CLOVER SKIN ADHESIVES 3833

Ambu Study ID: CIS-015

Version: 4.0

Date: 27th of September 2019

English title:

A Single Centre Comparison Study on Adhesion Properties of Three (3) Skin Adhesives on Healthy, Female, Adult Volunteers

Danish title:

Et single center komparativt studie om klæber egenskaber for tre (3) hudklæbere på raske voksne kvindelige frivillige

Ambu Study ID: CIS-015

To be initiated: Fall 2019

Expected final report: Winter 2019

Revision history

Version No.	Release Date	Description of Change	Initiator
1	12-JUN-2019	First version	ACLU
2	15-AUG-2019	Two adhesives are excluded due to processing difficulties of the adhesives	SYGN
3	26-AUG-2019	Update according to EC comments	ACLU
4	27-SEP-2019	Reviewed according to EC requests	ACLU

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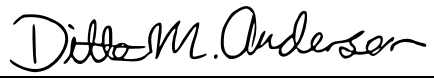

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30. September 2019

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Contents

1. CLINICAL INVESTIGATION SYNOPSIS

Clinical Investigation Title	A Single case control Study on Adhesion Properties of Three (3) Skin Adhesives on Adult and Healthy Female Volunteers.
Investigational Product	Clover Skin Adhesives 3833
Clinical Investigation Duration	4 months
Clinical Investigation Design	Single Centre, Comparative, randomized study within subjects
Study objective	The aim of the study is to compare three silicone adhesives' adhesion ability (on adult female skin over 72 hours) and skin reaction (itch, grated skin reactions and pain) in order to identify the most suitable adhesive for clinical use.
Hypothesis	All adhesives adhere equally on female adult skin over 72 hours.
Planned number of subjects	39 subjects
Clinical Investigation Population	Adult and Healthy Female Volunteers
Inclusion criteria	i. Female Healthy Volunteers. ii. Age 18 - 40 years old. iii. Willing to attend two scheduled visits iv. The investigational area of the skin is intact v. Able to assess itch and adherence at 24h, 48h and 72h. vi. Provide written informed consent.
Exclusion criteria	i. Non-intact skin barrier (e.g. eczema, rash, cut, scar tissue, wound, etc.). ii. History of inflammatory skin diseases (e.g. atopic dermatitis or psoriasis). iii. History of contact allergy iv. Swimming or engaging in sport activities causing sweat during study period. v. Use of medication (e.g. corticosteroids) which could affect skin reactions.
Follow-up duration	Not applicable
Criteria for Withdrawal	i. Subjects have the right to withdraw from the study at any time for any reason. ii. The investigator may withdraw subjects from the study in the event of intercurrent illness, AEs, lack of compliance with study and study procedure or any other reasons where the investigator feels it is in the best interest of subject. Reasons for withdrawal must be documented and explained to the subject.
Clinical Investigation Primary Endpoints	– 72-hours skin adhesion rating
Clinical Investigation Secondary Endpoints	– Rate of skin reaction after wearing the adhesive for 72 hours – Ease of removal after 72 hours. – Rate of the pain level when removing the adhesive from the subject's skin after 72 hours. – Rate of itch while wearing the adhesive at T24, T48 and T72. – Any adhesive residue left on skin after removal of the adhesive?
Sites	Denmark
Sponsor	Ambu A/S

2. ABBREVIATIONS

AE	Adverse effect
CV	Curriculum Vitae
CIP	Clinical Investigation Plan
CRF	Case Report Form
CIR	Clinical Investigation Report
DKKR	Danish Krone
EC	Ethics Committee
EU	European Union
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
ICF	Informed Consent Form
ISO	International Standard Organisation
PPE	Personal Protective Equipment
SAE	Serious Adverse Event
VAS	Visual Analogue Scale

3. INTRODUCTION

A medical adhesive or tape can be used to secure a device (i.e. tape, dressing, catheter, electrode, and ostomy pouch) to the skin. There are many types of adhesives such as acrylates, latex, hydrocolloids, polyurethane, and silicone-based adhesives. The backings of the adhesive can be made of paper, plastic, silk, cloth, elastic and foam which provide the stretch, conformability and rigidity of the adhesive (1).

Medical adhesives are made from different types of polymers and the most popular ones are nylon (polyamides), polyethylene, polypropylene, polyvinyl, polyacrylates, cellulose derivatives, chitosan, carrageenan and silicone polymers (2). They are composed of several layers including backing and adhesives which will determines the properties and performance of the adhesive product. The backing may consist of paper or a paper blend, plastic, silk (woven polyster), soft (nonwoven) cloths, traditional cloth or foam and/or elastic. Types of adhesives used in tapes and dressings are acrylates, silicones, hydrogels, hydrocolloids, and polyurethanes, as well as those that are natural-rubber latex based or contain zinc oxide (3).

Tissue trauma caused by the removal of adhesives can exacerbate pain, increase wound size and delay healing, thereby increasing health-care costs and reducing patients' quality of life (4). Skin injury occurs when the skin to tape adhesion is stronger than adhesive forces between the skin cells and skin layers so that they separate when the tape is peeled off (1).

Among the different types of adhesives, the silicone adhesive or gel is considered to be unique in their application. Silicone polymers possess unique properties, which make them suitable for many different applications, for example in the pharmaceutical and medical industry (2). Silicone have a lower surface tension and fill in gaps between adhesives and irregularities skin quickly and maintain the same level of adherence over time. Others adhesives, such as the acrylates, act more slowly, and adherence increases over time (5). Therefore, this study aims to investigate three different silicone adhesives ability to remain attached to the skin for minimum 3 days (72 hours) while minimizing tissue trauma and pain when the adhesive is removed from the skin. The CIP was made in accordance with the Helsinki Declaration (6) and good clinical practice (GCP) as outlined in ISO 14155 (7) to the extent possible considering that the products investigated in the study are not classified as medical devices.

4. IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL PRODUCT

4.1 Description

Adhesive Name	Physical Properties	Intended Use
3M™2475P Single Sided Thermoplastic Elastomer [TPE] Tape (8)	Tape Caliper: Single-coated Film Tape on Clear Polyester Liner. Backing: Translucent Thermoplastic Elastomer [TPE] Film. Adhesive: Medical Grade Gentle 3M Silicone Adhesive. Release Liner: Clear Polypropylene Film, one side Fluoropolymer Release.	Medical Tape
Scapa Soft-Pro® Silicone RX1449P (9)(10)	Carrier: Polyurethane Film Adhesive: Silicone Gel Liner: Polycarbonate Film	Pressure Sensitive Tape
P-DERM® PS-1243 (11)	Carrier: Polyurethane Adhesive: Silicone Gel Liner: 75 micron matte polycarbonate	Medical Tape

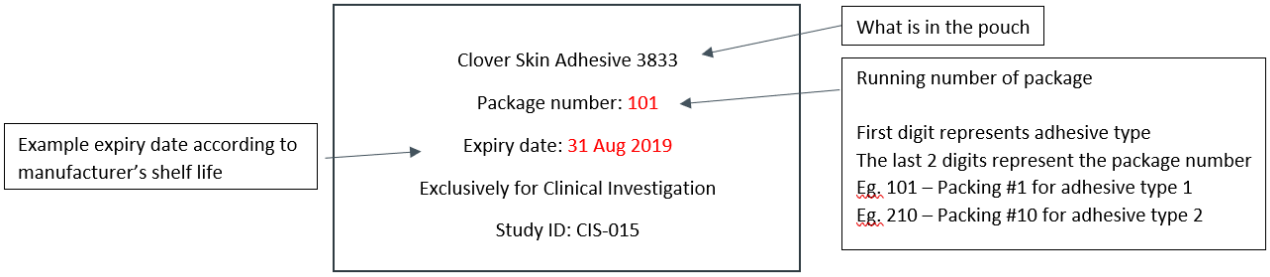
4.2 Manufacturer

Adhesive Name	Manufacturer
3M™2475P Single Sided Thermoplastic Elastomer [TPE] Tape (12)	3M (Medical Solutions Division) 3M Center, St. Paul, MN 55144-1000, USA.
Scapa Soft-Pro® Silicone RX1449P (9)	Scapa North America LLC, 111 Great Pond Drive, Windsor, CT 06095.
P-DERM® PS-1243 (13)	Polymer Science, Inc. 2577 South Freeman Road, Monticello, IN 47960.

4.3 Models/type of the investigational Product

Code	Adhesive Name
1	3M™2475P Single Sided Thermoplastic Elastomer [TPE] Tape Device traceability
2	Scapa Soft-Pro® Silicone RX1449P
3	P-DERM® PS-1243

Labelling of the Package:
The package will be labeled as diagram below:



Each package will have their own unique package number which the first digit represents the adhesive type and the last 2 digits represent the package number (running number).

4.4 Investigational product procedures

All three adhesives will be cut into clover shape and packed accordingly. There will be fifteen (15) clover shape adhesive in one (1) pack for each adhesive. The designated personnel have to place the adhesives on subject's skin according to study procedure.

5. JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

Ambu is using adhesives in several products and is interested in increasing the general knowledge on adhesion quality and skin tolerance. Due to its widespread use, this study focuses on silicone adhesives and aims to identify if one of the three silicone solutions tested guarantee prolonged adhesion and at the same time ensures skin tolerance.

The study population for this study is exclusively females to avoid chest hair on the investigational skin area, as this study only intend to investigate the adhesion to skin. In theory, males could be included if the hair was removed prior to placement of the adhesives. However, as hair removal could result in abrasion of the skin, it was decided not to include any male subjects. Subjects with inflammatory skin diseases such as psoriasis and atopic dermatitis will be excluded from this study as well, as this could affect the adhesion and as it could affect or complicate the assessment of skin reaction and pain.

In this study, the subject will be its own control, and each subject will wear two of each adhesive. This is done to reduce the number of subjects (14).The adhesive will be placed on the subject for 72 hours to assess adhesion quality and skin tolerance during prolonged wear.

All three adhesives have been tested for biocompatibility and toxicological and their results has been summarized in table below.

Code	Adhesive Name	Biocompatibility	Toxicological
1	3M™2475P Single Sided Thermoplastic Elastomer [TPE] Tape Device traceability	Test conducted: In vitro cytotoxicity, MEM elution, Primary skin irritation, Guinea pig sensitization. Results: All the test met the requirement and was not considered to be a sensitizer in the guinea pig maximization test (15).	No health effects are expected for inhalation, skin contact, eye contact and ingestion (12).
2	Scapa Soft-Pro® Silicone RX1449P	Test conducted: Cytotoxicity, irritation and sensitization. Results: All the test met the requirement (16).	Not applicable, considered to be a non-hazardous manufactured article (9).
3	P-DERM® PS-1243	Test conducted: Cytotoxicity, systemic toxicity, intracutaneous reactivity, implantation, skin sensitization and pyrogen. Results: All the test met the requirement (17).	No health effects are expected for inhalation, skin contact, eye contact and ingestion (13).

Based on the tests conducted on the three adhesives, it is proven that, the products are safe for human use.

6. RISK AND BENEFITS OF THE INVESTIGATIONAL PRODUCT AND CLINICAL INVESTIGATION

The use of adhesives can cause allergic reactions characterized by erythema, edema and itch. In addition, removal of the adhesives from the skin can cause discomfort. However, all the adhesives used in this study have been tested for biocompatibility and toxicology (as described in section 5 Justification for the design of the clinical investigation) and they all met the test requirements.

There are no clinical benefits for the subjects participating in the study as healthy volunteers are used and as the product cannot facilitate any treatment or diagnostic procedures. Therefore, the subjects will be compensated for the inconvenience with 800 DKKR for study participation including payment of expenses for transportation. If the subject signs the informed consent, but doesn't complete any of the study visits, no compensation will be made. If the subject completes the first study visit, but withdraws before the follow-up visit, a compensation of 400 DKKR will be paid.

7. OBJECTIVES AND HYPOTHESES

The aim of the study is to compare three silicone adhesives' adhesion ability (on adult female skin over 72 hours) and skin reaction (itch, graded skin reactions and pain) in order to identify the most suitable adhesive for clinical use.

H_0: All adhesives adhere equally on female adult skin over 72 hours.
H_A: All adhesives do not adhere equally on female adult skin over 72 hours.

7.1 Primary endpoint

- 72-hour skin adhesion rating
  - Did the adhesive stay attached to the skin for 72 hours (Yes/No)
  - Before removal of the adhesive, adhesion will be assessed on a scale from 0-4 (18).
    - 0 = ≥90% adhered (essentially no lift off the skin).
    - 1 = ≥75% to <90% adhered (only some edges lift off the skin).
    - 2 = ≥50% to <75% adhered (less than half lifts off the skin).
    - 3 = >0% to < 50% adhered (more than half lifts off the skin without falling off).
    - 4 = 0% adhered (detached and is completely off the skin).
  - If the adhesive scores 0 or 1, the adhesive is defined as staying attached for the 72 hours (yes).
  - If the adhesive scores 2, 3 or 4, the adhesive is defined as not staying attached for the 72 hours (no).

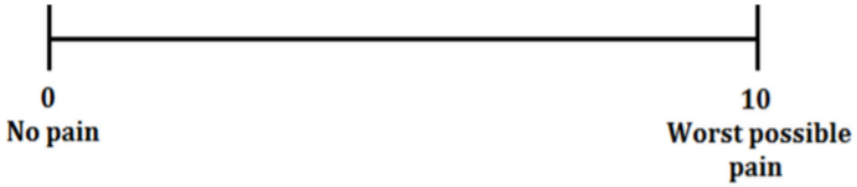
7.2 Secondary endpoints

7.2.1 Rate of itch while wearing the adhesive at T24, T48 and T72 (measured on a visual analogue scale, VAS) (19).

7.2.2 Ease of removal after 72 hours (5-point scale)

- 1: Very difficult
- 2: Difficult
- 3: Acceptable
- 4: Easy
- 5: Very easy

7.2.3 Rate of the pain level when removing the adhesive from the subject's skin after 72 hours (measured on a visual analogue scale, VAS)(20)



7.2.4 Rate of skin reaction after wearing the adhesive for 72 hours (21).

- After removal, the skin reaction is assessed on a scale from 0-7
  - 0: No evidence of irritation
  - 1: Minimal erythema that is barely perceptible
  - 2: Definite erythema that is readily visible and minimal edema or minimal papular response
  - 3: Erythema and papules
  - 4: Definite edema
  - 5: Erythema, edema and papules
  - 6: Vesicular eruption
  - 7: Strong reaction spreading beyond the application site.

7.2.5 Any adhesive residue left on skin after removal of the adhesive (Yes/No).

7.3 Claims and intended performance

The 3M™2475P Single Sided Thermoplastic Elastomer [TPE] Tape Device traceability and P-DERM® PS-1243 claims their intended use as medical tape, whereas Scapa Soft-Pro® Silicone RX1449P claims their intended use as pressure sensitive tape.

8. DESIGN OF THE CLINICAL INVESTIGATION

8.1 General

This clinical investigation is a single centre, double blinded, case control study in healthy adult females. This study will be conducted in private rooms at Gentofte Hospital (Hjertemedicinsk Forskning, post 835, Kildegårdsvej 28, 2900 Hellerup) and/or at Ambu A/S (Baltorpbakken 13, 2750 Ballerup), Denmark.

The investigation centre will enroll 39 subjects including a 20% drop out within a four (4) months period. The subject will not be enrolled before approval of investigation protocol by the local ethics committee. If the number of subjects cannot be included in time, the sponsor will decide whether the investigation period should be extended or if the investigation should be closed.

The subjects need to meet the inclusion and exclusion criteria to be included in this clinical investigation. Each volunteer enrolled in the investigation can only participate once in a procedure. The testing period for each subject will be minimum 72 hours.

The principal investigator's qualifications will be verified through his/her CV. The principal investigator is required to be a medical doctor with at least one year's experience in using similar medical adhesives (e.g. by being experienced in using electrodes where medical adhesives are included) and at least one year's experience with clinical research. In addition, the investigator must be trained in GCP before the study is initiated.

If any subject withdraws from the study, they will not be replaced as drop-out rate is included in the sample size.

eCRF must be completed for each subject that has signed the Informed consent form (ICF) and enrolled into this clinical investigation. Subjects are required to complete the home assessment as given.

8.2 Investigational Products and comparators

8.2.1 Product exposure

Each subject will be exposed to the three adhesives described in the table below for at least 72 hours. If the subjects experience unbearable itch or discomfort when wearing the adhesives, they are allowed to remove them. It must be recorded in the CRF if the adhesives are removed or fall off before the second investigational visit.

Code	Adhesive Name	Exposure
1	3M™2475P Single Sided Thermoplastic Elastomer [TPE] Tape Device traceability	This product is considered to be an article which does not release or otherwise result in exposure to a hazardous chemical under normal use conditions. No engineering controls or personal protective equipment (PPE) are necessary.
2	Scapa Soft-Pro® Silicone RX1449P	Standard room ventilation usually adequate for most operations. No engineering controls or personal protective equipment (PPE) are necessary.
3	P-DERM® PS-1243	This product is considered to be an article which does not release or otherwise result in exposure to a hazardous chemical under normal use

		conditions. No engineering controls or personal protective equipment (PPE) are necessary.

8.2.2 Choice of comparator

Not applicable.

8.2.3 Other investigational devices or medications

Not applicable.

8.2.4 Number of investigational products to be used

Each subject will use two of each adhesive. A total number 150 units of each adhesive is ordered for the study. This includes an additional 72 units of each adhesive in case any miscellaneous happen to the adhesives such as fall down during placement, tear while removing from liner etc. If the adhesives fall off after they have been placed correctly, they will not be replaced. However, it will be noted in the CRF when the adhesives fell off.

Code	Adhesive Name	Quantity
1	3M™2475P Single Sided Thermo-plastic Elastomer [TPE] Tape De-vice traceability	150
2	Scapa Soft-Pro® Silicone RX1449P	150
3	P-DERM® PS-1243	150
TOTAL		450

8.3 Subjects

In order to get a 90% power to detect (i.e. get a two-sided p-value less than 0.0167) if the proportion of adhesives classified as success is 5% and 30%, respectively, then 77/2=39 subjects should be included if we assume 20% drop-out rate.

8.3.1 Inclusion criteria

Subjects will be enrolled responding to the following criteria:

i. Female Healthy Volunteers.
ii. Age 18 - 40 years old.
iii. Willing to attend two scheduled visits
iv. Able to assess itch and adherence at 24h, 48h and 72h.
v. Provide written informed consent.

8.3.2 Exclusion criteria

Subjects responding to the following criteria are excluded from participation:

i. Non-intact skin barrier (e.g. eczema, rash, cut, scar tissue, wound, etc.).
ii. History of inflammatory skin diseases (e.g. atopic dermatitis or psoriasis).
iii. History of contact allergy
iv. Swimming or engaging in sport activities causing sweat during study period.
v. Use of medication (e.g. corticosteroids) which could affect skin reactions.

8.3.3 Subject withdrawal or discontinuation

Subjects will be withdrawn from the clinical investigation for any of the following reasons:

a. Subject requests early discontinuation.
b. Subject is lost to follow up.
c. Withdrawal by investigator for e.g. safety reasons
d. The adhesives are not kept dry during the study period

The subject can leave the investigation at any time, at the subject's request. The reason for withdrawal will be documented in the appropriate section of the electronic case report form (eCRF).

8.3.4 Recruitment and point of enrolment

Healthy volunteers will be recruited through social media (e.g. facebook), recruitment websites (e.g. forsoegsperson.dk) and/or physical posters placed at educational institutions etc. Contact information on contact persons will be stated in the recruitment text, so interested subjects can contact the study personnel to hear more about the study. First contact with the subjects will be on phone, text (e.g. email) or face-to-face. If a subject is interested in participating in the study, information about the study will be given verbally (over the phone or face-toface in a private room) by the investigator or a person named by the investigator and the first study visit will be arranged. Then, the subject information (Deltagerinformationen) will be send to the subject latest the day (minimum 12 hours) before the first study visit, to ensure that the subject has time to read it carefully and consider participation in the study. At the first study visit, the subject information will be reviewed with the Investigator or a person named by the investigator in a private room to allow the subject to ask any questions that have arisen. Subjects are allowed to bring relatives or friends for the information and study initiation. If subjects agree to participate, they must sign the informed consent before start of the investigation. No subjects should undergo study specific screening procedures before signing the informed consent.

A subject is considered enrolled in the investigation when they have signed the informed consent form. Subjects who are enrolled (signed informed consent) and found eligible shall be documented on the recruitment log.

Participation in the investigation is voluntary and the subject can at any time withdraw from the investigation without any consequence for further examinations and treatment.

When a subject is included, the investigator assures that the subject meets all inclusion criteria and none of the exclusion criteria, by checking the relevant boxes in the eCRF.

8.3.5 Duration of the clinical investigation

The recruitment period will be maximum four months and it will take three (3) days for each subject to complete the procedures.

8.4 Procedures

The eCRF must be filled in for each subject that has signed the informed consent and therefore is enrolled in the investigation.

8.4.1 Screening

Subjects will have a physical examination of investigational area and discuss the subject's medical history to access if they can be included in the clinical investigation.

If any abnormal clinical findings are detected, it must be documented in the eCRF.

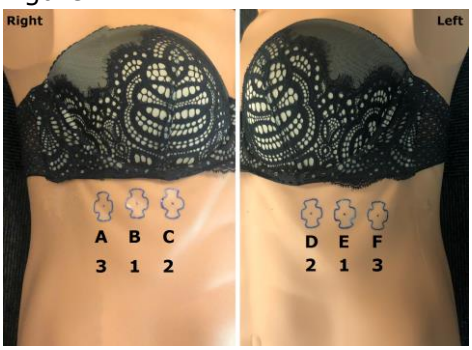
8.4.2 Randomization and Blinding

The adhesives will be placed on the trunk, just below the bra on costae 8-9 level as shown on Figure 1. A set of adhesives includes the three (3) types of adhesives. One set of adhesives will be placed on the right side (position A, B and C) while the other will be placed on the left side (D, E and F). See Table 1 as example. The placement of the three (3) adhesives are randomly allocated to places A, B and C. As well the three (3) adhesives are randomly placed on places D, E and F. The placements are identical on each patient which guarantee that the adhesives in reality are placed equal number of times – in a random order – on each possible place. The placement of the adhesives will be carried out by designated study personnel who are not blinded. After 72 hours, the adhesives will be removed and assessed by a medical doctor, who is blinded.

Table 1

Position		Adhesive	
Side	Code	Code	
Right	A	1	1st Set
Right	B	3	
Right	C	2	
Left	D	2	2nd Set
Left	E	1	
Left	F	3	

Figure 1



8.4.3 Investigational procedures

The study will consist of two visit and three home assessments. The first visit will be conducted by designated personal from Ambu, to ensure that the investigator performing the assessment on the second visit is blinded for the positioning of the different adhesives. In between the two visits, the subject will fill out an electronic questionnaire 24, 48 and 72 hours after placement of the adhesives. The second visit will be performed by the investigator, who is a medical doctor.

Visit 1: Completion of sections in the eCRF.
After signing of informed consent, the investigator must complete the following sections in the eCRF:

- Centre identification.
- Date of enrolment.
- Inclusion/exclusion criteria.
- Confirmation on signed informed consent.
- Demographic data.
- Medical history.

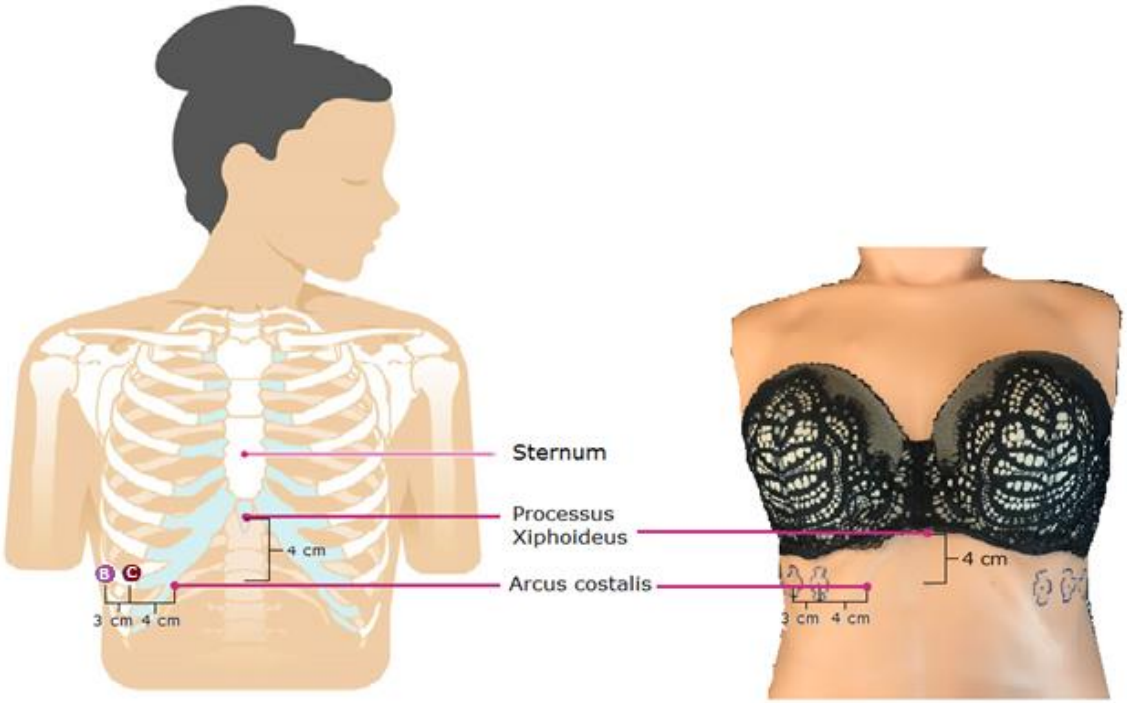
Visit 1: Placement of adhesives.

6 adhesives will be placed on the subject's thorax by designated personnel, as described below and illustrated on figure 2.

- Place the adhesives in a line on the thoracic wall starting four (4) cm below the processus xiphoideus (on the same level as costae 8-9).
- Ensure that the centre of the adhesive closest to the midline is placed 4 cm from arcus costalis.
- Ensure that a distance of 3 cm between the middle of each adhesive.

Ensure that the adhesives are placed below the bra and on the thoracic wall, in order to avoid unnecessary rubbing of the adhesives.

Figure 2: Placement of the adhesives.



After placing the adhesives, the investigator must complete the following sections in the eCRF:

- Date and time of adhesive placement.
- Position of each adhesive.
- Accountability.

Home assessment

After the adhesives have been placed, the subject can go home. The subject must wear the adhesives for minimum 72 hours. The adhesives must be kept dry during all 72 hours and they should only be removed from the body if they cause unbearable itchiness or discomfort for the subject. After wearing the adhesives for 24, 48 and 72 hours, the subject must assess the following in an electronic questionnaire send out by the eCRF system:

- Date and time of assessment.
- If the adhesives were exposed to water or sweat.
- Detachment of adhesives
    - Date and time for each adhesive which detached or was removed.
- Itchiness caused by the adhesives
    - Using the VAS score.

Visit 2: Removal and assessment of adhesives.

After minimum 72 hours the subject will attend the second visit, where a blinded medical doctor will remove the adhesives from the subject's skin.

Before removal of the adhesives, the medical doctor will assess the adherence of each adhesive according to a scale ranging from 0-4 (18) in the eCRF:

- 0 = ≥90% adhered (essentially no lift off the skin)
- 1 = ≥75% to <90% adhered (only some edges lift off the skin)
- 2 = ≥50% to <75% adhered (less than half lifts off the skin)
- 3 = >0% to < 50% adhered (more than half lifts off the skin without falling off)
- 4 = 0% adhered (detached and is completely off the skin).

The adhesives will be removed one-by-one. After removal of each adhesive the following will be assessed in the eCRF:

- Ease of removal, assessed by the medical doctor on a 5-point scale (1=very difficult, 2=difficult, 3=acceptable, 4=easy, 5=very easy).
- Pain during removal, assessed by the subject on the VAS scale (0=no pain, 10=worst imaginable pain).
- Skin condition, assessed by the medical doctor on a scale from 0-7 (21)
    - 0: No evidence of irritation
    - 1: Minimal erythema that is barely perceptible
    - 2: Definite erythema that is readily visible and minimal edema or minimal papular response
    - 3: Erythema and papules
    - 4: Definite edema
    - 5: Erythema, edema and papules
    - 6: Vesicular eruption
    - 7: Strong reaction spreading beyond the application site.
- Residue on the skin, assessed by the medical doctor by answering yes or no.

Once the assessment is completed, the subject has completed the study. In case of any skin reactions, the medical doctor will assess if treatment is needed. In case any treatment is prescribed, it must be documented in the eCRF.

8.4.4 Follow-up procedures

Not applicable.

8.4.5 Lost to follow-up

Not applicable.

8.4.6 Procedures performed by sponsor representatives

Sponsor will assist with recruitment of subjects and placement of the adhesives.

8.4.7 Subject Identification and Confidentiality

Subjects will be identified on the eCRF and any other document transmitted to the sponsor by the principal investigator or site staff, by a unique identification number.

Data entered on the eCRF 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 will maintain as part of the Investigator Binder a list identifying all subjects entered into the clinical investigation.

8.5 Monitoring plan

The sponsor is responsible for ensuring appropriate monitoring of the clinical investigation activities. During the period of the investigation a representative of the sponsor (Anna Charlotte Lundgaard, +45 29 64 37 48) will act as monitor of the investigation. The investigator may contact Anna Charlotte at any time. 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.

8.5.1 Monitoring visits

A minimum of three visits will be performed including one initiation visit, one monitoring visit and one closeout visit. The visits will be performed on site or remotely. The monitor is responsible for planning the monitoring visit.

8.5.2 Initiation visit:

The aim of this meeting is to train the investigator on the investigation procedure, perform a page-by-page revision of the CIP with emphasis on reporting of deviations, adverse events and how to complete the eCRF. Moreover, contract signature and approvals from authorities will be verified, and monitoring arrangements will be discussed.

Initiation visit will be conducted once ethics approval has been obtained. During this visit, the investigation team will be trained on the investigation procedure, how to complete the eCRF and other relevant documents. This training will be documented. A report will be prepared after this visit and will be filed.

8.5.3 Routine Visit

The aim of these monitoring visits is to corroborate the clinical investigation progress and perform source data verification. eCRF will be monitored for completeness and correctness of the data against source data (where available). Completeness and correctness of the informed consent forms will be monitored as well. It is required that the investigator or designated personnel is available during monitoring visits. At least one routine monitoring will be conducted, if needed more monitoring activities will be planned ongoing. A report will be prepared after each visit and will be filed.

8.5.4 Close-out visit:

The aim of this meeting is to close financial aspects, check that all essential documents are complete and up to date, all outstanding queries are resolved, current state of all adverse events is documented, arrangement for achieving all clinical investigation documentation, product accountability, and notification of the corresponding authorities.

This close out visit will be carried out once all the data query is completed and database is locked. A report will be prepared after this visit and will be filed.

8.5.5 Source data verification

This study will not have access to the subject's medical record and all data will be collected directly into the eCRF as source data. However, to ensure that the randomization is followed, the placement of the adhesives entered into the eCRF will be verified against the original randomization list (source data) for all subjects.

9. AUDIT

Audit of the clinical investigation may be conducted by the sponsor or third parties designated by the sponsor to evaluate compliance with the CIP, written procedures and good clinical practice. These audits may cover all involved parties, systems and facilities and are independent from routine monitoring. The aims of the audit are:

- to assess the effectiveness of the monitoring,
- whenever there are repetitive deviations from the CIP,
- to prepare the investigation for a regulatory inspection,
- when requested by a regulatory authority, etc.

Audits may be performed during the investigation. All parties will be informed in advance of the date and objective of the audit.

10. STATISTICAL CONSIDERATIONS

10.1 Pass/fail criteria

The adherence will be measured on a 5-graded scale:
- 0 = ≥90% adhered (essentially no lift off the skin).
- 1 = ≥75% to <90% adhered (only some edges lift off the skin).
- 2 = ≥50% to <75% adhered (less than half lifts off the skin).
- 3 = >0% to < 50% adhered (more than half lifts off the skin without falling off).
- 4 = 0% adhered (detached and is completely off the skin).

An adherence of 0 and 1 is defined as success and 2, 3 and 4 as not success. Each adherence will be classified as success or not success and the sample size calculations will be based on comparing the proportion of adherences classified as success. The original scale (i.e. 0, 1, 2, 3 and 4, will not be used in the statistical analyses as if an adhesive is classified as 2 or higher it is a failure and it is a success of the adhesive is classified as 0 or 1 and it does not matter if the category is 0 or 1.

10.2 Statistical analyses

10.2.1 Statistical design, method and analytical procedures

The study will compare three different types of adhesives (which can be used for electrodes measuring the electrical signals from the heart) on healthy adults. Each subject will have all three adhesives placed on the skin for 72 hours and then the adhesives performance will be evaluated.
The primary endpoint will be to evaluate if the adhesive will stay attached to the skin for the minimum requirement of 72 hours. The adherence will be measured on a 5-graded scale:
- 0 = ≥90% adhered (essentially no lift off the skin).
- 1 = ≥75% to <90% adhered (only some edges lift off the skin).
- 2 = ≥50% to <75% adhered (less than half lifts off the skin).
- 3 = >0% to < 50% adhered (more than half lifts off the skin without falling off).
- 4 = 0% adhered (detached and is completely off the skin).

An adherence of 0 and 1 is defined as success and 2, 3 and 4 as not success. Each adhesive will be classified as success or not success and the sample size calculations will be based on comparing the proportion of adhesives classified as success.

The following hypotheses will be tested (π_X is the true probability that adhesive X will be classified as success):

$$H_{01}: \pi_1 = \pi_2 \text{ versus } H_{11}: \pi_1 \neq \pi_2$$
$$H_{02}: \pi_1 = \pi_3 \text{ versus } H_{12}: \pi_1 \neq \pi_3$$
$$H_{03}: \pi_2 = \pi_3 \text{ versus } H_{15}: \pi_2 \neq \pi_3$$

Prior to start of the statistical analysis it will be randomised which one of each adhesive that will be compared. This means that if for example adhesive 1 and adhesive 2 will be compared then it will be randomised which of the two of the adhesive type 1 that will be compared to each of the two adhesive type 2.
In the statistical analysis of these objectives the results will be presented in a 2x2 table like the table below.

Presentation of the results for each of the 3 hypotheses				
n_{ij} is the number of subjects in that category.		Adhesive X is classified as success		
		No	Yes	Total
Adhesive Y is classified as success	No	n_{11}	n_{12}	$n_{11}+n_{12}$
	Yes	n_{21}	n_{22}	$n_{21}+n_{22}$
	Total	$n_{11}+n_{21}$	$n_{12}+n_{22}$	$n_{11}+n_{12}+n_{21}+n_{22}$

Each of the objectives will then be the same as testing

$$H_0: n_{12} = n_{21} \text{ versus } H_1: n_{12} \neq n_{21}$$

The test to be used is then the Binomial test (exact version).

10.2.2 Sample size

In order to get a 90% power to detect (i.e. get a two-sided p-value less than 0.0167) if the proportion of adhesives classified as success is 5% and 30%, respectively, then 77/2=39 subjects should be included if we assume 20% drop-out rate.

10.2.3 The level of significance and the power of the clinical investigation

In order to preserve the Family-Wise Type I error on 5% each of the 3 null-hypotheses above will be rejected if the p-value is below 0.05/3=0.0167.

10.2.4 Expected drop-out rates

The expected drop-out rate is 20%.

10.2.5 Pass/fail criteria to be applied to the results of the clinical investigation

The result of the trial will be based on the primary objectives and as there are 3 primary objectives it is not possible to classify the study as "pass" or "failed".

10.2.6 The provision for an interim analysis

No interim analyses will be applied.

10.2.7 Criteria for the termination of the clinical investigation on statistical grounds

There will be no possibility to terminate the study based on any statistical ground.

10.2.8 Procedures for reporting any deviation(s) from the original statistical plan

The statistical analyses will start when the data base is clean and thereafter locked. Prior to start of the statistical analyses any deviations from the statistical plan stated in the clinical

investigational plan will be defined and documented. In the clinical study report it will be described which (if any) deviations from the statistical analyses plan that was conducted.

10.2.9 The specification of subgroups for analysis

No sub-group analyses are planned.

10.2.10 Procedures that take into account all the data

All included subjects will also be included in the statistical analyses.

10.2.11 The treatment of missing, unused or spurious data, including drop-outs and withdrawals

Subjects dropping out, or are withdrawn, will not be replaced. The expected drop-out rate is included in the sample size calculations.
Prior to data base lock spurious data will be defined and handled.
Missing data will not be imputed.

10.2.12 The exclusion of particular information from the testing of the hypothesis, if relevant, and in multicentre clinical investigations, the minimum and maximum number of subjects to be included for each centre

There is no minimum or maximum number of patients for each site. No exclusion of information will be done.

10.2.13 Special reasoning and sample size(s) may apply for the early clinical investigation(s), e.g. feasibility clinical investigation(s)

Not applicable.

11. DATA MANAGEMENT

Data will be entered directly into an electronic data capturing system on an eCRF. When the data is collected, and all queries are resolved data will be exported to an Excel master file. Thereafter, data transfer from the Sponsor site to the statistician, StatCons (C/O Mikael Åström, Högerudsgatan 8B, SE-216 18 Malmö, Sweden); transfer will be done according to the regulation of the Danish law for treatment of personal information.

11.1 Data review and cleaning

Data will be collected through an electronic data capturing system on the eCRF, a secure, internet based CRF and image transfer software. This system will be used to record all subject information collected in the study for secure data tracking and centralized data monitoring ("remote monitoring"). A representative of the sponsor will be responsible of setting up the eCRF. Sponsor will add collaborators (e.g. investigator) and assign them to their respective tasks.

Automated, real time data analyses built into the database enable complete control on study outcomes and safety assessments. Automated alerts (emails) are generated by the system for enrolment of patients, adverse event notification, and upcoming or late follow up visits. Additional specific alerts and reports may be setup as required by the sponsor to ensure full control and easier compliance to the clinical investigation plan.

The principal investigator will perform primary data collection by entering the data into the eCRF, using a standard internet-browser. Only the principal investigator or other pre-designated study personnel will be authorized to enter data via internet-based eCRF, using a unique username and pass code. All involved personnel will each be assigned a unique username and pass code to access the eCRF. Each user access to the system is tracked, so that all data operations can be monitored and verified.

The sponsor's designated monitor shall ensure appropriate training on data entry is provided prior to the start of the clinical investigation to all site personnel involved.

The principal investigator can delegate tasks to his/her collaborators, however the roles and responsibilities as time period of involvement involved personnel must be documented on the personnel log as well as training received before getting involved with the clinical investigation.

Personnel not trained and not officially identified by his/her name, signature and personal login for the eCRF system cannot access the system nor enter data in the eCRFs.

The principal investigator, using his/her personal login information shall approve and date each CRF section in the eCRF system.

The monitor, using his/her personal login information shall verify all critical data points and issue electronic queries for the authorized personnel to answer.

A eCRF section shall be considered complete when all data are completed, verified by the monitor, outstanding queries resolved and signed off by the principal investigator.

A critical quality control shall be performed for the first insert 5 subjects by the sponsor's designated data management team and queries issued where needed. Such queries must be reviewed by the monitor and released in the system as a query to be resolved by the site personnel.

After the monitor has done the source document verification (of adhesives placement) and obtained satisfactory answers to eventual queries from the study personnel, a full quality control shall be performed on the monitored data throughout the clinical investigation by the designated data management team and queries issued where needed. This process will be repeated till the end of the clinical investigation so as to allow for a timeline freezing of the data base for statistical analysis.

11.2 Electronic clinical data systems

Test persons will validate the eCRF system by filling out all sections of the eCRF. If any issues are found during data entry, they will be corrected, and the entire system is tested again. The system will be tested by minimum three different test persons. In addition, the system will be tested at least once in a setting simulating the investigational procedure.

11.3 Data retention

The sponsor and principal investigator shall maintain the clinical investigation documents as required by the applicable regulatory requirements. The investigator binder, including CIP, CIR, eCRF's data, Patient Registration List and Informed Consent, must be kept by the principal investigator for at least 5 years after the clinical investigation report has been signed.

The sponsor will file original CRFs, adverse event forms, statistical analysis, agreements, approvals, investigators' CVs and CIR for 10 years

12. AMENDMENTS TO THE CIP

No changes in the clinical investigation procedures shall be affected 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.

All changes require notification to the EC. Substantial changes may require approval from the EC prior to implementation.

13. DEVIATIONS FROM THE CLINICAL INVESTIGATION PLAN

The investigator is not allowed to deviate from the CIP, except a deviation from the CIP is defined as an event where the clinical investigator or site personnel did not conduct the study according to the CIP, GCP and any national or local regulatory requirements. Any discrepancies compared to the procedures described in this CIP shall be documented in the CRF together with an explanation for the deviation and reported to the Sponsor or monitoring person who is responsible for analyzing them and assessing their significance.

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 eCRF and reviewed with the sponsor's designated monitor for the need for reporting to the EC, 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.

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. PRODUCT ACCOUNTABILITY

The sponsor will keep records of the number of products used for each subject. If any adhesives are disposed, e.g. during placement, it will be noted in the eCRF, apart from this, the products will not be accounted for.

15. STATEMENTS OF COMPLIANCE

Not applicable.

15.1 Declaration of Helsinki

The clinical investigation will be conducted according to the guidelines established in the Declaration of Helsinki (6). Subjects will be free to withdraw from the clinical investigation at any stage without prejudice to their subsequent treatment.

15.2 Good clinical practice

The clinical investigation processes will comply with good clinical practice as outlined in ISO 14155 (7) to the extent possible considering that the products investigated in the study are not classified as medical devices.

15.3 Ethics Committee Approval

The final version of the CIP with the subject information and consent forms and any other national or local required document(s) will be submitted to an appropriately constituted EC by the principal investigator prior to the commencement of the clinical investigation. A copy of the EC opinion/approval together with the list of EC voting members will be provided to the sponsor prior to initiating the investigation at a particular clinical investigation site.

The principal investigator shall:

- Submit the appropriate documentation if any necessary extension or renewal of the EC approval must be obtained. In particular amendments to the CIP, the informed consent, or other written information provided to subjects, and/or clinical investigation procedures directly affecting the subject must be approved in writing by the EC.
- Report in writing to the EC, any serious adverse event within the by the EC required timelines but no longer than 10 days after first learning about the event.
- Report any major deviation from the clinical investigation requirements as outlined in this CIP, GCP and applicable national or local regulations. With major deviation is meant any deviation that affects subject's rights, safety and well-being, or the scientific integrity of the clinical investigation. Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of subjects may proceed without prior approval of the sponsor and the EC. Such deviations shall be documented and reported to the sponsor within 24 hours and to the EC within the local required timelines but no later than 10 days after the emergency occurred.
- Report to the EC any new information that may affect the safety of the subjects or the conduct of the investigation. Written summaries of the investigation status shall be sent by the principal investigator to the EC annually or more frequently when requested (according to the local requirements).
- Upon completion of the investigation, provide the EC with a report of the outcome of the investigation as required by the local EC.

15.4 Competent Authority Notification

Not applicable.

15.5 Regulatory compliance

The clinical investigation processes shall be performed in compliance with all applicable regulatory requirements in addition to the above defined requirements for good clinical practices. Where regulatory requirements are less or more stringent than the requirements outlined GCP the most stringent requirements will need to be complied with.

16. INFORMED CONSENT PROCESS

16.1 Patient information

The patient information is a brief summary of the investigation written in a language understandable for the subject. The patient information describes the aim of the investigation, benefits and risks to the subject and the possibility of compensation. Furthermore, it includes an explanation of alternative methods and consequences of withdrawal from the investigation.

The subject information reflects product investigations and is provided according to GCP and Helsinki Declaration (6). The subject information may be modified as per relevant EC instructions for each site. In such case, a final version of the patient information must be provided to the sponsor before starting the investigation.

The investigator will review the subject information with each possible subject and explain the investigation to him/her. The subject will be given sufficient time to consider participation and it is recommended that a witness from the subject side is present during the information procedure. If the subject requests more time to consider participation in the investigation the investigator will schedule a new time for the examination of the subject. The subject information describes the contact details of the investigator.

16.2 Informed consent

Informed consent is the voluntary confirmation and documentation of the willingness of a subject to participate in a particular investigation, after information has been given orally and in writing to the subject. Point of enrolment is from the time when informed consent is signed. The subject and investigator must each sign and date the informed consent.

The investigator signs to confirm that information has been given to the subject. One copy is for the subject and the other one for the investigator binder.

The informed consent may be modified as per the relevant EC instructions for each site. A final copy of this informed consent must be provided to the sponsor prior to first use.

Participation in the investigation is voluntary and the subject can at any time chose to be withdrawn from the investigation.

The principal investigator or authorized designee must obtain from the subjects or their legally authorized representative, written informed consent to their inclusion in the clinical investigation, after explaining the rationale for and the details, aims and objectives of the clinical investigation, the risks and benefits of the product, and the extent of the subject’s involvement. All subjects must sign and date the informed consent.

The principal investigator is responsible for ensuring that no subject is undergoing any clinical investigation-related examination or activity before subjects have given their written informed consent.

After obtaining signature of the subject, duly signed informed consents, as well as a copy of the written information given to subjects shall be kept and archived in the investigator binder, according to the requirements of the country's health regulations, but for a minimum of 5 years after completion of the investigation.

The principal investigator or authorized designee shall forward for review, to the sponsor or monitor any changes to the content of the subject information sheet and informed consent and any other written information to be provided to the subject, prior to submission to the EC.

All information provided to subjects including any advertisements for the clinical investigation within the clinical investigation site or in the public press needs approval of both sponsor and EC prior to being presented to the subjects under any format.

17. ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

17.1 Definitions (2,3)

Product deficiency:

The inadequacy of the product which is not reported in the study endpoints.

Adverse event (AE):

Any untoward medical occurrence, unintended disease or injury or untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational product.

Note 1: This includes events related to the investigational product or the comparator.

Note 2: This includes events related to the procedures involved.

Note 3: For users or other persons this is restricted to events related to the investigational product.

Serious adverse effect (SAE):

An adverse product effect that has resulted in any of the consequences characteristic of a serious adverse event.

Serious adverse event (SAE):

An adverse event that:

a) led to a death,
b) led to a serious deterioration in the health of the subject user or other persons that either resulted in:
    1. a life-threatening illness or injury, or
    2. a permanent impairment of a body structure or a body function, 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.
    5. chronic disease,
c) led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note: A planned hospitalization for pre-existing condition or a procedure required by the CIP without a serious deterioration in health is not considered to be a serious adverse event.

17.2 Investigator requirements

Investigator must record and document all AE and product deficiencies in the adverse event form/product deficiency form.

The principal investigator shall report all AE and product deficiencies in the appropriate sections of the eCRF and provide where requested by the sponsor, the necessary clinical or technical information that may contribute to clarifying the circumstances.

The principal investigator shall report all SAE: if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate, to the sponsor within 24 hours after knowledge of the event using the appropriate eCRF.

Reporting of AE start from the time point the subject is enrolled in the clinical investigation – signed informed consent. This means that any AE related to or reported during the screening assessments are to be reported. Any clinical occurrence that is detected during the screening but can clearly be considered as a pre-existing condition is not to be reported as an AE but as physical exam findings and, if appropriate, medical history e.g. should the patient be diagnosed with diabetes during screening, then this is not to be reported as an adverse event but as medical history, however if a patient is developing an allergic reaction to a contrast medium used in one of the screening assessments, this is to be reported as an AE.

When required by national or local regulations, the principal investigator shall also notify the EC of all reportable events according to applicable national law within the required timelines and may also be requested by the EC to provide annual reports. The principal investigator shall document all AE and product deficiencies in the eCRF from the point of enrollment until the subject is exited from the study.

All SAE shall be reported to the sponsor by e-mail immediately but no later than three calendar days.

Emergency contact details are stated on the form and are as follows:

CLINICAL DEPARTMENT

Anna Charlotte Lundgaard
aclu@ambu.com
+45 29 64 37 48

After termination of the AE/SAE a copy of all relevant medical documents must be sent to the sponsor including the finalised adverse event form.

17.3 Information provided by the clinical investigation site

The principal investigator will provide the following information, at a minimum, for each AE or product deficiency:

- Date of the AE or product deficiency
- Date principal investigator (or authorized designee) became aware of AE or product de ficiency
- Description of AE or product deficiency, relevant diagnostic findings
- Treatment
- Resolution

- Assessment of:

a) Severity of the event

   i) Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
   ii) Moderate: minimal, local or noninvasive intervention indicated; limiting
   iii) Severe: medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling

b) Life-threatening: urgent intervention indicated, disabling

c) Fatal: death related to AE

d) Relationship of the event to the investigational device (related, unlikely related, possible related, probable related or causal relationship)

e) Relationship of the event to the index procedure (related, unlikely related, possible related, probable related or causal relationship)

f) Causality

   i) disease under study
   ii) lack of performance of the investigational device or comparator/worsening of treated condition
   iii) medical history
   iv) concomitant or previous medication
   v) other (specify).

17.4 Sponsor requirements

The sponsor is responsible for the classification of all AE and ongoing safety evaluation of the clinical investigation and shall:

1. Review the investigator's assessment of all AE and determine and document in writing their seriousness, severity and relationship to the investigational device; in case of disagreement between the sponsor and the principal investigator, the sponsor shall communicate both opinions to concerned parties.
2. Ensure the reporting to the EC by the principal investigator.
3. Review and report all reportable events according to national regulations in acceptable timely conditions and shall monitor for increased incidence and severity.
4. Ensure that the EC is informed of significant new information about the clinical investigation, and

The sponsor shall report all AE to the EC with the following timelines (22):

All serious adverse events must be reported by the sponsor immediately – no later than 2 calendar days to EC.

- All AE shall be informed to the sponsor immediately - within 7 calendar days after occurrence to the EC.

17.5 Expected clinical occurrences

The use of adhesives can cause allergic reactions characterized by erythema, edema and itch. In addition, removal of the adhesives from the skin can cause discomfort. However, all the adhesives used in this study have been tested for biocompatibility and toxicology (as described in section 5 Justification for the design of the clinical investigation) and they all met the test requirements.

18. VULNERABLE POPULATION

Not Applicable.

19. SUSPENSION OR TERMINATION OF THE CLINICAL INVESTIGATION

The sponsor, investigator or EC may decide to interrupt the investigation in case of detecting repetitive SAEs, in case of unexpectedly poor performance of the product, repetitive major deviations from the protocol, etc.

Sponsor will withdraw from sponsorship of the clinical investigation if

- major non-adherence to the CIP 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.

20. PUBLICATION POLICY

The clinical investigation will be registered on a public accessible database before recruitment of the first subject, e.g. https://clinicaltrials.gov/. A summary of the results of the clinical investigation will be published in the same public accessible database. The subjects' identity will remain confidential.

All information supplied by Ambu A/S to the investigator in connection with this investigation shall remain the sole property of Ambu A/S and is to be considered confidential information. No confidential information shall be disclosed to others without prior written consent from Ambu A/S.

The involved investigator has the right to write a publication for a relevant scientific journal or present the results at relevant international/national meetings after CIR has been approved. The principal investigator and sponsor have the right to comment on the manuscript within two weeks. If no comments have been received after two weeks the submission will proceed. Primary investigator will have the right of being first author if the data from the study is published.

21. RESPONSIBILITIES

The sponsor is responsible for the investigation and must ensure that the study is conducted according to GCP and that all responsibilities to the EC is committed.

The monitor appointed by Ambu A/S is responsible for monitoring the investigation according to GCP.

The principal investigator is responsible for conducting the investigation as described in the CIP, the study agreement (filed in the study file), according to the Helsinki Declaration (6) and GCP.

22. INSURANCE

Ambu A/S will within the limitations of their legal responsibility, accept responsibility for any damage suffered by a subject as a result of using the test products in the clinical investigation as described in this CIP.

Ambu A/S is insured in the insurance company Zurich and all subjects will be fully covered throughout the investigation.

23. PRINCIPAL INVESTIGATOR AND SPONSOR COOPERATION

23.1 Study agreement

A written agreement is made between the principal investigator and the Sponsor and shall be signed before start of the clinical investigation. The agreement describes the responsibility and liability for sponsor and investigator respectively, during the investigation.

23.2 Clinical Investigation Report (CIR)

The CIR will be prepared according to GCP by the sponsor. The sponsor has one month to finalise the CIR after receipt of the final statistical report. The principal investigator has two weeks to comment on and approve the final CIR.

The principal investigator and the sponsor are required to sign the report.

24. CONFLICT OF INTEREST

The investigation is initiated and payed by Ambu A/S. No financial support has been provided by sources outside of Ambu A/S (e.g. manufactures of the investigated products). Ambu's interest in the study outcome does not favorize one product over the others.

Principal Investigator does not have any financial interest in the study outcome. Principal investigator is reimbursed on an hourly basis according to the consultant agreement made with Ambu A/S. The time consumption is estimated to be around 50 hours for the principal investigator equivalent to approximately 35.000 DKKR.

Gentofte Hospital will be paid for rental of rooms to cover consumption and maintenance costs.

25. DATA PROTECTION

All subject data will be handled according to Regulation (EU) 2016/679 of the European Parliament and of the Council of 27. April 2016 and the Danish Data Protection Act No. 502 of 23 May 2018.
All patient data collected during the course of this investigation will be kept strictly confidential. An investigation number will identify subjects and the monitor will have limited access to subject's files/documentation for source data verification. Any information, which could identify a subject, will remain with the investigator where it will be filed with investigation documents. Subjects will remain anonymous for data analysis.

Should the investigation require future review, it may be necessary to allow limited access to regulatory authorities for audit purpose only.

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