duration of wound
- Previous wound treatment (if applicable)
- Wound size (photo)
- Wound location (upper extremity, lower extremity- leg, lower extremity-foot, abdomen, thorax, back, buttock/sacrum, other)
- Reason of burn (thermal, Chemical, other)

[redacted]

If other relevant wound care products or secondary dressings are required to be used in addition to the test product as part of standard of care, this must be recorded.

5.6. Potential compromising factors

The subjects are not allowed to receive antibiotics (also for other reasons than wound infection) 1 week upon inclusion. If, during the study period, the subject should acquire a condition requiring antibiotics, the condition must be registered as an AE and the antibiotic treatment must be registered as part of concomitant medication with start and end date.

5.7. Equipment

The wound area is measured by an [redacted] delivered by [redacted] that enables the PI or delegate to take a photo of the wound at every scheduled site visit. The photos are uploaded, stored, and analysed within an Imaging system delivered by [redacted] (Please refer to section 11 Data Management).

5.8. Randomisation Procedure

Not applicable

5.9. Blinding

Not applicable

5.10. Total expected duration of the clinical investigation

The dates below are approximate, and no subjects will be enrolled before all required approvals have been obtained. If changes are required, applicable EC and regulatory authorities will be notified.

First subject enrolled (07/2023)

Last subject enrolled (01/2024)

Last subject complete (01/2024)

Final report (02/2024)

6. Clinical Investigation population

The clinical investigation will be conducted in 50 subjects enrolled at multiple clinical investigation sites. The enrolment is competitive.
According to the sample size calculations (See section 10.4) 44 subjects are required to complete the investigation. Considering a drop-out rate of 10%, the required total number of subjects to be enrolled in the trial shall be 50.

6.1. Eligibility criteria

To be included in the investigation, the subjects must comply with the selection criteria described below.

6.1.1. Inclusion criteria

Table 1: Inclusion criteria

Inclusion criteria	Justification

1. **Has signed informed consent**	To meet the Helsinki Declaration
2. **Is between 18 - 65 years (both included)**	To minimize the risk of non-device SAE
3. **Is capable of following study procedure (assessed by investigator).**	To ensure study protocol is followed in between site visits
4. **Has a partial thickness burn wound**	Selected indications
5. **Has a burn wound that is infected or at risk of infection (assessed by investigator)**	Selected indications (infected or risk of infection)
6. **The size of burn (including both study wound and non study injuries) has a Total Body Surface Area (TBSA) less than 10% (assessed by investigator).**	To minimize the risk of non-device related SAE
7. **The wound should fit under a 20x30 cm dressing (600 cm2) or smaller**	To fit with the test product size
8. **The shape and location of the wound should be suitable for photo capture (assessed by the investigator).**	To minimize errors in the wound area measurement method
9. **Has a wound that has medium to high level of exudate (assessed by the investigator)**	According to the IFU
10. **Is suitable to use the test product for wound treatment (assessed by the investigator).**	No single treatment is completely successful for wound healing as complete wound healing depends on the type of wound, as well as the variation in the rate of production of wound exudates and the variation in the appearance of the wound surface in relation to wound type and healing phase

6.1.2. Exclusion criteria

Table 2: Exclusion criteria

Exclusion criteria	Justification
1. **Is pregnant/breastfeeding**	Vulnerable group
2. **Is currently receiving or has within the past 60 days received radio- and/or chemotherapy (low doses radio- and/or chemotherapy is allowed for other indications than cancer if assessed by investigator not to influence study wound area)**	The skin undergoes major changes because of radio- and/or chemotherapy, and therefore it can be more fragile during wound management

3. Known history of skin sensitivity to any components of the test dressings	According to IFU
4. >72 hours from time of injury	For the healing not to be influenced by the initial product used and to be comparable to other studies
5. Intake of antibiotics within one week before the start of the enrolment	To ensure any antimicrobial effect observed is due to the dressing and not the antibiotic
6. Use of chemical debridement	Chemical debridement can be used in a selected group of patents. Use of chemical debridement is excluded to ensure a homogeneous population in the study
7. Participation in any other clinical studies that can compromise this study treatment (assessed by the investigator).	To avoid bias.

6.1.3. Pregnancy and breastfeeding

All female subjects with childbearing potential (they have had at least one period during the last 12 months), must at V0 confirm that they are not pregnant or breastfeeding. Furthermore, they will be informed that no pregnancy is allowed during participating in the investigation.

If the subject becomes pregnant during the investigation, it is important, that the subject informs the Investigator or delegate immediately. The PI will then consider whether she should continue in the investigation.

6.2. Recruitment and enrolment

The recruitment of potential subjects will commence only once authorisation has been received from the respective EC and CA. Recruitment will occur through competitive enrolment in UK. The recruitment period from first subject enrolled to last subject enrolled will be approximately 5 months.

Recruitment will be via admitted patients in recruiting sites with hospitals and outpatient clinics, subject screening visits and advertisement in paper form and/or digital platforms.

6.3. Screening of potential subjects

If a subject is potentially eligible and interested in participating, written information about the investigation (Participant Information Sheet) will be provided to the subject to ensure they are given the opportunity to understand what the investigation is about. Subjects will have time to ask the PI, or delegate, any questions they may have. The subject information provides information to subjects about how to contact the local PI or a representative thereof if they wish to learn more about the investigation.

If a potentially eligible subject is interested in participating in the investigation a screening visit (V0) will be arranged. When arranging the visit, the subject must receive the Participant Information Sheet (PIS) and given adequate time to review it. The subject will receive both written and verbal information about the possibility of bringing a companion to the visit and to any possible subsequent visits.

The subject has the right to wait before deciding to participate. If/when the subject decides to participate, he/she will be asked to sign the Informed Consent Form. If a subject so desires, and it is certain that it is understood what the investigation entails, and the Informed Consent Form has been signed, the subject is considered enrolled/included in the investigation.

For subjects with more than one eligible wound, only a single wound can be included in the investigation.

The monitor will be in close contact with each site during the recruitment period. The PI, or delegate, at each site will notify the monitor when a subject is enrolled and all future planned visits.

When the Coloplast Clinical Manager becomes aware that 50 subjects have been included and the recruitment will stop.

Recruitment method	Hospital/Outpatient clinic	Advertising
Potential subjects	Recruitment will go through hospital ward or outpatient clinic at the hospital site. Potential subjects are identified by the following searching criteria: • Is 18 years or above • Is capable of following study procedure (assessed by investigator). • Has a partial thickness burn wound • Has a burn wound that is infected or at risk of infection (assessed by investigator) • The size of burn (including both study wound and non study injuries) has a Total Body Surface Area (TBSA) less than 20% (assessed by investigator). • The wound should fit under a 20x30 cm dressing (600 cm2) or smaller • The shape and location of the wound should be suitable for photo capture (assessed by the investigator). • Has a wound that has medium to high level of exudate (assessed by the investigator) • Is suitable to use the test product for wound treatment (assessed by the investigator).	Recruitment may go through an advertisement. The advertisement will state the contact information of relevant Principal Investigator(s) that potential subjects are asked to contact for further information.
First contact	The potential subjects will be contacted by mail, phone call or contacted during a visit in at the hospital/ outpatient clinic. If a subject is eligible and interested in participating in the investigation upon a short introduction, then written information about the investigation (Participation Information Sheet /Informed Consent Form) will be distributed to the subject. The Principal Investigator or delegate will invite the subject to a Screening Visit (V0).	The potential subjects will mail or call the Principal Investigator. If a subject is eligible and interested in participating in the investigation upon a short introduction, then written information about the investigation (Participation Information Sheet/ Informed Consent Form) will be sent to the subject and the subject will be re-directed to a recruiting site near the subjects' home for a potential Screening Visit (V0).

Recruitment method	Hospital/Outpatient clinic	Advertising
Screening Visit (V0)	At the scheduled Screening Visit (V0) the Principal Investigator or delegate will introduce the investigation and review the inclusion and exclusion criteria. If the subject wishes to reconsider his/her participation at V0, the subject has the rights to wait minimum 24 hours before deciding on participation. If the subject hereafter decides to participate in the clinical investigation a Baseline Visit (V1) will be scheduled unless performed the same day as the Screening Visit. The Screening Visit can be formed at the site or as a phone call. If the subject does not meet the inclusion criteria or meet the exclusion criteria, this will be registered at the Subject Pre-Screening Log.	At the scheduled Screening Visit (V0) the Principal Investigator or delegate will introduce the investigation and review the inclusion and exclusion criteria. If the subject wishes to reconsider his/her participation at V0, the subject has the rights to wait minimum 24 hours before deciding on participation. If the subject hereafter decides to participate in the clinical investigation a Baseline Visit (V1) will be scheduled unless performed the same day as the Screening Visit. The Screening Visit can be formed at the site or as a phone call. If the subject does not meet the inclusion criteria or meet the exclusion criteria, this will be registered at the Subject Pre-Screening Log.
Baseline Visit (V1)	If the subject decides to participate and it is certain that it is understood what the investigation entails, the subject will be asked to sign the PIS/ICF. When the PIS/ICF is signed the subject is considered included in the investigation.	If the subject decides to participate and it is certain that it is understood what the investigation entails, the subject will be asked to sign the PIS/ICF. When the PIS/ICF is signed the subject is considered included in the investigation.

6.4. Subject withdrawal criteria

The subject is allowed to withdraw from the investigation at any time for whatever reason without any consequences for their future treatment outside the clinical investigation. The PI may withdraw a subject from the investigation at any time if they judge it to be the subject's interest.

The PI must withdraw a subject from the investigation due to:

- Noncompliance with the CIP impacting the scientific integrity of the investigation.
- If subject's safety and wellbeing is compromised by further participation.
- Subjects lost to follow-up. At least three documented attempts will be made to verify subjects lost to follow-up.

Withdrawn subjects will not be replaced by new subjects.

A subject who is withdrawn from the investigation, for any reason, will be encouraged to contact the PI if problem arises, that the subject believes are related to the clinical investigation. Subject who has not experienced any adverse events, will not be followed up. For subjects who experience adverse events see section 18.1.

6.5. Screening failure

Subjects that have signed the Informed Consent Form but fails to comply with inclusion or exclusion criteria are considered screening failures. A screening failure can be replaced by a new subject if the subject can complete the investigation within timelines (before last subject last visit and within visit windows).

6.6. Point of enrolment

A subject is considered enrolled in the investigation when the written informed consent is obtained. The expected duration for each subject is described in section 5.1.

6.7. Subject Identification and Confidentiality

Subjects will be identified on the electronic CRF (e-CRF), and any other document transmitted to the sponsor by the principal investigator or delegate, by a unique identification number.

Data entered on the e-CRF are confidential and will only be available to the sponsor (including sponsor delegates), members of data management teams, the statistician, data monitoring board members or clinical event committee members if involved, members of the EC and if requested to regulatory authorities.

The principal investigator for each clinical investigation site will maintain as part of the investigational file a list identifying all subjects entered into the clinical investigation.

7. Procedures

7.1. Clinical investigation related procedures and assessments

Visit 0 (V0) Screening visit

- Introduction to the investigation and review of Participant Information Sheet and Informed Consent Form
- Review in- and exclusion criteria
- Schedule Baseline visit (V1) within 72 hours since injury, unless performed at the same day as Screening visit V0
- Register the potential subject on the Pre-screenings log.

Baseline visit (V1)

- Review Participant information Sheet and Informed Consent Form
- Check in- and exclusion criteria
- Informed Consent signed
- Inclusion in the study and allocation of subject number
- Collect baseline information:
  - Age (years)
  - Weight (kg)
  - Height (cm)
  - Gender (male/female)
  - Nutritional status (well-nourished, malnourished)
  - Mobility status (good mobility, bad mobility)
  - Smoking (yes/no)
  - Alcohol (Units/week)
  - Comorbidities (That can affect wound healing (diabetes, venous insufficiency, peripheral arterial disease, cardiopulmonary conditions, immune deficiencies, dementia, other) or none as deemed relevant by investigator)

- Relevant concomitant medication (that can impact wound healing e.g., NSAID, Glucocorticoid steroids and chemotherapeutic drugs)
- Use of antiseptics in study wound within the last week (yes/no) and reason for use.

- Cleansing of wound according to standard of care (record product applied)
- Photo of wound and upload to a digital [redacted]

Wound description/assessment

- Reason of burn (thermal, Chemical, other)
- Duration of wound
- Previous wound treatment/treatment at time of inclusion (if applicable)
- Wound size (measured by photo uploaded to a digital [redacted]
- Wound location (upper extremity, lower extremity- leg, lower extremity-foot, abdomen, thorax, back, buttock/sacrum, other)
- [redacted]

- Dressing application according to IFU
- Record applied additional relevant wound care products (e.g., secondary dressing or barrier cream)
- Instruction to the subject (including sheet for dressing change between scheduled visits)
- Scheduling Visit 2 in Week 1, 7 days (+/-2 days) after Visit 1 (Attention to compliance with maximum wear time of 7 days according to IFU)
- Complete eCRF
- Perform device accountability

Visit 2 (V2)

- Insurance of subject´s wellbeing. Review of AEs/ADEs/SAEs/SADEs/device deficiencies/Protocol Deviations
- [redacted]

- Cleansing of wound according to standard of care (record product applied)
- Photo of wound and upload to a digital [redacted]

Wound assessment

- [redacted]
- Wound healed (yes/no)

Test Product assessment

- [redacted]

- Dressing application according to IFU
- Record applied additional wound care products (e.g., sec. dressing or barrier cream)

- Record any changes in concomitant medication
- Record if use of antibiotics and antiseptics since last visit
- Scheduling next Study visit V3 in the following week. Visit 3 must be 14 days after Visit 1 (+/-2 days) (Attention to compliance with maximum wear time of 7 days according to IFU)
- Perform device accountability
- Complete eCRF

Visit 3 Termination

- Insurance of subject´s wellbeing. Review of AEs/ADEs/SAEs/SADEs/device deficiencies/Protocol Deviations
- [redacted]
- Cleansing of wound according to standard of care (record product used)
- Photo of wound and upload to a digital [redacted]

Wound assessment

- [redacted]
- Wound healed (yes/no)

Test Product assessment

- [redacted]

- Record any changes in concomitant medication
- Record if use of antibiotics and antiseptics since last visit
- Handover to routine care
- Perform device accountability
- Complete eCRF

Termination visit wound healed

- Insurance of subject´s wellbeing. Review of AEs/ADEs/SAEs/SADEs/device deficiencies/Protocol Deviations
- [redacted]
- Cleansing of wound according to standard of care (if applicable) (record product used)
- Photo of wound and upload to a digital [redacted]

Wound assessment

- [redacted]
- Wound healed (yes/no)

Test Product assessment

- [redacted]

- Record any changes in concomitant medication

- Record if use of antibiotics and antiseptics since last visit
- Perform device accountability
- Complete eCRF

7.2. Dressing changes between study site visits.

The dressing should be replaced when wound care practice indicates that a change is needed, or when it has reached its maximum, but no more than 7 days. If the wound care practice indicates that a change is needed (strike through) more than the scheduled study visit once per week, additional visits at the site can be scheduled for dressing changes.

In the event of a completed dressing change between the weekly scheduled visits, it must be documented at the next scheduled weekly visit in the eCRF to capture the total number of dressings changes since last scheduled visit and numbers of test products used simultaneously per dressing change.
The subject will be instructed to complete a sheet for dressing changes, date of the event, and numbers of test products used simultaneously between the scheduled weekly site. Furthermore, the subject will be instructed to document any use of antiseptics, and reason for use if known, between the scheduled visits.

Dressing change can also take place at the **subject's** home by a homecare nurse.
The subject will be provided with additional test products at each visit for use at home in case of additional dressing changes in between visits. An information sheet for the homecare nurse will be distributed to the subjects to be shared with the homecare nurse, providing information about the study and the study treatment to ensure that the protocol is followed between scheduled visits.

No clinical investigation-related wound assessments are conducted during the additional visits and/or dressing **changes at the subject's home.** Cleansing of wound must be done according to standard of care if needed.

7.3. Unscheduled visits.

If circumstances demand it, e.g., due to specific issues with the test product or events which need to be assessed by the PI or delegate, an unscheduled visit may be scheduled. No clinical investigation-related wound assessments are conducted during the unscheduled visits.

7.4. Wound healed

If the wound is evaluated by PI or delegate to be healed before or at the termination visit 3 the subject must be terminated according to the termination Wound healed and not according to termination visit 3 as these assessments are not relevant when the wound has healed.

7.5. Schedule of clinical-related procedures and assessments

Table 3. Chart showing the connection between visits and assessments.

	PER-FORMED BY	SCREENING VISIT	BASELINE VISIT	VISIT 2	TERMINATION VISIT WOUND HEALED	TERMINATION VISIT	UNS VISIT
VISIT	-	V0	V1	V2	-	V3	
WEEK	-	WEEK 0	WEEK 0	WEEK 1	-	WEEK 2	
DAY		DAY 0	DAY 0	DAY 7	-	DAY 14	

VISIT WINDOW	-	-	0-72 hours after injury	+/-2 days	-	+/-2 days	
GENERAL							
Introduction to the investigation and review of Patient Information Sheet/Informed Consent Form	Investigator or delegate	X	X				
Review of in- and exclusion criteria	Investigator or delegate	X					
Check and verification of in- and exclusion criteria	Investigator or delegate		x				
Informed Consent Signed	Investigator or delegate and Subject		X				
Enrollment in the investigation allocation of subject number	Investigator or delegate		X				
Collect Baseline information	Investigator or delegate		X				
Record concomitant medication	Investigator or delegate		X				
Review of AE/ADE/SAE/SADE/device deficiencies/Protocol Deviations	Investigator or delegate			X	X	X	X
Procedures/Assessments							
Cleansing of wound according to standard of care (record product used)	Investigator or delegate		X	X	X	X	X
Photo of wound and upload to a [redacted]	Investigator or delegate		X	X	X	X	
Wound area measurements using a digital [redacted]	Coloplast representative		X	X		X	
Wound healed (Yes/No)	Investigator or delegate			X	X	X	
[redacted]	Investigator or delegate		X	X		X	

[redacted]	Investigator or delegate			X	X	X	
[redacted]	Investigator or delegate		X	X		X	
[redacted]	Investigator or delegate		X	X		X	
[redacted]	Investigator or delegate		X	X		X	
[redacted]	Investigator or delegate		X	X		X	
[redacted]	Investigator or delegate			X	X	X	
[redacted]	Investigator or delegate		X	X	X	X	
Dressing application	Investigator or delegate		X	X			X
[redacted]	Investigator or delegate			X	X	X	
[redacted]	Investigator or delegate			X	X	X	
[redacted]	Investigator or delegate			X	X	X	
Record applied additional wound care products (e.g., sec. dressing or barrier cream)	Investigator or delegate		X	X			X
Record any changes in concomitant medication	Investigator or delegate			X	X	X	
Perform device accountability	Investigator or delegate		X	X	X	X	
Sheet for capture dressing changes and numbers of test products used simultaneously	Subject			X	X	X	
Instruction to the subject (including sheet for dressing changes and numbers of test products used simultaneously)	Investigator or delegate		X				

Handover to routine care	Investigator or delegate					X	
Complete eCRF	Investigator or delegate		X	X	X	X	X
Schedule Baseline Visit 1	Investigator or delegate	X					
Schedule Visit 2	Investigator or delegate		X				
Schedule Termination Visit V3	Investigator or delegate			X			
ADDITIONAL ASSESS-MENTS							
Use of antibiotics and anti-septics since last visit	Investigator or delegate			X	X	X	

7.6. Concomitant treatment

Only concomitant medication/treatment that can impact wound healing should be registered. These include NSAID, glucocorticoid steroids and chemotherapeutic drugs. If subject use antibiotics or antiseptics after baseline V1, this must be documented in the eCRF with description on reason for use and which treatment used.

7.7. Supplementary materials and equipment

The Sponsor will provide the Principal Investigators with supplementary materials for the investigation such as computers with access to eCRF if needed and phones with the [redacted] installed to obtain photos.

8. Risk – benefit analysis and ethical considerations

8.1. Risk-benefit analysis of the investigational device

A risk analysis according to ISO 14971 Application of risk management to medical devices has been conducted. Risks have been proven minimized or eliminated through appropriate design control, confirmed by pre-clinical bench and laboratory testing.

All unacceptable risks related to the device have been mitigated as far as possible and have been deemed acceptable for the clinical study.

8.2. Risk-benefit for subjects participating in the clinical investigation

The investigation is conducted in accordance with current law and applicable standards, see section 15, Statement of Compliance. The rights, safety and well-being of human subjects shall prevail over the interest of science of society.

Risks in this investigation are considered equal to the use of other wound care products on the marked (with silver). Risks associated with the use of wound care products are skin irritation/inflammation, allergic skin reaction, maceration, pain, hyper-granulation, and blistering. See section 18, Adverse Events and Adverse Device Effects for details.

There is no known interaction between the use of the test product and the medication participants can take – except from what is stated in the exclusion criterions. Disadvantages of testing (trial engagement) may be the time spent on visits and transport.

The overall clinically benefits of Biatain Fiber Ag may include, to be investigated in the study; moist wound healing, [redacted] Adequately exudate management provides a moist wound healing environment and together with sufficient antimicrobial effect this will pave the way for healing of wounds with delayed healing due to bacteria or wounds at risk of infection. [redacted]

8.3. Risk Analysis for the conduct of the clinical investigation

A risk assessment of the clinical investigation will be conducted initially prior to the first subject enrolment and periodically re-assessed based on any new risks identified through the process. This assessment will be completed throughout the duration of the investigation, as defined by the study team. A risk-based monitoring strategy may be implemented including on-site remote, and central monitoring. Details of the strategy are defined in the monitoring plan in section 9.

8.4. Delegation of responsibility

Before initiation of the clinical investigation, sponsor must be provided with key personnel signed and dated curriculum vitae (not more than 2 years old) to verify their qualifications. Key site personnel are those, who treat or evaluate subject data in the clinical investigation. Also, the sponsor will ensure that all site personnel are trained in the investigation procedures, how to complete the CRFs, procedure for reporting an adverse event or serious adverse event (how, when, to whom), and who to contact in case of emergency related to the investigational device.

9. Monitoring Plan

The sponsor is responsible for ensuring appropriate monitoring of the clinical investigation activities as described below.
The monitors will be the primary contact for the principal investigator and clinical investigation site personnel.

Monitoring activities are mandatory as per good clinical practice, however the extend and depth of these activities depend on the criticality of the clinical investigation, speed of enrolment, the experience of the clinical investigation site personnel in carrying out clinical investigations and specific study designs.

For the purpose of this clinical investigation the below described monitoring procedures have been determined.

9.1. Site selection visit

Depending on the prospective clinical investigation sites experience with the specific investigational device, an on-site qualification or site selection visit shall be performed during which the feasibility of the clinical investigation requirements will be discussed and common agreement between sponsor and principal investigator shall be reached. This visit may also be replaced by one or more phone calls or conducted remotely, using Microsoft Teams.

9.2. Initiation visit

All clinical investigation sites will complete an initiation visit with full training on all aspects of the clinical investigation. The initiation visit can be held as a physical meeting or remotely, using Microsoft Teams, Skype or Face Time. Initiation visit will be held as close to study start as possible.

9.3. Monitoring visit(s)

The site dedicated monitor is to ensure adherence to the clinical investigation plan, accurate data recording on the e-CRFs and to monitor recruitment rates and adherence to follow-up schedules. The principal investigator shall permit and assist the monitor to carry out verification of completed e-CRFs against data in the source documents.

The principal investigator can delegate tasks to his/her collaborators, however the roles and responsibilities as time period of involvement for each clinical site personnel must be documented on the Site Personnel signature and delegation list as well as training received before getting involved with the clinical investigation must be documented in the Clinical investigation training log.

The monitor shall inform the sponsor about any problems relating to facilities, technical equipment or medical staff at the clinical investigation site. During the clinical investigation, monitors shall check that appropriate written informed consents have been obtained. The monitor shall also be responsible for notifying such deficiencies in writing to the principal investigator and convene with the clinical investigation site personnel appropriate and timely corrective actions.

The sponsor, or delegate, will provide clinical monitoring, including review of eCRF with verification to the source documentation, as defined in the monitoring plan.

The monitor shall make written reports to the sponsor, after each visit and provide written action items if any, to the principal investigator or clinical investigation site personnel.

All data collected can be directly entered into the eCRF and the EDC system will via edit checks ensure that all fields are completed in the eCRF. Monitor will ensure by 100% monitoring, that all queries are timely resolved.

Source data verification will be performed to the extent it is possible. The Source Data Specification Form must be completed at the initiation visit detailing the location of the source data for each data point. Where no source data (besides the eCRF) is available the contents of the eCRF will be monitored.

The Informed Consent Forms and AE/ADE will be 100% monitored for timely completeness.

Only the investigator, delegated site personnel and the sponsor representatives will have access to all the eCRFs.

9.4. Source data verification

A source document is a document in which data collected for a clinical trial is first recorded. This data is usually later entered in the electronic case report form (eCRF).
Source documents are defined as "original documents, data, and records. Source documents contain source data, which is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

All documents and data related to the clinical investigation handled by site personnel, shall be produced and maintained in a way that assures reliability, integrity, control and traceability, and shall be appropriately stored to provide a complete history.

The Principal Investigator shall assure the accuracy, attribution, completeness, legibility and timeliness of the data reported to the sponsor in the eCRFs and in all required reports. All printed copies of electronic source documents shall be certified, as indicated by a dated signature by the investigational site personnel at the time the document is printed. Special requirements should be applied to the capture, review and retention of electronic source data, to ensure reliability, quality, integrity and traceability.

The data reported in the eCRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. In some cases, the eCRF can serve as the source document and this must be documented on the Source Data Specification Form. The Source Data Specification Form must be completed at the initiation visit detailing the location of the source data for each data point.

10. Statistical considerations

10.1. Definition of analysis populations

Intention to Treat (ITT) and Safety populations will be defined at a formal data review meeting before database lock. As a minimum, the data manager, the clinical manager, and the statistician will be involved in the classification of subjects.

The Safety population will constitute by subjects who have given informed consent. Due to the design, the ITT population is identical to the safety population.

The full analysis set (FAS) will be constituted by all subjects with valid informed consent who have been exposed to the Test Product, with information on at least either primary or secondary endpoints.

All statistical analysis will be based upon the FAS population whereas adverse events and Device deficiencies will be assessed based on the safety/ITT population. Invalid individual data points may be omitted from analysis even though the corresponding subject is part of the FAS population. Any exclusion of data points will be documented.
A formal per protocol (PP) population will be performed for the primary, secondary and exploratory endpoints. Considering the data obtained it might also be considered to make additional explorative analyses based on a subset of the ITT population.

10.2. Analysis of endpoints, individual questions, and assessments

All collected data including withdrawals will be accounted for in listings. All endpoints and baseline information will be listed and summarized by descriptive statistics. The summaries will be done in total and by the different population groups. Summaries and listing will include both safety/ITT and FAS population.

Summary statistics for continuous variables are presented with N, Mean, SD (standard deviation), Median, Min and Max, where N denotes the number of subjects contributing with non-missing data. For discrete variables, summary statistics are presented with N and percentage, where percentage is based on the total number of subjects/observations with non-missing data.

Other summaries and analyses can be made, if relevant.

10.3. Analysis of primary endpoint

The primary endpoint proportion of wounds healed will be analyzed using a binomial proportion test.

The purpose of the primary analysis is to show non-inferiority to the performance of the similar product Aquacel Ag (a silver containing gelling fiber) on proportion of wounds healed, 77 %, with a non-inferiority margin of 20 %. (1)

Since the performance of Aquacel Ag is a fixed proportion, this is equivalent to testing whether the performance of Biatain Fiber Ag is superior to 77 – 20 = 57 %.

Let the null hypothesis and the alternative hypothesis be defined as:

- H_0: μBiatain Fiber Ag ≤ 57 % wounds healed
- H_1: μBiatain Fiber Ag % > 57 % wounds healed

Where Non-inferiority will be demonstrated if H_0 is rejected.

This will be done using the proc freq procedure with a binomial test and if the lower limit of the 95 % confidence interval is above 57 % H_0 is rejected, and the success criteria fulfilled.

Furthermore, as a conservative estimate, a sensitivity analysis will be performed on the primary endpoint, where patients lost to follow-up, or otherwise missing information, will be considered not healed in regards to their wound.

The exploratory endpoints will be analysed descriptively and presented with confidence intervals.

10.4. Sample size

The primary endpoint is proportion of wounds healed and the sample size calculation is based on a proportion of 77 %. The design is a non-inferiority design, where we want to show noninferiority with a margin of 20 %. *This gives*

The POWER Procedure
Z Noninferiority Test for Binomial Proportion

Fixed Scenario Elements	
Method	Normal approximation
Number of Sides	U
Null Proportion	0.77
Margin	-0.2
Alpha	0.025
Binomial Proportion	0.77
Nominal Power	0.8
Variance Estimate	Null Variance

Computed N Total	
Actual Power	N Total
0.801	44

Meaning a total of 44 completers gives a sufficient (80%) power. Accounting for dropouts (10%) gives us 50 subjects.

10.5. Level of significance and power

The study is designed with a power of 80 % and testing of the primary analysis will be done using a one-sided 0.025 significance level. No other statistical test as pre-planned.

11. Data management

Data management and the final statistical analyses of all measurements described in this protocol are car-ried out by Clinical Strategies, Coloplast A/S.

Data will be collected through an electronic data capturing (EDC) system on electronic Case Report Form (eCRF), a secure, internet-based case report form. This system will be used to record all subject information collected in the investigation for secure data tracking and centralised data monitoring ("remote monitoring") done by monitors, as defined in the monitoring section.

[redacted]The system is designed to be compliant with the FDA requirements of 21 CFR part 11. It is a validated data management system allowing only qualified and trained personnel to enter the system. The system has full audit trail and electronic signature.

The data management system has restricted role-based access control. The principal investigator or delegate must be trained in the system prior to getting access. The sponsor will be responsible for training the investi-gator or delegate, in completion of the eCRF. The training is web-based and must be completed be-fore access to the investigation is granted. Training will be documented in the data management system. The data manager will also demonstrate the system on a virtual meeting. Only the principal investigator, or delegate, will be au-thorised to enter data in the eCRF.

The monitor, using his/her personal login information shall verify all critical data points against the source documents and issue electronic queries for the authorised clinical site personnel to respond, as defined in the monitoring section.

A critical quality control will be performed by the sponsor's data management team and queries issued where needed. Such queries must be resolved by the site personnel.

The principal investigator, using his/her personal login information, shall sign each eCRF.

Automated, real-time access to the data enable control on study compliance and safety assessments.

A full audit trail ensures, that each user's (site personnel, monitor, sponsor, data manager) access to and actions in the system is tracked.

The Data Validation Plan describes which edit checks, range checks, and other consistence checks that will be done on the clinical data during conduct of the investigation. The Data Validation Plan will be devel-oped in collaboration with the Clinical Manager and the Statistician and will be aligned with the monitoring section.

Principal Investigator, or delegate, at the clinical site will perform primary data collection directly into the eCRF or drawn from source-document (i.e., medical records) reviews. The eCRF will be completed on a continuous basis starting from the point of enrolling the subject to final follow up.

The eCRF will be completed by the investigator, or delegate, who have signed the Site Personnel Signature and Delegation List and Clinical Investigation Training Log. It will be the responsibility of the investigator to ensure that all measurements and observations are correctly noted in the eCRF.

All assessments and observations throughout the investigation for each subject must be carefully recorded in an eCRF during the visit or immediately after. The eCRF makes it possible to enter data right away when they are obtained. This is the preferred way of collecting data. In case this is not possible the data should be entered no later than 7 days after the visit / procedure.

In the unforeseen situation, where site cannot establish connection to the EDC system, a paper CRF (pCRF) has been printed and supplied by sponsor.

The wound area is measured by an [redacted] delivered by [redacted] The PI, or delegate, will download an app to a Smartphone. The app can be used to take a photo of the wound. The photo is then uploaded to [redacted] Imaging platform where a designated person will perform the area measurement. The results will afterwards be entered into [redacted]

At the end of the study a formal data review meeting will be performed before the database will be locked.

The Data Management Procedures are further described in the Data Management SOPs.

The investigator will keep a separate list of the subjects' ID numbers, names, and addresses in a locked room/cabinet. Only data referred to in this clinical investigation plan will be recorded in the CRFs.

Adverse events should be registered following the timelines described in the Adverse Event section.

11.1. Remote monitoring

Remote or centralized monitoring is a remote evaluation carried out by sponsor personnel or representatives (e.g., data management personnel, statisticians, or clinical monitors) at a location other than the site(s) at which the clinical investigation is being conducted. Remote monitoring processes can provide many of the capabilities of on-site monitoring as well as additional capabilities.

In addition to onsite monitoring visits, remote monitoring of the data entered in the e-CRF system could be used to achieve the following:

- Conduct activities such as: standard checks of range, consistency, and completeness of data and checks for unusual distribution of data, such as too little variance)
- Special attention will be given in case of frequent data anomalies or errors, protocol violations or excessive dropouts.
- Augment on-site monitoring by performing monitoring activities that can only be accomplished using centralized processes (e.g., statistical analyses to identify data trends not easily detected by on-site monitoring)
- Monitor data quality through routine review of submitted data in real-time to identify missing data, inconsistent data, data outliers, and potential protocol deviations that may be indicative of systemic and/or significant errors in data collection and reporting at the site
- Verify source data remotely, provided that both source data and CRFs can be accessed remotely
- Conduct aggregate statistical analyses of study data to identify subject data that are outliers relative to others and to evaluate individual subject data for plausibility and completeness
- Conduct analyses of site characteristics, performance metrics (e.g., high screen failure rates, high frequency of eligibility violations, and delays in reporting data), and clinical data to identify early on corrective actions needed for characteristics correlated with poor performance or noncompliance.

11.2. Data retention

The PI file must be archived for a minimum period of 10 years after the final clinical investigation report has been signed.

12. Amendments to the Clinical Investigation Plan

No changes in the clinical investigation procedures shall be affected without mutual agreement between the PI and the sponsor. The agreement of the changes must be documented by signing the corresponding clinical investigation plan amendments and registered in the Change Log.

All significant changes require notification to the EC and applicable regulatory authority. Substantial changes may require approval from the EC and applicable regulatory authority prior to implementation. (Example of significant change: Changes of inclusion criteria, end points or assessment methods)

13. Deviations from the Clinical Investigation Plan

Deviations to the Clinical Investigation Plan occurs when the activities during the clinical investigation do not comply with the EC/CA approved investigation plan. Minor deviations are **defined as those that don't** increased risk, decrease benefit, or **don't have a significant** effect on the subject's rights, safety or welfare; and/or on the integrity of the data. If a deviation increases risk or decreases benefit and/or has a significant effect on the subject's rights, safety, or welfare and/or has a significant effect on the integrity of the data it is defined as a major deviation and the Investigator must inform the monitor immediately, and the monitor will report and inform the Clinical Manager or designee immediately.

The investigator is not allowed to deviate from the Clinical Investigation Plan unless, under emergency circumstances or to protect the rights, safety, and welfare of the subject(s).

For the purposes of this investigation, any variance from the protocol is considered a deviation and is to be reported.

The site will complete a deviation eCRF for all data-related deviations and all deviations that are **not** related to the data (for example, an untrained nurse performing study procedures) are reported by the monitor in the Site Report – Periodic Monitoring and actions are addressed to the Investigator for completion.

If any deviations to the investigation plan are detected during the monitoring visit, the Monitor shall ensure the site reports all deviations in the eCRF or on the Deviation log in the Investigator File. Additionally, the monitor must report any deviation noted during the visit in the Periodic Monitoring Report.

Monitor will align with data management in each investigation, how data management will be informed about all deviations.

The following information about the deviation will be collected:

- **Site ID,** Subject ID
- Date the deviation took place.
- State what the deviation is related to.
- Does the deviation affect data integrity?
- Does the deviation affect the **subject's** safety?
- Clear and concise description of the event.
- Corrective action taken.

14. Device Accountability

All access to the investigational devices used in the clinical investigation is controlled by storage procedures and device accountability logs as described below. The investigational devices must only be used in this clinical investigation and only according to the CIP.
Sponsor keeps a device accountability log that states the physical location of all investigational devices from shipment of investigations devices to the investigational sites until return of or disposal.

The PI or delegate, keeps records documenting the receipt, use and return and disposal of the investigational devices, which includes:

- Name of product received
- Date of receipt.
- Identification of each investigational device (batch no./serial no./unique code).
- The expire date (if applicable)
- Number of products received
- The date(s) of use.
- Number of products distributed to subjects
- Subject identification.
- The date on which the investigational device was returned/explanted from the subject, if applicable.
- The date of return unused, expired or malfunctioning investigational devices, if applicable.

15. Statement of compliance

The clinical investigation is conducted in accordance with:

- Ethical principles that have their origin in the Declaration of Helsinki, 1964, Last amended at the 59th WMA General Assembly, Brazil, October 2013.
- MDR (EU) 2017/745
- ISO 14155:2020 **"Clinical Investigation of medical devices for human subjects** – Good clinical practices**".**
- Any applicable regional or national regulations will be specified in the country specific CIP.

15.1. Ethics committee and regulatory authorities

The CIP and/or other relevant documents are submitted to the appropriate EC(s) and regulatory authorities. This clinical investigation will not begin until the required approval from the EC and regulatory authorities have been obtained. Any amendment to the protocol will be submitted to the same EC(s) and regulatory authority.

Sponsor will notify the relevant regulatory authority and EC(s) concerned of the end of the clinical investigation.

15.2. Data protection

As part of the investigation Coloplast A/S, [redacted] **("Coloplast") will collect and process the personal information the subject provides for the investigation ("subject personal data"). This** includes identification and contact information (which may be anonymised depending on the nature of the investigation) as well as information about product usage experience and your health. Coloplast will only process the **subject's** personal data:

1. To conduct the investigation and carry out related research based on subject consent (primary use), cf. article 9(2)(a) of the EU General Data Protection Regulation (GDPR),
2. To comply with applicable legal obligations to e.g., ensure reliability and safety, cf. article 6(1)(c) in conjunction with article 9(1)(i) of GDPR, and
3. If separate consent is given for secondary use of subject personal data, cf. article 9(2)(a) of GDPR –carry out research outside the clinical protocol **to improve Coloplast's products and** services, and for use in education.

Part of Coloplast's **processing** is carried out on third-party platforms (clinical trial databases) and certain third parties are assisting Coloplast in the processing (e.g., the investigator). Such cases will imply a transfer of your personal data to the third parties, but solely for the specified purposes and with the third parties acting on instruction from Coloplast. Data may be collected and processed across the Coloplast network, which may entail processing of personal data outside the European Economic Area. In such cases, an adequate level of protection will be ensured by the third parties being subject to the standard contractual clauses on data protection adopted by the EU or to an EU-approved certification mechanism on data protection. For further information about this please the subject can always **consult Coloplast's data protection officer (details below)**.

Subject personal data will be kept as long as required under applicable laws and regulations. The EU Medical Device Regulation obligates Coloplast to keep the data for a period of at least ten years after the investigation is completed, or, in the event that the device is subsequently placed on the market, at least ten years after the last device has been placed on the market. Subject personal data will be deleted at the end of the mandatory retention period.

If the subject **has questions or queries regarding Coloplast's handling of personal information**, the subject can always **contact Coloplast's Data Protection Officer at** [redacted] Complaints related **to Coloplast's handling of** subject personal information may similarly be sent to the Data Protection Officer, and the subjcet are also entitled to file a complaint with the relevant supervisory authority, which in the case of Denmark is the Danish Data Protection Agency (www.datatilsynet.dk).

The subject can write to [redacted] at any time to request:

1. Access to personal data
1. Correction of errors in personal data or to erase personal data
1. Limit what can be done with personal data
1. To receive personal data in machine-readable format (data portability).
1. Withdrawal of consents the subject has given Coloplast to process personal data

15.3. Indemnity

All subjects are fully covered by Coloplast A/S insurance throughout the investigation:

[redacted]

15.4. Financial conditions

Coloplast A/S will compensate all investigators involved in the clinical investigation for their time and resources spent on the investigation. All financial agreements with the investigation sites involved in the clinical investigation will be specified in a sponsor investigator agreement.

The expenses include the salary to the Principal Investigator, the cost of external clinical support, study supplies, eCRF, Investigator and site personnel training and patient expenses including travel expenses.
The Principal Investigator and site personnel have no financial interests in the investigation.
The total budget for the investigation is [redacted] covering 50 subjects.

16. Informed consent process

Written informed consent is obtained from all subjects participating in the investigation after thorough written and verbal information. The information is given by the investigator or his/her representative in the subjects' native non-technical language. Each subject will be fully informed about the aim of the investigation, procedures, potential risks, or inconveniences and/or expected benefits, all anticipated adverse device effects and then have a minimum of 24h before deciding on participation. The subjects will be informed that their participation is voluntary and that they may leave the investigation at any time, without this having any influence on their further treatment.

The informed consent signature form includes personally dated signatures of the subject and the PI or his/her representative responsible for conducting the informed consent process. A copy will be provided to the subject.

If new information is to be given during the investigation, sponsor will inform the investigators, and the new information is given to the subjects by the investigator. If new information becomes available that can significantly affect a subject's future health and medical care that information will be provided to the subject in written form. The Clinical Manager is responsible for writing the information and providing it to investigators that will further provide it to the subjects. If applicable, all affected subjects shall be asked to confirm their continuing informed consent in writing.

17. Subject compensation

17.1. Compensation in case of injury

Product liability and No-Fault Clinical Investigation Insurance covering the duration of the clinical investigation are in place, to enable compensation in the event of an injury to a participating subject. Se section 15.3

17.2. Compensation for participating in the clinical investigation

Subjects are compensated for any transportation costs.

Reimbursement of transportation expenses are not taxable per local legislation. Transport expenses will be paid in appropriate portions that justify the administration throughout the investigation period.

Subjects will be compensated with a voucher per test visit, paid by Coloplast A/S with the value as described below:

Visits	Subjects
Visit 1 (V1)	[redacted]
Visit 2 (V2)	
Visit 3 (V3)	

18. Adverse events, adverse device effects and device deficiencies

18.1. Adverse events

An adverse event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, whether or not related to the investigational medical device(s), or the procedures involved. The adverse event shall be marked with the intensity mild, moderate, or severe. This could include events such as headache or dizziness.

18.2. Adverse device effect

An adverse event, which is related to the use of the investigational medical device, is an adverse device effect, and should be marked as unlikely related, possible related, probably related or with causal relationship on the adverse event form.

The definition of an adverse device effect includes any event resulting from insufficiencies or inadequacies in the instruction for use, or any malfunction of the medical device, as well as any event resulting from use error or from intentional misuse of the device.

The anticipated adverse device effects in this investigation are considered equal to the use of other wound care products on the marked (with silver). Risks associated with the use of wound care products are skin irritation/inflammation, allergic skin reaction, maceration, pain, hyper-granulation, and blistering.

Table 4 lists anticipated adverse device effects that may occur, and their likely incidence rates based on adverse event reported in clinical studies on other silver containing products (2-7)

Table 4. Anticipated adverse device effects and their likely incidence rates

ANTICIPATED ADE	INCIDENCE RATE
Skin irritation/inflammation	10 %
Allergic skin reaction	1%
Maceration	10%
Pain	10%
Hyper-granulation	5%
Blistering	2%

18.3. Device deficiency

A device deficiency is the inadequacy of the investigational medical device or comparator with respect to its identity, quality, durability, reliability, safety, or performance. This includes malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labelling.

18.4. Serious adverse events (SAE)

A serious adverse event is an adverse event that:

- Led to death,

- Led to a serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:
  1) a life-threatening illness or injury, or
  2) a permanent impairment of a body structure or a body function including chronic diseases, or
  3) in-patient or prolonged hospitalization, or
  4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

- Led to foetal distress, foetal death or a congenital abnormality or birth defect including physical or mental impairment.

This includes device deficiencies that might have led to a serious adverse event if:
1) Suitable action had not been taken, or
2) Intervention had not been made, or
3) Circumstances had been less fortunate.

These are handled under the serious adverse event reporting.

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.

18.4.1. Serious adverse device effect (SADE)

A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

18.4.2. Anticipated serious adverse device effect (ASADE)

Anticipated serious adverse device effect is any event that by its nature, incidence, severity, or outcome has been previously identified in the risk analysis report.

18.4.3. Unanticipated serious adverse device effect (USADE)

An unanticipated serious adverse device effect is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

18.5. Medical care of subjects

Principal investigator shall ensure that adequate medical care is provided to a subject experiencing an adverse event during and after participation in the clinical investigation. All ongoing ADEs, SAEs, SADEs and DDs, that could have led to a SAE at subject termination, will be followed according to the Risk Benefit analysis (see 8.2) and will be followed until a resolution is addressed for a period of 2 months after subject termination. An ongoing adverse event at subject termination visit is documented as the current status for the adverse event and will not be followed up.

The subjects shall be informed of any new significant findings occurring during the clinical investigation, including the need for additional medical care that can be required, and of the nature and possible cause of any adverse events experienced

Principal Investigator or delegate shall provide the subject with the necessary instructions on proper use, handling, storage and return of the test products, when it is used or operated by the subject.

18.6. Reporting and timelines

All adverse events and device deficiencies will be reported in the eCRF. If, for some reason, the system is off-line, investigators (or designee) are required to report the event to: [redacted]

18.7. Investigator's reporting responsibilities

- PI at each site must assess all (S)AE`s that occur at his/her site.
- All serious adverse events and serious adverse device effects must be reported to sponsor within 24 hours of the site becoming aware of the event.
- A device deficiency that could have led to a serious adverse event but did not because suitable action was taken, intervention had been made or because of fortunate circumstances should be reported to sponsor within 24 hours of the site becoming aware of the event.
- New findings and/or updates in relation to already reported serious events should also be reported to sponsor within 24 hours of the site becoming aware of the event.
- Device deficiencies and all adverse device effects must be reported to the sponsor within 24 hours of becoming aware of the event.

When reporting the SAE, the relationship to the test material shall be described whether the event is considered

- **Not related**, the event has no temporal relationship with the use of the test material or the procedures.
- **Unlikely related,** the relationship with the use of the test material seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
- **Possibly related,** the relationship with the use of the test material is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an 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.
- **Probably related,** the relationship with the use of the test material seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.
- **Definitely related/Causal relationship,** the event has a temporal relationship with the test material use/application or procedures.

and the intensity of the event should be considered, as such:

- **Mild,** the intensity of the event is mild with no further action or intervention
- **Moderate**, the intensity of the event will lead to an action or intervention to solve the event
- **Severe**, the intensity of the event will lead to follow up on the action or intervention, as the effect of the action or intervention may not decrease the symptoms.

All above events must be reported by use of the relevant adverse event/serious adverse event/device deficiency form.

Please report to: [redacted] and [redacted] In cases where accessing e-mail is not possible, please call [redacted]

18.8. Sponsors reporting responsibilities

It is the responsibility of sponsor to ensure that the following are reported to national regulatory authorities immediately, but no later than 7 calendar days following the date of awareness by sponsor.

- All serious adverse events.
- All serious device effects.
- All device deficiencies that could have led to serious adverse events but did not because suitable action was taken, intervention had been made or because of fortunate circumstances.
- New findings and/or updates in relation to already reported events.

If the serious adverse event results in imminent risk of death, serious injury, or serious illness that requires prompt remedial action for other subjects, users or other persons or a new finding to such a serious adverse event, sponsor must immediately but no later than 2 calendar days after awareness by sponsor report the event to national regulatory authorities.

It is the responsibility of sponsor to inform all investigators in writing within 10 working days if device deficiencies, adverse events, adverse device effects, near-incidents, serious adverse events, serious adverse device effects or unanticipated serious adverse device effects lead to corrective actions (*e.g.,* change of IFU).

18.9. Data Safety and Monitoring Board (DSMB)

The review of all safety data will be conducted on an ongoing basis to identify any potential safety issues. If needed, the coordinating investigator can call for a Data Safety and Monitoring Board meeting with relevant members, to discuss potential safety issues and further recommendations, if relevant.

Based on the safety data review, the coordinating investigator along with the DSMB may recommend that the sponsor modifies, temporarily suspends, or terminates the clinical investigation.

Correspondence, decisions, and recommendations regarding safety in the Clinical Investigation from the Data Safety and Monitoring Board must be documented in meeting minutes and saved electronically in the Sponsor File.

All final decisions, however, regarding clinical investigation modifications, remain with the Sponsor.

19. Suspension or premature termination of the clinical investigation

Sponsor may suspend or prematurely terminate an investigation site or the entire clinical investigation for documented significant reasons.

If a suspicion of an unacceptable risk to subjects develops during the clinical investigation, sponsor will suspend the investigation while the risk is assessed. Sponsor will terminate the investigation if an unacceptable risk is confirmed. Sponsor will ensure that the premature termination will be justified in writing and will promptly inform the regulatory authorities and relevant EC(s). If monitoring or auditing of the clinical investigation identifies serious or repeated deviations at one of the participating investigation sites, sponsor will suspend or terminate the particular investigation site. The sponsor or investigator will inform the regulatory authority as appropriate and notify the EC about the termination of the site.

20. Clinical investigation report

At completion of the investigation sponsor is responsible for writing the clinical investigation report. The report is retained on file. The report contains a critical evaluation of all data, which have been collected during the investigation. The report describes the methodology and design and a data analysis, including statistical preparation and conclusion.

Sponsor and national coordinating investigators must sign the final version of the clinical investigation report or an affidavit, indicating their agreement with the contents. If no coordinating investigators are appointed, then the signatures of the principal investigators should be obtained.

The clinical investigation report must be submitted to EC and the CA

20.1. Publication policy

Publication policy is specified in Sponsor Investigator Agreement.

20.2. General

The investigation will be registered on a public accessible database, e.g., www.ClinicalTrial.gov, before recruitment of the first subject. The results of the investigation, positive as well as negative, may be communicated by abstracts, posters, or oral presentations provided that opportunity is given for sponsor to discuss the contents and any conclusions drawn, before the abstract, paper or visual presentations are finalised. In all cases the subject's identity will remain confidential.
Sponsor will undertake to comment on the draft documents within 30 working days of receipt, but the final decision on the contents and format of the publication from the conclusions drawn, will remain with the authors.

No preliminary results will be published.

Data from the investigation is considered confidential until it is published according to the conditions of this CIP.

Sponsor may publish single subject case stories at any time during and after the investigation.

Sponsor reserves the right to use the data (published and unpublished) for reimbursement or regulatory purposes.

20.3. Joint publication

A joint paper will not be published before all PIs have approved the content of the clinical investigation re-port. If a site cannot approve the results/conclusions drawn, an independent EC will be asked to review, and all investigators must follow its conclusion.

Decisions regarding authorship credit will follow the "Uniform Requirements for Manuscripts submitted to Biomedical Journals" (the Vancouver group) according to which an author of a publication must fulfil the following criteria:

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data.
- Drafting the article or revising it critically for important intellectual content.
- Final approval of the version to be published.

Investigators who do not meet all the above criteria for authorship will be listed in the acknowledgment section under the heading "clinical investigators" and their function or contribution described. All persons must give written permission to be acknowledged.

20.4. Individual publication

Individual sites may only publish their own data from the investigation (case histories not included) in the case that:

- No joint publication is planned, or a joint paper has already been published.
- Approval from sponsor has been obtained.

21. Suspension/termination of the clinical investigation

Sponsor will withdraw from sponsorship of the clinical investigation if

- major non-adherence to the clinical investigation plan is occurring

- it is anticipated that the subject recruitment will not be adequate to meet the investigation objectives at least 75% of the subjects should be entered within the recruitment time.

In case sponsor withdraws, sponsorship for the subjects already recruited into the clinical investigation will continue.

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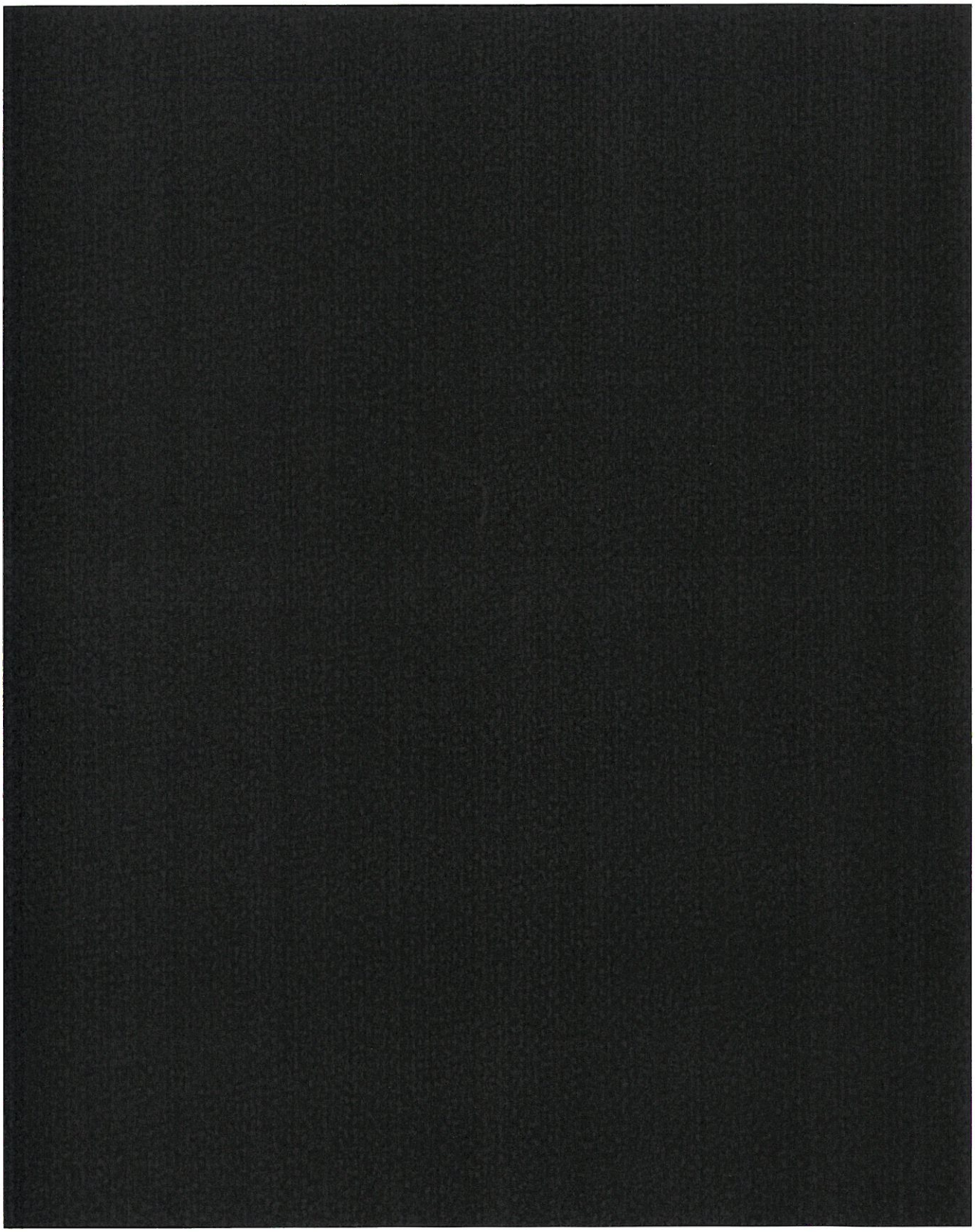
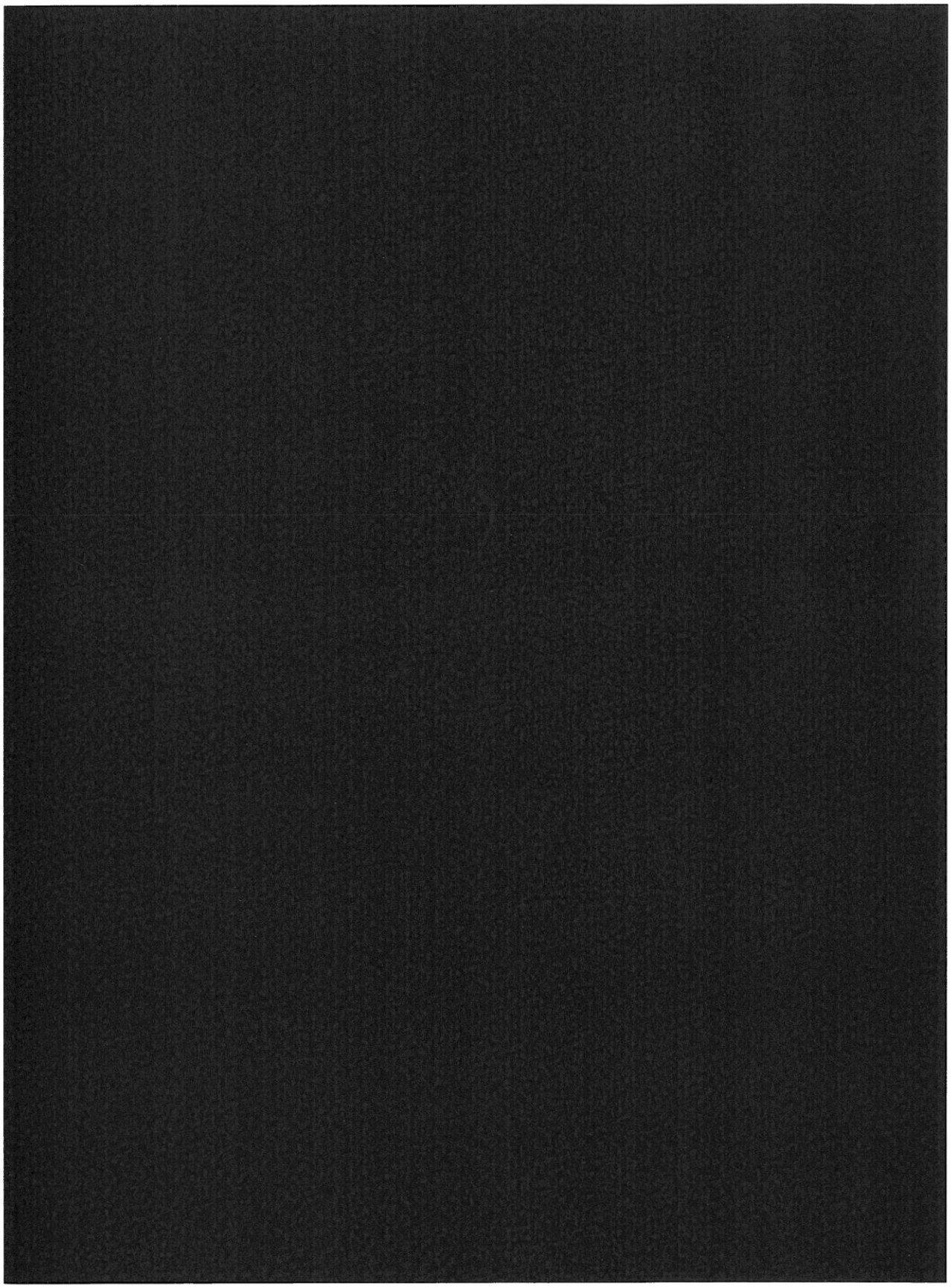
23. Appendix 1: IFU Biatain Fiber Ag





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