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Study protocol #18E1721
Related to quote #18D1721-2

**EVALUATION OF THE EFFICACY AND THE CUTANEOUS
ACCEPTABILITY OF A DERMOCOSMETIC PRODUCT IN THE
REPIGMENTATION OF VITILIGO
-STUDY REALIZED BY A DERMATOLOGIST-**

Product ref : 16300.04 Lot 120918A
Placebo Ref : 16300.06 Lot 120918B

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Document 1/1 including 24 pages

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KEY ELEMENTS OF THE STUDY #18E1721

EVALUATION OF THE EFFICACY AND THE CUTANEOUS ACCEPTABILITY OF A DERMOCOSMETIC PRODUCT IN THE REPIGMENTATION OF VITILIGO -STUDY CONDUCTED BY A DERMATOLOGIST-																																																																																										
Objectives	<u>Primary objective :</u> <ul style="list-style-type: none">Evaluate the percentage of repigmentation observed one month after the end of three months of treatment measured on an objective layer by image analysis; <u>Secondary objectives:</u> Evaluate: <ul style="list-style-type: none">the percentage of repigmentation observed after one, two and three months of treatment measured on an objective layer by image analysis;the ability of the product to maintain the human body in good condition (cutaneous acceptability) by clinical examination by the dermatologist;Patient satisfaction using a visual analogue scale from 0 to 10.The illustrative effect using standardized photographs;The quantity of product by weighing the tubes.The occurrence of possible adverse effects.																																																																																									
	<u>Methodology</u> <ul style="list-style-type: none">Study in proof of concept;Double blind study;Comparative study, versus placebo in intra-individual;Three parallel groups testing different dosages / combinations of treatments;Randomized.																																																																																									
Kinetics	<table><tr><td></td><td>Selection visit</td><td>D0</td><td>M1</td><td>M2</td><td>M3</td><td>M4</td></tr><tr><td>Weighing products</td><td></td><td>•</td><td></td><td></td><td>•</td><td></td></tr><tr><td>Information of the volunteer about the conditions of the study and collection of his informed consent</td><td>•</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Verification of inclusion and non-inclusion criteria</td><td>•</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Realization of a standardized photograph of each target lesion</td><td></td><td>•</td><td>•</td><td>•</td><td>•</td><td>•</td></tr><tr><td>Shifting and identifying the perimeter of each target lesion on a layer sheet</td><td></td><td>•</td><td>•</td><td>•</td><td>•</td><td>•</td></tr><tr><td>Clinical examination by the dermatologist</td><td></td><td>•</td><td>•</td><td>•</td><td>•</td><td></td></tr><tr><td>Application of the product by the patient at home</td><td></td><td colspan="4">•</td><td></td></tr><tr><td>Scoring on a visual analogue scale by the patient</td><td></td><td></td><td></td><td></td><td></td><td>•</td></tr><tr><td>Collection of adverse effects</td><td></td><td>•</td><td>•</td><td>•</td><td>•</td><td>•</td></tr><tr><td>Distribution (d) / return (r) of daily log</td><td></td><td>• (d)</td><td>• (r/d)</td><td>• (r/d)</td><td>• (r/d)</td><td>• (r)</td></tr><tr><td>Distribution (d) / return (r) of the studied product</td><td></td><td>• (d)</td><td></td><td></td><td></td><td>• (r)</td></tr></table>							Selection visit	D0	M1	M2	M3	M4	Weighing products		•			•		Information of the volunteer about the conditions of the study and collection of his informed consent	•						Verification of inclusion and non-inclusion criteria	•						Realization of a standardized photograph of each target lesion		•	•	•	•	•	Shifting and identifying the perimeter of each target lesion on a layer sheet		•	•	•	•	•	Clinical examination by the dermatologist		•	•	•	•		Application of the product by the patient at home		•					Scoring on a visual analogue scale by the patient						•	Collection of adverse effects		•	•	•	•	•	Distribution (d) / return (r) of daily log		• (d)	• (r/d)	• (r/d)	• (r/d)	• (r)	Distribution (d) / return (r) of the studied product		• (d)				• (r)
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Distribution (d) / return (r) of the studied product		• (d)				• (r)																																																																																				

Foreseen dates	Product reception	Study start	Study end	1 st results by e-mail
	October 31, 2018	October, 2019	May, 2020	August, 2020
Products	Reference		Form	Application zone
	Product ref : 16300.04 Lot 120918A			
	Placebo Ref : 16300.06 Lot 120918B			

Study Population	Specific inclusion criteria			
	<ul style="list-style-type: none"> • Sex: female and male; • Age: 18 years old and above; • Patients with stable non-segmental vitiligo lesions (defined by no new lesions or lesions existing for at least 3 months, absence of hypochromic margins in Wood's light and absence of confetti depigmentation); • Patients with 2 to 6 symmetrical lesions (1 to 3 on each side). These lesions (macules) will be treated for a minimum surface of 2 cm² and a maximum surface of 100 cm². 			
	Number of subjects minimum			
	12 distributed into groups of 4			

1. STUDY PROCESS

The study is carried out on cosmetic products whose safety has been assured by the Sponsor.

Its aim is to further confirm, under normal and reasonably foreseeable use conditions, the capacity of products to maintain human body in good condition.

+ See ethical requirements and regulatory standards in **Appendix 6**.

This study will be conducted under the following conditions:

1.1. POPULATION

1.1.1. Selection

INCLUSION CRITERIA	
Specific	
<ul style="list-style-type: none">• Sex: female and male;• Age: 18 years old and above;• Patients with stable non-segmental vitiligo lesions (defined by no new lesions or lesions existing for at least 3 months, absence of hypochromic margins in Wood's light and absence of confetti depigmentation);• Patients with 2 to 6 symmetrical lesions (1 to 3 on each side). These lesions (macules) will be treated for a minimum surface of 2 cm² and a maximum surface of 100 cm².	
General	
<ul style="list-style-type: none">• Healthy subject;• Subject having given his/her free informed, written consent;• Subject willing to adhere to the protocol and study procedures.	

NON-INCLUSION CRITERIA

- pregnant or nursing woman or woman planning to get pregnant during the study;
- Patient with segmental or mixed vitiligo;
- Patient with vitiligo on the external genitalia;
- Patient with vitiligo on hands and feet only;
- Patient with a history of skin cancer or pre-cancerous skin lesions;
- Patient taking topical or systemic vitiligo treatments within the previous month of the study;
- Patient taking concomitant local or general corticosteroid therapy or immunomodulatory treatment;
- Patient with a history of photodermatoses or taking photosensitizing medications;
- Patient planning to expose himself (artificial sun or UV) during the study on the zones to be treated and / or having been exposed during the previous month to the study and having an obvious acquired pigmentation (tanning);
- Patient who had been treated with phototherapy within 4 weeks before randomization;
- Patient with lithium allergy.

1.1.2. Study requirements and constraints

HAVE TO	DURING THE STUDY, THE SUBJECTS	
	MUST NOT	ARE ALLOWED TO USE* (except on visiting days)
<ul style="list-style-type: none"> • respect dates and hours of hospital visits; • follow the conditions of use of the investigational product at home; • complete the daily-log and bring it back with the investigational product at the end of the study; • avoid excessive UV exposure (including artificial UV). 	<ul style="list-style-type: none"> • apply any product to test areas the days of the visits* to the hospital; • apply any other similar product to test areas; • modify their usual make-up, hygiene or care products and/or use new products; • allow the use of the investigational product by another person than himself/herself. 	<ul style="list-style-type: none"> • usual cleansing products.

1.1.3. Compliance assessment

The compliance is controlled by checking the daily log and by weighing the products before distribution (D0) and after use (M3).

+ See Appendix 5.2.

1.1.4. Protocol deviations

A protocol deviation can be defined as any non-adherence to the final protocol, including:

- wrong inclusion (inclusion criteria or non-inclusion criteria not fulfilled);
- start of a prohibited concomitant treatment;
- non-adherence of the subjects to the study schedule (missed or postponed visit);
- missing data for one or several evaluation criteria;
- low compliance of the subject to the study product(s) application;
- premature study end or untraceable subject;
- no respect of the constraints envisaged by the protocol.

Deviations to the protocol 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 for the subject and/or do not have a significant effect on the integrity of the data collected,
- **major (or protocol violations)** if they affect the rights, safety or well-being of participants. They increase the risk for the subject and/or have a significant effect on the integrity of the study data.

In case of minor protocol deviation, the technician or the investigator repeats the instructions and reminds the subject to follow protocol requirements / study procedures. In case of persistent or major protocol violations, the subject is declared non-compliant and withdrawn from the study because of non-compliance.

1.2. INVESTIGATIONAL PRODUCT

1.2.1. Description

Reference	Batch#	Form	Packaging	Confidentiality procedure	Storage temperature
Product ref: 16300.04	120918A	Yellowish liquid	Tube	Encoded	Room temperature
Placebo ref: 16300.06 Lot 120918B	120918B	Yellowish liquid	Tube	Encoded	Room temperature

1.2.2. Application

	Zone	Frequency	Mode
Product ref : 16300.04 Lot 120918A	Body	<ul style="list-style-type: none"> • <u>Group A</u> : 4 patients; Lithium liposome <u>1 application / day (evening)</u> on target lesions on <u>one side</u> of the body, placebo <u>1 application / day (evening)</u> on contralateral target lesions and excimer lamp on target lesions on the two sides; 	
Placebo ref: 16300.06 Lot 120918B	Body	<ul style="list-style-type: none"> • <u>Group B</u> : 4 patients; <u>Liposomal Lithium 2 applications / day (morning and evening)</u> on target lesions on one side of the body, <u>placebo 2 applications / day (morning and evening)</u> on contralateral target lesions and excimer lamp on target lesions on the two sides; • <u>Groupe C</u> : 4 patients; Lithium liposome <u>2 applications / day (morning and evening)</u> on one side, placebo <u>2 applications / day (morning and evening)</u> on contralateral target lesions. 	

1.2.3. Labelling

Example of labelling of each product by EUROFINS Dermscan and translation:

DERMSCAN Etude n°	DERMSCAN Study #
N° vol :	Subject#:.....
Côté :	Side :
Posologie :	Posology :
En cas d'urgence : n° tél	In case of emergency : Tel #
Conservation :	Conservation :
<p>A tenir hors de portée et de la vue des enfants. A utiliser sous stricte surveillance médicale pour essai clinique, médicale pour essai clinique.</p>	<p>Keep out of reach and sight of children. To be used only under strict medical supervision for clinical trial.</p>

1.2.4. Storage

Until the beginning of the study, products are kept at room temperature in a dedicated air-conditioned room, which is locked and access controlled.

1.2.5. Attribution to the subjects

→ Products

Each product is attributed to volunteers according to the randomization in **Appendix 5.1**.

→ Application zones

The application side (right/left) of the products (product/ placebo) are randomized according to the randomization list set previously.

1.2.6. Handing-out

The products are delivered to the subjects by the investigator with an explanation of the application mode and frequency.

1.2.7. Future

As far as possible, one sample of the study products is kept by the investigation center for a period of six months after its receipt.

- By default, the products (used and not used) are destroyed at the end of the study according to the current internal EUROFINS Dermscan/Pharmascan procedures.

1.3. STUDY STAGES

BEFORE THE BEGINNING OF THE STUDY

Technician:

- weighs the study products before their use.

Twice a week:

Patients of both groups A and B come to the hospital where the lesions will be exposed with a Quantel 308 excimer lamp that delivers a narrow UVB spectrum centered of a wavelength of around 308nm. This lamp makes it possible to perform phototherapy localized on the target lesion. Fluences will be performed twice a week throughout the duration of the study.

ON D0

Patients:

- come to the investigation center without having applied any product to the body since the previous evening;
- are informed about the trial objectives, the procedures and the risks of the study with the information sheet;
- sign two copies of the Consent Form.

Dermatologist:

- verifies inclusion and non-inclusion criteria;
- performs a standardized photo of each target lesion;
- traces and identifies the perimeter of each target lesion (1 to 3 on each side) on a tracing sheet (the natural marks such the scars, moles, tattoos or others will be also reported on the tracing sheet in order to easily find the target lesions);
- performs a clinical examination of the skin on the application area;
- asks the subjects about their usual unpleasant sensations;
- explains to the subjects the product application conditions and frequency;
- gives to the subjects:
 - the **product** to be used according to the instructions in 2.1.2 and 2.2.2,
 - the **daily log** to write down their possible unpleasant sensations or medications,

ON M1 (last application being done the previous day)

Subjects:

- return to the hospital with no product applied to the body since the previous evening;
- bring back their daily log;

Dermatologist:

- performs a standardized photo of each target lesion;
- traces and identifies the perimeter of each target lesion (1 to 3 on each side) on a tracing sheet (the natural marks such the scars, moles, tattoos or others will be also reported on the tracing sheet in order to easily find the target lesions);
- performs a clinical examination of the skin on the application area;
- asks the subjects about the unpleasant sensations they felt during the study and assesses the cutaneous acceptability of the study product;
- collection of the concomitant treatments and undesirable effects.

On M2 (the last application being done the previous night):**Subjects:**

- return to the hospital with no product applied to the body since the previous evening;
- bring back their daily log;

Dermatologist:

- performs a standardized photo of each target lesion;
- traces and identifies the perimeter of each target lesion (1 to 3 on each side) on a tracing sheet (the natural marks such the scars, moles, tattoos or others will be also reported on the tracing sheet in order to easily find the target lesions);
- performs a clinical examination of the skin on the application area;
- asks the subjects about the unpleasant sensations they felt during the study and assesses the cutaneous acceptability of the study product;
- collection of the concomitant treatments and undesirable effects.

On M3 (the last application being done the previous night):**Subjects:**

- return to the hospital with no product applied to the body since the previous evening;
- bring back their daily log and the products;
- stop the treatment.

Dermatologist:

- performs a standardized photo of each target lesion;
- traces and identifies the perimeter of each target lesion (1 to 3 on each side) on a tracing sheet (the natural marks such the scars, moles, tattoos or others will be also reported on the tracing sheet in order to easily find the target lesions);
- performs a clinical examination of the skin on the application area;
- asks the subjects about the unpleasant sensations they felt during the study and assesses the cutaneous acceptability of the study product;
- collection of the concomitant treatments and undesirable effects.

On M4 (one month after the last product application):**Subjects:**

- return to the hospital with no product applied to the body since the previous evening;
- bring back their daily log and the products;
- performs clinical scores on an analog visual scale.

Dermatologist:

- performs a standardized photo of each target lesion;
- traces and identifies the perimeter of each target lesion (1 to 3 on each side) on a tracing sheet (the natural marks such the scars, moles, tattoos or others will be also reported on the tracing sheet in order to easily find the target lesions);
- performs a clinical examination of the skin on the application area;
- asks the subjects about the unpleasant sensations they felt during the study and assesses the cutaneous acceptability of the study product;
- collection of the concomitant treatments and undesirable effects.

AT THE END OF THE STUDY**Technician:**

- weighs the study products after their use.

1.4. DATA ANALYSIS

The following data are analyzed:

	Parameter(s)	Unit(s)	Variation(s) DX/D0 Kinetics	Statistical analysis (tick if yes)	Expected result(s)
Cutaneous acceptability	Clinical signs observed Functional and physical signs reported	/	D28/D0	/	No worsening
Efficacy	Lesions surface	cm ²	M4/D0 M3/D0 M2/D0 M1/D0	/	Decrease
Subjective evaluation	Analog visual scale from 0 to 10	Score	/	/	/

Individual data are presented in raw value tables. These tables also show the descriptive statistics: means, medians, minima, maxima, standard errors of the means (SEM) and confidence intervals of 95% (95% CI).

Variation tables present raw variations, percentage variations and descriptive statistics.

1.4.1. Calculation formulas

Product	Placebo
$\Delta \text{Pdt} = (\text{Pdt ti} - \text{Pdt t0})$	$\Delta \text{Pla} = (\text{Pla ti} - \text{Pla t0})$
$\Delta\% \text{Pdt} = \frac{(\text{Pdt ti} - \text{Pdt t0})}{\text{Pdt t0}} \times 100$	$\Delta\% \text{Pla} = \frac{(\text{Pla ti} - \text{Pla t0})}{\text{Pla t0}} \times 100$

$$\Delta\Delta = \Delta \text{Pdt} - \Delta \text{Pla}$$

$$\Delta\Delta\% = \Delta\% \text{Pdt} - \Delta\% \text{Pla}$$

with: Pdt: value obtained on the zone treated by the tested product
Pla: value obtained on the zone treated by the placebo
t0: before product application
ti: at each measurement time after product application

1.4.2. Statistical method

Only descriptive analysis (Mean, SEM, frequency...) is calculated.

1.4.3. Statistical software

The software used is EXCEL.

1.5. AUDIT AND TRIAL MONITORING VISIT

An audit and/or trial monitoring visit may be carried out at the Sponsor's request or by the appropriate regulatory authority. The aim of the monitoring visit is to verify that the study is conducted according to the determined protocol and current regulations.

2. PRINCIPLES AND RESULTS

2.1. STANDARDIZED PHOTOGRAPHS

A standardized photograph of each lesion will be taken on the visits D0, M1, M2, M3 and M4.

The following parameters will remain fixed from one visit to another:

- Ambient lighting (use preferably a blind room without window).
- Setting the camera (speed and diaphragm).
- Distance device / lesion: constant.
- Position device / lesion: constant (perpendicular axis of the lens to the lesion).

The person in charge of the photographs will have to photograph the identification of the patient and the visit, for example on the heading of the data collection notebook or on a printed card for this purpose.

2.2. ANALYSIS OF THE LESIONS SURFACE

2.2.1. Principle

On each visit, the perimeter of each target lesion and any possible repigmentation ranges inside it will be traced and identified on a tracing sheet. Natural marks such as scars, moles, tattoos or others will also be reported on the tracing sheet in a manner to find the target lesions easily.

An entire body drawing, front view and back view, must be present in the data collection notebook so that the lesions can be represented and numbered. The number of each lesion must also appear on the tracing sheet.

The surface measurement of each lesion (in cm²) will be made by the Sponsor, by image analysis of the tracing sheet under a video camera using a classical image analysis software.

2.3. LESIONS EXPOSURE TO EXCIMER LAMP

The lesions will be exposed to a Quantel 308 excimer lamp that delivers a narrow UVB spectrum centered around the 308nm wavelength. This lamp makes enables to carry out phototherapy localized on the target lesion. The fluences will be performed twice a week during the whole study according to the recommendations of the French Society of Dermatology regarding phototherapy. The initial dose of 50 mJ / cm² will be increased then progressively every 2 sessions until getting a franc erythema lasting less than 48h and not causing phlyctenes.



excimer lamp Quantel 308

2.4. CUTANEOUS ACCEPTABILITY

Before (D0) and after product use (M1, M2, M3), the subjects body is examined by the dermatologist to assess each of the following parameters:

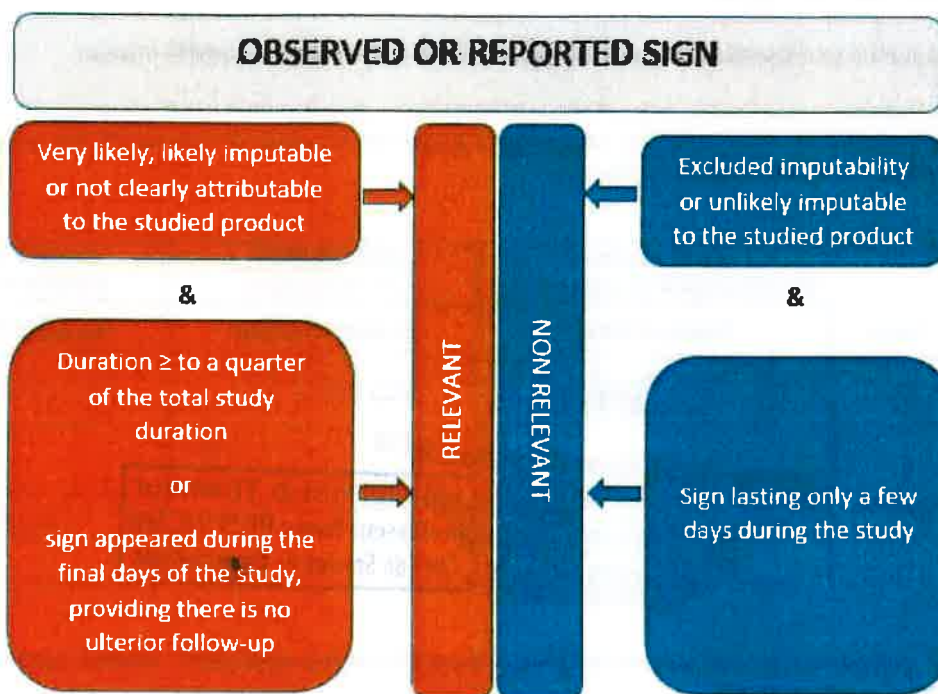
	NONE	VERY MILD	MILD	MODERATE	SEVERE
Erythema	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Edema	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Dryness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Desquamation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Roughness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Others	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Please define:					

On D0, the subjects are also asked about their usual functional habits:

	NONE	VERY MILD	MILD	MODERATE	SEVERE
Tightness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Stinging	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Itching	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Warm, burning sensation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Others	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Please define:					

At the end of the study, the cutaneous acceptability of the product is assessed by taking into account the relevant elements reported by the subject (functional and physical signs) as well as those noted during the examination (clinical signs).

The confrontation of these signs is used to conclude the final cutaneous acceptability of the studied product.



2.5. PATIENTS SCORING ON AN ANALOG VISUAL SCALE

On M4, the patient will be asked about their satisfaction with the treatment, on each side of the body:

Left side :

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
0	1	2	3	4	5	6	7	8	9	10
Not satisfied at all										Very satisfied

Right side:




<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
0	1	2	3	4	5	6	7	8	9	10
Not satisfied at all										Very satisfied

3. CERTIFICATION

The study is conducted according to Helsinki Declaration (1964) and its successive updates. Data are obtained using the study protocol, current internal procedures and as closely as possible to the guidance on Good Clinical Practice CPMP / ICH / 135 / 95 (R2).

This study is totally performed under the responsibility of EUROFINS Dermscan/Pharmascan.

All the observations and numerical data collected throughout the study are reported in this document and are in accordance with the obtained results.

	Study monitor (dermatological laboratory ACM)	INVESTIGATOR - (Dermatologist)	PROJECT MANAGER (DERMSCAN TUNISIA)
Name	Thierry LEVEILLE	Pr Samy FENNICHE	Houneida BOUSSETTA
Date	29/10/2019	30/10/19	30/10/19
Signature	 LABORATOIRE Dermatologique ACM SAS au Capital de 814 000 Euros 17, rue de Neuilly - Impasse Passow 92110 CLICHY LA GARENNE RCS NANTERRE B 433 367 497 SIRET 433 367 497 00024	 Hopital Habib Thameur Professeur Samy FENNICHE Chef de Service de Dermatologie	

Any modifications are the sole responsibility of the author of the modification, whether he/she is acting for the Sponsor or independently.

The on-line publishing, on the Internet, of this study protocol with the names and signatures is strictly prohibited.

4. BIBLIOGRAPHY

Regulatory

1. ICH TOPIC E6 (R2)/ Note for guidance on Good Clinical Practice- CPMP / ICH / 135 / 95, November 2016.
2. WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI/ Ethical Principles for Medical Research Involving Human Subjects- Helsinki Declaration (1964) and its successive updates.

Cutaneous acceptability

1. IGIELSKA-KALWAT J, GOŚCIAŃSKA J, WITKOWSKA B, NOWAK I. / *In vivo* studies of substances used in the cosmetic industry - Advances in Dermatology and Allergology. 2016; 33(3):163-169.
2. SALVERDA et AL. / Results of a cosmetovigilance survey in The Netherlands - Contact Dermatitis. 2013; 68: 139-148.
3. BROECKX W., BLONDEEL A., DOOMS-GOOSSENS A., ACHTEN G. / Cosmetic intolerance - Contact Dermatitis. 1987; 16: 189-194.
4. ROBERT P. and coll. / *Dermopharmacologie clinique* - EDISEM MALOINE, 1985.

APPENDICES:

**STUDY DOCUMENTS,
&
ETHICAL REQUIREMENTS AND REGULATORY STANDARDS**

5. APPENDICES – STUDY DOCUMENTS**5.1. RANDOMIZATION LIST (GROUPS ATTRIBUTION)****RANDOMIZATION LIST****STUDY 18E1721****17/09/2019**

ID	Groupe	Côté Droit	Côté Gauche
1	A	Produit A	Produit B
2	B	Produit B	Produit A
3	C	Produit A	Produit B
4	A	Produit B	Produit A
5	A	Produit B	Produit A
6	B	Produit A	Produit B
7	B	Produit B	Produit A
8	A	Produit A	Produit B
9	C	Produit B	Produit A
10	C	Produit A	Produit B
11	C	Produit B	Produit A
12	B	Produit A	Produit B

Groupe A: 1 application/ jour (le soir) + lampe

Groupe B: 2 applications/ jour (matin et soir) + lampe

Groupe C: 2 applications/ jour (matin et soir)

بطلقة متفجرة يومية

CE TABLEAU DOIT ETRE COMPLETE CHAQUE JOUR. Lorsqu'il n'y pas d'application de produit, notez "0" dans la colonne "Nombre".
يجب تعبئة هذا الجدول يوميا، عندما لا يكون هناك استعمال للمنتج، تكتب (0) في خانة عدد

En cas d'inconfort et/ou d'intolérance, merci de noter la nature (rairements, picotements, émanations, sensations de brûlure...) à zone, l'insistance (léger, modéré, sévère, très sévère) et la durée de ces sensations ainsi que le début d'apparition par rapport à l'application (immédiate, retardée ou après quelques minutes).

ملاحظة: في حالة الشعور بعدم الراحة و/أو التحمل، يرجى ملاحظة الطبيعة (نقرات، وخزجات، انبعاثات، إحساس بالحرقان...) في المنطقة، الإلحاح (خفيف، معتدل، شديد، شديد جدًا) ومدة هذه الأحاسيس وكذلك بداية ظهورها فيما يتعلق بالتطبيق (فورية، متأخرة أو بعد بضع دقائق).

[illegible]

..../**M1/M2/M3**

6. APPENDICES - ETHICAL REQUIREMENTS AND REGULATORY STANDARDS

6.1. ADVERSE EVENT

6.1.1. Adverse Event (AE)

Any noxious symptom, occurring in a subject taking part in a clinical trial, whether or not this symptom is related to the study or the study product(s) (e.g. flu, headache, abnormal biological analysis...).

6.1.2. Undesirable Effect (UE) / Adverse Reaction (AR)

An **undesirable effect** is defined as an adverse reaction for human health attributable to the normal or reasonably foreseeable use of the cosmetic product(s).

There are 5 levels of imputability: very likely, likely, not clearly attributable, unlikely and excluded (ANSM methodology).

The severity/intensity of undesirable effects/adverse events can be graded on a three-point scale:

- **mild**: discomfort noted, that does not disturb normal daily activities;
- **moderate**: discomfort sufficient to reduce or affect normal daily activities;
- **severe**: inability to work or have normal daily activities.

6.1.3. Serious Adverse Event (SAE) / Serious Undesirable Effect (SUE)

Any event that:

- results in death (note: death is the outcome, not the event);
- is life threatening;
- requires in-patient hospitalization (at least one night) or prolongation of existing hospitalization (does not include hospitalization scheduled before the inclusion);
- results in temporary or permanent functional incapacity or disability;
- is a congenital anomaly;
- is considered like by the investigator.

6.1.4. Documentation

All concomitant treatments are reported in the CRF; only those started after the beginning of the study are reported in the study report.

All Undesirable Effects are reported in the CRF and the study report.

If it requires the temporary or definitive termination of the study product, the need for a corrective treatment or the withdrawal of the subject, an Adverse Event form is completed.

All SAE/SUE are reported in the CRF and the study report.

6.1.5. Notification

The investigator declares to the Sponsor, by e-mail, the occurrence of adverse reactions according to their severity and their unexpectedness (according to the investigator's advice).

All SAE/SUE are transmitted by e-mail to the Sponsor without delay, at the latest 24 hours after knowledge of their occurrence.

A SAE/SUE declaration form signed by a physician is sent, within 48 hours, by e-mail with acknowledgement of receipt.

6.1.6. Follow-up

When an adverse event linked to the investigational product or the protocol persists at the end of the study, the Investigator ensures that the subject is followed up until total resolution of the event or stabilization of the symptoms without releasing the Sponsor of any obligation or responsibility.

6.1.7. Occurrence of pregnancy

The occurrence of a pregnancy (reported or diagnosed) after inclusion in the study is considered as an intercurrent event not related to the study product(s) nor the protocol and induces the immediate dropping out of the subject. Any pregnancy that occurs during the study period is reported by e-mail to the Sponsor within 24 hours following its discovering.

A follow-up is done according to the current internal procedures until the completion/termination of the pregnancy or its interruption.

6.2. PREMATURE TERMINATION OF SUBJECT PARTICIPATION

In compliance with the Helsinki Declaration (1964) and its successive updates, subjects have the right to exit from the study at any time and for any motive.

The investigator can also interrupt the subject participation in the study prematurely in the case of a disease occurrence, a pregnancy or the occurrence of an adverse reaction.

The Sponsor can demand that any subject be excluded from the study for major infringements to the protocol, for administrative reasons or any other motive however this would need to be clearly documented with a rationale as to why.

Nevertheless, premature removal of a high percentage of subjects from the study can make it difficult or impossible to interpret. Consequently, any premature exit without valid motives should be avoided as much as possible and is carefully documented in the case report form, the final report and, if necessary, in the Adverse Event form.

Every premature exit must be classified under one of the following headings:

- presence of a non-inclusion criteria;
- Undesirable Effect / Adverse Event occurrence;
- Serious Adverse Event / Serious Adverse Effect occurrence;
- withdrawal of consent;
- lost to follow-up;
- appearance of non-inclusion criteria;
- non-adherence to the protocol;
- other reason.

No replacement is foreseen as 10% additional subjects are planned to be included in the study.

6.3. CONFIDENTIALITY AND GENERAL DATA PROTECTION REGULATION

In this study, DermScan processes personal data of subjects on behalf of the Sponsor, in accordance with the rules on the protection of personal data. For this purpose, EUROFINS DermScan/PharmScan limits the collection and use of personal data to that which is needed for analysis and control purposes, by insuring their security and integrity and by guaranteeing their confidentiality.

DermScan makes 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 after obtaining their consent,

- to implement and maintain appropriate technical and organisational measures.

An identification code is attributed to each subject for the purpose to keep his/her identity confidential. This code consists of: the first two letters/first letter of the subject's name and the first letter of his/her first name.

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. However, considering the objective of the study, to avoid any bias in the investigational product evaluation, the identity of the Sponsor is not revealed to the subject participating.

6.4. DATA COLLECTION AND VALIDATION

The staff in charge of the study (doctors, technicians, ...) collects the data in the CRF and on computer support.

The simple data entry is carried out from the observation books by a designated operator (s), without any interpretation, in MS EXCEL specific databases.

Then the Project Manager or his assistant checks the coherence of the computer data with those present in the documents of the study. It also checks the formulas used in the EXCEL spreadsheet (calculation formulas, data ranges, etc.).

The consistency of the data coming directly from the measurement software is also verified and validated by the Project Manager or his assistant.

When all the notebooks are entered and all the checks are done, the database is frozen.

The personnel in charge of the study collects data to a computerized data base.

If applicable, the Project Manager or assistant checks the double data entry by comparing both databases.

Then the coherence of the whole data set is checked as well as formulas used in the EXCEL tables (calculation formulas, selected data...).

When all the controls are done, the database is locked.

6.5. QUALITY MANAGEMENT

In order to ensure that the clinical trials are in compliance with the Sponsor's requirement, EUROFINS Dermscan/Pharmascan has implemented a quality management system which has been certified ISO 9001: 2015. This quality assurance system includes Good Clinical Practices (GCP) and regulation requirements.

Each study report is subjected to a quality inspection by a member of the EUROFINS Dermscan/Pharmascan Proofreading Committee. The proofreader is chosen because he/she is not involved in the audited study. The inspection of the study report allows to confirm that the results reflect exactly the study raw data and that the study fulfils any standard and regulatory requirements.

A certificate of quality inspection signed by the person who checked the report is enclosed in each study.

6.6. ARCHIVES OF STUDY DOCUMENTS