Cover page

The Clinical Investigation plan for study **CP319**

A clinical pilot study of newly developed ostomy tapes and how they adhere to the skin.

NTC ID: 04544566

Document date: 12/11/2020

Clinical Investigation Plan

CP319

A clinical pilot study of newly developed ostomy tapes and how they adhere to the skin

March 2020 – August 2020

SYNOPSIS OF THE CLINICAL INVESTIGATION

Aim and objective(s)

The aim of the study is to explore different recipes of ostomy tapes and understand their ability to adhere to the skin without affecting it.

The primary objective is to explore the adherent area after use.

Secondary objective is to explore the skin after application of the ostomy tapes.

Design of the investigation

This investigation is a randomised, open-label, comparative, cross-over study, with three test periods. In total, 12 subjects will be included and randomised, and each subject will have an inclusion visit and four test visits overseen by the Principal Investigator, or delegate. Each subject will be enrolled for three times 7-9 days in total for the entire investigation, thus for a maximum of 27 days – equal to at least 3 baseplates + tape change in each period. The subjects will test two new recipes of ostomy tapes and a comparator product in randomised order.

Between visits the subject will change products at home. At each product change every user should record experience at home by taking picture of the peristomal skin, and answer questions. All tapes should be removed from the baseplate and saved for the next visit at CP.

Test products and comparator

The test products are non-CE marked stoma tape products. The two test products are adhesive strips designed to support the edges of the ostomy baseplate by providing additional adhesion to the intact peristomal skin. [redacted]

The comparator is [redacted].

Primary endpoint and secondary endpoint(s)

Primary endpoint:

- Mean adherent area measured by photo of used tape (area (cm^2) per baseplate change)

Secondary endpoints:

- Erythema measured after each treatment period by spectrophotometric method
- Erythema measured after tape removal by photos
- Feeling of security
- Adhesion of tape
- Comfort
- Skin issues in the area covered by the tape
- Adverse Events

User experience with feeling of security, adhesion of tape, comfort and skin issues in the area covered by tape, will be assessed by interviews at Coloplast visit and self-reported by user at home.

Population/subjects

The population in this investigation includes 12 subjects with an ileostomy, colostomy or urostomy that comply with the following in- and exclusion criteria:

Inclusion criteria	Exclusion criteria
Has given written informed consent	Currently receiving or have within the past 2 months received radio-and/or chemotherapy
Be at least 18 years of age and have full legal capacity	Currently receiving or have within the past month received topical steroid treatment in the peristomal skin area or systemic steroid (tablet(injection) treatment
Have had a stoma for more than ½ year	Is pregnant or breastfeeding
Have intact skin on the area used in the study (Assessed by investigator, see Appendix 1.).	Having dermatological problems in the peristomal area (assessed by investigator)
Willing to change baseplate every second day or less frequent	Currently receiving or have within the past 2 months received radio-and/or chemotherapy
Willing to avoid using Concave baseplate during the study.	Currently receiving or have within the past month received topical steroid treatment in the peristomal skin area or systemic steroid (tablet(injection) treatment
Willing to avoid the use of barrier creams or similar that affect the skin/adhesive interface under the tape.	Is pregnant or breastfeeding

Investigation approval

The investigation will be approved by the Ethical committees and the competent authorities before investigation initiation.

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1. List of personnel involved in the Investigation

1.1. Sponsor representatives

COORDINATING CLINICAL MANAGER	STATISTICIAN
[redacted]	[redacted]
HEAD OF CLINICAL OPERATIONS	**SCIENTIFIC MANAGER**
[redacted]	[redacted]
DATA MANAGER	**HEAD OF PRE-CLINICAL**
[redacted]	[redacted]

In case of emergency, please contact the coordinating Clinical Manager.

1.2. Investigators

The Clinical Manager is responsible for maintaining an updated list of all PIs, investigation sites and institutions.

PRINCIPAL INVESTIGATOR
Tonny Karlsmark [redacted]

2. Rational/justification for conducting the clinical investigation

People with abdominal stomas have, despite development of better ostomy products, still problems with leakage and peristomal skin disorders which influence their quality of life negatively [1,2].

To minimize the risk of leakage on clothing, ostomy tape can be used. [redacted] and is used to support the rim of the ostomy base plate/adhesive by providing additional adhesion to the intact peristomal skin.

The adhesives in the ostomy tapes are developed to make the tape seal to the skin and thereby minimise the risk of leakage episodes. At the same time, the tape should be easy to remove without affecting the skin.

This evaluation investigates two newly developed adhesives and their ability to adhere to the skin without affecting it. Based on the knowledge obtained in this investigation, an improved ostomy tape can be developed and thereby give ostomists new supporting products that reduce the risk of leakage episodes.

3. Objective(s) of the clinical investigation

The purpose of the study is to explore different recipes of ostomy tapes and understand their ability to adhere to the skin without affecting it.

The primary objective is to explore the adherent area after use.

Secondary objective is to explore the skin after application of the ostomy tapes.

4. Investigational device and comparator(s)

4.1. Description of investigational device

The test products are non-CE marked stoma tape products. The products are adhesive strips designed to support the edges of the ostomy baseplate by providing additional adhesion to the intact peristomal skin. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.1.1. Manufacturing

[redacted]

4.2. Identification and traceability of the device

For this study the test products are packed in GRIPPIE zip lock bags (LDPE). Labels are placed on these bags. [redacted] (standard of care) used in CP319 is already CE marked and is labelled accordingly.

4.3. Intended use of the device in the clinical investigation

The product is intended to support the rim of the ostomy base plate/adhesive by providing additional adhesion to the intact peristomal skin.

4.4. Intended population for the device

Brava Tape Innovation is indicated for people who use an ostomy bag and base plate/adhesive. The product is indicated for both male and female adults.

4.5. Handling of the investigational device

The handling of the test products is described in details in the Instruction for Use (IFU), which is included in all bags with test products. It is stated in the IFU that the test products are for single-use and must be stored horizontally under dry and not freezing conditions and should be kept away from direct sunlight.

4.6. Description of the comparator product(s)

The comparator product is [redacted] which is already on the market and will be used within the intended use in this clinical investigation. Therefore, it is not considered an investigational device according to ISO 14155:2011 and is thus not described here. Please refer to the ISO 14155:2011 for details.

5. Design of the clinical investigation

5.1. General

This investigation is a randomised, open-label, comparative, cross-over study, with three test periods.

In total, 12 subjects will be included and randomised, and each subject will have an inclusion visit and four test visits overseen by the Principal Investigator, or delegate. Each subject will be enrolled for three times 7-9 days in total for the entire investigation, thus for a maximum of 27 days – equal to at least 3 baseplates + tape change in each period. The subjects will test two new recipes of ostomy tapes and a comparator product in randomised order.

Between the test visits, the subjects will change products at home. At each product change, subjects will take a photo of the peristomal skin using a smartphone with a specially designed Clinical Trial app installed. Furthermore, they will answer questions about feeling of security, adhesion of tape, comfort and potential skin issues.

5.2. Primary endpoint

- Mean adherent area measured by photo of used tape (area (cm^2) per baseplate change)

5.3. Secondary endpoints

- Erythema measured after each treatment period by spectrophotometric method
- Erythema measured after tape removal by photos
- Feeling of security:
  - How was the feeling of security while wearing the tape?
    (5-point scale from Very poor to Very good)
  - Did you feel confident that the tape would keep your base plate securely in place?
    (5-point scale from Very little to Very much)

- Adhesion of tape:
  - How was the immediate adhesion to the skin?
    (5-point scale from Very poor to Very good)
  - Did the edge of the tape lift/roll during use?
    (5-point scale from Very poor to Very good)

- Comfort:
  - How comfortable was the tape to wear?
    (5-point scale from Very discomfortable to Very comfortable)
  - Did the tape allow you freedom of movement?
    (5-point scale from Very little to Very much)

- Skin issues in the area covered by the tape:
  - Do you experience any **bleeding from the skin** under the tape **right now** when changing your product? (Experiencing/Not experiencing)
  - Once you have cleaned and dried the skin, do you experience any **weeping or moisture on the skin** under the tape right now when changing your product? (Experiencing/Not experiencing)
  - Are you experiencing any **ulcers or sores** under the tape **right now** when changing your product? (Experiencing/Not experiencing)
  - Did you experience complications where the tape was applied (like pain, stinging, itching, heat swelling or shiny skin)? (Yes/No)

- Please rate how painful the skin under the tape has been at its worst, since you last changed your product. (10-point scale from no pain (1) to worst pain possible (10))
- Please rate how itchy the skin under the tape has been at its worst, since you last changed your product. (10-point scale from no itch to worst itch possible)

- Adverse events

User experience with feeling of security, adhesion of tape, comfort and skin issues in the area covered by tape, will be assessed by prior mentioned questionnaires which will be assessed by interviews at Coloplast visit and self-reported by user at home.

5.4. Rationale for selection and measurement of endpoints

The endpoints are parameters describing the adherence of the ostomy tape to the skin and the potential effect on the skin. These are essential to investigate to understand, if the newly developed ostomy tapes have the ability to adhere to the skin without affecting it.

Adherent area: The adherent area after use shows how effectively the ostomy tape adheres to the skin. After removal of the ostomy tape, a photo of the tape is taken. The adherent area is measured from the photo and an image analysing program.

Erythema: A change in the surface skin colour is known to be related to a change in the blood flow. This can be measured non-invasively with a spectrophotometric instrument (Derma-spectrophotometer, Cortex Technology A/S, Hadsund) where both the redness and the colour of the skin are measured. Furthermore, visual assessments of photos have been used in several exploratory clinical investigations by Coloplast A/S to explore how adhesives affect the skin. The visual assessment is conducted by trained personnel and is a valuable tool for assessing newly developed adhesives and their impact on skin in the early development phases.

Feeling of security, adhesion of tape, comfort and skin issues: User experience is a very important part of product development in Coloplast A/S, and questions related to feeling of security, adhesion of tape and comfort relate to the user experience of how the ostomy tape adhere to skin while questions regarding skin issues relate to how the ostomy tape affects the skin.

Adverse Events: All Adverse Events are captured and documented throughout the study.

5.5. Demography and potential compromising factors

The following baseline information will be collected at V0:
- Gender
- Age
- Height/weight
- Reason for stoma
- Type of stoma
- Years with stoma
- Use of ostomy tape (Y/N)
- Use of other accessories (ring and paste)
- Usually stoma product used

To avoid treatments that may affect the skin, subjects may not be given chemotherapy or radiation treatment for two months prior to or while participating in the investigation. Subjects may not receive or have within the past month received systemic steroid or local treatment in the peristomal area and other areas of the skin tested.

The subjects can use ring or paste as they normal do during the study. But they are not allowed to use barrier creams or similar that affect the skin/adhesive interface under the tapes. Furthermore, the subjects may not use concave baseplate because the ostomy tapes are not designed for these baseplates.

5.6. Randomisation Procedure

All subjects that meet the inclusion and exclusion criteria will be randomised to one of six treatment arms. Each arm examines the comparator product and the 2 test products. The six possible arms are:

- Arm 1: Test product A, Test product B, and then comparator
- Arm 2: Test product B, Test product A, and then comparator
- Arm 3: Comparator, Test product A and then Test product B
- Arm 4: Comparator, Test product B and then Test product A
- Arm 5: Test product B, Comparator and then Test product A
- Arm 6: Test product B, Test product A and then Comparator

The randomisations list will consist of blocks of 6 and is centralised.

5.7. Blinding

No blinding will be used in this investigation, as it is not possible to blind the products due to visible differences, except for the statistician who will be blinded until DBL.

5.8. 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 (03/2020).
- Last subject enrolled (05/2020).
- Last subject completed (06/2020).
- Final report (10/2020).

6. Clinical Investigation population

The clinical investigation will be conducted in 12 subjects enrolled in a clinical facility at Coloplast A/S, [redacted]

6.1. Eligibility criteria

Subjects interested in participating the clinical investigation must comply with the following criteria:

6.1.1. Inclusion and exclusion criteria

Below, in Table 1 and Table 2 inclusion and exclusion criteria are presented.

Table 1: Inclusion criteria

Inclusion criteria	To be included in the investigation a subject must comply with the following inclusion criteria:	Justification for inclusion criteria
1.	**Has given written informed consent**	To ensure that the subject has been given written and oral information regarding the investigation, and know enough about the investigation to decide participation
2.	**Be at least 18 years of age and have full legal capacity**	To meet the Helsinki declaration
3.	**Have had a stoma for more than ½ year**	To ensure subjects are recovered from ostomy surgery
4.	**Have intact skin on the area used in the study (Assessed by investigator, see Appendix 1).**	The skin has to be intact in order to explore the peristomal skin after use of ostomy tape
5.	**Willing to change baseplate every second day or less frequent**	To ensure at least two days wear time and baseplates cannot be changed without changing the tapes

Inclusion criteria	To be included in the investigation a subject must comply with the following inclusion criteria:	Justification for inclusion criteria
6.	**Willing to avoid using Concave baseplate during the study.**	The ostomy tape is not designed for this type of baseplate
7.	**Willing to avoid the use of barrier creams or similar that affect the skin/adhesive interface under the tape.**	Barrier creams may interfere with the study end-points by interfering with the performance of the ostomy tapes.

Table 2: Exclusion criteria

Exclusion criteria	A subject is not allowed to participate in case he/she:	Justification for exclusion criteria:
1.	**Currently receiving or have within the past 2 months received radio-and/or chemotherapy**	The skin undergoes major changes because of radio-and/or chemotherapy, and therefore, the skin might be more fragile to product changes.
2.	**Currently receiving or have within the past month received topical steroid treatment in the peristomal skin area or systemic steroid (tablet(injection) treatment**	Steroid product on peristomal skin may interfere with the study endpoints by making the peristomal skin thinner and more fragile.
3.	**Is pregnant or breastfeeding**	Even though the ingredients and the recipes have been approved for humans, their effect on embryos, foetuses, and infants are unknown.
4.	**Having dermatological problems in the peristomal area (assessed by investigator)**	The skin has to be intact in order to see a potential damage of the skin.

6.1.2. Pregnancy and breastfeeding

For female subjects with childbearing potential (they have had at least one period during the last 12 months), a urine pregnancy test will be performed at the inclusion visit, to ensure the subject is not pregnant. The urine pregnancy test will be performed by dipstick at the trial site. Furthermore, the female subjects should not be breastfeeding, when participating in the clinical investigation.

6.2. Recruitment and enrolment

Recruitment of potential subjects will begin once approval have been obtained from the Ethics Committee of the Capital Region Denmark and the Danish Medicines Agency.

The recruitment time is estimate to approximately 1 month.

Recruitment method	Coloplast Database
Potential subjects	Recruitment will go through Coloplast own subject database (stoma care users) in Denmark. Potential subjects are identified by the following searching criteria in the Coloplast database: • Has an ileostomy, colostomy or urostomy • Currently not using [redacted] product Be at least 18 years of age
First contact	The identified potential subjects will as first contact be sent an Invitation and Reply Letter by mail or email. If a potential subject does not return the reply letter or answer the email, they may be contacted by phone, mail or email to make sure that they have received the approach.

Second contact	If potential subjects return the Reply Letter/reply to the email or have called the investigator as first contact and are interested, the Investigator or delegated site personnel will contact the subjects by phone and give a short introduction to the investigation and go over the inclusion and exclusion criteria. If the subjects do not meet the inclusion criteria or meet the exclusion criteria, this will be registered in the Subject Screening Log.
Subject Information Form	If subjects are eligible and interested in participating, then written information about the investigation (subject information) will be sent to the subjects to ensure that they are given the opportunity to read about the investigation before a possible informational visit, and so that they can prepare any possible questions they may have. Information visit V0 will be booked at this point and the subjects are instructed to contact the investigator or delegated study personnel if they, after having read the subject information, no longer are interested in participation in the study.
First visit Information visit	If an eligible subject is interested in participating, baseline visit (V0) will be arranged in a room ensuring quiet surroundings at Coloplast. When arranging the visit, it will be ensured, that the subject has received the Subject Information prior to the visit. The subjects will receive both written and verbal information about the possibility of bringing a companion to the informational visit and to any possible subsequent visits. See section 16. for information to be given to the subjects, as well as the informed consent process.
Enrolment and Baseline visit (V0)	The subjects have the right to wait 24h before deciding on participation. If/when the subject decides to participate he/she will be asked to sign the relevant forms (see section 16). If a subject so desires, and it is certain that it is understood what the investigation entails, and the relevant forms have been signed the subjects are considered enrolled in the investigation.

6.3. 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 Investigator may withdraw a subject from the investigation at any time if they judge it to be the subject's interest.

The investigator 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 investigator if problems arise that the subject believes are related to the clinical investigation. Subjects who have not experienced any adverse events will not be followed up. For subjects who experience adverse events, see section 17.

6.4. 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

6.5. 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 clinical site staff, 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, and members of the EC or regulatory authorities if requested.

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

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.

See section 7.3 Flow-charts for a more detailed overview of the clinical investigation-related procedures at visits.

7.2. Visits

Baseline visit (V0):
- Introduction to the study
- Informed Consent and letter of authority signed
- Check of in- and exclusion criteria
- Visual evaluation of skin for inclusion
- Pregnancy test - dipstick (for women of child-bearing potential only)
- Inclusion in study and allocation of subject number
- Collect baseline information
- Possibility to accept interview by User Insight/development engineers/project members

Test visit 1:
- Randomisation
- Instruct subject in use of smartphone and Clinical Trial app and remind the subject to bring it for every study visit
- Remove tape/product with use of adhesive remover
- Photo of peristomal skin (digital camera)
- Acclimatization of peristomal skin for ½ hour
- Photo of peristomal skin after acclimatization (digital camera)
- Measurements of erythema
- Provide randomized test products or comparator products for the subject for change at home and apply 2 ostomy tapes on the peristomal skin (after ostomy product has been applied).
- Provide storage material for used ostomy tapes and adhesive remover
- Instruct and remind the subject to follow the study specific procedures between visits
- Schedule next visit in 7-9 days

Test visit 2 and 3:
- Follow up on subjects use of smartphone and Clinical Trial app and remind the subject to bring it for every study visit
- Ostomy tapes are removed with use of adhesive remover (before removing, mark the lifted tape area with a pen on the adhesive part)
- Photo of peristomal skin (digital camera)
- Photo of skin (smartphone – Clinical Trial App)
- Smartphone: Questionnaire about feeling of security, adhesion of tape, comfort & skin issues in the area covered by the tape
- Acclimatization of peristomal skin for ½ hour
- Photo of peristomal skin after acclimatization (digital camera)
- Measurements of erythema

- Provide randomized test products or comparator products for the subject for change at home and apply 2 ostomy tapes on the peristomal skin (after ostomy product has been applied).
- Provide storage material for used ostomy tapes and adhesive remover
- Instruct and remind the subject to follow the study specific procedures between visits
- Schedule next visit in 7-9 days
- Collect all used tapes and measure the adherent area
- Review AEs/ADEs/SAEs/SADEs
- Possibility to accept interview by User Insight/development engineers/project members

Termination visit 4:

- Follow up on subjects use of smartphone and Clinical Trial app
- Ostomy tapes are removed with use of adhesive remover (before removing, mark the lifted tape area with a pen on the adhesive part)
- Photo of peristomal skin (digital camera)
- Photo of skin (smartphone – Clinical Trial App)
- Smartphone: Questionnaire about feeling of security, adhesion of tape, comfort & skin issues in the area covered by the tape
- Acclimatization of peristomal skin for ½ hour
- Photo of peristomal skin after acclimatization (digital camera)
- Measurements of erythema
- Application of stoma product which subject normally use
- Collect all used tapes and measure the adherent area
- Review AEs/ADEs/SAEs/SADEs
- Collect smartphone
- Possibility to accept interview by User Insight/development engineers/project members
- Fill in termination form

Product change and study specific procedures, to be followed at home:
Between visits the subject will change at home. At each product change, the subject should record experience at home by taking photo of the peristomal skin and answer questionnaires (with a Clinical Trial app on a handed-out smartphone).
At home:

a) Remove tape with use of adhesive remover (before removing mark the lifted tape area with a pen on the adhesive part).
b) Remove the tape from baseplate and save the tapes in the provided storage material for the next visit
c) Take photo of peristomal skin.
d) Answer questions (about feeling of security, adhesion of tape, comfort & skin issues in the area covered by the tape)

7.3. Flow-chart

Table 3 chart showing the connection between visits and assessments.

		BASELINE	TEST PERIOD	TEST PERIOD	TEST PERIOD	TERMINATION
	PERFORMED BY	V0	V1	V2	V3	V4
VISIT WINDOW (DAYS)	-	-	-	7 - 9	7 - 9	7 - 9
GENERAL						
Subject information	Investigator	X				
Signed informed consent	Subject / Investigator	X				
Signed letter of authority	Subject / Investigator	X				

Allocation of subject number	Investigator	X				
Check of in- and exclusion criteria	Investigator	X				
Visual evaluation of skin for inclusion	Investigator	X				
Pregnancy test, dipstick (If applicable)	Investigator	X				
Randomization	Investigator		X			
Insurance of subjects' wellbeing and compliance with CIP	Investigator	X	X	X	X	X
COLLECTION AND REGISTRATION OF BASELINE DATA						
Demographics: Gender, age, height and weight	Investigator	X				
Stoma: Type, reason and duration	Investigator	X				
Use of ostomy tape (Y/N)	Investigator	X				
Use of other accessories (Ring and paste)	Investigator	X				
Usually stoma product used	Investigator	X				
Optionally interviews	Development engineers/project members			X	X	X
PROCEDURES						
Instruct in and follow up on subjects use of smartphone and Clinical Trial app	Investigator		X	X	X	X
Remind the subject to bring the smartphone at every study visit	Investigator		X	X	X	X
Mark the lifted tape area with a pen on the adhesive part, before removing the ostomy tapes	Investigator			X	X	X
Remove tape/product with use of adhesive remover.	Investigator		X	X	X	X
Photo of peristomal skin (digital camera)	Investigator		X	X	X	X
Photo of peristomal skin (smartphone)	Subject			X	X	X
Acclimatize peristomal skin for ½ hour	Subject		X	X	X	X
Smartphone, Questionnaire: Feeling of security, adhesion of tape and comfort	Subject			X	X	X
Smartphone, Questionnaire: Skin issues in the area covered by the tape	Subject			X	X	X
Photo of peristomal skin, after ½ hour acclimatization (digital camera)	Investigator		X	X	X	X
Measure erythema	Investigator		X	X	X	X
Provide test products to the subject	Investigator		X	X	X	
Apply ostomy product and ostomy test tapes (Test tapes should be applied at the edges of the baseplate)	Subject		X	X	X	
Provide storage material for used ostomy tapes and adhesive remover	Investigator		X	X	X	
Instruct and remind the subject to follow the study specific procedures between visits	Investigator		X	X	X	X

Schedule next visit	Investigator	X	X	X	X	
Collect all used tapes and measure the adherent area by photography	Investigator			X	X	X
Registration of AEs/ADEs/SAEs/SADEs	Investigator		X	X	X	X
Complete eCRF	Investigator	X	X	X	X	X
REGISTRATION OF TERMINATION						
Termination form	Investigator					X

7.4. Case Report Forms

All assessments and observations throughout the investigation for each subject must be carefully recorded in an electronic CRF (eCRF), or an application (Clinical Trial App) in a provided phone for each subject. Details about data capture can be found in section 11.

CRFs will be filled in by the investigator and/or delegated site personal, who have signed the Site Personnel Signature and Delegation List and Clinical Investigation Training Log. If eCRFs are used delegated site personal will be required to complete e-learning prior to system access. Delegated personal will receive credentials.

7.5. Concomitant treatment

Subjects may not be given chemotherapy or radiation treatment for two months prior to or while participating in the investigation.

Subjects may not receive or have within the past month received systemic steroid or local treatment in the peristomal area and other areas of the skin tested.

The subjects can use ring or paste as they normal do during the study. But they are not allowed to use barrier creams or similar that affect the skin/adhesive interface under the tapes.

The subject may not use concave baseplate.

7.6. Supplementary materials and equipment

The Sponsor will provide the Principal Investigator, or delegate with supplementary materials for this investigation. Supplementary materials would be:

- Computer with access to eCRFs
- Smartphones with Clinical Trial app.

8. Risk – benefit analysis and ethical considerations

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

The intended purpose of the test products is to support the rim of the ostomy base plate by providing additional adhesion to the intact peristomal skin. It is known from previous Coloplast market research that up to 40% of people with stomas worry about leakage. This potentially influences their health-related quality of life negatively. The use of ostomy tapes may reduce the worry for leakage episodes. This study will investigate newly developed ostomy tapes and their ability to adhere to the skin without affecting it. Potential benefits are that subjects can worry less for leakage episodes without affecting their skin.

No risks are expected to the subjects other than the adverse events mentioned in section 17, all of which are well known in connection with the use of ostomy tapes. The risk assessment of the test products is carried out in accordance with the requirements of ISO 14971. There is no known interaction between the use of ostomy tapes and the medication subjects can take – except from what is stated in the exclusion criteria. Disadvantages of testing may be the time spent on visits and responding questions regarding product change.

Risks have been proven minimized or eliminated through appropriate design control, confirmed by pre-clinical bench, laboratory and biological safety evaluations. Therefore, the risks are considered to be equal to the use of ostomy tapes already on the market. Risks associated with the use of ostomy tapes are skin irritation and mechanical trauma.

To mitigate and reduce the risks, the subjects will be trained, according to the IFU, in application of product (e.g. correct position), removal of product and storage of the product.

The outcome of this investigation will contribute with important information for development of products for subjects with a stoma.

Disadvantages during the investigation could be the extra workload related to completion of questionnaires, or visits at Coloplast A/S and using the clinical trial app at each change of product.

9. Monitoring Plan

The sponsor is responsible for ensuring appropriate monitoring of the clinical investigation activities.

The monitor 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.

9.1.1. Initiation visit

The clinical investigation site will get an on-site initiation visit during which full training on all aspects of the clinical investigation will be provided.

9.1.2. Monitoring visit(s)

The site dedicated monitor is to ensure adherence to the clinical investigation plan, accurate data recording on the eCRFs 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 eCRFs 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 delegation log as well as training received before getting involved with the clinical investigation must be documented in the 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.

9.2. 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. Statistical design, method and analytical procedures

Definition of analysis populations

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

The ITT population (full analysis set) will be constituted by all included subjects who:

- Have provided valid informed consent
- Have measurements for at least one of the endpoints or assessments

The Safety population will constitute by subjects who have given informed consent.

All statistical analysis and summaries will be based upon the ITT population whereas adverse events and Device deficiencies will be assessed based on the safety population. Invalid individual data points may be omitted from analysis even though the corresponding subject is part of the ITT population. Any exclusion of data points will be documented.

A formal PP population is not planned due to the explorative nature of the investigation.

Analysis of endpoints, individual questions and baseline data

All endpoints and individual questions as well as baseline/demographic data will be listed and summarized by descriptive statistics. The summaries for the endpoints and individual questions will be made for each product separately.

To explore potential indications of differences in adherent area the following analysis will be performed, if relevant. Adherent area can be analysed by a mixed repeated measures model using mean of the two adherent areas for each individual baseplate change as the observational unit. The model will consider that observations corresponding to different subjects are independent; whereas observations corresponding to the same subject are correlated. The correlation between observations corresponding to the same product can be larger than observations corresponding to different products. Hence the model includes a fixed effect of product (comparator product, test product A, test product B), a fixed period effect (period 1, 2, 3), a random effect of subject and a random interaction effect of product and subject. The model might be reduced by removing non-significant fixed effects, if relevant. All combinations of differences between the three products will be estimated.

Erythema measured by end of each period can be analysed by a linear mixed model like the model for the adherent area, as there is 3 measurements per subject for each product.

As it is an exploratory study no adjustment for multiple testing will be applied.

Other summaries and analyses can be made, if relevant.

All statistical analyses and summaries are made with SAS version 9.4 (SAS Institute Inc., Cary, NC).

10.2. Sample size

Due to the conceptual nature of this trial (pilot evaluation of ostomy tapes under development) no formal sample size calculation has been performed. The evaluation will be supported by data from laboratory models. Twelve subjects are expected to provide enough information for further adjustment of the recipe.

10.3. Level of significance and power

If a statistical analysis is performed a two-sided significance level of 5% will be applied. As this is an exploratory study no power has been applied.

10.4. Pass/fail criteria

Because the investigation is explorative, pass/fail criteria has not been applied. A positive as well as a negative outcome will provide knowledge that is useful in the further decision-making/development of the product.

10.5. Interim analysis

There is no planned interim analysis for this investigation.

10.6. Statistical reason for termination of investigation

There will be no interim analysis and therefore no reason to terminate the investigation based on statistical considerations.

10.7. Deviation(s) from statistical design, method or analytical procedures

Any deviations from the statistical plan will be documented in the clinical investigation report.

11. Data management

11.1. Data Collection in the clinical investigation

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 plan.

The EDC system used is Rave EDC, version 2018.2.2, delivered by Medidata Solutions Inc. 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 sponsor will be responsible for training the investigator, or delegate, in completion of the eCRF.

Principal Investigator, or delegate, at the clinical site will perform primary data collection directly into the eCRF or drawn from source-document 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 subject will receive an iPhone with the Clinical Trial App installed. The app is developed on behalf of Coloplast A/S by the app development company Nodes. This Clinical Trial App is used during the investigation every time the subject makes a product change.

The photos and the data completed in the Clinical Trial App are transferred via an encrypted connection to a Coloplast controlled Azure environment. Photos will be stored and can be assessed at Azure. All other data will be transferred automatically into the EDC system.

In the unforeseen situation, where site cannot establish connection to the EDC system a paper CRF (pCRF) can be printed and supplied by sponsor. It will be the responsibility of investigator that all measurements and observations on the site are correctly noted with a pen (permanent writing utensil) in the pCRF. Any corrections in the pCRF must be clearly signed and dated by authorised site personnel.

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.

11.2. Database Management, Queries and Quality Control

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 training is web-based and must be completed before access to the investigation is granted. Training will be documented in the data management system. Only the principal investigator, or delegate, will be authorised 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 plan.

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. Automated alerts (emails) are generated by the system to ensure full control and easier compliance to the clinical investigation plan.

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

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

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

Data management and the final statistical analyses of all measurements described in this protocol are carried out by the Medical Affairs, Coloplast A/S.

11.3. Data retention

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

All investigation site documents will 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 effected without mutual agreement of the principal investigator 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 the competent authority (when appropriate). Substantial changes may require approval from the EC and the competent authority prior to implementation (example of significant change: Changes of inclusion criteria, endpoints or assessment methods).

13. Deviations from the Clinical Investigation Plan

A deviation from the clinical investigation plan is defined as an event where the clinical investigator or site personnel did not conduct the study according to the clinical investigation plan, ISO 14155:2011 and any national or local regulatory requirements.

For reporting purposes, the sponsor classifies study deviations as major and minor:

Major deviation: Any deviation that may either have an impact on the rights, safety and well-being of the subjects or the scientific outcome of the clinical investigation.

Minor deviation: Any deviation that has no impact on the rights, safety and well-being of the subject or that may impair the scientific outcome of the clinical investigation.

Deviations, along with explanations of why these occurred, are recorded by the principal investigator in the appropriate section of the e-CRF and reviewed with the sponsor's designated monitor for the need for reporting to the EC/IRB, and any corrective and/or preventative actions to be taken.

Major deviations are to be reported immediately by the principal investigator to the overseeing EC and where required by national regulations to the competent authority by the sponsor.

Repeated deviations after discussion with the sponsor's designated monitor and after implementation of corrective and preventative actions by the site personnel may lead to a decision from the sponsor to suspend temporarily the clinical investigation in a given site until full corrective actions have been put in place. Failure to do so may lead to termination of the clinical investigation in this site.

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 principal investigator or an authorized designee keeps records documenting the receipt, use and return and disposal of the investigational devices, which includes:

- Date of receipt.
- Identification of each investigational device (batch no./serial no./unique code).
- The date(s) of use.
- Subject identification.
- Date of returned investigational device

15. Statement of compliance

The clinical investigation is conducted in accordance to:

- Ethical principles that have their origin in the Declaration of Helsinki, 1964, Last amended at the 59th WMA General Assembly, Brazil, October 2013.
- MDD 93/42/EEC as amended by Directive 2007/47/EC (commonly known as the Medical Device Directive).
- MDR 2017/45
- ISO 14155:2011 “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] 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 comply with the EU General Data Protection Regulation (GDPR) and the Danish act on data protection (“databeskyttelsesloven”), including in connection with transfer of data to third countries, cf. chapter V of GDPR, Coloplast will only process the subjects personal data:

1. To conduct the investigation and carry out related research based on subject consent (primary use), cf. articles 6(1)(a) and 9(2)(a) of 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. articles 6(1)(a) and 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 dataprotectionoffice@coloplast.com. 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 privacyrequests@coloplast.com 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

The investigation is initiated and sponsored by Coloplast A/S and Coloplast A/S will compensate the investigator for the time and resources spent on this investigation. The expenses include salary to the investigator and study staff, cost of products, transportations and gift certificates.

The investigation expenses are expected to be approximately [redacted] per subject.

Subjects will be compensated for their participation in the study and receives a gift voucher equivalent in value to [redacted] per visit 1, 2, 3 and 4, in total [redacted] if the subject completes the investigation. The subjects will also be compensated for any transport expenses. Reimbursement of transport expenses are not taxable whereas payment for participation in the study is taxable per local legislations. Subjects will be paid for their participation after each visit and transport expenses will be paid in appropriate portions that justify the administration, throughout investigation period.

All financial agreements with the investigator will be specified in a sponsor investigator Agreement. The Investigator has no financial conflict of interest in the investigation.

16. Informed consent process

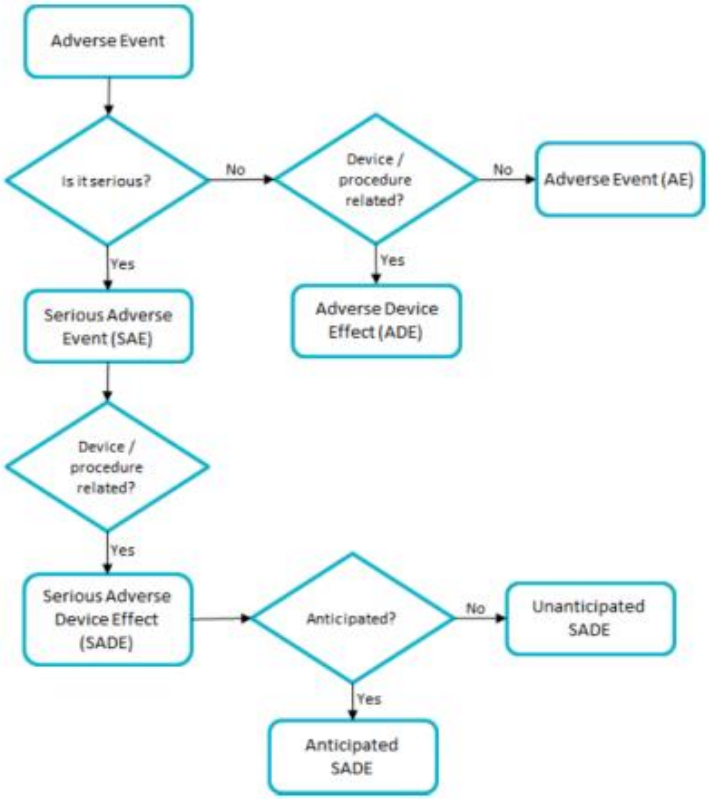
Written informed consent is obtained from all subjects participating in the investigation after thorough written and verbal information. The information is given by the investigator or his/her representative in the subjects' native non-technical language. Each subject will be fully informed about the aim of the investigation, procedures, potential risks or inconveniences and/or expected benefits and 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. Furthermore, the subjects will be informed that the investigator, sponsor, sponsor representatives and regulatory authorities can get access to relevant information from patient journals necessary to conduct the investigation and to audit the investigation.

The informed consent signature form includes personally dated signatures of the subject and the investigator 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 investigator, 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 investigator that will further provide it to the subjects. If applicable, all affected subjects shall be asked to confirm their continuing informed consent in writing.

This procedure also applies to informed consent obtained from a subject's legal representative. The procedure cannot waive the subjects' legal rights.

17. Adverse events, adverse device effects and device deficiencies



17.1. Adverse events

An adverse event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other parties, whether or not related to the medical device(s), or the procedures involved. This could include events such as headache or dizziness.

17.2. 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 related or possibly related 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 are well known in connection with the use of new adhesives. Allergic peristomal skin irritation occurs very rare, but information about possible allergic reactions will be collected.

Temporary redness upon removal of the ostomy tape plate is not considered to be an adverse device effect. However, an abnormal development in the intensity or duration of redness should be considered an adverse device effect.

Table 5 lists anticipated adverse device effects that may occur.

Table 4 Anticipated adverse device effects and their likely incidence rates

ANTICIPATED ADE	INCIDENCE RATE
Peristomal skin irritation (incl. mechanical trauma and skin maceration)	< 10%

Allergic peristomal skin irritation (dermatitis)	< 1%

17.3. 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.

17.4. 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 fatal distress, fatal death or a congenital abnormality or birth defect.

This includes device deficiencies that might have led to a serious adverse event if:

- Suitable action had not been taken, or
- Intervention had not been made, or
- 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.

17.4.1. 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.

17.4.2. 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.

17.4.3. 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.

17.5. 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 serious adverse events will be followed until a resolution is addressed.

The current status of all ongoing adverse events is documented during site close-out.

17.6. Reporting and timelines

17.6.1. Investigator's reporting responsibilities

- PI 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 sponsor within 10 days 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 were 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.

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

Please report to:

clinical-studies@coloplast.com

17.6.2. 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 the national regulatory authorities and Ethic Committee, as applicable.

18. 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.

If suspension or termination of the clinical investigation occurs, the investigator(s) will promptly inform the enrolled subjects. Sponsor will provide resources to fulfil the obligations from the CIP for follow-up of the subjects as necessary.

19. 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 coordinating investigator must sign the final version of the clinical investigation report or an affidavit, indicating their agreement with the contents. If no coordinating investigator is appointed, then the signatures of the principal investigator(s) should be obtained.

The clinical investigation report must be submitted to EC and regulatory authorities.

20. Publication policy

20.1. General

In connection with the publication policy Coloplast is referring to the internal document 'Clinical Publication Policy' that will be available for internal and external persons involved in the publication process.

The investigation will be registered on a public accessible database before recruitment of the first subject. The results of the investigation, positive as well as inconclusive and negative will be published in the same public accessible database. The subjects' identity will remain confidential. Publication of results in the database will be conducted per the law of personal data protection and will be initiated as soon as scientifically acceptable, however, within one year after the last subject has completed the investigation. Data from the investigation is considered confidential until it is published per the conditions of this protocol and the 'Clinical Publication Policy'. Sponsor may publish anonymous single subject case stories (or public, if the subject consents) at any time during and after the investigation. The identification of the participant must not be possible. Sponsor reserves the right to use the data (published and unpublished) for reimbursement or regulatory purposes.

The results may be submitted to a scientific journal.

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.

22. Bibliography

[1] Porret T et al. DialogueStudy: An international real-life study of stoma care nursing using a new ostomy appliance. Gastrointestinal Nursing. 2011 Mar 9(2) (Supplement): 1-24.

[2] Nybaek H, Knudsen DB, Laursen TN, Karlsmark T, and Jemec GB. Quality of life assessment among patients with peristomal skin disease. Eur J Gastroenterol Hepatol. 2010 Feb; 22(2): 139-43

23. Appendix 1

Intact skin/mucosa and Injured skin/mucosa
Definitions by Coloplast

Scope:

This document includes Coloplast definitions of skin and mucous membrane conditions relevant to the interpretation of Medical Device Regulation (EU) 2017/745 [1].

1. Skin

a. Intact skin
b. Injured skin

2. Mucous membrane

3. Intact mucous membrane
4. Injured mucous membrane

These definitions shall be considered in product development, product classification, product intended use in instructions for use (IFU) and in promotional material.

Regulatory background

The terms “injured skin”, “injured mucous membrane”, and “intact skin” appear currently in the Medical Device Regulation of 5th April 2017 as follows [1]:

A. in Annex VIII “Classification Rules”, Chapter I, 2.8:

“Injured skin or mucous membrane” means an area of skin or a mucous membrane presenting a pathological change or change following disease or a wound.

B. Annex VIII, Chapter III, 4.4 (rule 4):

All non-invasive devices which come into contact with injured skin or mucous membrane are classified as:

- *class I if they are intended to be used as a mechanical barrier, for compression or for absorption of exudates*
- *class IIb if they are intended to be used principally for injuries to skin which have breached the dermis or mucous membrane and can only heal by secondary intent*
- *class IIa if they are principally intended to manage the micro-environment of injured skin or mucous membrane; and*
- *class IIa in all other cases*

C. in Annex VIII “Classification Rules”, Chapter III, 7.5 (rule 18) [14]:

“All devices manufactured utilizing tissues or cells of human or animal origin, or their derivatives, which are non-viable or rendered non-viable, are classified as class III, unless such devices are manufactured utilizing tissue or cells of animal origin, or their derivatives, which are non-viable or rendered non-viable and are devices intended to come into contact with intact skin only”

Coloplast Definitions:

1. Skin

1.a. Intact skin

Intact skin is skin where the basement membrane is unbroken (anatomically based definition). The basement membrane consists of the stratum basale (basal epithelial layer), the basal lamina and the reticular lamina. [2]

The epithelial cells can replicate from the stratum basale and normal anatomical structure and function can quickly be restored [3].

If the basement membrane is broken the vascularized dermis is exposed and the skin is no longer considered intact.

For products intended for pediatric use, please refer additionally to relevant document(s).

1.b. Injured skin

Injured skin is skin presenting pathological changes or changes following disease or trauma.

Injured skin can be distinguished in two levels, depending on the depth of the above-mentioned changes:

1) Intact injured skin (superficially injured skin): skin which presents with superficial pathological changes or changes following disease or trauma but where the basement membrane is unbroken. Skin changes of this kind are expected to heal with no permanent damage or scarring to the skin [3]
2) Non-intact injured skin: skin which present with pathological changes or changes following disease or trauma and where the basement membrane is breached. Healing is by secondary intend (if left to heal on its own) and scarring is expected [3].

2. Mucous Membrane

2.a. Intact mucous membrane

Intact mucous membrane is mucous membrane (mucosa) whose basement membrane is intact. Mucous membrane consists of epithelium, lamina propria, muscularis mucosae and sub mucosa. [2] The basement membrane is the basal part of the non-vascularized epithelium, separating it from the underlying vascularized tissues.

If the basement membrane is broken the blood vessels in the underlying tissue are exposed and the mucus membrane is no longer considered intact.

2.b. Injured mucous membrane

Injured mucous membrane is mucous membrane presenting pathological changes or changes following disease or trauma.

Injured mucous membrane can be distinguished in two levels, depending on the depth of the above-mentioned changes:

1) Intact injured mucous membrane (superficially injured mucous membrane): mucous membrane which presents with superficial pathological changes or changes following disease or trauma but where the basement membrane is unbroken. Mucous membrane changes of this kind are expected to heal with no permanent damage or scarring to the mucosa [4].
2) Non-intact injured mucous membrane: mucous membrane which presents with pathological changes or changes following disease or trauma and where the basement membrane is breached.

References

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2. Gray's Anatomy, 40th Edition. The Anatomical Basis of Clinical Practice. Susan Standring. Ed. Churchill Livingstone, 25th September 2008
3. Madeleine Flanagan: Wound Healing and Skin Integrity, 2013, page 34, re to Enoch and Leaper 2005
4. Larsson P, Chamorro CI, Fossum M (2016) A Review on Bladder Wound Healing after Mechanical Injury. J Tissue Sci Eng 7:170. doi:10.4172/2157-7552.1000170

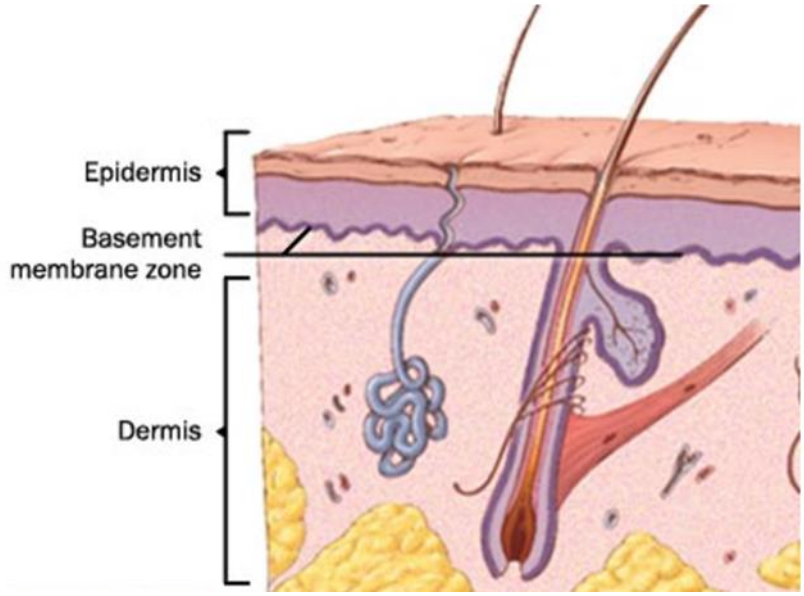

Figure 1: Skin [from: http://www.mayoclinic.org/diseases-conditions/epidermolysis-bullosa/multimedia/basement-membrane-zone/img-20005890]

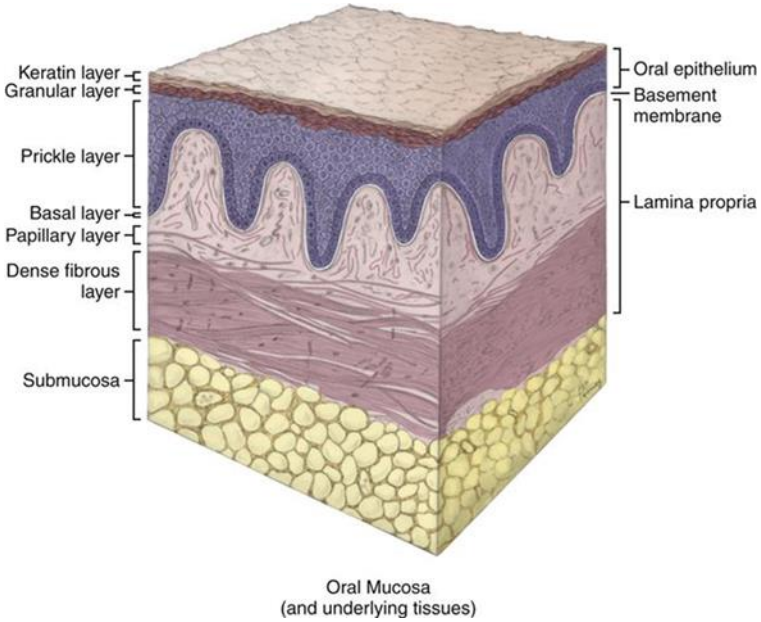

Figure 2: Example of a mucous membrane: oral mucosa [from: https://pocketdentistry.com/9-oral-mucosa/]