CLINICAL INVESTIGATION PLAN (CIP)

INVESTIGATIONAL DEVICE:

EPADERM® Cream

INVESTIGATION TITLE:

A prospective post market clinical follow-up investigation with Epaderm® Cream to confirm performance and safety parameters

CO-ORDINATING INVESTIGATOR:
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CLINICAL INVESTIGATION PLAN (CIP) SYNOPSIS

INVESTIGATION TITLE:

A prospective post market clinical follow-up investigation with Epaderm® Cream to confirm performance and safety parameters

Objectives
To confirm safety and performance of Epaderm Cream when used as intended in daily practice

Overall Design
This investigation is designed as a prospective, non-randomised, single arm clinical investigation. Data will be collected from approximately 120 evaluable subjects, divided into three groups of approximately 40 subjects; infants (0-36 months old), children (3-18 years old) and adults (>18 years old), with the following indications: eczema, psoriasis and other dry skin conditions. Each subject will be followed during 4 weeks treatment, with a visit at baseline (visit 1), at 2 weeks (visit 2) and at 4 weeks (visit 3) treatment.

Primary Endpoint

Subject evaluation of skin moisturisation (hydration) after treatment with Epaderm Cream up to 4 weeks, using a questionnaire.

Secondary Endpoints

1. Subject evaluation of skin softness after treatment up to 4 weeks, using a questionnaire.
2. Evaluation of the subject's dry skin/xerosis after treatment with Epaderm Cream up to 4 weeks, by investigator/nurse using "Overall dry skin score, ODS", (Masson P, 1995).
3. Skin hydration after treatment with Epaderm Cream up to 4 weeks, using a non-invasive device MoistureMeterEpiD.
4. Subject evaluation regarding:
   - Frequency of application and amount used of Epaderm Cream
   - Comfort during treatment
   - Time of onset of effect (moist and soft)
   - Overall effect
   - Was the investigational device used as a skin cleanser?
5. Concomitant and previous medication and treatment
6. Number of Adverse Device Effects (ADEs) related to the use of Epaderm Cream during the investigation.

Inclusion Criteria

1. Subjects suitable for treatment with Epaderm Cream, as deemed by the investigator and according to intended use (eczema, psoriasis and other dry skin conditions).
2. Subject or subject's legal representative must be able to read and sign the Patient Information and Consent Form.

Exclusion Criteria

1. Known allergy/hypersensitivity to any of the components of Epaderm Cream.

2. Subject not suitable for the investigation according to the investigator's judgement.
3. Subject participating in other ongoing similar clinical studies or other clinical studies which could interfere with this investigation, as judged by the investigator.
4. Subject previously enrolled in the current clinical investigation.

Investigational Device

Epaderm Cream

Mölnlycke will provide the investigational device, to the investigation sites and subjects, free of charge. The treatment with the investigational device will be according to the prescription by the investigator together with the instruction stated on the investigational device (e.g. when used as an emollient: *Apply liberally to the affected area and massage well into the skin. Use as often as required or as directed by your health care professional.* When used as a skin cleanser: *Use as required when washing or in the shower.)*.

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LIST OF ABBREVIATIONS

ADE	**Adverse Device Effect**
AE	**Adverse Event**
CIP	**Clinical Investigation Plan**
eCRF	**Electronic Case Report Form**
DD	**Device Deficiency**
EC	**Ethics Committee**
IRB	**Institutional Review Board**
PMCF	**Post-Market Clinical Follow-up Investigation**
SAE	**Serious Adverse Event**
SADE	**Serious Adverse Device Effect**

Clarification

Investigator/Nurse: **In the CIP, it refers to the Physician(s) and Nurse(s) participating in the investigation.**

1. INTRODUCTION AND BACKGROUND

Epaderm® Cream is an emollient formulated with ingredients that hydrate, aid moisture retention and soften the skin. Epaderm Cream provides all the protective benefits of paraffin-based emollients and can be used in the management of eczema, psoriasis and other dry skin conditions. The emollient can also be used as a skin cleanser. Epaderm Cream is suitable for all ages including babies (PD-537170-01, appendix G). This emollient is a low risk device (Class IIa device under Medical Device Directive MDD 93/42/EEC) and is formulated with well-established ingredients commonly used in topical formulations. Epaderm Cream has been on the market in its present formulation since 2012 and with over 5.8 million sold items.

The ingredients of Epaderm Cream moisturise and softens the skin. Yellow soft paraffin and liquid paraffin are used for the softening and moisturising characteristics and to reduce water loss from the skin. Epaderm Cream also contains glycerine which is used for its hydration properties.

Whilst there is no need for a Post-Market Clinical Follow-up investigation (PMCF) from a safety perspective for Epaderm Cream, there is a need for a PMCF investigation to confirm the performance of Epaderm Cream in accordance with MEDDEV 2. 12/2 Rev: 2, see Clinical Evaluation Report PD-420529 Rev: 02. The investigation should cover dry skin conditions, eczema and psoriasis, as well as different age groups including babies.

2. OBJECTIVES

To confirm safety and performance of Epaderm Cream when used as intended in daily practice.

3. CLINICAL INVESTIGATOR(S) AND INVESTIGATION ADMINISTRATIVE STRUCTURE

3.1 PI at Investigation Sites

Name and addresses of Principal Investigators are listed in appendix A.

3.2 Mölnlycke Investigation Personnel

Relevant personnel, included in appendix A.

3.3 Other Participants

Supplier of the eCRF system
PCG Clinical Services AB
Viedoc
Kungsängsvägen 19, 1 tr.
753 23 Uppsala, Sweden

4. INVESTIGATION PLAN AND PROCEDURES

4.1 Overall Design

This investigation is designed as a prospective, non-randomised, single arm clinical investigation. Data will be collected from approximately 120 evaluable subjects, divided into

three groups of approximately 40 subjects; infants (0-36 months old), children (3-18 years old) and adults (>18 years old), with the following indications: eczema, psoriasis and other dry skin conditions. Each subject will be followed during 4 weeks treatment, with a visit at baseline (visit 1), at 2 weeks (visit 2) and at 4 weeks (visit 3) treatment. An evaluable subject is a subject with a baseline visit and at least one follow-up visit.

4.2 Investigation Endpoints

4.2.1 Primary Endpoint

Subject evaluation of skin moisturisation (hydration) after treatment with Epaderm Cream up to 4 weeks, using a questionnaire.

4.2.2 Secondary Endpoints

7. Subject evaluation of skin softness after treatment up to 4 weeks, using a questionnaire.
8. Evaluation of the subject's dry skin/xerosis after treatment with Epaderm Cream up to 4 weeks, by investigator/nurse using "Overall dry skin score, ODS", (Masson P, 1995).
9. Skin hydration after treatment with Epaderm Cream up to 4 weeks, using a non-invasive device MoistureMeterEpiD.
10. Subject evaluation regarding:
    - Frequency of application and amount used of Epaderm Cream
    - Comfort during treatment
    - Time of onset of effect (moist and soft)
    - Overall effect
    - Was the investigational device used as a skin cleanser?
11. Concomitant and previous medication and treatment
12. Number of Adverse Device Effects (ADEs) related to the use of Epaderm Cream during the investigation.

4.3 Procedures and Assessments

Data will be collected at the baseline visit, visit 1 (day 0), at visit 2 (2 weeks, day 14) and at visit 3 (4 weeks, day 28). Collected data will be entered into an eCRF (electronic Case Report Form).

The subject should be instructed not to shower or put on Epaderm Cream before the follow-up visits.

If the subject cannot come to a follow-up visit, the investigator/nurse should collect as much information as possible (at least one documented attempt to reach the subject) and enter this into the eCRF.

4.3.1 Schedule of Assessments

Visits	Baseline Visit Visit 1 Day 0	Follow up visit Visit 2 Day 14 (+/-2)	Final visit Visit 3 Day 28 (+/-2)
Informed consent, dated and signed	√		
Inclusion/Exclusion criteria	√		
Subject's age and sex	√		
Relevant medical history	√		
Relevant previous medication or treatment	√		
Concomitant medication/ treatment relevant for the investigation	√	√	√
Did the subject have a shower before the visit	√	√	√
Skin disease/condition	√		
Severity of disease/condition	√	√	√
Subject's evaluation of itching in relation to skin condition/diagnosis (VAS scale)	√	√	√
Ongoing flare	√	√	√
Overall Dry Skin Score (ODS)	√	√	√
Body location of target area for skin hydration evaluation	√	√	√
Non-invasive device measuring skin hydration	√	√	√
Subject's treatment compliance		√	√
Subject Questionnaire		√	√
Investigator/nurse Questionnaire	√	√	√
Non-invasive device measuring skin hydration	√	√	√
New relevant medical events		√	√
ADE/DD/SADE		√	√

4.4 Selection of Population for Investigation

4.4.1 Inclusion Criteria

1. Subjects suitable for treatment with Epaderm Cream, as deemed by the investigator and according to intended use (eczema, psoriasis and other dry skin conditions).
2. Subject or subject's legal representative must be able to read and sign the Patient Information and Consent Form.

4.4.2 Exclusion Criteria

1. Known allergy/hypersensitivity to any of the components of Epaderm Cream.
2. Subject not suitable for the investigation according to the investigator's judgement.
3. Subject participating in other ongoing similar clinical investigation or other clinical investigations which could interfere with this investigation, as judged by the investigator.
4. Subject previously enrolled in the current clinical investigation.

4.4.3 Discontinuation of treatment and Lost to follow-up

Subjects will be categorised as lost to follow-up when the investigation staff has done at least one documented attempt to reach the subject, after the baseline visit. When a subject discontinues investigation, the reason will be reported in the eCRF.

4.4.4 Withdrawal of Subjects from treatment

Subjects are free to discontinue participation from the investigation at any time, and without prejudice to further treatment. Subjects who withdraw from the investigation should always be asked about the reason(s) for the discontinuation and about the presence of any Adverse Device Effect (ADE) and, if possible, be assessed by an investigator.

Subjects may be withdrawn from investigation treatment and assessments at any time, at the discretion of the investigator.

4.5 Investigational Device

Epaderm Cream
Mölnlycke will provide the investigational device, to the investigation sites and subjects, free of charge. The treatment with the investigational device will be according to the prescription by the investigator together with the instruction stated on the investigational device (e.g. when used as an emollient: *Apply liberally to the affected area and massage well into the skin. Use as often as required or as directed by your health care professional.* When used as a skin cleanser: *Use as required when washing or in the shower.)*

Epaderm Cream is an emollient formulated with ingredients that hydrate, aid moisture retention and soften the skin. It provides all the protective benefits of paraffin-based emollients and can be used in the management of eczema, psoriasis and other dry skin conditions. The emollient can also be used as a skin cleanser. Epaderm Cream is suitable for all ages including babies. Epaderm Cream is a Class IIa device. This device is CE-marked and has been on the market in its present formulation since 2012. The ingredients of Epaderm Cream are listed below:

Ingredients

	% (w/w)
Yellow Soft Paraffin BP	15
Liquid Paraffin Ph.Eur	10
Glycerine BP	5
Cetomacrogol Emulsifying Wax BP (SLS Free)	5
Chlorocresol	0.1
Purified Water EP	64.9

4.5.1 Labelling

Labelling of the investigational device, will be in accordance with ISO 14155, the Medical

Devices Directive (MDD) and Mölnlycke Quality Management System.

4.5.2 Accountability

At the follow-up visits (at 2 and 4 weeks), the subject will be asked by the investigator/nurse about treatment compliance. The subject will be asked by the investigator/nurse if the investigational device was used according to instructions and frequency of application:

Frequency of application:
- Once a day
- Twice a day
- Three times a day
- Four times a day
- More than four times a day

Daily use:
- Every day
- 5 days or more per week
- 2-4 days per week
- Less than 2 days a week

Number of bottles used:
- Less than one bottle
- At least one bottle
- At least two bottles
- At least three bottles
- At least four bottles

4.5.3 Storage conditions

A description of the appropriate storage is specified on the investigational device label. According to the instructions, the Epaderm Cream should be stored in dry conditions, below 25°C. Epaderm Cream should be kept out of the reach of children.

4.5.4 Method of Assigning Subjects to Product Groups

N.A.

4.6 Concomitant Treatments

Concomitant treatment relevant for the investigation and the skin disease/condition, according to the investigator's judgement, will be recorded in the electronic Case Report Form (eCRF).

4.7 Performance and Safety

4.7.1 Non-invasive device measuring skin hydration

As an additional measurement of skin hydration, besides the subjective scale used for both investigator/nurse and subject, a non-invasive device, MoistureMeterEpiD from Delfin Technologies, will be used (please see appendix E for instructions on use).

The MoistureMeterEpiD is an all-in-one measurement unit that is composed of an integrated probe, a built-in contact force sensor and a display. The OLED display shows non-invasively measured values in percentage of local tissue water (0 to 100 %) effectively in the epidermis and normal values are typically between 30-50 %. Change of some %-units of percentage tissue water means improvement of hydration.

Measurement principle
The MoistureMeterEpiD generates a high frequency, low power electromagnetic (EM) wave into the skin. The reflected EM wave is analysed and the obtained value is a tissue dielectric constant (TDC), which is proportional to the water content of the measured site. This TDC value is converted to water percentage and displayed. The value increases with increasing hydration.

4.7.2 Subject Characteristics

See appendix C for details.

- Dated and signed informed consent
- Age (months, years)
- Sex
- Skin disease e.g. eczema, psoriasis and other dry skin conditions

4.7.3 Performance Measurements and Variables

Primary Endpoint Variable

Subject evaluation of skin moisturisation (hydration) after treatment with Epaderm Cream up to 4 weeks (at 2 and 4 weeks), using a questionnaire (the evaluations should be done on the same affected spot):

- Improved Moisturisation (Strongly agree, Agree, Neither agree nor disagree, Disagree, Strongly disagree)

Secondary Endpoints Variables

1. Subject evaluation of skin softness after treatment up to 4 weeks (at 2 and 4 weeks), using a questionnaire (the evaluations should be done on the same affected spot).
   - Improved Softness (Strongly agree, Agree, Neither agree nor disagree, Disagree, Strongly disagree)
2. Evaluation of the subject's dry skin/xerosis after treatment with Epaderm Cream up to 4 weeks (at baseline, 2 and 4 weeks), by investigator/nurse using "**Overall dry skin score, ODS**". ODS, a scoring scale combining all the major and minor signs of dry skin (xerosis),
   0= Absent
   1= Faint scaling, faint roughness and dull appearance
   2= Small scales in combination with a few larger scales, slight roughness, whitish appearance
   3= Small and larger scales uniformly distributed, definite roughness, possibly slight redness and possibly a few superficial cracks
   4= Dominated by large scales, advanced roughness, redness present, eczematous changes and cracks
3. Skin hydration using non-invasive device MoistureMeterEpiD (measuring the same treated spot on the skin during baseline and follow-up visits). The device displays percentage water content (%) in the epidermis (appendix G).
4. Subject evaluation (at 2 and 4 weeks), regarding:
   a. Frequency of application and amount used of Epaderm Cream (please see Accountability 4.5.2)
   b. Comfort during treatment (Very poor/Poor/Average/Good/Excellent)
   c. Time of onset of effect, regarding moist and soft skin
      - Immediately
      - Within 2 weeks
      - Within 2 to 4 weeks

- Not at all

d. The overall effect of the investigational device (Very poor/Poor/Average/Good/Excellent)
e. Did you use the investigational device as a skin cleanser (Yes/No)?

5. Concomitant and previous medication and treatment
6. Number of Adverse Device Effects (ADEs) related to the use of Epaderm Cream during the investigation.

Further investigation variables/data

Baseline procedure as specified in appendix C:

1. Subject's age and sex
2. Relevant Medical History (skin condition, date of diagnosis past/current, ongoing medication)
   a. Classification (eczema, psoriasis and other dry skin conditions)
   b. Location (Please specify)
   c. Duration (Weeks/Months/Years)
   d. Severity of diagnosis/condition according to local definition (Mild/Moderate/Severe)
3. Type of Relevant Previous Treatment
   a. Topical: which type of medication/treatment
   b. Systemic: which type of medication/treatment
   c. Phototherapy
4. Concomitant medication or treatment relevant for the investigation
5. Instructions on frequency of treatment with Epaderm Cream
6. Did the subject shower and put on a moisturiser in the morning before visit? Instruct the subject not to shower nor put on Epaderm Cream before the follow-up visits.
7. Is the subject experiencing a flare of his/her skin condition at present (Yes/No/Not applicable)
8. Subject evaluation of itching in relation to skin condition/diagnosis (VAS scale)

Follow- Up visit, Visit 2 procedure will be registered for all enrolled subjects as specified in appendix C:

1. New relevant medical event? If Yes, please specify
2. Did the subject shower and put on a moisturiser in the morning before visit? (Yes/No)
3. Is the subject experiencing a flare of his/her skin condition at present (Yes/No/Not applicable)
4. Subject evaluation of itching in relation to skin condition/diagnosis (VAS scale)
5. Changes of concomitant treatment relevant for the investigation
   a. Topical: which type of medication/treatment
   b. Systemic: which type of medication/treatment
   c. Phototherapy

End of Investigation Visit/Visit 3 procedure will be registered for all enrolled subjects as specified in appendix C:

1. New relevant medical event? If Yes, please specify
2. Did the subject shower and put on a moisturiser in the morning before visit? (Yes/No)
3. Is the subject experiencing a flare of his/her skin condition at present (Yes/No/Not applicable)
4. Subject evaluation of itching in relation to skin condition/diagnosis (VAS scale)
5. Changes of concomitant treatment relevant for the investigation
   a. Topical: which type of medication/treatment
   b. Systemic: which type of medication/treatment
   c. Phototherapy

4.7.4 Safety Measurements and Variables

Only events related to the use of the investigational device and events related to inadequacies of the investigational device and the non-invasive device measuring the skin hydration, will be recorded as safety issues i.e. Adverse Device Effect (ADE), Serious Adverse Device Effect (SADE) and Device Deficiencies (DD). The definition of ADE, SADE and DD and procedures for reporting SADE and DD that could have led to a SADE are presented in section 8 of this CIP. All ADE, SADE and DD must also be recorded in the appropriate section of the eCRF. It is of utmost importance that all staff involved in the clinical investigation are familiar with the content of section 8. It is the responsibility of the Principal Investigator to ensure this.

4.7.5 Anticipated ADEs

Epaderm Cream has been on the market in its present formulation since 2012 with over 5.8 million sold items (PD-420529 Rev: 02). Epaderm Cream has a low risk and is formulated with well-established ingredients commonly used in topical formulations.

The following events have been identified in the Product Risk Management Record:

- 1 skin reaction registered as Adverse Event – Non-reportable.
- 7 cases of skin reaction (3), rash (3) or burning skin (1) were registered as Adverse Events – Non-reportable in the Mölnlycke Quality Management System during the period July 2015 to Oct 2017.

The conclusion of the Product Risk Management Record is as following: Residual risks are negligible/tolerable and will be managed through provision of information from a Health Care professional, information on the product package or patient information.

Individuals hypersensitive to any of the ingredients may experience skin irritation. Epaderm Cream should not be used if you have any known allergy or sensitivity to any of the ingredients.

The Investigational Device should be used according to instructions for use (appendix D).

4.8 Data Quality Assurance

4.8.1 Monitoring, Audits and Inspections

During the investigation, the monitor will have regular contacts with the investigation site. This contact will include visits to confirm that the facilities remain adequate to specified standards and that the investigation site team is carrying out the procedure stated in the CIP and supports the investigator. All data must be accurately recorded in the eCRF. Source data verification (a comparison of data in the eCRF with the subject's hospital/practice and other records at the investigation site) with direct access to records will also be performed.

The monitor, delegate or other Mölnlycke personnel will be available between visits if the investigator or other staff at the site needs information and/or advice.

Authorised representatives of Mölnlycke and/or a Competent Authority (CA) and/or the Ethics Committee (EC)/Institutional Review Board (IRB) may visit the investigation site to perform audits/inspections, including source data verification.

4.8.2 Training of Staff

The Principal Investigator will ensure that appropriate training relevant to the investigation is given to the medical, nursing and other staff at the site involved and that new information of relevance to the performance of this investigation is forwarded to the staff involved.

4.8.3 Data Management

The Data Management process includes all activities related to data handling regarding:

- Set-up of eCRF and database
- Specification of on-line checks
- Data entry / Data editing
- Export of data from Viedoc to SAS
- Creation of post-entry checks and listings
- Reconciliation of SADE, ADE and DD
- Clean-file process including execution of post-entry checks and listings
- Post clean-file tasks

Viedoc, a web based electronic CRF system, will be used to capture data in this investigation. The eCRF system complies with FDA Title 21 CFR part 11 (ER/ES) requirement.

eCRF training will be given to appropriate personnel before/at initiation of the investigation sites.

Data entry will be performed by investigators and other authorised personnel at the sites. When entering data, on-line checks are incorporated in Viedoc for consistency and validation. Pharma Consulting Group will support with a helpdesk function taking care of system user questions regarding Viedoc.

When data has been entered, authorised personnel at Mölnlycke can immediately view the data, send queries if necessary and lock eCRF pages when they have been validated.

All data entered in Viedoc will be encrypted. The physical database will be stored in Sweden.

Programs for post-entry checks and data listings will be created and executed for validation of data.

Completeness will be checked by authorised personnel at Mölnlycke so that there are no unexplainable empty fields in Viedoc. This is done to prevent data have being overlooked by personnel entering the data.

A clean-file meeting will be held prior to database lock. All decisions on the evaluability of the data from each individual subject for the statistical analysis must be made and documented before locking the database.

4.9 Statistical Methods and Determination of Sample Size

4.9.1 Analysis populations

Safety population

The safety population includes all subjects who had applied Epaderm Cream.

Intention to treat population

The intention to treat population consists of all subjects attending the baseline visit and meets the Inclusion/Exclusion criteria.

Per protocol population

An evaluable subject is a subject with a baseline visit and at least one follow-up visit. At the clean file meeting a decision will be made as to which patients to include in the per protocol population. These decisions will be based on the protocol violations affecting skin hydration.

4.9.2 Statistical Evaluation

The results from the investigation period will be presented with descriptive statistics by visit. For continuous variables mean, standard deviation, median, minimum and maximum will be presented and for categorical data number and percentage will be presented.

To evaluate change in skin hydration (Improved Moisturisation) evaluated by subject from baseline to 4 weeks (strongly agree/agree/neither agree nor disagree/disagree/strongly disagree) Sign test will be used. This will be made totally and for each of the three groups (infants, children and adults). This will be presented descriptively.

Change over time for continuous variables will be tested using Wilcoxon signed rank test and for ordered categorical and dichotomous variables signed rank test will be used.

All tests are two-sided with alpha 0.05.

All efficacy analyses will be performed for an ITT/Full analysis set and also for a per protocol population. The safety variables will be studied for the Safety population. All results will be presented totally and for the three groups (infants, children and adults).

Applicable data will be collated into summary tables and figures. Those summary tables and figures will be integrated into the body of the Clinical Investigation Report. Data listings will be prepared for all captured data. The listings will be incorporated into applicable appendices of the Clinical Investigation Report (CIR).

4.9.3 Determination of Sample Size

The sample size is based on that the investigation is looking at performance of Epaderm Cream measured as Improved Moisturisation evaluated by the subject. The answers will be recoded as three categories strongly agree/agree/neither agree nor disagree/disagree/strongly disagree. The expected distribution of the answers is strongly agree/agree 40%, neither agree or disagree 50% and disagree/strongly disagree 10%. Assuming a power of 80% and using a Sign test a total of approximately 40 subjects is needed in each subgroup (infants, children and adults).

4.10 Changes to the Clinical Investigation Plan

No change in the investigation procedure will be effected without the mutual agreement between the Principal Investigator and Mölnlycke.

An amendment to the CIP may require notification or approval from EC/IRB and, in many countries, also the CA before implementation. Local requirements must be followed.

Mölnlycke will distribute CIP amendments to the Principal Investigator who is responsible for the distribution of these documents to the EC/IRB and staff concerned at his/her site. The distribution of these documents to the CA will be handled according to local practice.

5. STATEMENTS OF COMPLIANCE

5.1 Ethics

5.1.1 Ethics review

The final CIP, including the final version of the Subject Information and Consent Form, must be approved or given a favourable opinion in writing by an EC in accordance with local requirements before enrolment of any subject into the investigation.

The Principal Investigator is responsible for informing the EC of any amendment to the CIP in accordance with local requirements.

5.1.2 Ethical Conduct of the Investigation

The clinical investigation will be performed in accordance with the ethical principles that have their origin in the most recent version of the Declaration of Helsinki, and with applicable regulatory requirements.

5.1.3 Subject Information and Consent Form

The Principal Investigator will ensure that the subject/subject's legal representative is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the investigation. Subjects/subject's legal representative must also be notified that they are free to discontinue participation in the investigation at any time. The subject/subject's legal representative should be given the opportunity to ask questions and time for consideration. The subject/subject's legal representative signed informed consent must be obtained before conducting any procedure specifically for the investigation. The original must be filed by the Principal Investigator. A copy of the Patient Information including the signed Consent Form should be given to the subject.

A sample of the Patient Information and Consent Form is enclosed (appendix B). If modifications are made according to local requirements, the new version must be approved by Mölnlycke.

If subject's legal representative is a parent, both parents' signatures are required.

The ICF process should be reflected in the source documents.

5.2 Regulatory and standards

5.2.1 Standards and other

The most recent version of ISO 14155 will be followed in addition to national regulations.

5.2.2 Subject data protection and confidentiality

The written Subject Information explains that the data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation and that authorised representatives of Mölnlycke and/or a CA and/or EC/IRB, require direct access to those parts of the hospital/practice records relevant to the investigation, including medical history, for verification of data. All data computerised by Mölnlycke will be identified by subject number only.

The clinical investigation will be conducted in accordance with EU General Data Protection Regulation 2016/679.

5.3 Subject Protection Procedures

5.3.1 Procedures in Case of Medical Emergency

The Principal Investigator is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the investigation.

5.3.2 Insurance

Mölnlycke has product liability insurance.

5.4 Use of Information and Publications

The investigation data will be used internally by Mölnlycke in accordance with its post-market surveillance activities. The data may be used by Molnlycke without revealing the identity of the subject. It may be used in printed and digital (e.g. websites) forms for internal and external scientific, educational and promotional purposes, e.g. peer-reviewed journal articles, conference posters, conference presentations, brochures, training materials, etc.

5.5 Record Retention

The Sponsor will retain all investigation documents for 10 years after the device leaves the market. The site is required to keep the documentation in accordance with local regulation.

5.6 Public Domain Access to the Clinical Investigation

A description of this clinical investigation will be available on http://www.ClinicalTrials.gov together with the NHI website.

6. INVESTIGATION TIMETABLE AND TERMINATION

Investigation start:	Anticipated Q1 2019
Inclusion completed:	Anticipated Q3 2019
Last subject out:	Anticipated Q3 2019
Data base lock:	Anticipated Q3 2019
Investigation Report:	Anticipated Q4 2019

Mölnlycke retains the right to suspend or terminate this investigation at any time. The investigation could be prematurely discontinued if the investigation site is unable to fulfil the inclusion period according to the Clinical Investigation Agreement.

7. LITERATURE REVIEW AND REFERENCES

To determine the scientific background for this clinical investigation as well as to assess risks/benefits of the device, a literature review was conducted. The literature listed below was evaluated before serving as background information.

1. Medical Device Directive MDD/93/42/EEC as amended.
2. Clinical Evaluation MEDDEV 2.7/1, Rev 4; Jun 2016.
3. Post Market Clinical Follow up Studies MEDDEV 2.12/2 Rev 2; Jan 2012.

4. Internal Report: Clinical Evaluation Report, Epaderm Cream with Glycerine (SLS free), PD-420529 Rev: 02
5. Masson P, Rodrigues FL, Berardesca E, Leveque JL, Loden M, Pierard G et al. EEMCO guidance for the assessment of dry skin (xerosis) and ichthyosis: Clinical scoring systems. Skin Res. Technol. 1995, 1, 109-114

8. DEFINITIONS AND PROCEDURES FOR REPORTING OF ADVERSE DEVICE EFFECT, SERIOUS ADVERSE DEVICE EFFECT AND DEVICE DEFICIENCY

Definitions:

Device Deficiency (DD)
Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Note: Device Deficiencies include malfunctions, use errors, and inadequate labelling.

All Device Deficiencies that might have led to a Serious Adverse Device Effect shall be reported in accordance with Serious Adverse Event reporting procedures, as specified below.

Adverse Event (AE)
Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device

Note:

- This definition includes events related to the investigational medical device or the comparator.
- This definition includes events related to the procedures involved.
- For users or other persons, this definition is restricted to events related to investigational medical devices.

Adverse Device Effect (ADE)
Adverse Event related to the use of the investigational medical device and the hydration measuring device.
Note:

- This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, or operation, or any malfunction of the investigational medical device.
- This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Serious Adverse Event (SAE)
Adverse Event that:

a) led to death,
b) led to a serious deterioration in the health of the subject, 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 hospitalisation or prolonged hospitalisation or,
4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

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

Serious Adverse Device Effect (SADE)
Adverse Device Effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.

PROCEDURES FOR SAE AND/OR SADE REPORTING OR REPORTING OF DD THAT COULD HAVE LED TO A SADE

The investigator must inform Mölnlycke within 1 calendar day of awareness of the event. When a SAE/SADE has been entered into the eCRF by the investigator /authorised site staff, the eCRF system will automatically generate a report to:
Clinical_Investigations_Event_Reporting@molnlycke.com.

In case of problem with the eCRF, a paper based version of the SAE/SADE report form (available in the investigator Site File) shall be used and sent by email to:
Clinical_Investigations_Event_Reporting@molnlycke.com.

All SAEs/SADEs that occurs during the Clinical Investigation shall be reported, whether or not they are considered causally related to the investigational device.

Device Deficiencies that might have led to SADE if either a) suitable action had not been taken, b) if intervention had not been made, or c) if circumstances had been less fortunate must be reported as a SADE.

The investigator is responsible for informing the EC/IRB and/or the Competent Authority of the SAE/SADE as per local requirements.

PROCEDURES FOR DD REPORTING

All DD shall be reported to Mölnlycke as soon as possible, without unjustified delay. If the DD might have led to a SADE, the reporting requirements for SADE described above must be followed. DDs can be either subject related or non-subject related depending on if the investigational device was used by a subject or not. Separate forms are used for subject related and non-subject related DDs. When a subject related DD has been entered into the eCRF by the investigator /authorised site staff, the eCRF system will automatically generate a report to:
Clinical_Investigations_Event_Reporting@molnlycke.com

Non-subject related DDs are reported using the paper based report form located in the Investigator Site File. The completed form shall be sent by email to
Clinical_Investigations_Event_Reporting@molnlycke.com

Procedures for ADE reporting

All ADE shall be reported by the investigator to Mölnlycke as soon as possible without unjustified delay. When a ADE has been entered into the eCRF by the investigator /authorised site staff, the eCRF system will automatically generate a report to:
Clinical_Investigations_Event_Reporting@molnlycke.com

Causality Assessment

The relationship between the use of the investigational device and the occurrence of each ADE/SADE shall be assessed by the investigator and the sponsor and classified as device related or not related to the device.

CLINICAL INVESTIGATION PLAN (CIP)

Appendix A

INVESTIGATIONAL DEVICE:

Investigational Device

INVESTIGATION TITLE:

Investigation Title

Signature of Clinical Investigation Plan Author:

14 MAR 2019

CATHARINA FLODIN: DDMMMYYYY

Signature of Clinical Project Manager:

Cat. Flod.

14 MAR 2019

CATHARINA FLODIN: DDMMMYYYY