EVALUATION OF THE EFFICACY AND TOLERANCE OF CRYSTAL PEEL, A SALICYLIC ACID BASED PEEL IN THE TREATMENT OF ACNE

Clinical Investigation Plan for Medical Device according to ISO standard 14155:2020

Clinical Investigation plan #:	**22E2387**
Clinical investigation single identification #:	**To be determined**
Investigational device(s):	**CRYSTAL PEEL**
Form(s):	**Liquid peeling**
Application(s):	**Topical performed by Investigator**
CRO/Investigation site:	**Eurofins Dermscan Poland** ul. Matuszewskiego 12 80 - 288 GDANSK POLAND
Coordinating/Principal Investigator:	**Beata IMKO-WALCZUK**
Sponsor:	**DERMOSCIENCES FRANCE** **15 Chemin des presses** **06800 Cagnes sur Mer** **FRANCE**
Clinical Investigation Plan date and version:	Final version 1.0 of 16/08/2022

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1- GENERAL INFORMATION AND SIGNATURES

1.1 INTRODUCTION

The primary objective of the study is to evaluate the efficacy and clinical performance of Crystal Peel, a salicylic-based peel, for the treatment of acne. The targeted population consists of male and female subjects presenting mild acne on the face. Treatment with the tested medical device will be performed by the investigator (dermatologist) in 3 sessions every 3 weeks. Total number of subjects to be included is 33 in order to obtain 30 evaluable results. The total duration of the study for the subject will be 78 days.

1.2 IDENTIFICATION OF THE CLINICAL INVESTIGATION PLAN (CIP)

TITLE OF THE CIP: EVALUATION OF THE EFFICACY AND TOLERANCE OF CRYSTAL PEEL, A SALICYLIC ACID BASED PEEL IN THE TREATMENT OF ACNE

CLINICAL INVESTIGATION #: 22E2387

VERSION AND DATE OF THE CIP: FINAL 1.0 16/08/2022

Summary of the revision history:

Date	Version	Amendment
16/08/2022	1.0	Creation

ABBREVIATION LIST

ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
CA	Competent Authority
CE	Conformité Européenne - European Conformity
CIP	Clinical Investigation Plan
CRA	Clinical Research Associate
CRO	Contract Research Organization
D	Day
DMC	Data Monitoring Committee
EC	Ethics Committee
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
95% CI	95% Confidence Interval
IB	Investigator Brochure
IFU	Instruction for use
INCI	International Nomenclature of Cosmetic Ingredients
Investigation	= study = research = trial
ISF	Investigator Site File
ITT	Intent To Treat
MD	Medical Device
NA	Not Applicable
PMCF	Post-Market Clinical Follow-up
PP	Per Protocol
SADE	Serious Adverse Device Event
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
USADE	Unanticipated Serious Adverse Device Effect

1.3 SPONSOR AND FUNDING SOURCE

DERMOSCIENCES FRANCE 15 Chemin des presses 06800 Cagnes sur Mer FRANCE	
CONTACT	**DATE AND SIGNATURE**
Monory POT **Function: Formulator and R&D Manager** Tel.: +33 (0)6 07 23 82 49 email: monory.p@dermaceutic.com	Signé par Monory POT Le 19/08/2022 Signed with universign
Rana MTEIREK **Function: Head of Regulatory Affairs, Vigilance Alternate** Tel.: +33 (0)7 87 15 64 29 email: rana.m@dermaceutic.com	Signé par Rana MTEIREK Le 19/08/2022 Signed with universign
Nicola FAGIUOLI **Function: Director** Tel.: +33 (0)6 64 14 55 53 email: nicola.f@dermaceutic.com	Signé par Nicola FAGIUOLI Le 18/08/2022 Signed with universign

The sponsor is responsible for the clinical investigation funding in its totality including the investigators payment, subject's compensation and treatment of potential AE connected with the study product/procedures.

1.4 PRINCIPAL INVESTIGATOR, COORDINATING INVESTIGATOR, CRO AND INVESTIGATION SITE(S)

COORDINATING/PRINCIPAL INVESTIGATOR

CONTACT	DATE AND SIGNATURE
Dr. Beata IMKO-WALCZUK **Principal/Coordinating investigator, Dermatologist**	Beata Imko-Walczuk 05 Sept 2022

CLINICAL RESEARCH ORGANISATION (CRO)

We agree to conduct the study in accordance with the clinical investigation plan described in this document and in compliance with ISO 14155:2020 and applicable regulatory requirements.

Eurofins Dermscan Poland **ul. Matuszewskiego 12** **80 - 288 GDANSK** **POLAND**	
CONTACT	**DATE AND SIGNATURE**
Aleksandra TARASZKIEWICZ **Project Manager** **Tel: +48 58 732 02 90** **e-mail: ata@dermscan.pl**	29/08/2022 Taraszkiewicz
Cédric JUNG **Biostatistician** Tel: +33(0)4 72 89 36 56 email: CJU@dermscan.com	August 29th, 2022

INVESTIGATION SITES

Centre # 1
Eurofins Dermscan Poland ul. Matuszewskiego 12 80 - 288 GDANSK POLAND
Coordinating and principal Investigator: **Dr Beata IMKO-WALCZUK, Dermatologist** Tel.: 58 732 02 90 email:bimko@wp.pl

1.5 OVERALL SYNOPSIS OF THE CLINICAL INVESTIGATION

Clinical investigation single identification #:	To be determined
Clinical investigation plan #:	22E2387
Title of the clinical investigation:	EVALUATION OF THE EFFICACY AND TOLERANCE OF CRYSTAL PEEL, A SALICYLIC ACID BASED PEEL IN THE TREATMENT OF ACNE
Sponsor:	DERMOSCIENCES FRANCE 15 Chemin des presses 06800 Cagnes sur Mer FRANCE
Development phase:	Post market study Confirmatory Interventional Device used according to IFU
Objectives:	Principal aim: The primary objective of the study is to evaluate the efficacy and clinical performance of Crystal Peel, a salicylic-based peel, for the treatment of acne by lesions counting (front, 2 cheeks, the chin above the jaw line (excluding the nose)) using both visual observation and palpation. Total lesions will be defined as the sum of inflammatory lesions (papules, pustules), non-inflammatory lesions (whiteheads and blackheads) and other acne lesions (nodules). Secondary aims: • Pores and texture analysis (will be performed by Newtone with Colorface acquisitions) • Visual effect (Standardized anonymized photographs (face, 45° at left, 45° right) with Colorface) • Investigator Global Assessment • Patient Global Assessment • Local and overall tolerance of the Crystal Peel, a salicylic acid-based peel, used under the normal conditions of use recommended by the manufacturer. • Subject's self-evaluation on D78 using a questionnaire. • Potential adverse events collection.
Design:	Open, monocentric study with intra-individual comparisons.
Planned Sample Size:	33 included subjects for 30 results at sponsor's request
Number of investigational study sites:	1 Center in Poland

Inclusion criteria:	1. Healthy subjects 2. Gender: female and/or male. 3. Age: 18 – 45 4. Phototype I to IV according Fitzpatrick scale. 5. Healthy subject with normal physical examination results and a medical history compatible with the requirements of the study. 6. A healthy male or female subject with a medical diagnosis of mild to moderate facial acne vulgaris defined by at least 6 (six) inflammatory lesions, 12 (twelve) non-inflammatory lesions and no more than 2 (two) nodules (the nose is excluded for lesion count purposes). 7. Subject declares to avoid exposure to UV radiation (tanning booths, phototherapy and sun) on the face for at least three months prior to the selection visit and agrees to avoid it throughout the study. 8. Subject agrees not to apply any cosmetic, medical or aesthetic treatments outside the study protocol on the face for the duration of the study. 9. For female subjects: Female subject not in childbearing status (tubal ligation, hysterectomy, bilateral oophorectomy), or Female subjects of childbearing potential who, in the opinion of the investigator, are using a reliable method of contraception (pill or contraceptive patch, IUD, implant or vaginal ring, condoms) for at least one month prior to the screening visit. Subject willing to continue using contraception during the study and one month after the end of the study.
Exclusion criteria:	1. Pregnant or nursing woman or planning a pregnancy during the study. 2. Subject who had been deprived of their freedom by administrative or legal decision or who is under guardianship. 3. Subject in a social or sanitary establishment. 4. Subject participating to another clinical research or being in an exclusion period for a previous study. 5. Intensive exposure to sunlight or UV-rays within the previous 3 months and foreseen during the study. 6. Subject with any skin or systemic disease (acute and/or chronic), in the previous year, likely to interfere with the measured parameters or to put the subject to an undue risk. 7. Subject having history of allergy or hypersensitivity to one of the components of the tested device. 8. Subject receiving any treatment that, in the opinion of the clinical investigator, may interfere with test results or put the subject to undue risk. 9. Subjects on topical or oral treatments (such as Benzoyl Peroxide, Retinoic Acid, Isotretinoine) that did not stop the treatment 30 days before their first peel (risk of over-peeling). 10. Subjects with known salicylism or related medical indications.

Investigational device: **Name / code** **Galenic form** **Dosage and duration** **Administration route**	 CRYSTAL PEEL Liquid 3 applications performed by the dermatologist: 2.5 ml of Crystal Peel applied with a cotton swab on the face. Apply up to 3 coats, waiting 1 minute between each coat. Leave the last coat on for up to 5 minutes, while observing the skin's reaction. Topical administration
Endpoints:	<u>Primary endpoint:</u> Comparison of the change from baseline of total sum of lesions on each visit. <u>Secondary endpoints:</u> Pores and texture analysis Visual effect - photographs Investigator Global Assessment score Patient Global Assessment score Local and overall tolerance of the Crystal Peel Subject's self-evaluation on D78 using a questionnaire. Adverse events number
Study Procedures:	D0, D15 (peeling act), D36 (peeling act), D57 (peeling act), D78

Statistical methods:	The following analysis populations will be studied and will be considered for the statistical analysis: - Safety population: any subject having used the investigational device. - ITT (Intent-to-Treat) population: any subject included in the study with at least a post-basal value. - PP population: any subject having used at least once the investigational device and without any major deviation to the CIP. ***Descriptive analysis:*** Quantitative data will be summarized using adapted statistics (number of values, mean, median, standard deviation, minimum and maximum values) by time point. Categorical data will be summarized in frequency (N) and percentage (%) by time point. ***Inferential analysis:*** For each continuous variable obtained from devices: A mixed linear model for repeated measurements (PROC MIXED) will be fitted to raw data. Using the adjusted means obtained from this model (LS-Means), the contrast of interest will be built: o To assess the change from first measurement at each time The underlying assumptions (normality and homoscedasticity of residuals) will be checked using Shapiro-Wilk test (α=0.01) and graphical representations. In case of strong deviation, a transformation of the data or a non-parametric approach (Wilcoxon signed rank tests) will be performed. The raw score will be summarized using descriptive statistics for quantitative data by time point. A Wilcoxon signed rank test will be applied to test whether the change from baseline is statistically significant. The categorical data will be summarized in frequency (N) and percentage (%) associated with its 95% confidence interval by time point. The questionnaire will be summarized in frequency (N) and percentage (%). The adverse events will be analysed. Each statistical analysis test will be two tailed and the type I error will be set at α=0.05.
Foreseen study duration:	Clinical investigation beginning: Q4 2022 Clinical investigation end: Q1 2023 Clinical investigation global duration: 17 weeks Duration by subject: 78 days

FLOW-CHART

Procedure (time-points)	**V1**	**V2**	**V3**	**V4**	**V5**
Intervals	**D0**	**D15 (+/-1)**	**D36 (+/-2)**	**D57 (+/-2)**	**D78 (+/-3)**
Checking the inclusion/non-inclusion inclusion/non-inclusion criteria	●				
Physical examination/Vital signs / medical history and treatment	●				
Informed Consent Form	●				
Pregnancy test	●				
Exclusion criteria	●	●	●	●	●
Use of associated treatment			●		
PEELING ACT		●	●	●	
Colorface Standardized Photos (X3)	●	●	●	●	●
Lesions counting	●	●	●	●	●
pores analysis by Newtone	●	●	●	●	●
texture analysis by Newtone	●	●	●	●	●
Local tolerance		●	●	●	●
Dispense cosmetic products and daily log	●				
Collect daily log		●	●	●	●
Subjective evaluation questionnaire					●
IGA					●
PGA					●
Adherence control, record of AE, concomitant treatments	●	●	●	●	●
End of study form					●

2- IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

2.1 SUMMARY DESCRIPTION

The investigational device is a class IIA according to the rule N°4 of the Medical device regulation (UE) 2017/745.

Crystal Peel is a medical device for which we are requesting a CE certification. It belongs to the family of the chemical peel products.

Crystal Peel is a medical device intended for the treatment of Melasma, Solar and Senile lentigines, Post-inflammatory pigmentation, Mild -Acne and Hyperkeratosis.

Crystal Peel is a superficial chemical peel composed of Salicylic Acid (20%), Mandelic Acid (5%) and Citric Acid (5%). The main components of Crystal Peel have a keratolytic effect. They are considered as exfoliants. They work through a chemical removal of the keratinized structure of the epidermis.

Crystal Peel active ingredients aim to accelerate the elimination of the keratinized structures of the epidermis (the outer layer of the skin) to promote its renewal and reduce the thickness of the stratum corneum. The device reduces the cohesion between corneocytes (dead cells) by weakening the lipid matrix responsible for their cohesion on the surface of the skin.

Crystal Peel is a non-sterile and non-invasive device for a very short term-use and limited area.

Crystal Peel is intended to adults and can only be used by a trained healthcare professional.

Crystal Peel is presented as a kit:

- Crystal Peel as a glass bottle (30ml) contained in a kit with these accessories:
- One bottle of a Foamer 15 (40ml).
- Cottons buds
- One cup (Glass).
- The instruction of use.

2.2 DETAILS CONCERNING THE MANUFACTURER

2.2.1 Investigational device:

Name	DERMOSCIENCES France
Address	15 Chemin des Presses, 06800 Cagnes-sur-Mer, France
Phone number	+33 (0)4 86 87 24 24
Representative	Nicola FAGIUOLI
Mail contact	contact@dermaceutic.com
Website	www.dermaceutic.com

2.3 NAME OR NUMBER OF THE MODEL/TYPE

2.3.1 Investigational device:

SRN Code of manufacturer	FR-MF-000003058		
Basic-UDI (Family code or Global Model Number)	376013501318251916 53T		
Model	Model	Product	UDI-ID
	Kit selling size	Kit	3760135011834
		Bottle 30 ml	3760135011827
	Kit sample size	Kit	3760135011810
		Bottle 4 ml	3760135011803

2.4 TRACEABILITY

The devices will be sent to each investigation site by the sponsor. Once the devices are received, the management and traceability of the devices during the investigation are done by each site using appropriate documentation.

Each device will be assigned a batch number to insure its traceability from its production to its destruction. During the study, each device will be labelled with a specific label.
The labelling of the investigational devices will be realized by Eurofins Dermscan Pharmascan.
Here is an example of the label which will be pasted on device packaging:

Subject #: XXX
Centre # 1
Principal investigator: Dr Beata IMKO-WALCZUK
Study #: 22E2387
Storage: between 5° and 25°C
Name: CRYSTAL PEEL
Batch #: XXXX
Expiry date: XXXX
Legal mention: For clinical investigation only. To be used only by a legally qualified practitioner. External use. Do not swallow. Keep out of reach of children.

The label will be translated in each site language.

The devices will only be handled by qualified practitioner. They will not leave the centre nor be distributed to subjects during the investigation.

2.5 INTENDED PURPOSE OF THE INVESTIGATIONAL DEVICE IN THE PROPOSED CLINICAL INVESTIGATION

The objectives of the clinical evaluation are to demonstrate that:

- The Crystal Peel used according to the instructions for use is successful in treating or reducing the symptoms of the mild acne for which it is intended,
- Clinical performance meets end-user needs and expectations, validating the design of the medical device,
- The benefits to patients outweigh the risks,
- The conditions of application and frequency of use are sufficient to treat mild acne.
- The objectives regarding safety and performance requirements are met.

2.6 POPULATION AND INDICATIONS FOR WHICH THE INVESTIGATIONAL DEVICE IS INTENDED

Crystal Peel is a superficial chemical peel intended for the treatment of Melasma, Solar and Senile lentigines, Post-inflammatory pigmentation, Mild -Acne and Hyperkeratosis.

• Acne: Acne vulgaris is a chronic inflammatory condition of the pilosebaceous unit. It manifests as open or closed comedones or both and inflammatory lesions including papules, pustules or nodules. Acne vulgaris is one of the most prevalent dermatologic condition worldwide.

• Post-inflammatory pigmented lesions: Post-inflammatory hyperpigmentation (PIH) is a common dermatological disorder occurring after various dermatoses, injuries, exogenous stimuli, dermatologic procedures photosensitive drugs or light therapies. Acne is one of the leading causes of PIH in skin of colour. PIH occurs at all ages, with equal incidence in males and females and more frequently in individuals with dark phototypes. It presents as irregular, asymptomatic, darkly pigmented macules or patches occurring in the same distribution as the initial skin insult. The clinical course of PIH is chronic and unpredictable, although the probability of resolution of epidermal hyperpigmentation is better than those of dermal hyperpigmentation. The severity of PIH is determined by the inherent skin colour, degree, and depth of inflammation, of dermo-epidermal disruption, and stability of melanocytes. PIH can be prevented or alleviated,

• Solar and Senile lentigines: Solar/senile lentigines are hyperpigmented lesions ranging in size from a few millimeters mainly localized on photodamaged body sites, whose onset is commonly observed along with aging. They tend to be multiple with individual lesions gradually increasing in size to larger macules or patches. Around 90% of the White population aged over 60 years are affected, but this condition may also occur in Asian populations and other ethnicities. The underlying mechanisms responsible for the occurrence and maintenance of these spots are not yet completely defined. Depending on the body area, specific differences in the etiology of lentigines seem to occur. Lentigines on the face or hand could result from cumulative sun exposure and not from sunburn events. Solar lentigines on the back have been associated with frequent sunburn and with recreational sun exposure but not with lifetime exposure. Constituents of ambient air pollution may also contribute to the development of solar lentigo Molecules related to inflammatory and fatty acid metabolism are induced in solar lentigines, probably linked to chronic UV exposure. Solar lentigines are associated with increased age, and individuals seek treatment options to decrease perceived age. Under the dermatoscope, the solar lentigo can display diffuse brown pigmentation, light-brown fingerprint-like structures and a fine regular network. The surface may be rough on palpation and dermoscopically there may be comedo-like openings, as these lesions are often in the process of evolving into seborrheic keratoses.

• Hyperkeratosis: Hyperkeratosis is an umbrella term that describe a number of skin conditions. It manifests by the thickening of the outer layer of the kin, associated with keratin abnormality and an increase in the granular layer of the skin. Thickening is often the skin's normal protection against rubbing, pressure and other forms of irritation, causing calluses and corns on the hands and feet or whitish areas inside the mouth. Other forms of hyperkeratosis occur as part of the skin's defense against chronic inflammation, infection and the radiation of sunlight or irritating chemicals. Less often, hyperkeratosis develops on skin that has not been irritated. These types may be part of an inherited condition, may begin soon after birth and can affect skin on large areas of the body. Hyperkeratotic skin disorders affect 10-20 % of the Western population, with the incidence increasing with age. Hyperkeratotic skin may appear red and dry with brow or grey scaly patches. Hyperkeratosis may involve a small, isolated area or larger skin surfaces, for example on the lower limb. A variety of treatment options are available for hyperkeratosis including keratolytics moisturizer.

The device is for professional use only, as indicated on the packaging as well as on all the labels of the range's device and instruction of use. It is intended for trained clinicians and dermatologists.

The targeted patient population is adults who present the skin disorders listed above. Since Crystal Peel is a superficial chemical peel system, the use is topical and external as it is clearly mentioned on the instruction of use.

In this clinical investigation the population presenting mild Acne vulgaris will be included.

2.7 DESCRIPTION OF THE INVESTIGATIONAL DEVICE

2.7.1 Investigational device

Reference	Crystal Peel Kit
Classification	Class IIa medical device
Formula	18258.L4
Galenic form	Liquid
Route and mode of administration/use	Topical application
Packaging	Glass vial of 30 ml
Preservation and storage	At room temperature (5°C-25°C)

2.8 SUMMARY OF THE TRAINING AND EXPERIENCE NEEDED TO USE THE INVESTIGATIONAL DEVICE

The investigational device and comparator will only be used by legally qualified medical practitioners, trained and experienced in use of chemical peeling. Before any intervention in the study, the investigators will familiarize themselves with the devices, their complete instruction leaflets/ investigator brochure and the CIP.

2.9 DESCRIPTION OF THE SPECIFIC MEDICAL OR SURGICAL PROCEDURES INVOLVED IN THE USE OF THE INVESTIGATIONAL DEVICE

No additional medical nor surgical procedures are involved in the study.

3- JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

Crystal Peel is a medical device intended for the treatment of Melasma, Solar and Senile lentigines, post-inflammatory pigmentation, Mild -Acne and Hyperkeratosis.

Only biocompatibility studies have been performed on the Crystal Peel medical device (see section 3.1) but no clinical investigation yet. In the framework of the medical device regulation the collection of clinical data is mandatory during the life of the medical devices.

This clinical investigation will allow the collection of data on the performance of the medical device Crystal Peel on mild acne which is one of the intended uses of the medical device.

3.1 BIOCOMPATIBILITY DATA

3.1.1 Cytotoxicity test

Based on the results, interpreted according to ISO 10993-5:2009, **Crystal Peel must be considered cytotoxic**. However, the cytotoxicity test has an extreme sensitivity and unlike the other test utilized in biological evaluation, it is not a pass/fail test.

3.1.2 Hypersensitivity test

The hypersensitivity test has been investigated by the manufacturer, in order to assess this endpoint hazard for the patients. Under the experimental conditions, the test item applied to the skin of Guinea pigs caused no alterations in the challenge period. Therefore the Crystal Peel is classified as **non-sensitizer**.

3.1.3 Irritation test

Crystal Peel was considered “negligible irritant”. This is expected due to acidics properties of the agent peels available in the product.

3.1.4 Safety assessment

On the basis of the available toxicological data on the ingredients of **Crystal Peel** formulation, on the VOCs (Volatile Organic Coumpound) and elementary impurities analysis, and considering the results of the biocompatibility toxicological studies, it can be concluded that **Crystal Peel** does not represent neither a major risk of cutaneous intolerance nor a risk of cutaneous allergy under normal conditions of use, unless specific individual sensitivity to some of the ingredients. A cutaneous reaction is predicted due to cytotoxic (desired) properties of the formulation. Yet, **Crystal Peel** is applied for very short time (1 – 5 minutes) and then rinsed off; this short exposure time reduces the risk and the severity of the skin reaction.

3.1.5 Skin Absorption test

A skin absorption test for the main active ingredients (Salicylic, Mandelic and Citric acids) has been performed by a qualified and independent laboratory under the manufacturer request. The Goal was to assess the rate of absorbed quantity to rule out any metabolic activity of these compounds. The assessment has been conducted in appropriate way, following the instruction of use to reflect the more probable conditions of use.

In summary, the absorbed quantity of Salicylic acid (0.0026 % < average < 0.00541%) is very negligible compared to what is found in scientific publications and should not generate a systemic absorption.

Mandelic acid is a large molecule, unlikely to go deeply on the skin, and this is confirmed by the permeability tests showing even less absorption rate compared to Salicylic acid (either in minutes or after 24h), law average between 1-5 minutes (0.001% < average < 0.003%)

Citric acid was not measurable (either in minutes or after 24h) since the values are out the limit of quantification of the analytical method.

These results evoke that absorption rates were very low for the three substances, essentially for the most critical one (Salicylic acid) suggesting that **Crystal Peel** is unlikely to induce systemic absorption or subchronic adverse effect.

4- BENEFITS AND RISKS OF THE INVESTIGATIONAL DEVICE, CLINICAL PROCEDURE AND CLINICAL INVESTIGATION

4.1 ANTICIPATED CLINICAL BENEFITS

Anticipated clinical benefit is an improvement of skin quality (texture and pores), especially the improvement in the number of acne lesions.

4.2 ANTICIPATED ADVERSE DEVICE EFFECTS

As described in the instruction leaflet of the investigational device, the following potential adverse events may occur immediately or may be delayed.

Side effects such as edema, erythema, desquamation, persistent redness, itching, burning sensation or pigmentation disorder may appear after the treatment. If these symptoms persist for longer than 72 hours, arrange a consultation with the patient.
As with any product prescribed for topical use, there is a risk of allergic reaction to one of the components.

4.3 RISKS ASSOCIATED WITH PARTICIPATION IN THE CLINICAL INVESTIGATION

There will be no additional risk for the subjects, associated with their participation in the clinical investigation. All measurements scheduled are non-invasive, without risks.

4.4 POTENTIAL INTERACTIONS WITH CONCOMITANT MEDICAL TREATMENTS

Treatment with CRYSTAL PEEL in combination with drugs and other devices has not been clinically evaluated.

4.5 STEPS THAT WILL BE TAKEN TO CONTROL OR MITIGATE THE RISKS

Risks are mitigated by including only those subjects that meet the study entry criteria.

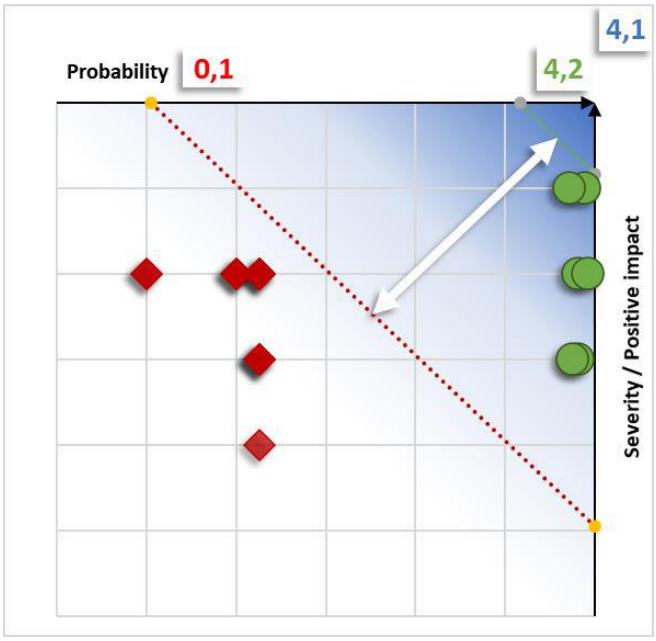
4.6 RATIONALE FOR BENEFIT-RISK RATIO

A risk analysis documentation that identifies hazards and measures to reduce risks has been established It is provided as an excel document and can be sent upon a request.

The figure below, represents the global risk mapping of **Crystal Peel**. It considers the different factors from conception, manufacturing process, use, transport and stockage), all associated in **Crystal Peel** risk analysis.

Each individual benefit and individual risk have been identified and evaluated according to a risk product analysis procedure. After having identified risk measures and procedures to control or to reduce these risks an overall benefit level and an overall risk level are identified.

As a conclusion the ratio of these two factors exhibits a positive benefit/risk balance.



Regarding all risks associated with the use of the Crystal Peel during the clinical investigation are identified in the Risk Analysis and are classified as minor and acceptable. We state that the Crystal Peel has a favourable benefit/risk profile.

All risks identified in the Risk Analysis are addressed in the report and considered low. A review of safety data of each excipient used in the Crystal Peel indicated low risk of possible hypersensitivity to the ingredients. Furthermore, the performance of the Crystal Peel, which is based on three combined acids which are Salicylic (20%), Mandelic (5%) and Citric acids (5%) dissolved in a mixture of alcohol-water solvent, is identified and substantiated by literature sources.

In summary, we state that the Crystal Peel is effective for the treatment of the symptoms of mild acne when the product is used according to the Instruction for Use and has a favourable benefit/risk profile due to the minimal risks associated with the use of the Crystal Peel.

5- OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION

5.1 CLAIMS FOR CLINICAL PERFORMANCE, EFFECTIVENESS AND SAFETY OF THE INVESTIGATIONAL DEVICE THAT ARE TO BE VERIFIED

- The Crystal Peel used according to the instructions for use is successful in treating or reducing the symptoms of the mild acne for which it is intended,
- Clinical performance meets end-user needs and expectations, validating the design of the medical device,
- The benefits to patients outweigh the risks,
- The conditions of application and frequency of use are sufficient to treat mild acne.
- The objectives regarding safety and performance requirements are met.

5.2 OBJECTIVES

5.2.1 Primary objective

The primary objective of the study is to evaluate the efficacy and clinical performance of Crystal Peel, a salicylic-based peel, for the treatment of acne by lesions counting (front, 2 cheeks, the chin above the jaw line (excluding the nose)) using both visual observation and palpation.

Total lesions will be defined as the sum of inflammatory lesions (papules, pustules), non-inflammatory lesions (whiteheads and blackheads) and other acne lesions (nodules).

5.2.2 Secondary objective(s)

• Pores and texture analysis (will be performed by Newtone with Colorface acquisitions)
• Visual effect (Standardized anonymized photographs (face, 45° at left, 45° right) with Colorface)
• Investigator Global Assessment
• Patient Global Assessment
• Local and overall tolerance of the Crystal Peel, a salicylic acid-based peel, used under the normal conditions of use recommended by the manufacturer.
• Subject's self-evaluation on D78 using a questionnaire.
• Potential adverse events collection.

5.3 SCIENTIFIC JUSTIFICATION AND CLINICAL RELEVANCE

The primary endpoint of the study will be an objective counting of the acne lesions performed on every visit.

5.4 HYPOTHESES TO BE ACCEPTED OR REJECTED

Crystal Peel is effective in the treatment of mild acne.

5.5 RISKS AND ANTICIPATED ADVERSE DEVICE EFFECTS THAT ARE TO BE ASSESSED

The anticipated adverse device effects that are to be assessed are the one described in section 4.2.

6- DESIGN OF THE CLINICAL INVESTIGATION

6.1 GENERAL

6.1.1 Description of the design

The study will be:

- ♦ in open
- ♦ intra-individual
- ♦ multiple sessions of application
- ♦ single centre
- ♦ on healthy subjects

6.1.2 Description of the measures to be taken to minimize or avoid bias

Not applicable.

6.1.3 Primary and secondary endpoints with rationale for their selection and measurement

6.1.3.1 Primary endpoint

Comparison of the change from baseline of total sum of lesions on each visit- objective counting of the lesions by the investigator.

6.1.3.2 Secondary endpoints

1. Pores and texture analysis – analysis using Colorface photographs: For pores analysis: front face image and PP polarization; For texture analysis: profiles images and CP and Std 60 polarization.
2. Visual effect - Colorface photographs
3. Investigator Global Assessment score
4. Patient Global Assessment score
5. Local and overall tolerance of the Crystal Peel
6. Subject's self-evaluation on D78 using a questionnaire
7. Adverse events number

6.1.4 Method and timing for assessing, recording, and analysing variables

Procedure (time-points)	**V1**	**V2**	**V3**	**V4**	**V5**
Intervals	**D0**	**D15 (+/-1)**	**D36 (+/-2)**	**D57 (+/-2)**	**D78 (+/-3)**
Checking the inclusion/non-inclusion inclusion/non-inclusion criteria	●				
Physical examination/Vital signs / medical history and treatment	●				
Informed Consent Form	●				
Pregnancy test	●				
Exclusion criteria	●	●	●	●	●
Use of associated treatment			●		
PEELING ACT		●	●	●	
Colorface Standardized Photos (X3)	●	●	●	●	●
Lesions counting	●	●	●	●	●
pores analysis by Newtone	●	●	●	●	●
texture analysis by Newtone	●	●	●	●	●
Local tolerance		●	●	●	●

Procedure (time-points)	**V1**	**V2**	**V3**	**V4**	**V5**
Intervals	**D0**	**D15 (+/-1)**	**D36 (+/-2)**	**D57 (+/-2)**	**D78 (+/-3)**
Dispense cosmetic products and daily log	●				
Collect daily log		●	●	●	●
Subjective evaluation questionnaire					●
IGA					●
PGA					●
Adherence control, record of AE, concomitant treatments	●	●	●	●	●
End of study form					●

6.1.5 Equipment to be used for assessing, recording and analysing variables and arrangements for monitoring maintenance and calibration

The device used for the photographs taking will be the Colorface®. The maintenance of device used for the clinical investigation were checked before study beginning. The calibration of these devices (by the technician) is done regularly.

6.1.6 Procedure for the replacement of subject

Subjects will not be replaced. It is planned to include 33 subjects to reach 30 evaluable subjects.

6.1.7 Investigation sites

The clinical investigation will be done on 1 site:

Centre # 1
Eurofins Dermscan Poland ul. Matuszewskiego 12 80 - 288 GDANSK POLAND

6.1.8 Definition of completion of the clinical investigation

The investigation will be completed after the last subject last visit.

6.2 INVESTIGATIONAL DEVICE

6.2.1 Description of the exposure to the investigational device

6.2.1.1 Dosage

2,5 ml of Crystal Peel applied with cotton bud. Application of 2,5 ml of the product in 3 layers.

6.2.1.2 Instructions for use

- 1 | CLEANSE

Cleanse the face using 4 pumps of Foamer 15, rinse and dry.

- 2 | PEEL APPLICATION

Pour 2.5 ml of Cyrstal Peel into a cup and apply to the face using 1 cotton bud. Apply with vertical and horizontal strokes across all areas. Always start by applying the product on the T-Zone, followed by the jawline and mouth, and finish with the cheeks. Apply up to 3 layers, waiting for 1 minute between each layer. Leave the last layer up to 5 minutes, whilst observing skin reaction. Rinse abundantly with water and dry the face. Remove immediately in case of intense reaction or pain.

6.2.1.3 Precautions for use

For external use only and for use on a limited area, due to the presence of Salicylic Acid. For adults only.

- Skin preparation is recommended 15 days before the first peel.
- Must only be used by trained healthcare professionals. Required knowledge of complications associated with the application of medical devices and how to react is necessary.
- Always use protective gloves during the procedure and clean the glass cup carefully between each peel session. Cotton buds should be disposed of after each use.
- Do not use alcohol or acetone-based cleanser.
- Avoid the lip area and nasolabial folds. Do not swallow.
- Avoid eyes and mucous membranes: in the event of accidental contact, rinse thoroughly with water, and use a saline solution.
- Avoid sun exposure and use sun protection (K Ceutic or Sun Ceutic 50+) for 4 weeks after the treatment and in-between treatments.
- Keep out of the reach of children.
- In case of alteration in the product's appearance, do not use the medical device.
- Protocol variations should be based on assessment of patient skin type, treatment tolerance and desired results.
- Do not apply on a large area or other areas of the body to avoid a high absorption of Salicylic Acid.
- Never hold the medical device above the patient to avoid accidental spillage.
- If an allergic reaction is considered likely, apply the product to a 1 cm² sized area behind the ear, following the exact same protocol. If no unusual reaction is observed within 72 hours, the facial peel can go ahead.

The practitioners are asked to refer to the last version available of IFU/IB.

6.2.2 List of other medical device or medication to be used during the clinical investigation

No other medical device or medication is planned to be used according to the CIP. However the associated cosmetic products are to be used during the investigation.
Accompanying products are commercially available products developed by DERMOSCIENCES LTD. They are used to prepare and protect the skin during the peeling procedures and to maintain the effect of the peeling.

Foamer 15 (15 % glycolic acid foamer):
- Use as a pre-peel: Cleanse the face with 4 squeezes spread over the whole face, rinse thoroughly after 2 minutes or as soon as the first tingling appears and dry.
- Use at home: Apply a small amount of foam to the clean and dry face.
Massage and rinse with water after two minutes or as soon as you start to feel tingling.
- Precautions: You may feel a tingling sensation. If discomfort occurs, reduce the frequency of frequency of use.
- Do not apply to irritated or damaged skin, or to the eyes and mucous membranes.
Avoid exposure to the sun.

Hyal Ceutic (Intense moisturizing cream):
- Use: Apply when skin needs moisturising, all over the face during the day as required.
- Precautions for use: Avoid contact with eyes and mucous membranes. In case of contact, rinse with plenty of water. Do not apply to open wounds.

Sun Ceutic teintée (SPF 50+ product, slightly teinted):
- Use: Every morning, apply evenly to the face, neck and décolleté 10 minutes before sun exposure. Reapply frequently.
- Precautions for use: Do not apply to irritated or damaged skin, or to the eyes and mucous membranes.
In case of contact, rinse with plenty of water. Avoid prolonged exposure to the sun, even with the cream.

DUAL+ (Night cream):
- Use: Apply in the evening to the full face focusing especially on the areas of concern. Increase frequency progressively, up to 2 times per day.
PRECAUTIONS You may experience a tingling sensation, redness and slight desquamation. In case of discomfort, reduce the frequency of use.

Do not apply to irritated or broken skin. Do not combine this product with other retinol-based products.
Avoid direct contact with eyes and mucous membranes.
During use, avoid exposure to sunlight without high SPF protection.
Not recommended for sensitive and/or very dry skin.
NB: All these cosmetic products are in the market

6.2.3 Concomitant acts and treatments

6.2.3.1 Collection of concomitant acts and treatments

Any concomitant medication or act at selection of the subject into the study must be reported on the source document and in the study Electronic Case Report Form at the initial visit and will be taken into consideration by the investigator deeming study eligibility.
Any modification on these treatments/acts during the study must be reported on the source document and in the study eCRF.
Use of any concomitant treatment will be recorded in the eCRF with the following information:

- Name of the treatment and unit strength;
- Indication for use of the treatment;
- Dose administered;
- Route of administration;
- Duration of treatment (start and stop date).

Use of any concomitant act will be recorded in the eCRF with the following information:

- Description of the act;
- Indication;
- Result;
- Duration (start and stop date).

6.2.3.2 Rescue treatment(s)

In case of adverse device effect affecting subject well-being, the investigator is authorized to interrupt the use of the investigational device and prescribe to the subject a rescue treatment.
The adverse event will be recorded in the subject's eCRF and source document, including details on rescue medication.

6.2.4 Number of investigational devices to be used

1 investigation device will be used per 1 subject.

6.3 STUDIED POPULATION

6.3.1 Inclusion criteria for subject selection

1. Healthy subjects
2. Gender: female and/or male.
3. Age: 18 – 45
4. Phototype I to IV according Fristzpatrick scale.
5. Healthy subject with normal physical examination results and a medical history compatible with the requirements of the study.
6. A healthy male or female subject with a medical diagnosis of mild to moderate facial acne vulgaris defined by at least 6 (six) inflammatory lesions, 12 (twelve) non-inflammatory lesions and no more than 2 (two) nodules (the nose is excluded for lesion count purposes).
7. Subject declares to avoid exposure to UV radiation (tanning booths, phototherapy and sun) on the face for at least three months prior to the selection visit and agrees to avoid it throughout the study.
8. Subject agrees not to apply any cosmetic, medical or aesthetic treatments outside the study protocol on the face for the duration of the study.
9. For female subjects:

Female subject not in childbearing status (tubal ligation, hysterectomy, bilateral oophorectomy),

or

Female subjects of childbearing potential who, in the opinion of the investigator, are using a reliable method of contraception (pill or contraceptive patch, IUD, implant or vaginal ring,condoms) for at least one month prior to the screening visit. Subject willing to continue using contraception during the study and one month after the end of the study.

6.3.2 Exclusion criteria for subject selection

1. Pregnant or nursing woman or planning a pregnancy during the study.
2. Subject who had been deprived of their freedom by administrative or legal decision or who is under guardianship.
3. Subject in a social or sanitary establishment.
4. Subject participating to another clinical research or being in an exclusion period for a previous study.
5. Intensive exposure to sunlight or UV-rays within the previous 3 months and foreseen during the study.
6. Subject with any skin or systemic disease (acute and/or chronic), in the previous year, likely to interfere with the measured parameters or to put the subject to an undue risk.
7. Subject having history of allergy or hypersensitivity to one of the components of the tested device.
8. Subject receiving any treatment that, in the opinion of the clinical investigator, may interfere with test results or put the subject to undue risk.
9. Subjects on topical or oral treatments (such as Benzoyl Peroxide, Retinoic Acid, Isotretinoine) that did not stop the treatment 30 days before their first peel (risk of over-peeling).
10. Subjects with known salicylism or related medical indications.

6.3.3 Recommendations and restrictions

Subjects will be asked to comply with the following study recommendations:
Report any adverse events to the investigator,
Do not take any new medication without informing the investigator, even paracetamol
No sunlight or UV light on the face for the duration of the study,
No make-up on the face for 12 hours prior to the peel and assessment visits
No make-up on the face during the 12 hours prior to the peeling and evaluation visits,
In case of non-compliance with these recommendations, the investigator should report the in Deviation log or if necessary contact the sponsor
If these recommendations are not followed, the investigator can decide on the subject's withdrawal or should contact the sponsor to discuss the withdrawal of the subject if necessary,

6.3.4 Criteria and procedures for subject withdrawal or lost to follow-up

6.3.4.1 Criteria and modalities for drop out subjects

Subjects will be free to withdraw from the study at any time if they wish so and for any reason, without having to provide any justification to the investigator.
The investigator has the right to withdraw a subject for any reason, for its best interests, including illness or an adverse event.
The sponsor may decide to withdraw subjects for major deviation to the protocol, for administrative reasons or for any other valuable reason ethically justified.

Subjects may discontinue their participation in the study for the following reasons:

1. *Eligibility: Inclusion/Exclusion criteria*
2. *Adverse event:* the investigator has the right to withdraw a subject in case of intercurrent illness or adverse events or if in the investigator's opinion, continuation in the study would be detrimental to its well-being.
3. *Consent withdrawal:* subject have the right to withdraw his consent at any time and for any motive, without their right to treatment being affected.
4. *Untraceable subject* if a subject does not come to the scheduled visits, several attempts have to be done to try to contact him/her; to obtain the reasons for non-attendance.
5. *Protocol non-adherence:* the investigator has the right to withdraw a subject in case the subject does not respect the study procedures and/or restrictions.

6. *Other:* administrative or personal reasons for instance

6.3.4.2 Modalities of recording data for drop out subjects

In all cases, the reason for withdrawal must be recorded in the eCRF and the source document and should include any available and appropriate complementary information.

The investigator must make every effort to contact subjects who dropped-out of the study early. In the case where no visit is possible a registered letter with acknowledgement of receipt may be sent to the subject. All the documentation concerning that subject must be as complete as possible.

6.3.4.3 Modalities for the follow-up of drop out subjects

At the study end visit, the investigator will check subject's health and if there is no reason for additional follow-up, he will complete study end form accordingly.

In the case of early study termination, the investigator must make every effort to contact the subject. The subject must be followed up to state the reason for withdrawal and to establish whether the reason is an adverse event. Since the moment the investigator knows the early termination or exclusion, the withdrawal of the subject must be if possible formalized by a visit. If possible, all examinations scheduled for the final study day must be performed on all subjects who received the investigational device but do not complete the study according to the protocol.

When the premature exit is due to an adverse device effect or an adverse event linked to the CIP procedures, the subject must be followed by the investigator until the resolution or the stabilization of the symptoms.

6.3.5 Enrolment procedure

Subjects will be pre-selected by phone from Eurofins Dermscan Pharmascan data base, according to inclusion and exclusion study criteria. This data base is constituted from registration files of people wishing to participate in clinical studies at Eurofins Dermscan Pharmascan.
Advertisement will be placed in Eurofins Dermscan Pharmascan website.

Pre-selected subjects will come to the site for consent form signature on D0 visit and then will be included if eligible according to inclusion and exclusion criteria. The informed consent process is explained in section 13.

6.3.6 Randomization procedure

None.

6.3.7 Duration of the clinical investigation

Clinical investigation beginning: Q4 2022
Clinical investigation end: Q1 2023
Clinical investigation global duration: 17 weeks
Duration by subject: 78 days

6.3.8 Sample size

33 subjects will be included in total on Sponsor's request.

6.3.9 Enrolment period

The enrolment period will last approximately 6 weeks to include the 30 subjects.

6.3.10 Relationship of investigation population to target population

The investigation population and the target population are the same.

6.3.11 Information on vulnerable population

Not applicable.

6.3.12 Subjects' identification

Each subject having signed a consent form will be assigned a "screening subject number" according to his/her chronological order of arrival in the study, from 501, preceding by the letter "S" (i.e. S501).
Then, each subject included will be assigned a "subject number" identifying him/her according to his/her chronological order of selection in the study and from 01.
In addition, each subject will be identified with the first letter of name and first letter of first name.

6.3.13 Financial compensation

A **compensation of 300 PLN** for the constraints suffered and the incurred travel expenses will be paid following the end of subject's participation in the study, if the missing elements (product(s), questionnaire(s), daily-log etc.) are brought back and if all the visits, acts and measurements were made. In case of subject's withdrawal from the study, failure to follow instructions given in the information sheet or in case of premature study end for sanitary or administrative reason, the compensation will be paid proportionally to the duration of subject's participation in the study, to acts made (linked to the investigational device) and associated constraints and to the number of available evaluations.

6.3.14 ID card

Each subject receives, from the investigational site, a personal identification card to be kept for the duration of the study. The card will specify: subject name and number, sponsor name, study reference, beginning date and scheduled study end, investigation site address with the name and phone number of the investigator and the urgent phone number.

6.4 PROCEDURES

6.4.1 Description of all the clinical investigation-related procedures that subjects undergo during the clinical investigation

6.4.1.1 Staff involved in the study

There will be three different kinds of personnel involved in the study:
- Investigators performing the peeling act (qualified practitioners): they will oversee the inclusions of subjects and they will be in charge of the device application;
- Live independent evaluators (investigators): the follow-up of subject's and the scoring in live.
- Technicians: operators: they will oversee the photographs taking .

6.4.1.2 Study schedule

Visit 1: D0

- Subjects will come to the investigational site with their completed diary.
- Information of the subjects on study aims and schedule.
- Signature of consent form in two copies by the subject and the investigator in charge of the screening visit.
- Medical examination for verification of subject's health state, collection of previous medical history, previous and actual treatments.
- A urinary pregnancy test will be performed for women with childbearing potential.
- Checking of inclusion and exclusion criteria.
- Distribution to the subjects of accompany treatment with the instructions of use.
- Colorface standardized photos will be taken by the Technician.
- Acne lesions will be counted by the Investigator.
- Distribution of the ID card and diary so they can note the adverse events and concomitant treatments / acts.

Visit 2, 3 and 4: D15, D36 and D57

- Subjects will come to the investigational site with their completed diary.
- Checking of exclusion criteria.
- Colorface standardized photos will be taken by the Technician.
- Acne lesions will be counted by the Investigator.
- Peeling act will be performed by the Investigator.
- Record of AE and concomitant treatments.

Visit 5: D78

- Subjects will come to the investigational site with their completed diary.
- Checking of exclusion criteria.
- Colorface standardized photos will be taken by the Technician.
- Acne lesions will be counted by the Investigator.
-Subjective questionnaire.
-Scoring of Patient global assessment.
-Score of Investigator global assessment.
-Record of AE and concomitant treatments.

6.4.2 Description of effectiveness parameters

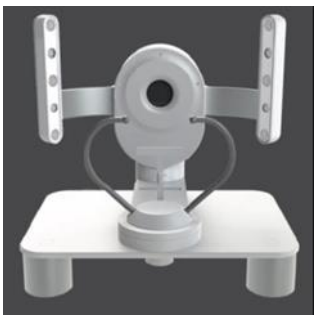
6.4.2.1 Counting of the acne lesions

Investigator will perform acne lesions counting (front, 2 cheeks, the chin above the jaw line (excluding the nose)) using both visual observation and palpation on each visit (baseline, D15, D36, D57 and D78.
Total lesions will be defined as the sum of inflammatory lesions (papules, pustules), non-inflammatory lesions (whiteheads and blackheads) and other acne lesions (nodules).

The change of the number of acne lesions from baseline will be calculated on each visit.

6.4.2.2 ColorFace©

The ColorFace© acquisition system is a dedicated solution developed by Newtone Technologies for standardized imaging in the clinical study setting for evaluation of a clinical effect [20]. This innovative solution is based on a high-resolution sensor to obtain high-quality standardized images (24M pixel sensor). In addition, specific lighting allows multimodal captures in cross polarization, parallel polarization, standard lighting and ultraviolet for analysis.



The ColorFace® ensures reliable and reproducible repositioning of subjects over time, thanks to an ear support coupled with a control of the head tilt and by a real-time visualization by the operator. Without chin strap or retention system on the forehead, it allows full exploitation of the face.

Three pictures of subject's face at rest (1 front face picture and 2 profiles 45° pictures) will be taken at D0 and at each time point after the baseline (D15, D36 and D57 before the MD application).
NB:
For pores analysis: front face image and PP polarization
For texture analysis: profiles images and CP and Std 60 polarization

6.4.2.3 Pores and texture analysis by NEWTONE

After thorough quality control of the images, the images will be analyzed with a focus to pores (in parallel polarized light in front views) and cheek (or other relevant area) texture (in cross-polarized (CP) light profile views or standard 60 light (std60) profile views.

Pores analysis will provide parameters of the pores visibility (conspicuous surface, length, volume, density of pores, and average surface of detected pores) and will enable conclusion on the evolution of these elements overtime under the effect of the treatment.

Texture will be analyzed either with a colorial texture analysis (in CP images) or the line marks approach (in std60 images).

- Colorial texture is an approach to apprehend the evolution of the skin contrasts and pixels luminosity organization evolution overtime, and possible consequence on the perception of the skin surface roughness. Colorial contrast and entropy parameters will be delivered. To reveal texture and roughness evolution of the skin this analysis should be performed in skin areas where the colour organization does not evolve significantly.

- Line marks analysis is an approach to apprehend the detection and followup of small oriented surface elements that contribute to the skin roughness perception. Paraleters related to these elements visibility will be provided. To reveal texture of and roughness evolution overtime, this analysis should be performed in skin areas where the colour organization does not evolve significantly. Gloss evolution may also impact this analysis and will be taken into account to the choice of the approach.

One or the other of these approaches will be used depending of the images received.
The region of interest will also be defined as regards analysis relevance in the context of the study endpoint.

6.4.2.4 Investigator Global Assessment

The investigator (the second evaluator not performing the peeling act) will evaluate the global effect of the medical device on D78.

☐	☐	☐	☐	☐
Worse -1	No improvement 0	Slight improvement 1	Good improvement 2	Very good improvement 3

6.4.2.5 Patient Global Assessment

The subject will evaluate the global effect of the medical device on D78.

☐	☐	☐	☐	☐
Worse -1	No improvement 0	Slight improvement 1	Good improvement 2	Very good improvement 3

6.4.2.6 Subjective questionnaire

Subjects will be asked to complete the satisfaction questionnaire on D78.

6.4.3 Description of safety parameters

6.4.3.1 Local tolerance

At the end of the study, the local tolerance on the skin of the product will be assessed during the clinical examination. Abnormal clinical signs and subjective signs reported by the subjects will be reported in the CRF.

According to these signs, the **local tolerance** of the product will be defined on the following scale:

0= Bad tolerance
1= Moderate tolerance
2= Good tolerance
3= Very good tolerance.

6.4.3.2 General tolerance

Collection of adverse events by the investigator.

6.4.4 Description of activities performed by sponsor representatives

The sponsor has delegated the following activities to the CRO (Eurofins Dermscan Pharmascan):

- Overall management of the study: document writing, coordination and training of staff participants, study realization and inclusions status follow-up.
- Submission of the study files to the Ethics Committee (EC) and Competent Authority (CA).
- Management of investigators contracts and fees payment.
- Data management
- Statistical analysis and clinical investigation report writing.

6.4.5 Any known or foreseeable factors that may compromise the outcome of the clinical investigation or the interpretation of results and the methods for addressing these factors

None.

6.4.6 Justification of follow-up period duration

The follow-up period of 78 days shall permit the demonstration of investigational device clinical effectiveness and safety. This period is sufficient to represent a realistic test of the investigational device and allow any risks associated with adverse device effects to be identified and assessed.

6.4.7 Medical care and follow-up to be provided for the subjects after the clinical investigation has been completed

No medical care nor follow-up will be provided after the clinical investigation end (Last Subject Last Visit; see section 6.1.9) unless the subject presents an ongoing adverse device effect or adverse event linked to the CIP procedures at its last visit. In that case, the subject will be followed-up by phone or with a visit to the laboratory until resolution of the adverse event.

6.4.8 Disposition/Future use of samples obtained from subjects

Not applicable. No samples will be taken for this investigation.

6.5 MONITORING PLAN

6.5.1 General outline of the monitoring

The monitoring of the study will be done by Eurofins Dermscan Pharmascan. The Clinical Research Associate (CRA) has the responsibility to familiarise the investigators and the investigation site staff involved in the study with all applicable study Standard Operating Procedures (SOPs). The CRA has the responsibility

of reviewing the ongoing study with investigators to verify adherence to the CIP and to deal with data queries as well as any problems that arise during the conduct of the study.

A monitoring plan will be written and validated by the sponsor before any monitoring activities can be performed.

6.5.2 Access to source data

In accordance with good clinical practices and the standards of the data protection law, data obtained during a research involving human beings must be treated confidentially to guarantee the subjects' data privacy.

The investigator agrees that, subject to local regulations and ethical considerations, the sponsor representatives' designee and/or and any regulatory agency have direct access to all study records, CRFs, corresponding subject medical records, study drug dispensing records and study drug storage area, and any other documents considered as source documentation. The investigator also agrees to assist the representative, if required.

6.5.3 Extent of source data verification

The monitoring strategy is defined in agreement with the sponsor and depends on several factors to take into consideration during the risk assessment:

- Monitoring type (on-site, a combination of on-site and remote (centralized), or centralized monitoring only).
- Monitoring frequency (early, initial assessment or throughout the study)
- Monitoring extent (100% data verification, targeted or random review of certain data).

The choice of monitoring strategy is also based on the following criteria:

- Study duration
- Number of subjects to randomize, populations of subjects
- Investigational sites (number, subsidiary or not, geography)
- Investigator experience in clinical trials and previous experience with him
- Study design / protocol complexity
- Principal endpoint of the study (subjective/objective, of effectiveness or safety or mixed)
- Type of collected data.

On Sponsor's request, a 100% documents review will be done.
The CRA ensures the coherence and the veracity of the data reported in the CRF compared to the source data and the CIP.

7- STATISTICAL DESIGN AND ANALYSIS

The statistical analysis will be performed by the CRO biostatistician.

The applicable statistical methods will be described, in this CIP section.

7.1 ANALYSIS POPULATION AND PROCEDURES THAT TAKE INTO ACCOUNT ALL THE DATA

The following analysis populations will be studied and will be considered for the statistical analysis:

- Safety population: any subject having used the investigational device.
- ITT (Intent-to-Treat): any subject included and randomized in the study with at least a post-basal value.
- PP population: any subject included and randomized having used at least once the investigational device and without any major deviation to the CIP.

In case the ITT and PP population differ by less than 10%, only the ITT population will be analyzed.

7.2 DESCRIPTIVE STATISTICS AND ANALYTICAL PROCEDURES

The analysis of the effectiveness parameters will be performed on the ITT and PP population.
The analysis of the safety/tolerance parameters will be performed on the "safety" population.

The continuous variables will be summarized using the descriptive statistics for quantitative data (number of valid values, number of missing values, means, standard deviations, standard errors of the mean, medians, minimum values and maximum values) for each time.
The categorical data will be summarized in frequency (N) and percentage (%) by time point.

7.2.1 Primary endpoint

Comparison of the change from baseline of total sum of lesions on each visit- objective counting of the lesions by the investigator.
Total lesions will be defined as the sum of inflammatory lesions (papules, pustules), non-inflammatory lesions (whiteheads and blackheads) and other acne lesions (nodules).

7.2.2 Secondary endpoint(s)

• Pores and texture analysis (will be performed by Newtone with Colorface acquisitions)
• Visual effect (Standardized anonymized photographs (face, 45° at left, 45° right) with Colorface)
• Investigator Global Assessment
• Patient Global Assessment
• Local and overall tolerance of the Crystal Peel, a salicylic acid-based peel, used under the normal conditions of use recommended by the manufacturer.
• Subject's self-evaluation on D78 using a questionnaire.
• Potential adverse events collection.

Analysis of primary and secondary endpoints 'parameters:

For each continuous variable obtained from devices: A mixed linear model for repeated measurements (PROC MIXED) will be fitted to raw data.

Using the adjusted means obtained from this model (LS-Means), the contrast of interest will be built:

- To assess the change from first measurement at each time

The underlying assumptions (normality and homoscedasticity of residuals) will be checked using Shapiro-Wilk test (α=0.01) and graphical representations.
In case of strong deviation, a transformation of the data or a non-parametric approach (Wilcoxon signed rank tests) will be performed.

The raw score will be summarized using descriptive statistics for quantitative data by time point. A Wilcoxon signed rank test will be applied to test whether the change from baseline is statistically significant.

The categorical data will be summarized in frequency (N) and percentage (%) associated with its 95% confidence interval by time point.

The questionnaire will be summarized in frequency (N) and percentage (%).

The adverse events will be analysed.

7.3 SIGNIFICANCE LEVEL AND POWER OF PRIMARY ENDPOINT(S)

All statistical tests will be assessed at α = 5% level of significance in a bilateral approach.

7.4 SAMPLE SIZE AND ITS STATISTICAL JUSTIFICATION

The number of subjects determined is standard for this kind of study and is considered as sufficient to reach the study objectives, and thus, based on previous experiences.

7.5 PASS/FAIL CRITERIA TO BE APPLIED

7.5.1 Primary endpoint

Not applicable

7.5.2 Secondary endpoint(s)

Not applicable

7.6 PROVISION FOR AN INTERIM ANALYSIS AND CRITERIA FOR THE TERMINATION OF THE CLINICAL INVESTIGATION ON STATISTICAL GROUNDS

As no interim statistical analysis has been planned, no statistical criteria for the termination of the clinical investigation have been defined.

7.7 MANAGEMENT OF BIAS

Not applicable.

7.8 MANAGEMENT OF CONFOUNDING FACTORS

No confounding factor was identified.

7.9 DESCRIPTION OF CONTROL PROCEDURES FOR MULTIPLICITY AND ADJUSTMENT OF ERROR PROBABILITIES

Not applicable.

7.10 SPECIFICATION OF SUBGROUPS FOR ANALYSIS

No subgroup analysis is planned to be made.

7.11 MANAGEMENT AND JUSTIFICATION OF MISSING, UNUSED OR SPURIOUS DATA, INCLUDING DROP-OUTS

No strategy for taking in charge missing data has been defined. Data that are not valid or missing will be considered and treated as missing data.

7.12 PROCEDURE FOR REPORTING DEVIATIONS FROM THE ORIGINAL STATISTICAL PLAN

Any modification to the statistical analysis plan due to a substantial modification of the CIP will be documented as an amendment and will be described in the final study report if applicable.

8- DATA MANAGEMENT

8.1 METHODS FOR DATA ENTRY AND COLLECTION

8.1.1 Identification of source data

Source data are all information in original records of clinical findings, observations, or other activities of the clinical investigation necessary for the reconstruction and evaluation of the clinical investigation.

The data related to the subjects' characteristics, to their current or previous medical state and to the safety of the device will be notified in the subject's source document and the eCRF.

Source data for photographs are acquisitions made at each kinetics and for each zone and will be saved on the device's specific software and then on Eurofins Dermscan internal network.

A list identifying the location of source data on each investigation site will be prepared by the CRO before the study start.

8.1.2 Data collection

At each visit of the subject, the investigator or delegate reports in the source document the data related to the subject's health state, and the safety and effectiveness of the device. These data are then reported in the subject's eCRF. Some effectiveness data are directly recorded within data capture software for measurement instruments and are not reported in the eCRF.
One source document and one eCRF must exist for each subject having signed an informed consent.
The eCRF is designed to identify each subject by a subject number and, where appropriate, subject's initials.
The eCRF pages are validated by the principal investigator by electronic signature before data analysis.
An eCRF guideline will be edited and distributed to investigational site.

8.1.3 Data entry

The solution used for the eCRF is the one from DataCapt.

8.2 PROCEDURES USED FOR DATA REVIEW, DATABASE CLEANING AND ISSUING/RESOLVING DATA QUERIES

8.2.1 Audit trail

The solution used for the eCRF contains an audit trail that will be extracted at the study end.

8.2.2 Data queries

Queries (missing data, inconsistencies…) will be edited by the CRA in charge of the monitoring directly in the eCRF. All queries must be answered before the database lock.

8.2.3 Medical coding

None.

8.2.4 Data Review

Data review will be performed by the project manager. Inconsistencies detected will be solved by the project manager or the concerned person.
The study review aims at determining the analysis population by:

- reviewing the conditions of study's realization,
- specifing all the CIP's deviations liable to lead the skew into statistical analysis,

- reviewing the statistical analysis plan if needed.

Following the data review, the statistical analysis populations will be defined and a report will be written and validated by the CRO and the sponsor.

8.2.5 Preparation of the Database and Locking

The database will be prepared in accordance with the data review conclusion.
The database will be locked upon resolution of all queries. A copy of the locked database will be sent to the sponsor certifying that the database has been locked. A signed database lock form will be provided.

After the database has been locked, any change to the database can only be done upon approval of the CRO and the sponsor. If the database needs to be corrected, unlocking/relocking must be clearly documented in the TMF (Trial Master File).

8.2.6 Data unblinding

Not applicable

8.2.7 Final Report

A final report according to ISO 14155:2020 will be written by the CRO project manager. A draft will be sent to the sponsor for validation. This final report will be signed by the coordinating investigator, the CRO, the biostatistician and the sponsor.

8.3 PROCEDURES FOR VERIFICATION, VALIDATION AND SECURING OF ELECTRONIC CLINICAL DATA SYSTEMS, IF APPLICABLE

An eCRF will be used for this study. eCRF conception and data-management will be managed with DataCapt which answers to all international regulatory requirements.

8.4 PROCEDURES TO MAINTAIN AND PROTECT SUBJECT PRIVACY

In this study, the CRO and investigation site will process personal data of subjects having signed a consent form on behalf of the sponsor, who is the data controller, in accordance with the rules of the protection of personal data and, in particular, the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data.
For this purpose, the CRO and investigation site commit themselves to only collect personal data which are needed for analysis and for the control of clinical data generated, by ensuring their security and integrity and by guaranteeing their confidentiality.
The CRO will make sure beforehand and throughout the duration of the data-processing:
- of the compliance with the obligations of the applicable data protection law,
- to inform subjects of their personal data-processing and obtain the prior consent for their collection,
- to implement and maintain appropriate technical and organisational measures.

To guarantee the confidentiality of collected data, the name and other information's allowing to identify the subject will not be included in the study results. Subject's will be identified only by a code composed of subject number and first letter of name and first name. Only the investigator and authorized personnel on site will be able to link this code to subject's name. The re-identification, if necessary, will be done according to a list or via this informed consent form which is kept and archived on site in the Investigator Site File (ISF). This list is only available on site and will not be sent to the CRO nor the sponsor.

According to Article 14 of GDPR, the concerned subject must be informed of the identity and the contact details of the controller and, where applicable, of the controller's representative.
In this clinical investigation, subject's may exercise their rights at any time from the investigator.

8.5 PROCEDURES AND PERIOD FOR DATA RETENTION

The sponsor must archive the CIP, documentation, approvals and all other essential documents related to the study, including certificates that satisfactory audit and inspection procedures have been carried out, for a duration of 15 years. Eurofins Dermscan Pharmascan will archive all documents concerning the study as detailed below:

- All documents must be archived in a secure place and treated as confidential material.
- Paper documents will be stored maximum during one year before being transmitted for archiving to an approved service provider or on site.
- Data will be archived securely as digital and/or paper version for 15 years from the date of dispatch of the final report's acceptance.

At the end of this period, the study archives will be destroyed unless otherwise stipulated in writing by the sponsor.

8.6 OTHER ASPECTS OF CLINICAL QUALITY ASSURANCE

In order to ensure the conformity of the studies entrusted to Good Clinical Practices (including Medical Devices' GCP as defined in ISO 14155:2020) and regulatory requirements, Eurofins Dermscan Pharmascan has implemented a quality management system which has been certified ISO 9001:2015.

9- AMENDMENTS TO THE CLINICAL INVESTIGATION PLAN

The sponsor or the principal investigator might modify the CIP for ethical, medical or scientific reasons.
No change can be implemented at investigational sites without having obtained the favourable opinion of the sponsor, unless there is an immediate risk for the safety or well-being of the subjects.

These changes will be documented in the TMF and communicated to investigational sites as soon as possible.

If the modifications are considered as substantial by the sponsor (that are likely to have a substantial impact on the safety, health or rights of the subjects or on the robustness or reliability of the clinical data generated by the investigation), changes will be submitted to obtain the opinion of EC and approval of the President of the Polish Competent Authority (Urząd Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych).

10- DEVIATIONS FROM CLINICAL INVESTIGATION PLAN

The investigators are not allowed to deviate from the CIP, except under emergency circumstances, to protect the rights, safety and well-being of the subjects.

10.1 PROCEDURES FOR EVALUATING SUBJECT COMPLIANCE

The devices will not be handled by subjects.

At each visit, subjects will be questioned concerning the use of any topical or systemic prescription or other products. Subjects will also be questioned about prohibited activities such as sun exposure.

The investigator will instruct the subject of the importance of adhering to the protocol. If it can be proven that the subject is obviously not compliant, the investigator can decide to withdraw him from the study.

10.2 PROCEDURES FOR RECORDING, REPORTING AND ANALYSING CIP DEVIATIONS

All CIP deviations will be managed according to Eurofins Dermscan Pharmascan Standard Operating Procedure (SOP).

Deviations to the CIP should be classified as:

- **Minor** if they don't impact the rights, safety or well-being of the subjects. They do not increase the risk or do not diminish the benefit for the subject and/or do not have a significant effect on the integrity of the data collected,
- **Major (or CIP violations**) if they affect the rights, safety or well-being of participants. They increase the risk or diminish the benefit for the subject and/or have a significant effect on the integrity of the data in the study.
- **Critical:** if violations of the protocol as mentioned above that necessarily require suspension or closure of the study.

If a major deviation is reported/observed during the study, the investigator may decide to drop-out the subject of the study or not.

If the deviation is detected after the study end, the case will be discussed during the « data review » which occurs before data analysis.

10.3 NOTIFICATION REQUIREMENTS AND TIME FRAMES

Major deviations, in case of emergency, to protect the rights, safety and well-being of the subjects are reported to the sponsor and the EC as soon as possible according to Eurofins Dermscan Pharmascan SOPs. Minor deviations are reported to the sponsor and the EC at the study end.

10.4 CORRECTIVE AND PREVENTIVE ACTIONS AND PRINCIPAL INVESTIGATOR DISQUALIFICATION CRITERIA

If major deviations from the investigator is observed during the study, the CRA will warn the investigator of the importance to respect the CIP. An investigator who continuously violates the CIP despite CRA warnings could be excluded from the investigation with the approval of the sponsor.

11- DEVICE ACCOUNTABILITY

Investigational devices should only be dispensed under the supervision of the investigator or personnel approved for the study.

The device will be used only under conditions defined in this CIP and only for included subjects.

The CRO must keep an updated dispensation form which contain the subject number, the amount of MD dispensed to and returned at each visit, with the corresponding dates. This will be collected on a specific form.

All devices supplied as part of the investigation (empty containers, as well as used, partly used or unused devices) must be available for inspection at every monitoring visit. The CRA should verify the investigational site's devices accountability records against record of administrated doses in the source document. All MD (wasted and unused) will be destroyed accordind to Dermscan Poland procedures at the end of the study.

At study end, a reconciliation of MD supplies will be done by the CRO.

12- STATEMENTS OF COMPLIANCE

12.1 REGULATORY ASPECT

The study will be performed in accordance with:

- this CIP,
- the Good Clinical Practices (GCP)
- the EU regulation 2017/745 of 5 April 2017 and ISO 14155:2020 standard,
- the ethical principles that have their origin in the Declaration of Helsinki and its later modifications,

- the European Directive 2001/20/CE transposed in Polish Law (version of 07.08.2009, amended by the European Regulation # 596/2009 dated on June 18, 2009 - Dziennik Urzędowy, # L188, page 14).

This CIP will be submitted for opinion to an Ethics Committee (EC) and for authorization to the Polish competent authority (URPL).

12.2 ETHICS COMMITTEE

It is the responsibility of the sponsor or its legally designated representative to submit a copy of the CIP and of the detailed subject information sheet and consent form to an ethics committee in order to obtain independent approval before the conduct of the study.
The clinical investigation cannot begin until the favorable opinion of the ethics committee has been obtained. The approval of the ethics committee must be sent in writing, to the sponsor or its legally designated representative and then to the investigator. The EC approval letter must mention the members and their quality. Any additional requirements imposed by the EC must be met, if appropriate.

12.3 COMPETENT AUTHORITY (CA)

After receiving EC approval, the sponsor or its legally designated representative must address an authorization request the Polish competent authority (URPL).

It is the responsibility of the sponsor or its legally designated representative to submit a copy of the CIP and detailed information regarding investigational device to the competent authority. The clinical investigation cannot begin until the approval of the CA has been obtained when required. Any additional requirements imposed by the CA must be met, if appropriate.

12.4 INSURANCE

The sponsor has subscribed an insurance contract covering the cost of treatment of subjects in the event of clinical investigation related injuries, if applicable, the financial consequences of the liability of all investigators, the sponsor itself and anyone involved in the study.

The collaboration agreements are established by the sponsor.
The copy of the insurance certificate is presented separately in the EC submission file.

12.5 FINANCING OF THE CLINICAL INVESTIGATION

The clinical investigation is entirely financed by the sponsor. The sponsor is responsible for the clinical investigation funding in its totality including the investigators payment, subject's compensation and treatment of potential AE connected with the study product/procedures.

An agreement has been signed between the sponsor and the CRO (Eurofins Dermscan-Pharmascan).
The sponsor has delegated to the CRO the signature of the agreements with the clinical investigation sites and investigators.

13- INFORMED CONSENT PROCESS

13.1 GENERAL INFORMATION

Voluntary written informed consent form must be obtained from each subject prior to perform any study related procedures in compliance with the recommendations of the declaration of Helsinki. Subject should not be screened or included before the subject has signed an approved informed consent form, written in a language that is understandable to him.

The investigator, or delegates, will give both verbal and written information and explain the nature, purpose, and risks of the study. The subject will be informed that he has the right to withdraw at any time from the study, without giving reasons. The informed consent process must take place under conditions where the

subject has adequate time to consider the risks and benefits associated with his participation in the study. The informed consent form should be personally signed and dated in two originals by the subject and the person who conducted the informed consent discussion.

The investigator is responsible for ensuring the appropriate content of the informed consent form and that informed consent is obtained from each subject in accordance with all applicable regulations. The informed consent form will be reviewed and approved by the sponsor and the EC.

Each subject should receive one original of the signed and dated written informed consent form.

The second original of the signed and dated informed consent form should be retained in the investigator's file. The investigator should maintain a log of all subjects who signed the informed consent form.

No copy of this log will be given to the CRO nor the sponsor.

In the case of new information, requiring the signature of a new informed consent, the subjects will be informed as soon as possible.

13.2 PROCESS FOR SUBJECT'S INFORMATION AND CONSENT OBTAINING ON INVESTIGATIONAL SITE

A first information about the study aims and investigational device will be given by phone by the centre recruitment team (see section 6.3.5; phone call lasts approximately 15 minutes).

At screening visit (at least 24h before D0 visit), the investigator or delegates will again inform the subject about the study aims and constraints as well as the investigational device and will give him two paper copies of the informed consent form. After a reflexion time of 20 minutes on site and after all further questions are resolved, if the subject agrees to participate to the study, he will be asked to date and sign the informed consent in two original copies.

14- ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

14.1 DEFINITIONS

Table below presents categorization of adverse events:

<table>
<tr><th>Adverse events</th><th>Non-device-related</th><th colspan="2">Device- or investigational procedure-related</th></tr>
<tr><td>Non-serious</td><td>Adverse Event (AE)[a]</td><td colspan="2">Adverse Device Effect (ADE) [c]</td></tr>
<tr><td rowspan="3">Serious</td><td rowspan="3">Serious Adverse Event (SAE)[b]</td><td colspan="2">Serious Adverse Device Effect (SADE)</td></tr>
<tr><td>Anticipated</td><td>Unanticipated</td></tr>
<tr><td>Anticipated Serious Adverse Device Effect (ASADE)</td><td>Unanticipated Serious Adverse Device Effect (USADE)</td></tr>
<tr><td colspan="4">a Includes all categories
b Includes all categories that are serious
c Includes all categories that are related to the device or the investigational procedure</td></tr>
</table>

14.1.1 Adverse event (AE)

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 and whether anticipated or unanticipated.

NOTE 1: This definition includes events related to the investigational medical device or the comparator.

NOTE 2: This definition includes events related to the procedures involved.

NOTE 3: For users or other persons, this definition is restricted to events related to the use investigational medical devices or comparators.

14.1.2 Adverse device effect (ADE)

Adverse event related to the use of an investigational medical device.

NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

NOTE 3: This includes 'comparator' if the comparator is a medical device.

14.1.3 Device deficiency

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance.

NOTE 1: Device deficiencies include malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labelling.

NOTE 2: This definition includes device deficiencies related to investigational medical device or the comparator.

14.1.4 Serious adverse event (SAE)

Adverse event that led to any of the following:

a) death,

b) serious deterioration in the health of the subject, that resulted in any of the following:

1. life-threatening illness or injury,
2. permanent impairment of a body structure or a body function,
3. hospitalisation or prolongation of patient hospitalization,
4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
5. chronic disease,

c) foetal distress, foetal death, or a congenital physical or mental impairment or birth defect.

NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

14.1.5 Serious adverse device effect (SADE)

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

14.1.6 Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current risk assessment.

NOTE 1: anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity, or outcome has been identified in the risk assessment.

14.1.7 Serious health threat

Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons.

NOTE 1: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

14.1.8 Severity definition

The severity of adverse events can be graded on a three-point scale:

* **Mild**: Slight inconveniences, without any effects on the daily activities, no concomitant treatment taking.
* **Moderate**: Some inconveniences, some effects on the daily activities and/or possibility to take concomitant treatment to resolve the event.
* **Severe**: Big inconveniences having an impact on the daily activities and/or concomitant treatment necessary.

14.1.9 Relationship to the investigational device and investigation procedures

The relationship between the use of the medical device (including the medical/surgical procedures described in section 2.9) and the occurrence of each adverse event shall be assessed and categorized as described in the MDCG-2020-10/1 guidelines.
The relationship of each adverse event to the investigation procedures must also be assessed and categorized in the same way.

During causality assessment activity, clinical judgement shall be used and the relevant documents, such as the Investigator's Brochure, the CIP or the Risk Analysis Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant treatments, the natural history of an underlying disease, other concurrent illness or risk factors shall also be considered.

Each AE will be classified according to four different levels of causality:

1. Not related
2. Possible
3. Probable
4. Causal relationship

The sponsor and the investigators will use the following definitions to assess the relationship of the adverse event to the investigational device or the investigation procedures.

1. **<u>Not related</u>:** Relationship to the device or procedures can be excluded when:
   - the event has no temporal relationship with the use of the device or investigation procedures;
   - the adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
   - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the adverse event;
   - the event involves a body-site or an organ that cannot be affected by the device or procedures;

- the serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the adverse event.

2. **Possible:** The relationship with the use of the investigational device, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

3. **Probable:** The relationship with the use of the investigational device, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

4. **Causal relationship:** the adverse event is associated with the investigational device or with procedures beyond reasonable doubt when:
   - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
   - the event has a temporal relationship with investigational device use/application or procedures;
   - the event involves a body-site or organ that
     - o the investigational device or procedures are applied to;
     - o the investigational device or procedures have an effect on;
   - the adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
   - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the adverse event (when clinically feasible);
   - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
   - harm to the subject is due to error in use;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the adverse event.

The sponsor and the investigators will distinguish between the adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the investigational device.

Complications caused by concomitant treatments, not imposed by the clinical investigation plan, are considered not related. If routine procedures are not imposed by the clinical investigation plan, complications caused by them are also considered not related.

In some particular cases the event may not be adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The sponsor and the investigators will make the maximum effort to define and categorize the event and avoid these situations. Where an investigator assessment is not available and/or the sponsor remains uncertain about classifying the adverse event, the sponsor should not exclude the relatedness; the event should be classified as “possible” and the reporting is not delayed.

Particular attention shall be given to the causality evaluation of unanticipated serious adverse events. The occurrence of unanticipated events related could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected beforehand.

14.2 LIST OF NON-REPORTABLE ADVERSE EVENTS AND RATIONALE

Not applicable, all adverse events will be reported to the sponsor at the study end.

14.3 PROCESS FOR REPORTING ADVERSE EVENTS AND DEVICE DEFICIENCIES

14.3.1 Recording adverse events

The following must be assessed and recorded by the investigator in the subject's medical record in a timely manner and then transcribed onto the eCRF adverse event form at each visit:

- Observed or reported problems
- Complaints
- Physical signs and symptoms
- Medical condition which occurs during the study, having been absent at baseline
- Medical condition present at baseline, which appears to worsen during the study.

The need to capture AEs is not dependent upon whether or not the clinical event is associated with the use of the medical device.

Each recorded AE must be described as follows:

- Describe the event by stating the diagnosis (or symptoms), the underlying cause, coexisting disease, or other if identifiable. Whenever possible, the AE should be recorded unambiguously in standard medical terminology. In case the subject's complaint cannot be characterized, the subject's own words should be recorded.
- Note duration by entering the date of onset and date of resolution. If the event is present at the final study visit, indicate that the event is ongoing.
- Note the severity of the event: mild, moderate or severe according to provided definitions.
- Note the action taken as none, medical and/or surgical. Any prescribed medication must be noted in the subject's medical records and then transcribed onto the eCRF concomitant medication section. Surgical interventions should be specified.
- Note the relationship to the study device, or procedure using the guidelines described above.

Any subject withdrawn from the study due to an AE will be followed until the outcome of the event is determined. The investigator will prepare a complete written summary of the event and its outcome, in addition to recording the event on the eCRF AE form.

All other AEs will be followed through to the end of this study. Any AE that is related to the study device and unresolved at the end of the study will be followed by the investigator.

The following categories of AE outcomes will be recorded:

- Resolved
- Ongoing
- Unknown.

All AEs information is reported at the end of the study in the clinical report.

14.3.2 Recording device deficiencies

All investigational device deficiencies shall be documented throughout the clinical investigation and appropriately managed by the sponsor.

Each recorded deficiency must be described as follows:

- Describe the deficiency.
- Declare if the deficiency is linked to an AE.
- If no, declare if the deficiency could have led to a serious adverse device effect.

14.3.3 Reporting by the investigator

The declaration of serious adverse events is a legal requirement. Timelines for reporting SAEs to the sponsor are described in the table below:

	Reporting by the investigator
What to report?	**a) All SAE** **b) Any device deficiencies that might have led to a serious adverse event** **c) Any new findings in relation to any event referred to in points a) and b)**
To whom?	Rana MTEIREK, Head of regulatory affairs and Vigilance Alternate DERMOSCIENCES FRANCE 15, Chemin des Presses 06800 Cagnes sur mer, France Tel.: +33 (0)7 87 15 64 29 email: materiovigilance@dermaceutic.com
How to report?	**1- First notification:** **immediately upon awareness** by telephone, or email. **2- Completed form sending:** the first notification is confirmed by sending the completed SAE form and AE documentation form by email with an acknowledgement of receipt, **within 3 calendar days of knowledge by the investigator**. **3- Additional follow-up reports:** send e-mail. *Note: As a part of monitoring of serious adverse events, if necessary, this first notification will be followed by additional detailed written reports. In notifications, subjects participating in the study will be identified by their code number.*

14.3.4 Reporting by the sponsor

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

a) review the investigator's assessment of all adverse events and determine and document in writing their seriousness and relationship to the investigational device and procedures required by the CIP; in case of disagreement between the sponsor and the principal investigator(s), the sponsor shall communicate both opinions to concerned parties, as defined in c), d), and e) given below,
b) review all device deficiencies and determine and document in writing whether they could have led to a serious adverse device effect; in case of disagreement between the sponsor and the principal investigator(s), the sponsor shall communicate both opinions to concerned parties, as defined in c), d), and e) given below,
c) report or ensure the reporting, to the CA of all serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by the CIP or by the CA,
d) report to competent authorities, within the required time period, all serious adverse events and device deficiencies that could have led to a serious adverse device effect, including serious health threat, if required by the CIP,
e) ensure that the CA are informed of significant new information about the clinical investigation,
f) in case of serious adverse device effects and device deficiencies that could have led to serious adverse device effects, determine whether the risk analysis needs to be updated and assess whether corrective or preventive action is required.

The modalities of vigilance declaration by the sponsor are presented below:

What to report ?	**a) All SAE with relationship to investigational device classified as "Causal relationship", "Probable" or "Possible"**
To whom?	Materiovigilance service of URPL
Within which timeframe ?	**SAE / SADE** with serious public health threat: **Immediately but not later than 2 days after awareness by sponsor** **SAE / SADE** leading a death or an unanticipated serious deterioration in a person's state of health: **Immediately but not later than 10 days** Other SAE: **Immediately but not later than 15 days**
Reporting format ?	Email to the URPL: **incydenty@urpl.gov.pl**

14.4 PROCESS FOR REPORTING A PREGNANCY

The occurrence of a pregnancy (reported or diagnosed) after screening visit but before inclusion (first use of the investigational device) in the study is not reported to the sponsor unless severity criteria (like SAE related to CIP procedures). If the pregnancy is confirmed, the studied device must not be administered and the subject immediately withdrawn from the study.

If the pregnancy is suspected during device administration phase, the device must be immediately stopped until result of the pregnancy test.
If the pregnancy is confirmed, the device is definitively stopped and the subject withdrawn from the study.

The investigator must immediately notify the sponsor of the pregnancy using specific form and reports the withdrawn from the study in the eCRF (study end).
Women who become pregnant during the study will be followed until the outcome of the pregnancy is known and the issue must be reported to the sponsor (baby health).

14.5 LIST OF FORESEEABLE ADVERSE EVENTS AND ANTICIPATED ADVERSE DEVICE EFFECTS

The anticipated adverse device effects and foreseeable adverse events are described in section 4.2.

14.6 INFORMATION REGARDING THE DATA MONITORING COMMITTEE (DMC)

For the purposes of this study, no data monitoring committee will be formed, because:

- studied population is not considered to be high-risk population: healthy subjects, young (< 35 years old) and female subjects of childbearing potential should use a medically accepted contraceptive regimen,
- investigational device contains known components and is available on the market.
- lastly, study duration is short enough (78 days).

15- VULNERABLE POPULATION

Not applicable. The population studied during the clinical investigation is not considered as a vulnerable population

16- SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

16.1 CRITERIA AND ARRANGEMENTS FOR SUSPENSION OR PREMATURE TERMINATION OF THE WHOLE CLINICAL INVESTIGATION OR OF THE CLINICAL INVESTIGATION IN ONE OR MORE INVESTIGATION SITES

Urgent security measures which involve the premature termination of the study might occur.

16.2 CRITERIA FOR ACCESS TO AND BREAKING THE BLINDING/MASKING CODE

Not applicable.

16.3 REQUIREMENTS FOR SUBJECT'S FOLLOW-UP AND CONTINUED CARE

Subjects participating in the study are informed of the urgent security measures by the investigator. A first information is made by phone, followed by a written document sent by email or post mail with receipt confirmation. A visit with the investigator is then planned as soon as possible.

17- PUBLICATION POLICY

The clinical investigation will be registered in a publicly accessible database before first subject first visit. At the clinical investigation end, the results will be made publicly available.

The sponsor reserves the right to review all the manuscript(s) and abstract(s) before their submission for publication or presentation.

This is not intended to restrict or hinder publication or presentation, but to allow the sponsor to protect proprietary information and to provide comments based on information that may not yet be available to the investigators.

18- BIBLIOGRAPHY

18.1 ETHICAL ASPECT

1. REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on medical devices

2. EN ISO 14155:2020 Clinical investigation of medical devices for human subjects - Good clinical practice

3. WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI/ Ethical Principles for Medical Research Involving Human Subjects- Helsinki Declaration (1964) and its successive updates

4. REGULATION (EU) 2016/679 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation)