

STUDY PROTOCOL

1. TITLE PAGE

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|----------------------------------|--|
| Study title | Multicentric, parallel, randomized, double blind study under dermatological control to evaluate the anti-acne efficacy of a dermo-cosmetic product (fla 688977 33) associated with the fixed combination Adapalene 0.1%/ benzoyl peroxide 2.5% treatment versus this treatment associated with a standard moisturizer (Hydréane légère, Cosmétique Active International) during a 12-week application period in male and female subjects presenting with mild to moderate acne |
| Sponsor | Cosmétique Active International, Direction médicale Vichy International A. BOULOC 62, quai Charles Pasqua 92300 LEVALLOIS-PERRET FRANCE |
| ID-RCB Number | 2018-A02481-54 |
| ClinicalTrials Number | To be completed after CPP approval |
| Coordinating Investigator | Pr B. DRENO Head of dermatology department CHU Nantes-Hôtel-Dieu |
| Study Centres | <ul style="list-style-type: none">● <u>Centre 1</u> Intertek France - Etudes Cliniques Paris 48, rue de la Colonie 75013 Paris - France Agreement N° 17-1223 ● <u>Centre 2</u> CHU Nantes-Hôtel-Dieu (Dermatology Department) 1 place Alexis Ricordeau 44093 Nantes cedex 01 Agreement : NA |
| Investigational products | <ul style="list-style-type: none">● <u>Studied product</u>: Dermo-cosmetic product fla 688977 33● <u>Comparative product</u>: Hydréane légère, Cosmétique Active International (on the market)● <u>Pharmaceutical Drug</u>: Adapalene 0.1%/ benzoyl peroxide 2.5% treatment (Epiduo® 0.1%/2.5% gel; Galderma Laboratoires, on the market) |





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Study Numbers

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Confidentiality Statement

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2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations:

| | |
|-------------|---|
| AE | : Adverse Event |
| ANSM | : Agence Nationale de Sécurité du Médicaments et des produits de Santé |
| CA | : Competent Authority |
| CL | : Casual Level |
| CPP | : Comité de Protection des Personnes |
| CRF | : Case Report Form |
| CRO | : Contract Research Organization |
| D | : Day |
| DCF | : Data Clarification Form |
| DNA | : Deoxyribonucleic acid |
| GCP | : Good Clinical Practice |
| GEA | : Global Acne Evaluation |
| ICH | : International Conference on Harmonisation of Technical Requirements for registration of Pharmaceuticals for Human Use |
| IP | : Investigational Product |
| n | : number of subjects |
| NA | : Not Applicable |
| PCR | : Polymerase Chain Reaction |
| QA | : Quality Assurance |
| RIPH | : Research Studies Involving the Human Person |
| SAE | : Serious Adverse Event |
| SOP | : Standard Operating Procedure |
| TMF | : Trial Master File |
| W | : Week |

Definitions of terms

Assessment

A (cluster of) characteristic(s) measured and/or recorded for a subject.

Concomitant Medication

Any medication taken by a subject during the study.

Source data

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

Source documents

Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study).



3. PROTOCOL APPROVAL

3.1. Sponsor

Sponsor's Representative

A. BOULOC
Medical director
Cosmétique Active International, Direction
médicale Vichy International

Signature/Date (DD-MMM-YYYY):

3.2. Coordinating investigator

Coordinating Investigator

Pr B. DRENO
Head of dermatology department at CHU Nantes-
Hôtel-Dieu

Signature/Date (DD-MMM-YYYY):



3.3. Investigators signatures page

Je, soussigné atteste :

- Avoir pris connaissance de ce protocole ;
- Conduire cette étude conformément à ce protocole et ses amendements éventuels, et à toutes autres instructions fournies par le promoteur ;
- M'engager à éviter toute déviation ou tout changement concernant ce protocole sans l'accord écrit préalable du promoteur, des autorités réglementaires, à l'exception de mesures nécessaires pour assurer la sécurité et la santé des sujets ;
- Connaître les modalités d'utilisation de ce produit pour cette étude, comme décrit dans le protocole ;
- Être informé et travailler dans le respect des principes de la déclaration d'Helsinki, des Bonnes Pratiques Cliniques (BPC), et de toute autre exigence réglementaire applicable à ces activités ;
- Assurer que toutes les personnes m'assistant pour cette étude ont bien été informées des modalités de cette étude.

I, undersigned attest:

- To be informed of this protocol;
- Conduct this study according to this protocol and its possible amendments, and to other instructions supplied by the sponsor;
- Undertake to avoid any deviation or any change in this protocol without the prior written consent of the sponsor, the regulatory authorities, with the exception of necessary measures to insure the safety and the health of the subjects;
- Know the use instructions of this product for this study, as described in the protocol;
- Be informed and work in the respect for the Helsinki declaration, Clinical Good Practice (GCP), and other regulatory requirement applicable to these activities;
- Assure that all the persons assisting me for this study were indeed informed about modalities of this study.

Investigator

Y. DROUAULT
Dermatologist
Intertek France - Etudes Cliniques Paris

Signature/Date (DD-MMM-YYYY):

Investigator

I. TARDY
Dermatologist
Intertek France - Etudes Cliniques Paris

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Investigator

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Signature/Date (DD-MMM-YYYY):



4. PROTOCOL SYNOPSIS AND FLOW CHART

| | |
|----------------------------------|--|
| Study title | Multicentric, parallel, randomized, double blind study under dermatological control to evaluate the anti-acne efficacy of a dermo-cosmetic product (fla 688977 33) associated with the fixed combination Adapalene 0.1%/ benzoyl peroxide 2.5% treatment versus this treatment associated with a standard moisturizer (Hydréane légère, Cosmétique Active International) during a 12-week application period in male and female subjects presenting with mild to moderate acne |
| Sponsor | Cosmétique Active International, Direction médicale Vichy International A. BOULOC |
| Coordinating Investigator | Pr B. DRENO Head of dermatology department at CHU Nantes-Hôtel-Dieu |
| Study Centres | <ul style="list-style-type: none">● <u>Centre 1</u> Intertek France - Etudes Cliniques Paris 48, rue de la Colonne 75013 Paris - France Agreement N° 17-1223 ● <u>Centre 2</u> CHU Nantes-Hôtel-Dieu (Dermatology Department) 1 place Alexis Ricordeau 44093 Nantes cedex 01 Agreement : NA |
| Objectives | |
| Primary objective | To evaluate the adjunctive anti-acne efficacy of a dermo-cosmetic product (fla 688977 33) associated with the fixed combination Adapalene 0.1%/ benzoyl peroxide 2.5% treatment versus this treatment associated with a standard moisturizer (Hydréane légère, Cosmétique Active International) during a 12-week application period in male and female subjects presenting with mild to moderate acne. |
| Secondary objectives | <ul style="list-style-type: none">● To evaluate the effects on the skin quality of the dermo-cosmetic product associated with the fixed combination Adapalene 0.1%/ benzoyl peroxide 2.5% treatment versus this treatment associated with a standard moisturizer. ● To demonstrate that the dermo-cosmetic product can improve the local tolerance of the fixed combination Adapalene 0.1%/ benzoyl peroxide 2.5% treatment compared to a standard moisturizer. |



- To evaluate the cosmetic acceptability of the dermo-cosmetic product versus a standard moisturizer.
- According to the results of the primary variable, to evaluate the impact on the microbiota of the dermo-cosmetic product associated with the fixed combination Adapalene 0.1% / benzoyl peroxide 2.5% treatment versus this treatment associated with a standard moisturizer.
- To collect safety data.

| | |
|---------------------|--|
| Study design | Multi centre Randomised Double blind Controlled Parallel (100 subjects per arm) Intra-subject & inter subject comparisons |
|---------------------|--|

Study procedures are summarised in the Flow Chart.

Variables

| | |
|---------------------|---|
| Primary variable | <ul style="list-style-type: none">• Anti-acne efficacy: Counting of the retentional (open & closed comedones) and inflammatory lesions (papulae, pustulae & nodules (if applicable)) on the face at W0 and W12 |
| Secondary variables | <ul style="list-style-type: none">• Anti-acne efficacy:<ul style="list-style-type: none">• Counting of the retentional (open & closed comedones) and inflammatory lesions (papulae, pustulae & nodules (if applicable)) on the face at W0, W4 and W8• Determination of the acne stage according to the GEA scale at W0, W4, W8, W12• Skin quality efficacy at W0, W4, W8, W12:<ul style="list-style-type: none">• Clinical assessments:<ul style="list-style-type: none">• of the residual marks visibility of acne (hyperpigmentation)• of the pores visibility• of the skin shininess• Instrumental measurements:<ul style="list-style-type: none">• Skin greasiness using sebumetry measurements• Skin moisturizing using corneometry measurements• Skin pH using pHmetry measurements• Confocal microscopy analysis at W0 and W12 only (Total number of hair follicles per cube at a mean depth of 38 µm, diameter of the infundibulum, aspect of the border (thickness), onion-like appearance, presence of amorphous material into the infundibulum, signs of |



inflammation, vascularization and presence of *Demodex* mites)
(n≈30; CHU Nantes study centre only)

- Efficacy questionnaire at W12
- Local tolerance:
 - Clinical assessments of the face skin condition at W0, W4, W8, W12
 - Physical signs: erythema, dryness and scaling
 - Functional signs: tightness, prickling, itching, burning sensation and others
 - Products overall tolerance appreciation by the Dermatologist and the subject at W12
- Cosmetic acceptability questionnaire at W12
- Microbiota analysis at W0 and W12 (if applicable)
- Safety

Adverse Events Collection

Number of subjects A total of 200 male and female subjects (100 per arm) will be included.

Inclusion criteria

1. Male and/or female subjects aged 16 to 35 years
2. Subjects presenting with mild to moderate acne (stage 2 or stage 3 according to the Global Acne Evaluation with at least 12 inflammatory lesions on face)
3. Female subjects of child-bearing potential who:
 - use **the same** reliable hormonal contraceptive method (oral contraceptive, implant, intra-uterine device, patch, vaginal ring and injection) for at least **3 months** prior to study inclusion and throughout the study or
 - use a reliable non-hormonal contraceptive method (copper intra-uterine device, condoms, diaphragm, cervical cap and spermicide) for at least **1 month** prior to study inclusion and throughout the study or
 - have no sexual intercourse and agreeing not to have any throughout the study or
 - are surgically sterile (oophorectomy, hysterectomy or tubal ligation),
4. Subjects and/or all legal representatives (for minor subjects) who have given written informed consent
5. Subjects who are willing to comply with the study requirements
6. Subjects with Social Security (health insurance) coverage (according to the French requirements)



Exclusion criteria

1. Subjects with any systemic disorder or face dermatoses other than acne that would in any way confound interpretation of the study results (e.g. atopic dermatitis, eczema, or psoriasis)
2. Subjects with a condition or receiving a medication and/or with a history of medical/surgical events which, in the opinion of the Investigator, could compromise the safety of the subject or affect the outcome of the study
3. Subjects with a history of skin cancer
4. Female subjects who are pregnant (positive urine pregnancy test) or lactating or who are planning to become pregnant during the study
5. Subjects who have started, stopped or changed of hormonal treatment (contraception, thyroid ...) in the **3 months** prior the study inclusion
6. Subjects with hypersensitivity to the active substances of Epiduo® (Adapalene and/or benzoyl peroxide) or to one of its excipients
7. Subjects who are sensitive to peroxides (oxygenated water)
8. Subjects who have received isotretinoin treatment in the **6 months** prior to study inclusion
9. Subjects who have been exposed to excessive UV light (natural or artificial) in the **1 month** prior to the study inclusion or having planned excessive UV light exposure during the study (e.g. ski holidays, holidays in the tropics...)
10. Subjects who have used systemic drugs for more than 3 consecutive days related to antibiotics, anti-inflammatory, corticoids, anti-acneic in the **4 weeks** prior to study inclusion
11. Subjects who have used topical drugs for more than 3 consecutive days related to antibiotics, anti-inflammatory, corticoids, anti-acneic in the **2 weeks** prior to study inclusion
12. Subjects who have used scrub, anti-seborrheic topical cosmetic products and/or who have applied self-tanning products on face in the **1 week** prior the study inclusion
13. Subjects who have applied cosmetic products for more than 5 consecutive days with alpha hydroxyl-acids, vitamin C, hyaluronic acids in the **1 week** prior the study inclusion
14. Subjects having washed the face and/or the hair the day of the study inclusion (only water is accepted the morning of the study inclusion)
15. Subjects having applied any topical products on face (including make-up) the day of the study inclusion
16. Subjects who have planned a major surgery during the study requiring hospitalization under general anesthesia and the use of systemic or topical drugs (e.g. antibiotics, anti-inflammatory) for more than 1 week



17. Subjects who declare to be deprived of their freedom by administrative or legal decision or who are under guardianship
18. Subjects who cannot be contacted by telephone in case of emergency
19. Subjects belonging to the staff of the study centre
20. Subjects in an exclusion period or participating in another biomedical research study

| | |
|---|--|
| Name and type of IP | <ul style="list-style-type: none">• <u>Studied product</u>: Dermo-cosmetic product fla 688977 33• <u>Comparative product</u>: Hydréane légère, Cosmétique Active International (on the market)• <u>Pharmaceutical Drug</u>: Adapalene 0.1%/ benzoyl peroxide 2.5% treatment (Epiduo® 0.1%/2.5% gel; Galderma Laboratoires, on the market) |
| Description | Skin care for the face & topical treatment drug for acne |
| Supply | IP (cosmetic products) will be supplied by the Sponsor, to arrive at the study site at least one week before the start of the study. Investigators will provide the treatment Epiduo® in its branded packaging funded by the Sponsor. |
| Safety Assessments | Certificates of confirming the safety of the studied product will be provided by the Sponsor and will be included in the Investigator's brochure. The comparative product (Hydréane légère) is already on the market (cf Appendix 3 for informations). The fixed combination of "Adapalene 0.1%/ benzoyl peroxide 2.5% treatment" will be the marketed pharmaceutical drug Epiduo® 0.1%/2.5% gel; Galderma Laboratoires, as tube of 30g (cf Appendix 4). |
| Dose Regime/ Application instructions/ Randomisation | At W0, W4 and W8, subjects will be supplied with 1 tube of Epiduo® and 1 of the 2 cosmetic products according to the randomisation for a 4-week application period. Once-a-day, on the morning , the subjects will apply about a hazelnut of IP (amount equivalent to the amount generally used for a product of this type) to their face (avoiding eyes contour) in place of their usual product. Once-a-day, on the evening (before bedtime) , the subjects will apply the IP "Adapalene 0.1%/ benzoyl peroxide 2.5% treatment" on their face (affected area) on a cleansed and dried skin. The product must be applied in thin layer evenly with fingertips, avoiding eyes, lips and nostrils. The subjects will have to wash carefully their hands after each application. All IP applications will be made at home from W0 until the day before the last visit (W12) (i.e. 12-week application period). |



| | |
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| Study duration | 12 weeks with 4 visits to the study site (W0, W4 ± 3 days, W8 ± 3 days and W12 ± 3 days) per subject. |
|-----------------------|---|

An interval of at least one month must be respected before the subject will be allowed to participate in another study.

| | |
|------------------------|-------------------------------------|
| Data Management | Double data entry will be employed. |
|------------------------|-------------------------------------|

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|----------------------------|---|
| Statistical methods | Comparisons of fla 688977 33 versus Hydréane légère |
|----------------------------|---|

Statistical analysis

All data will be described by product.

1. For quantitative parameters, comparison between products using a covariance analysis with Product and Time as fixed factors, Subject as random factor and the value at baseline as covariate.
2. For ordinal parameters, comparison between products using a generalized linear random model for multinomial data with Subject as random factor, Time and Product as fixed factors and the value at baseline as covariate.

Responsibilities

| | |
|--|---|
| Protocol writing | Intertek |
| Supply of labeled study products | <ul style="list-style-type: none">• Dermo-cosmetic & Hydréane légère: Sponsor• Epiduo®: Investigator funded by the Sponsor |
| Products liability | Sponsor |
| Safety Assessment of the studied product | Sponsor |
| Randomization | SYLIA-STAT LANCRENON |
| Conduct of clinical phase | Each study centre |
| Monitoring | Sponsor |
| Quality assurance | Sponsor |
| Data management | SYLIA-STAT LANCRENON |
| Statistical analysis | SYLIA-STAT LANCRENON |
| Report writing without microbiota analysis | SYLIA-STAT LANCRENON |
| Microbiota analysis (if applicable) | INRA Transfert & Mercurialis for the interpretation of the results |

| | |
|------------------------|--|
| Study timelines | The planned study schedule will be as follows: |
|------------------------|--|

| | |
|--------------------------|-----------------|
| First inclusion | JAN-2019 |
| Last subject, last visit | DEC-2019 |
| Final report | DEC-2020 |



FLOW CHART

| STUDY PROCEDURES | VISIT 1 W0 Baseline | VISIT 2 ⁽¹⁾ W4 | VISIT 3 ⁽¹⁾ W8 | VISIT 4 ⁽¹⁾ W12 Final |
|---|---------------------------|------------------------------|------------------------------|--|
| Informed consent | X | | | |
| Demographics | X | | | |
| Medical history ⁽²⁾ | X | | | |
| Previous ⁽³⁾ and concomitant medication | X | | | |
| Checking of inclusion / exclusion criteria | X | | | |
| Urinary pregnancy test for females of child-bearing potential | X | | | |
| Counting of the retentional (open & closed comedones) and inflammatory lesions (papulae, pustulae & nodules (if applicable)) on the face by the Dermatologist | X | X | X | X |
| Determination of the acne stage according to the GEA scale by the Dermatologist | X | X | X | X |
| Clinical assessments by the Dermatologist (skin quality efficacy and local tolerance) | X | X | X | X |
| Microbiota sampling by a technician and/or a nurse | X | | | X |
| Instrumental measurements by a technician and/or a nurse | X | X | X | X |
| Confocal microscopy (n≈30; CHU Nantes study centre only) | X | | | X |
| Dispense IP, daily log and instructions | X | X | X | |
| Daily application of IP at home | | | X ⁽⁴⁾ | |
| Completion of daily log | | | X ⁽⁵⁾ | |
| Return of IP and daily log | | X | X | X |
| Compliance, Health and Concomitant medication checks | X | X | X | X |
| Cosmetic acceptability and efficacy questionnaires | | | | X |
| Products overall tolerance appreciation by the Dermatologist and the subject | | | | X |
| Adverse Events | X | X | X | X |
| Complete CRF, final page 'End of study' ⁽⁶⁾ | | | | X |

⁽¹⁾ Visit flexibility = ± 3 days

⁽²⁾ Details of relevant medical or surgical history experienced over the subject's life time, including any allergies or sensitivities, may include physical examination.

⁽³⁾ Details any medication taken in the 4 weeks prior to Visit 1.

⁽⁴⁾ IP application made at home until the day before the visits.

⁽⁵⁾ Completed after each IP application.

⁽⁶⁾ At Final Visit, if subject completes study as planned, or at any time before that in case of withdrawal.



5. STUDY CONTACT LIST AND TESTING FACILITIES

| | |
|---|---|
| Sponsor's Representative | A. BOULOC Medical Director Cosmétique Active International, Direction médicale Vichy International Address: 62, quai Charles Pasqua 92300 LEVALLOIS-PERRET FRANCE Phone: +33 (0)1 49 64 31 52 E-mail: anne.bouloc@loreal.com |
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| CHU Nantes-Hôtel-Dieu (Dermatology Department) Scientific investigator | A. KHAMMARI PhD Phone : +33 (0)2 40 08 32 80 |
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Testing facilities and authorization number

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- Centre 2
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1 place Alexis Ricordeau
44093 Nantes cedex 01
Agreement : NA



6. INTRODUCTION AND RATIONALE

Acne is a chronic disease of the pilosebaceous follicle (sebum-secreting glands at the root of the hair). It is related to the hypersecretion of sebum (hyper-seborrhea) and abnormalities of keratinization which leads to obstruction of the excretory duct of the pilosebaceous follicle and to the formation of comedones and microcysts. These lesions, called "retentional" lesions, can be complicated by inflammation, secondary to an anaerobic bacterium of the cutaneous flora, *Cutibacterium acnes*, which proliferates in the sebum. The lesions became inflammatory lesions.

Acne is a skin condition or dermatosis, non-contagious affecting about 80% of adolescents but also affects adults. It can have psychological repercussions, in particular because of the lesions that it can leave on the face or on visible parts of the body.

A combination of benzoyl peroxide and topical retinoids is proposed in the recent guidelines as first-line treatment in patients with acne (1, 2, 3).

In order to improve the efficacy and the tolerance of this treatment, a specific dermo-cosmetic product has been developed containing salicylic acid which is a beta-hydroxy acid known for its keratolytic action that aims to soften the stratum corneum of the epidermis to promote its natural desquamation. By boosting the elimination of dead cells, salicylic acid makes the skin smoother and softer. Another advantage: its astringent and antibacterial powers that allow it to act on the pores of the skin and sebaceous glands to limit the proliferation of bacteria and limit excess sebum.

So, the purpose of the study is to demonstrate that the dermo-cosmetic product fla 688977 33 associated with the fixed combination Adapalene 0.1% / benzoyl peroxide 2.5% treatment amplify anti-acne effectiveness of this treatment, but also, to demonstrate the benefit of the product by improving items on skin quality (hydration, pores, seborrhea ...) and finally, to demonstrate that this dermo-cosmetic product can improve the local tolerance of the Adapalene 0.1% / benzoyl peroxide 2.5% treatment.

7. STUDY OBJECTIVES

7.1. Primary objective

To evaluate the adjunctive anti-acne efficacy of a dermo-cosmetic product (fla 688977 33) associated with the fixed combination Adapalene 0.1% / benzoyl peroxide 2.5% treatment versus this treatment associated with a standard moisturizer (Hydréane légère, Cosmétique Active International) during a 12-week application period in male and female subjects presenting with mild to moderate acne.

7.2. Secondary objectives

The secondary objective of the present study are:

- To evaluate the effects on the skin quality of the dermo-cosmetic product associated with the fixed combination Adapalene 0.1% / benzoyl peroxide 2.5% treatment versus this treatment associated with a standard moisturizer.
- To demonstrate that the dermo-cosmetic product can improve the local tolerance of the fixed combination Adapalene 0.1% / benzoyl peroxide 2.5% treatment compared to a standard moisturizer.



- To evaluate the cosmetic acceptability of the dermo-cosmetic product versus a standard moisturizer.
- According to the results of the primary variable, to evaluate the impact on the microbiota of the dermo-cosmetic product associated with the fixed combination Adapalene 0.1% / benzoyl peroxide 2.5% treatment versus this treatment associated with a standard moisturizer.
- To collect safety data.

8. STUDY DESIGN

This will be a multi-centre, randomised, double blind, controlled, parallel groups (2 groups of 100 subjects), intra-subject & inter subject comparisons study.

The study will be conducted under ambulatory conditions. All the assessments will be carried out at the study centres.

The duration of the study will be 12 weeks with 4 visits to the study site (W0, W4 ± 3 days, W8 ± 3 days and W12 ± 3 days) per subject.

9. STUDY POPULATION

For Intertek France centre:

Subjects will be recruited from the recruitment database, the Facebook page and Intertek internet site.

For CHU Nantes centre:

Subjects will be recruited as part of a consultation conducted by the investigator and using external mailings.

A radio, press or internet ad or advertising poster will be used after the CPP authorized them. These ads may contain information such as: age, sex, study objective, place of achievement, main eligibility criteria, conditions, the duration of the study and the number of visits.

The study will be performed in male and/or female subjects presenting with mild to moderate acne (stage 2 or stage 3 according to the Global Acne Evaluation with at least 12 inflammatory lesions on face) after counting of the lesions by the Dermatologist and who satisfy all the inclusion criteria and none of the exclusion criteria presented in Sections 9.2 and 9.3.

All subjects and all legal representatives (for minor subjects) will receive verbal and written information concerning the study. This information will emphasise that participation in the study is voluntary and that the subject may withdraw from the study at any time and for any reason. All subjects and all legal representatives (for minor subjects) will be given opportunity to ask questions about the study and will be given sufficient time to consider their participation before consenting.

The subject's and legal representatives (for minor subjects) written informed consent to participate in the study will be obtained prior to any study related procedure being carried out.

The subjects participating in the study will not be able to participate simultaneously in another study. An interval of at least one month must be respected before the subject will be allowed to participate in another study.



9.1. Number of subjects

A total of 200 male and female subjects (100 per arm) will be included.

9.2. Inclusion criteria

Subjects must satisfy all of the following criteria for inclusion in the study:

1. Male and/or female subjects aged 16 to 35 years
2. Subjects presenting with mild to moderate acne (stage 2 or stage 3 according to the Global Acne Evaluation with at least 12 inflammatory lesions on face)
3. Female subjects of child-bearing potential who:
 - use **the same** reliable hormonal contraceptive method (oral contraceptive, implant, intra-uterine device, patch, vaginal ring and injection) for at least **3 months** prior to study inclusion and throughout the study or
 - use a reliable non-hormonal contraceptive method (copper intra-uterine device, condoms, diaphragm, cervical cap and spermicide) for at least **1 month** prior to study inclusion and throughout the study or
 - have no sexual intercourse and agreeing not to have any throughout the study or
 - are surgically sterile (oophorectomy, hysterectomy or tubal ligation),
4. Subjects and/or all legal representatives (for minor subjects) who have given written informed consent
5. Subjects who are willing to comply with the study requirements
6. Subjects with Social Security (health insurance) coverage (according to the French requirements)

9.3. Exclusion criteria

All subjects will be excluded from the study if they meet any of the following exclusion criteria:

1. Subjects with any systemic disorder or face dermatoses other than acne that would in any way confound interpretation of the study results (e.g. atopic dermatitis, eczema, or psoriasis)
2. Subjects with a condition or receiving a medication and/or with a history of medical/surgical events which, in the opinion of the Investigator, could compromise the safety of the subject or affect the outcome of the study
3. Subjects with a history of skin cancer
4. Female subjects who are pregnant (positive urine pregnancy test) or lactating or who are planning to become pregnant during the study
5. Subjects who have started, stopped or changed of hormonal treatment (contraception, thyroid ...) in the **3 months** prior the study inclusion
6. Subjects with hypersensitivity to the active substances of Epiduo® (Adapalene and/or benzoyl peroxide) or to one of its excipients
7. Subjects who are sensitive to peroxides (oxygenated water)
8. Subjects who have received isotretinoin treatment in the **6 months** prior to study inclusion
9. Subjects who have been exposed to excessive UV light (natural or artificial) in the **1 month** prior to the study inclusion or having planned excessive UV light exposure during the study (e.g. ski holidays, holidays in the tropics...)



10. Subjects who have used systemic drugs for more than 3 consecutive days related to antibiotics, anti-inflammatory, corticoids, anti-acneic in the **4 weeks** prior to study inclusion
11. Subjects who have used topical drugs for more than 3 consecutive days related to antibiotics, anti-inflammatory, corticoids, anti-acneic in the **2 weeks** prior to study inclusion
12. Subjects who have used scrub, anti-seborrheic topical cosmetic products and/or who have applied self-tanning products on face in the **1 week** prior the study inclusion
13. Subjects who have applied cosmetic products for more than 5 consecutive days with alpha hydroxyl-acids, vitamin C, hyaluronic acids in the **1 week** prior the study inclusion
14. Subjects having washed the face and/or the hair the day of the study inclusion (only water is accepted the morning of the study inclusion)
15. Subjects having applied any topical products on face (including make-up) the day of the study inclusion
16. Subjects who have planned a major surgery during the study requiring hospitalization under general anesthesia and the use of systemic or topical drugs (e.g. antibiotics, anti-inflammatory) for more than 1 week
17. Subjects who declare to be deprived of their freedom by administrative or legal decision or who are under guardianship
18. Subjects who cannot be contacted by telephone in case of emergency
19. Subjects belonging to the staff of the study centre
20. Subjects in an exclusion period or participating in another biomedical research study

9.4. Subject identification

The subjects will be identified by their screening number (SCXXX) and their randomisation number (RDXXXX) at W0 in order to maintain their data confidentiality.

The format of the screening number consists in letters SC followed by 3 digits; the 3 digits start from 001 and are given to the subjects in a chronological order during the screening in each study centre.

The format of the randomisation number consists in letters RD followed by 4 digits (the 1st digit corresponds to the number of the study centre); this number will be assigned to the subjects in the order of inclusion at W0 in each study centre as follow:

Intertek: from n° RD1001 to RD1100

CHU Nantes: from RD2001 to RD2100

The subject numbers will be documented in the CRF.

Subjects will be identified to the Sponsor only by their subject numbers, date of birth and gender. All subjects included in the study will be listed in the study status table.



9.5. Randomization and blinding

In order to minimise the bias, the study will be conducted in double blind and randomized conditions.

9.5.1. Description of randomisation/blinding measures

Prior to the start of the study, a randomisation list will be drawn up by SYLIA-STAT LANCRENON to be transmitted to the clinical packaging organisations for labelling.

The labels of the product materials identify only the randomisation number.

Subjects who fulfils all criteria will be randomized at each study centre in 1:1 way to receive:

- The dermo-cosmetic product (fla 688977 33)
- The standard moisturizer

The first IP will be dispensed to the subjects in the chronological order of their inclusion in the study at the visit 1, and no number should be omitted or skipped. This number will be documented in the CRF.

9.5.2. Maintenance of randomisation codes and procedures for breaking codes

SYLIA-STAT LANCRENON will send codes to the study centres.

The randomisation code (contains in sealed envelopes) identifies the IP provided/administered to each subject, throughout the period of the study. The investigator may only open this envelope if needed following a SAE, i.e only if the circumstances of this SAE require knowledge of the product which has been applied. In this event the investigator will inform the Sponsor. The investigator should mark on the code envelope the reason for the envelope being opened, the date of opening and should sign the envelope. On request, all code envelopes will be returned to the Sponsor at the end of the study.

The randomisation code will be also broken after the database lock and with agreement from the Sponsor.

9.6. Screen failures, subject withdrawals and replacement criteria

Non-included subjects, that is, subjects who have signed informed consent but are removed from the study during the screening process because they do not meet the inclusion/exclusion criteria, are classed as screen failures. Subjects who leave the study after randomisation or assignment to study treatment are classed as withdrawals rather than screen failures, even if the subject had not started the study treatment.

Subjects not completing the study for any reason will be considered as withdrawals and will not be replaced.

Criteria for withdrawal:

1. Subject withdraws consent: subjects will be free to withdraw from the study at any time and for any reason. (In accordance with the Declaration of Helsinki),
2. Adverse event / Serious adverse event: any adverse event that the investigator considers it is not in the subject's best interest to continue,
3. Protocol deviation (after agreement of the Sponsor and/or the investigator),
4. Subject lost to follow-up,
5. Other reasons: other reasons than stated above which requires subject to be withdrawn as:
 - any other situation where, in the opinion of the investigator, continuation of the study would not be in the interest of the subject;
 - Discontinuation of the study by the Sponsor.



The CRF should be completed up to the time of screen failure or withdrawal.

A subject will be considered as "Lost to Follow-up" after 3 phone calls (recorded) and a mail (registered mail with Acknowledgement of receipt) stayed without answer.

All subjects who are prematurely discontinued from the study should have the reason carefully documented by the Investigator/study team in the CRF, final page 'End of study', and, as applicable, on the Adverse Event Form and/or Concomitant Treatment Form.

No follow-up will be planned for the withdrawn subjects.

10. INVESTIGATIONAL PRODUCTS

10.1. Description

Sponsor should supply the investigators with the following cosmetic products.

- Studied product: fla 688977 33
- Comparative product: Hydréane légère, Cosmétique Active International (on the market)

The Investigator's brochure will confirm the safety of the studied product for use in this study. It will state that the IP to be tested do not entail any serious foreseeable risk for the health of the subjects taking part in the study as long as the conditions specified in the protocol are followed. It will be sent to CPP for protocol submission.

The comparative product (Hydréane légère) is already on the market (cf Appendix 3 for informations).

The fixed combination of "Adapalene 0.1% / benzoyl peroxide 2.5% treatment" will be the marketed pharmaceutical drug Epiduo® 0.1%/2.5% gel; Galderma Laboratoires, as tube of 30g (cf Appendix 4). Investigators will provide the treatment in its branded packaging funded by the Sponsor.

10.2. Packaging and labelling

The IP (cosmetic products) will be packed and labelled by the Sponsor, separately for each subject as per the randomization, according to the French requirements.

The container labels will have the following information in French:

| | |
|------------------------|----------------------------|
| ➤ Study reference | Référence de l'essai |
| ➤ Product type | Type de produit |
| ➤ Randomisation number | Numéro de randomisation |
| ➤ Expiry date | Date de péremption |
| ➤ Storage conditions | Conditions de conservation |
| ➤ Precautions for use | Précautions d'emploi |

INTERDIT A LA REVENTE
A N'UTILISER QUE DANS LE CADRE ET POUR LA DUREE DU TEST



10.3. Storage conditions

The IP (cosmetic products) will be stored at ambient temperature in a secure limited access area of each study centre.

The subjects will be asked to store the IP at home at ambient temperature.

The IP (marketed pharmaceutical drug) will be stored at temperature not exceeding 25°C in a secure limited access area of each study centre. The subjects will be asked to store the IP at home at a temperature not exceeding 25°C.

10.4. Dosage and application of the IP

At W0, W4 and W8, subjects will be supplied with 1 tube of Epiduo® and 1 of the 2 cosmetic products according to the randomisation for a 4-week application period.

Once-a-day, on the morning, the subjects will apply about one hazelnut of IP (amount equivalent to the amount generally used for a product of this type) to their face (avoiding eyes contour) in place of their usual product.

Once-a-day, on the evening (before bedtime), the subjects will apply the IP “Adapalene 0.1%/ benzoyl peroxide 2.5% treatment” on their face (affected area) on a cleansed and dried skin. The product must be applied in thin layer evenly with fingertips, avoiding eyes, lips and nostrils.

The subjects will have to wash carefully their hands after each application.

All IP applications will be made at home from W0 until the day before the last visit (W12) (i.e. 12-week application period).

10.5. IP accountability, compliance and destruction

Receipt, checking, registration of storage and dispensing of the IP will be carried out in each study centre.

The subjects will record each IP (cosmetic product & drug) application in their daily log. Their compliance with this requirement will be checked by a member of the study team at each visit from a review of the daily log. The number of IP applications will be reported in the CRF in order to compute the compliance at each visit as follow:

Compliance will be expressed by the ratio of the number of applications of the IP actually applied to the theoretical number of IP applications.

The compliance of the cosmetic products should be comprised between 80-120% whereas the compliance of the drug treatment should not be inferior to 75%.

Any deviation from the required IP use regime will be documented in the study report.

At the end of the study, the used and unused IP (cosmetic products) will be checked and then returned to the Sponsor whereas the unused IP (marketed pharmaceutical drug) will be destroyed by each study centre.



11. STUDY ASSESSMENTS AND CONDUCT

11.1. General

The study will be conducted under ambulatory conditions. All the assessments will be carried out at the study centres.

No study procedures will be carried out before the subject and/or legal representatives (for minor subjects) has/have given written informed consent.

11.2. Study duration

12 weeks with 4 visits to the study site (W0, W4 ± 3 days, W8 ± 3 days and W12 ± 3 days) per subject.

An interval of at least 1 month must be respected before the subject will be allowed to participate in another study.

11.3. Study restrictions

Throughout the study, subjects will be instructed as follows:

- to replace their usual skin care products for the face with the IP according to the instructions and not to apply any other topical products
- to continue to use their usual non-comedogenic washing products and shampoo (no new product)
- to continue to use their usual make-up and remover (no new product)
- not to expose to excessive sunlight
- not to expose to artificial UV light
- not to undergo surgical/medical procedures on the face (deep cleansing, dermabrasion, peeling, light-therapy, laser...)
- not to use scrub, not to apply self-tanning product on the face
- not to manipulate the imperfections on the face (do not scratch, squeeze...)
- not to change as far as possible their routine lifestyle (food...)
- not to apply any topical products (including IP, make-up...) on face the day of the visits
- not to wash the face and/or the hair the day of the visits (only water is accepted the morning of the visits)
- to return the daily log and the IP at each visit
- to store the IP (cosmetic product) at ambient temperature and the IP (drug treatment) at a temperature not exceeding 25°C at home

Subjects will be informed of the restrictions verbally and in writing prior to consenting to take part in the study.

11.4. Prior and concomitant medication

Any topical or systemic therapy used in the 4 weeks prior the Visit 1 will be recorded in the CRF, with the following information:

- name of the drug, type of formulation, and unit strength,
- dose administered,
- start and stop dates,
- reason for treatment.



The following treatments are not allowed:

- isotretinoin treatment within the 6 months prior the Visit 1 and during the study
- surgical/medical procedures on the face (deep cleansing, dermabrasion, peeling, light-therapy, laser...) during the study,
- systemic drugs for more than 3 consecutive days related to antibiotics, anti-inflammatory, corticoids, anti-acneic in the 4 weeks prior the Visit 1 and during the study,
- topical drugs for more than 3 consecutive days related to antibiotics, anti-inflammatory, corticoids, anti-acneic in the 2 weeks prior the Visit 1 and during the study,

Any subject using a concomitant therapy during the study that could interfere with the assessment of the IP will be considered for withdrawal from the study, at the discretion of the investigator.

11.5. Study schedule

Having received all the written and verbal information and the answers to them questions, the subjects and all legal representatives (for minor subjects) must give their consent by signing the Consent Form.

For females of childbearing potential (except those who are surgically sterile): a urinary pregnancy test will take place on W0, before IP dispensation.

Investigators will provide the pregnancy test kit funded by the Sponsor.

Then the following examinations are made:

• VISIT 1 - W0

- Inform Consent
- Demographics
- Medical history ⁽¹⁾ / previous and concomitant medications ⁽²⁾
- Checking of inclusion and exclusion criteria
- Urinary pregnancy test for females of child-bearing potential
- Counting of the retensional (open & closed comedones) and inflammatory lesions (papulae, pustulae & nodules (if applicable)) on the face by the Dermatologist
- Determination of the acne stage according to the GEA scale by the Dermatologist
- Definitive inclusion
- Clinical assessments by the Dermatologist (skin quality efficacy and local tolerance)
- Microbiota sampling by a technician and/or a nurse
- Instrumental measurements by a technician and/or a nurse (different according to the study centre) & confocal microscopy by investigator (Nantes site only)
- Dispense IP according the randomisation and daily log
- Explanation of usage instructions

⁽¹⁾ Details of relevant medical or surgical history experienced over the subject's life time, including any allergies or sensitivities, may include physical examination.

⁽²⁾ Details any medication taken in the 4 weeks prior the Visit 1.



• **VISIT 2 – W4 (±3 days) (AFTER A 4-WEEK APPLICATION PERIOD)**

- Confirm health status of subject and record any concomitant therapies and adverse events
- Return of IP and daily log
- Check of subject completed daily log for compliance with products usage
- Dispense IP according the randomisation and daily log
- Counting of the retentional (open & closed comedones) and inflammatory lesions (papulae, pustulae & nodules (if applicable)) on the face by the Dermatologist
- Determination of the acne stage according to the GEA scale by the Dermatologist
- Clinical assessments by the Dermatologist (skin quality efficacy and local tolerance)
- Instrumental measurements by a technician and/or a nurse (different according to the study centre)
- Explanation of usage instructions

• **VISIT 3 – W8 (±3 days) (AFTER A 8-WEEK APPLICATION PERIOD)**

- Confirm health status of subject and record any concomitant therapies and adverse events
- Return of IP and daily log
- Check of subject completed daily log for compliance with products usage
- Dispense IP according the randomisation and daily log
- Counting of the retentional (open & closed comedones) and inflammatory lesions (papulae, pustulae & nodules (if applicable)) on the face by the Dermatologist
- Determination of the acne stage according to the GEA scale by the Dermatologist
- Clinical assessments by the Dermatologist (skin quality efficacy and local tolerance)
- Instrumental measurements by a technician and/or a nurse (different according to the study centre)
- Explanation of usage instructions

• **VISIT 4 – W12 (±3 days) (AFTER A 12-WEEK APPLICATION PERIOD)**

- Confirm health status of subject and record any concomitant therapies and adverse events
- Return of IP and daily log
- Check of subject completed daily log for compliance with products usage
- Completion of the cosmetic acceptability and efficacy questionnaires by the subject
- Counting of the retentional (open & closed comedones) and inflammatory lesions (papulae, pustulae & nodules (if applicable)) on the face by the Dermatologist
- Determination of the acne stage according to the GEA scale by the Dermatologist
- Clinical assessments by the Dermatologist (skin quality efficacy and local tolerance)
- Products overall tolerance appreciation by the Dermatologist and the subject
- Microbiota sampling by a technician and/or a nurse
- Instrumental measurements by a technician and/or a nurse (different according to the study centre) & confocal microscopy by investigator (Nantes site only)



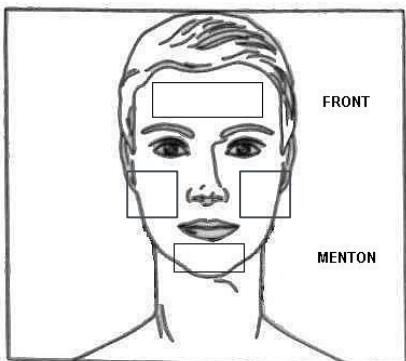
11.6. Study assessments

For 1 subject, clinical assessments should be performed by the same investigator for the whole study except in case of absolute necessity.

11.6.1. Primary variable: Counting of the retentional and inflammatory lesions (anti-acne efficacy)

At W0 (before any application) and W12 (after a 12-week application period), a counting of the retentional (open & closed comedones) and inflammatory lesions (papulae, pustulae & nodules (if applicable)) will be performed by a Dermatologist.

The counting will be broken down on several parts of the face according to the following pictures: forehead, left and right cheeks and chin.



The number and sum of open & closed comedones (retentional lesions) and of papulae, pustulae & nodules (if applicable) (inflammatory lesions) will be recorded in the CRF.



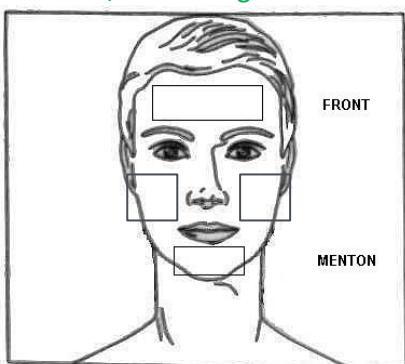
11.6.2. Secondary variables

11.6.2.1. Anti-acne efficacy

- Counting of the retentional and inflammatory lesions

At W4 (after a 4-week application period) and W8 (after an 8-week application period), a counting of the retentional (open & closed comedones) and inflammatory lesions (papulae, pustulae & nodules (if applicable)) will be performed by a Dermatologist.

The counting will be broken down on several parts of the face according to the following pictures: forehead, left and right cheeks and chin.



The number and sum of open & closed comedones (retentional lesions) and of papulae, pustulae & nodules (if applicable) (inflammatory lesions) will be recorded in the CRF.

- Determination of the acne stage

At W0 (before any application), W4 (after a 4-week application period), W8 (after an 8-week application period) and W12 (after a 12-week application period), determination of the acne stage will be performed by the Dermatologist according to the Global Acne Evaluation scale (cf Appendix 2) and will be recorded in the CRF.



11.6.2.2. Skin quality efficacy

- Clinical assessments

At W0 (before any application), W4 (after a 4-week application period), W8 (after an 8-week application period) and W12 (after a 12-week application period), clinical assessments will be performed under the same conditions by the Dermatologist:

- of the residual marks visibility of acne (hyperpigmentation)
- of the pores visibility
- of the skin shininess

using the scales below which include 10 grades (0 to 9).

| Residual marks visibility of acne (hyperpigmentation) | | | | | | | | | |
|---|----------------------------|---|---|--------------------------------|---|---|---------------------------------|---|---|
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Absence of visible residual marks | Few visible residual marks | | | Several visible residual marks | | | Numerous visible residual marks | | |

| Pores visibility | | | | | | | | | |
|--------------------------|-------------------|---|---|-----------------------|---|---|------------------------|---|---|
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Absence of visible pores | Few visible pores | | | Several visible pores | | | Numerous visible pores | | |

| Skin shininess | | | | | | | | | |
|---------------------------|-----------------------|---|---|-------------------------|---|---|---------------------|---|---|
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Absence of skin shininess | Slight skin shininess | | | Moderate skin shininess | | | High skin shininess | | |

All the scores will be recorded in the CRF.



- Instrumental measurements

At W0 (before any application), W4 (after a 4-week application period), W8 (after an 8-week application period) and W12 (after a 12-week application period), instrumental measurements will be performed by a technician at Intertek and a nurse at CHU Nantes.

The subjects will rest in a climatized temperate room for at least 30 minutes before instrumental measurements.

- Skin greasiness using sebumetry measurements*

The CL measurements (quantity of sebum (casual level)) will be taken using a SEBUMETER® (COURAGE + KHAZAKA).

The measurement is based on grease-spot photometry. A special tape becomes transparent in contact with the sebum on the skin surface. For the determination of the sebum, the measuring head of the cassette is inserted into the aperture of the device, where the transparency is measured by a light source sending light through the tape which is reflected by a little mirror behind the tape. A photocell measures the transparency. The light transmission represents the sebum content on the surface of the measuring area. A microprocessor calculates the result, which is shown on the display in $\mu\text{g sebum}/\text{cm}^2$ of the skin.

Only one measurement per subject will be taken in the middle of the forehead (if it will be possible on a nonlesional skin). The value will be reported in the CRF.

- Skin moisturizing using corneometry measurements*

The measurements will be taken using a CM 825 PC CORNEOMETER® (COURAGE + KHAZAKA).

The skin acts as a condenser with a high dielectric constant, for which the capacity depends on the amount of water contained in the epidermis (water rises ion mobility). The Corneometer measures the dielectric capacity of the epidermis using a condenser.

The hydration values are expressed in arbitrary units ranging from approximately 0 to 120.

Three measurements per subject will be taken on the right cheekbone (if it will be possible on a nonlesional skin). The values will be reported in the CRF.

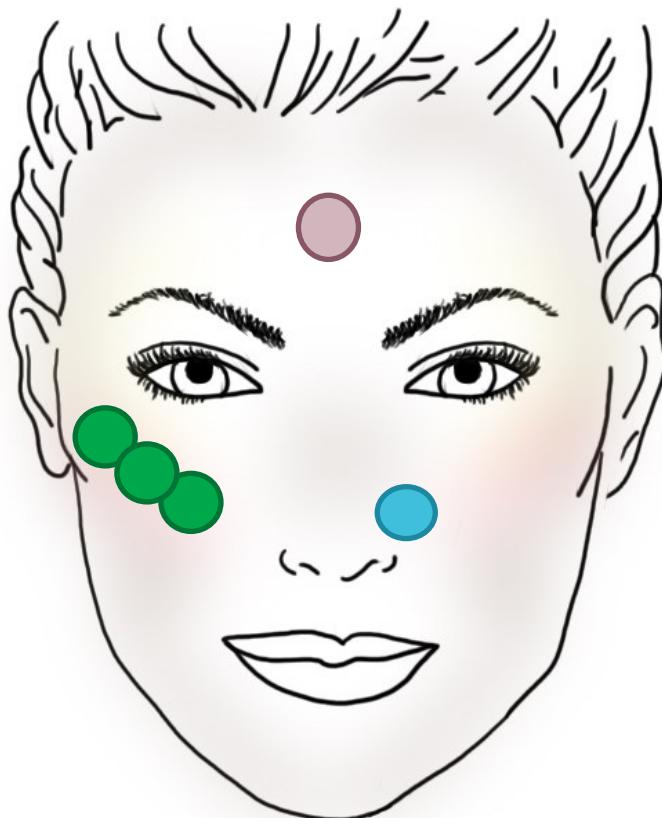
- Skin pH using pHmetry measurements*

The measurements will be taken using a SKIN PH METER 900® (COURAGE + KHAZAKA).

The measurement is based on the principle of electrochemistry. PH measurement allows obtaining the acidity and alkalinity of the skin. The value is determined by the hydrogen ion concentration (protons H+) and by the hydroxide ion concentration (OH- anions) and will be expressed in pH units.

The pH measurement is preferably carried out with a glass electrode. The interior of the electrode is filled with a buffer (mercury / calomel or silver / silver chloride). This buffer is separated from the measurement solution by a thin glass membrane. In contact with the solution, the buffer transports the ionic potential of the solution on the interior side toward the outer side of the glass membrane. A flat disc in front of the membrane allows direct contact on surface of the skin.

Only one measurement per subject will be taken on the left cheek, near to the side of the nose (if it will be possible on a nonlesional skin). The value will be reported in the CRF.



Sebumetry measurement



Corneometry measurements



Phmetry measurement



- *Confocal microscopy analysis (only for CHU Nantes; n≈ 30) (5)*

From the beginning of the inclusions and until the number of subjects will be reached (n≈ 30), the investigator will propose a complementary examination that the subjects will be free to refuse.

At W0 (before any application) and W12 (after a 12-week application period), instrumental measurements will be performed by investigator at CHU Nantes.

a) Acquisitions:

RCM Vivascope® (1500/3000) is a confocal laser scanning microscope for *in vivo* use, with an imaging wavelength of 830 nm, used to acquire standardized pictures of the skin. Confocal images are obtained by analyzing the reflection of a diode laser in the skin. Resolution allows analyzing the epidermis and upper layers of the stratum reticulare, up to a depth of 200 µm with a lateral resolution <1.25 µm. The lens will be directly applied onto the selected skin area (on 3 nonlesional skin area: forehead, right temple and right mandibular). Crodamol oil will be used as a conductive interface between the skin and the lens. Each image corresponded to a 500 µm x 500 µm horizontal section. A Vivacube® of 3 mm x 3 mm is a mosaic of 36 images, on three horizontal section levels.

b) Analysis:

Confocal images will be analyzed by two confocal microscopy experts (Dr. Vourc'h Jourdain, Dr. Muguet Guenot).

The assessments features will be:

- Total number of hair follicles per cube at a mean depth of 38 µm
- Diameter of the infundibulum
- Aspect of the border (thickness)
- Onion-like appearance
- Presence of amorphous material into the infundibulum
- Signs of inflammation
- Vascularization
- Presence of *Demodex* mites



- Efficacy questionnaire

Subjects will complete an efficacy questionnaire at the last visit (after a 12-week application period of the IP (cosmetic product & drug)).

The following items will be evaluated by the subjects:

| | ITEMS |
|----|---|
| 1 | Les imperfections sont moins visibles <i>Imperfections are less visible</i> |
| 2 | La peau est assainie/purifiée <i>The skin is cleansed/purified</i> |
| 3 | Le teint est homogène/uniforme <i>The complexion is homogeneous / uniform</i> |
| 4 | La peau est confortable <i>The skin is comfortable</i> |
| 5 | La peau est comme hydratée <i>The skin is like hydrated</i> |
| 6 | La peau est plus lisse <i>The skin is smoother</i> |
| 7 | La peau est plus douce <i>The skin is softer</i> |
| 8 | La peau est plus souple <i>The skin is suppler</i> |
| 9 | La peau est moins brillante <i>The skin is less brilliant</i> |
| 10 | La peau est matifiée <i>The skin is matified</i> |
| 11 | L'excès de sébum est réduit <i>Excess sebum is reduced</i> |
| 12 | La peau a un toucher mat <i>The skin has a matte touch</i> |
| 13 | Les pores de la peau sont resserrés <i>The pores of the skin are tightened</i> |
| 14 | Les rougeurs de la peau sont atténuées <i>Redness of the skin are reduced</i> |
| 15 | Le grain de peau est affiné <i>The skin texture is refined</i> |
| 16 | Les marques de la peau sont moins visibles <i>The marks of the skin are less visible</i> |

The following scale will be used:

- Agree (“D'accord”)
- Somewhat agree (“Plutôt d'accord”)
- Neither agree, nor disagree (“Ni d'accord ni pas d'accord”)
- Somewhat disagree (“Plutôt pas d'accord”)
- Disagree (“Pas d'accord”)



11.6.2.3. Local tolerance

- Clinical assessments

At W0 (before any application), W4 (after a 4-week application period), W8 (after an 8-week application period) and W12 (after a 12-week application period), a clinical assessment of the face skin condition will be performed by the Dermatologist:

- Physical signs: erythema, dryness and scaling
- Functional signs*: tightness, prickling, itching, burning sensation and others

The following scale will be used:

Rating 0: none ("absence")

Rating 1: slight ("léger")

Rating 2: moderate ("modéré")

Rating 3: severe ("sévère")

* During the study, the subjects will have to record any skin discomfort, intensity (slight, moderate or severe) and duration in their daily log. Functional signs will be assessed by the Dermatologist from a review of the daily log and interrogatory of the subject.

- Overall tolerance

In addition, at W12 (after a 12-week application period), the Dermatologist and the subject will state about the overall tolerance of the IP (cosmetic product & drug) based on rating scale:

- Excellent tolerance
- Good tolerance
- Medium tolerance
- Poor tolerance



11.6.2.4. Cosmetic acceptability

Subjects will complete a cosmetic acceptability questionnaire concerning the cosmetic product at the last visit.

The following items will be evaluated by the subjects:

| | ITEMS |
|----|---|
| 1 | Le produit est facile à étaler <i>The product is easy to spread</i> |
| 2 | Le produit est facile à appliquer <i>The product is easy to apply</i> |
| 3 | Le produit pénètre vite <i>The product penetrates quickly</i> |
| 4 | La couleur du produit est agréable <i>The color of the product is pleasant</i> |
| 5 | L'odeur du produit est agréable <i>The scent of the product is pleasant</i> |
| 6 | L'aspect du produit est agréable <i>The aspect of the product is pleasant</i> |
| 7 | La texture du produit est agréable <i>The texture of the product is pleasant</i> |
| 8 | La texture est confortable <i>The texture is comfortable</i> |
| 9 | Le produit ne laisse pas la peau collante <i>The product doesn't leave the skin sticky</i> |
| 10 | Le produit ne laisse pas de film gras sur la peau <i>The product doesn't leave a greasy film on the skin</i> |
| 11 | Le produit laisse un effet soyeux <i>The product leaves a silky effect</i> |
| 12 | Le produit ne peluche pas <i>The product does not go noodles</i> |

The following scale will be used:

- Agree (“D'accord”)
- Somewhat agree (“Plutôt d'accord”)
- Neither agree, nor disagree (“Ni d'accord ni pas d'accord”)
- Somewhat disagree (“Plutôt pas d'accord”)
- Disagree (“Pas d'accord”)



11.6.2.5. Microbiota analysis (6)

a) Sampling:

At W0 (before any application) and at W12 (after a 12-week application period), microbiota sampling will be performed by the same sampler (technician or nurse).

Skin microbiota sample will be collected on one test site of 4 cm² (square of 2 cm x 2 cm) which will be delineated using a template (to ensure that the same area will be sampled at each visit) on the middle of the left cheek and using aseptic techniques under sterile airflow generated by a portable hood.

Single use sterile square-sized cotton-tipped swabs (165KS01, COPAN SPA, Brescia, Italy) will be moistened with a sterile solution (filtered at 0,22 microns before use) of deionized water containing 0.15 M NaCl and 0.1% Tween 20.

Cotton tips containing the samples will be stored at -80°C until the end of the study and shipped for processing using dry ice to INRA Transfert.

b) Analysis (if applicable):

According to the results of the primary variable, the Sponsor will decide to go ahead with the microbiota analysis which will be done by INRA Transfert.

DNA Extraction, PCR Amplification, and Sequencing

DNA will be extracted from the swabs using the MoBio PowerSoil-htp 96-well Soil DNA Isolation Kit (MoBio, Inc., Carlsbad, CA, USA) following the manufacturer's instructions. PCR amplification will be performed for each DNA sample. DNA will be PCR amplified with barcoded primers that targets the V1-V3 region of bacterial. Cleaned pools will be sequenced on the Illumina MiSeq platform at Genotoul Next Generation Sequencing Facility, France.

Sequence Processing

Sequences will be processed as previously described. Sequences will be then de-replicated and a database containing one sequence for each operational taxonomic unit (OTU) will be generated at the 97% nucleotide identity level. Sequencing reads from the full dataset will be then clustered to the database to generate an OTU table. Taxonomy will be assigned to each OTU using Greengene database.

Interpretation of these results will be done by Mercurialis.

11.6.2.6. Safety: Adverse Events Collection

All AE reported during the study will be recorded in the CRF.



11.7. Adverse events and serious adverse events

11.7.1. Adverse events

11.7.1.1. *Definition of adverse events*

An **adverse event** is any untoward medical occurrence in a subject who has been administered an IP, which does not necessarily have a causal relationship with this IP.

An **Adverse Event** (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, whether or not related to the IP.

Thus any new sign, symptom or disease, or clinically significant increase in the intensity of an existing sign, symptom or disease, should be considered as an adverse event.

Notes:

- Clinically significant worsening of the disease/condition being evaluated, which occurs during the study, may be considered as an adverse event according to the Dermatologist judgment.
- Lack of efficacy of the IP is not considered an adverse event unless it leads to other unfavourable medical occurrence.
- Any new sign or symptoms suffered by the subject as results of accidental or intentional overdose or misuse of the IP should be reported as an adverse event. The overdose itself is not an adverse event.
- Pregnancy is not per se an adverse event. Any incidents of pregnancy during a study will be reported to the Sponsor immediately by letter to the Sponsor. The Sponsor will advise on the appropriate course of action. The subject will be immediately withdrawn from the study and the pregnancy will be documented as required by the protocol.
- Planned hospitalisation for elective treatment of a pre-existing condition that has not worsened from baseline is not considered an AE.

The expected AE of the drug treatment are listed in the “Résumé des Caractéristiques du Produit” (cf Appendix 4).

11.7.1.2. *Reporting of adverse events*

Events reported by the subject, or observed by the investigator, should be described in the following manner.

The **NATURE** of the event should be described in precise, standard medical terminology (i.e., not necessarily the exact words used by the subject). Where possible, a specific diagnosis should be stated (e.g., allergic contact dermatitis).

TIME OF THE EVENT will be described by the terms:

- Onset date (ie the date the first symptoms were experienced by the subject or the date the AE was discovered)
- End date (or left blank for event not resolved at the end of the follow up).

SERIOUSNESS of the event will be described by the terms:

- Minor i.e. not serious
- Serious



CAUSAL RELATIONSHIP of the event to the use of the IP will be according to the investigator's clinical judgement and described by the terms:

- Not related The event is clearly related to other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject or no IP has been used (where applicable)
- Unlikely The event was most likely produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject; and do not follow a known response pattern to the IP.
- Possible The event follows a reasonable temporal sequence from the time of IP administration; and/or follows a known response pattern to the study treatment; but could have been produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject.
- Probable The event follows a reasonable temporal sequence from the time of IP administration; and follows a known response pattern to the IP; and cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications administered to the subject.
- Definite As for Probable AND either occurs immediately following IP administration, or improves on stopping the IP, or reappears on repeat exposure, or there is a positive reaction at the specific application site.
- Unknown There is insufficient information to make a judgment

ACTION WITH RESPECT TO IP will be described by the terms:

- None
- Discontinue product (the subject continues on the study, if the protocol allows it, with or without re-introduction of the IP)
- Adjust dosage if the protocol allows it
- Withdraw from study

CORRECTIVE TREATMENT to be reported as a concomitant medication.

- None
- Medication
- Non-medication therapy

FREQUENCY of the event

- Isolated
- Intermittent
- Constant

SEVERITY of the event will be described in terms of mild, moderate or severe according to the investigator's clinical judgement.

- Mild: Did not interfere with normal everyday activities
- Moderate: Interfered to some extent with everyday activities
- Severe: Was not tolerated and interfered with normal everyday activities

EXPECTED / UNEXPECTED will be described by the terms:

- Expected AE conforms with known AEs associated with the IP as described in the supporting literature (i.e. Investigator Brochure)
- Unexpected



IMMEDIATE OUTCOME and FOLLOW UP OUTCOME of the event will be described by the terms:

- Ongoing
- Resolved
- Stabilized / discharged
- Lost to follow up (except for immediate outcome)

During the subject's study participation, all adverse events should be followed up to determine the final outcome. When an AE persists at the end of the subject's participation in the study, follow-up will be required for those adverse events classified as "possible", "probable" or "definite" related to the IP.

Follow-up should continue until

- the event has resolved or,
- the event is considered to be stabilized (at discretion of investigator and/or Sponsor) or,
- the subject has been discharged to the care of their own physician

11.7.2. Serious adverse events

11.7.2.1. Definition of serious adverse events

Serious Adverse Event (SAE): Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires insubject hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity or
- is a congenital anomaly/birth defect

or

- other medically important conditions*

* Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

11.7.2.2. Reporting of serious adverse events

Any Serious Adverse Event (SAE), related or unrelated to any IP or procedures occurring after informed consent has been obtained, and until the subject's completion of the study, must be reported to the Sponsor within ONE working day of the investigator becoming aware of the event. This may be done by email or telephone call.

SAEs must be reported using a Serious Adverse Event (SAE) form. The information provided on the form must include a description of the clinical course of the SAE and an assessment of the intensity, causal relationship to the IP and/or study procedures, the action taken and the outcome to date.

Reporting and completed SAE form must be emailed to the Sponsor:

A. BOULOC
Medical Director
62, quai Charles Pasqua
92300 LEVALLOIS-PERRET FRANCE
Phone: +33 (0)1 49 64 31 52
E-mail: anne.bouloc@loreal.com



The initial report should be followed by a detailed description as more information becomes available which may include copies of hospital records and other documents when requested and applicable.

If an investigator is in doubt whether to regard an adverse event as serious or not, the event is to be considered as serious until otherwise established.

All SAEs and Suspected, Unexpected Serious Adverse Reactions (SUSARs) are subject to expedited reporting to competent authorities and CPP and all concerned investigators, unless otherwise required as per local requirements.

For all SAEs, the investigator will follow-up the final outcome and ensures all queries have been resolved. Details of follow-up should be recorded (e.g. discontinuation of IP, if specific treatment is required, if hospitalisation is required etc.).

11.7.2.3. Pregnancy

Pregnancy which occurs during a study with an IP must be reported to the Sponsor by use of the Serious Adverse Event (SAE) Form and handled as a SAE with regard to reporting time frame. All pregnancies must be followed-up until conclusion.

11.7.3. Vigilance

- The suspicions of serious adverse event,
- The suspicions of other adverse events where a medical treatment was required and those that seem to have a serious nature,
- The new facts,

Will have to be declared to ANSM by the Sponsor according to article of law R.1123-49 of the "Code de la Santé Publique".

12. CODE AND HANDLING OF SAMPLES

12.1. Samples coding

Samples for microbiota analysis will be coded as follows:

- Study number (VCA 18-01)
- the randomisation number (RD1001 to RD1100 & RD2001 to RD2100),
- the visit (W0, W12)

12.2. Sample collection -preparation-storage and transfer

Cotton tips containing the samples will be stored in dry ice, then at -80°C (± 5) in each study centre until their shipment to INRA Transfert, for analysis (if applicable).

12.3. Remaining samples and archive samples

Remaining of samples will be destroyed by:

- INRA Transfert if analysis will be done
- Each centre if no analysis will be done.



13. DATA MANAGEMENT

13.1. Database set up

The data collection system (including database and data entry screens) is specifically designed with Ennov Clinical software for recording the data required by the protocol. The data entry system will be developed by SYLIA-STAT LANCRENON.

13.2. Data entry

A double data entry of all data collected during the study will be performed by two independent data entry operators on an interactive mode. Data entry operators will be trained to the study specificities by the data-manager in charge of the study.

All steps of data entry, coding and data handling as well as software used for data entry will be documented by SYLIA-STAT LANCRENON.

Any queries arising after data entry in the database must be answered using DCFs. The Investigator is responsible for resolving any query and must sign every DCF to confirm that the data is accurate.

All electronically issued documents will be identified with the subject number.

13.3. Database lock – individual data listing

Once the database is clean, a blind review will be organized with the Sponsor to check the consistency of the data.

Prior to the database lock, all the following prerequisites will be checked:

- Data entry of all collected data,
- Resolution of all data inconsistencies,
- Validation of data coding (if applicable),
- Proofreading of all non coded texts,
- Blind review performed,
- Determination of protocol deviations,
- Approval of the statistical analysis plan.

After authorization by the sponsor, the database will be locked and a certificate attesting of the lock will be sent to the Sponsor.

13.4. Data transfer

The SAS database will be transferred to the sponsor as a compressed file protected by password.

14. SAMPLE SIZE / STATISTICAL ANALYSIS

A statistical analysis plan (SAP) will be prepared by the SYLIA-STAT LANCRENON and validated by the Sponsor prior to the database lock. Statistical analyses will be performed with SAS® version 9.4 or higher (SAS institute, North Carolina, USA).



14.1. Sample size calculation

The primary objective of this study is to demonstrate the superiority of fla 688977 33 versus Hydréane légère on the total number of lesions at W12.

The following hypotheses, based on previous studies (4) were used for the estimation of the sample size calculation:

- Power $(1 - \beta) = 80\%$
- Two-sided significance level $(\alpha) = 5\%$
- Expected inter-treatment difference (on the changes W12-W0) = 1.15
- Standard deviation = 5.0
- Correlation between the baseline and the endpoint $R^2 = 0.70$

Using the sample size calculation method for covariance analysis (7), the number of evaluable subjects is estimated at 90 by treatment group (180 subjects total).

If we anticipated 10% of drop-out, the total number of subjects required is 200.

14.2. Study population for analysis

Efficacy evaluation will be done on “per protocol” PP population (randomized subjects without Major Deviations) while safety evaluation will be done on “Intent-To-Treat” ITT population (all subjects randomized with at least 1 application of each IP).

* Major deviations will be defined during the blind review

14.3. Data description and statistical analysis

Subject disposition

Data from subjects of all defined populations, from subjects who completed the study, and from subjects who withdrew from the study will be summarized by product group using descriptive statistics.

Data from subjects who withdrew from the study will also be summarized by reason for withdrawal using descriptive statistics.

Demographic and Baseline Characteristics

Subjects demographic and baseline characteristics will be summarized by product group using descriptive statistics. For continuous variables, descriptive statistics (n, mean, standard deviation, standard error, median, minimum, and maximum) will be provided. For categorical variables, subject counts and percentages will be provided. Categories for missing data will be presented if necessary.

Efficacy analyses

Analyses will use 2-sided tests at the 5% significance level, except the normality tested at the threshold of 1% (Shapiro-Wilk test).

For all parameters, descriptive statistical tables along with graphics will be performed.

For quantitative parameters (such as clinical counting of cutaneous lesions, sebumetry, corneometry, pHmetry), products will be compared by a covariance analysis with Product and Time as fixed factors, Subject as random factor and value at baseline as covariate (mixed models for repeated longitudinal using SAS® Mixed procedure). The interaction Time x Product will be tested. **Contrasts between products will be evaluated at each time. For the total number of cutaneous lesions, W12 will be considered as the primary contrast.**



Ordinal parameters such as the GEA will be analysed using generalized linear random model for multinomial data (a model for binary data can also be used according to the results of the descriptive analysis), with Subject as random factor, Time and Product as fixed factors and the value at baseline as covariate (SAS® Glimmix Procedure).

All comparisons will be carried out using contrasts. Tests will be followed by a Benjamini-Hochberg adjustment for multiple comparisons.

Data collected [from the efficacy and cosmetic acceptability questionnaires](#) at W12 will be described and compared between products by a chi-square test.

Safety analyses

Physical and functional signs will be described and analysed using a generalized linear random model for multinomial data (a model for binary data can also be used according to the results of the descriptive analysis), with Subject as random factor, Time and Product as fixed factors (SAS® Glimmix Procedure).

The overall tolerance will be compared between treatments using a chi-square test.

The adverse events will be described and the number of subjects with at least one AE related to the study product will be compared between products by a chi-square test.

15. REPORT

A study report will be prepared in English by [SYLIA-STAT LANCRENON](#).

16. REGULATORY STATUS, ETHICS AND ADMINISTRATION

16.1. Regulatory status

According to French "Décret n°2017-884", the regulatory status of this study has been confirmed by the Sponsor as an "interventional study with minimal risks and constraints" (RIPH 2 mentioned to the 2° Article of the French Low L.1121-1) and has been submitted to Ethic Committee (CPP [SUD-OUEST ET OUTRE-MER II](#)).

16.2. Ethical conduct of the study

The study will be conducted in compliance with the protocol and all amendments to the protocol.

The protocol and all corresponding amendments affecting the design, rationale or objectives of the study, or the burden of or health risks for the subjects will only be implemented after having received written approval of the Ethic Committee (CPP).

The study will be conducted in accordance with:

- The World Medical Association - Declaration of Helsinki, (see Appendix 1)
- Local regulations.

16.3. General Data Protection Regulation

According to the General Data Protection Regulation (GDPR), data recorded during the study will be kept confidential and processed electronically, unless the subject objects, by the study centres and/or the sponsor



on its behalf in order to carry out a statistical analysis of the results obtained from the entire study population.

The Sponsor will also comply with the “Méthodologie de Référence MR001”.

16.4. Insurance

The Sponsor hold liability insurance in line with local regulatory requirements.

16.5. Confidentiality

The information contained in this document and any additional information supplied by the Sponsor contains commercially sensitive information. This information is privileged and confidential and may not be disclosed without the Sponsor’s permission unless such disclosure is required by law or regulations.

Persons to whom such information is disclosed also must be informed that the information is privileged or confidential and may not be further disclosed by them.

16.6. Protocol amendment

Any protocol amendment (change of the protocol) should be approved by the Sponsor and the investigator before implementation.

Any substantial modification will only be implemented after having received written approval of the Ethic Committee (CPP).

16.7. Subject information and informed consent process

All subjects and all legal representatives (for minor subjects) will receive verbal and written information concerning the study in accordance with the applicable local regulations, guidelines and the current SOP of each study centre. This information will explain the nature, purpose and risks of the study and will emphasise that participation in the study is voluntary and that the subject may withdraw from the study at any time and for any reason. All subjects and all legal representatives (for minor subjects) will be given opportunity to ask questions about the study and will be given sufficient time to consider their participation before consenting.

The subject’s and all legal representatives (for minor subjects) written informed consent to participate in the study will be obtained prior to any study related procedure being carried out.

The subject information sheet and informed consent must be written in a language that is understandable to the subject. The consent form should be signed and personally dated by the subject and/or all legal representatives (for minor subjects) and the investigator who conducted the informed consent discussion.

Two copies will be signed, one to be kept by the subject and one to be retained in the TMF.

16.8. Case report form / Source documents

The CRF and questionnaire will be written by Intertek and printed in duplicate.

The investigator will be responsible for the timely recording, completeness and accuracy of the information in the CRF.

Documents in which study data are first recorded/captured constitute Source Documents (see definition in Section 1, List of Abbreviations and Definitions of Terms).



In this study, the following documents will be considered as source documents for the following data:

1. Informed consent
2. Subject file: medical history, date of birth, sex, demographics (for CHU Nantes).
3. CRF: visit dates, physical examination, counting of the lesions, clinical assessments, corneometry, sebumetry and pH measurements, concomitant medication and adverse events,
4. Questionnaire
5. Laboratory results: confocal microscopy analysis, microbiome analysis.

The duplicate will be sent to SYLIA-STAT after monitoring for data entry.

16.9. Premature termination of the study

The study may be prematurely suspended or terminated by the Sponsor or the study centres. In case of premature suspension or termination, the study centres will promptly inform all study subjects and will provide appropriate follow-up.

If the clinical study is terminated for any reason, the sponsor should provide a written statement as to why the premature termination has taken place and notify the Ethics Committee and the Regulatory Authority as applicable.

If the study is prematurely suspended or terminated by the study centres without the prior agreement of the Sponsor, the study centres will inform the Sponsor as soon as possible and will provide the Sponsor with a detailed written explanation of the termination or suspension.

17. CONTROL OF THE DATA (MONITORING)

The initiation, monitoring and close down visits will be performed by the Sponsor.

The investigator makes a commitment to permit trial-related monitoring, audits, ethical review and regulatory inspections and provide direct access to source data/documents.

The Sponsor is responsible for establishing the schedule and procedures to be followed for monitoring this study. On-site visits will be made prior to study initiation and at regular intervals during the study. Communications by telephone, fax or email may be used as needed to supplement site visits. Prior to the beginning of this study, the investigator will be informed as to the anticipated frequency of the monitoring visits. In addition, the investigator will receive reasonable notification prior to each monitoring visit during the course of the study.



The purpose of these visits is to verify:

- adherence to the protocol;
- and the completeness and accuracy of the case report forms, and study related source document.

At each visit, the investigator will be expected to cooperate with Sponsor representative(s) for the review and verification of all case report forms, the product supply and inventory records and any additional records as may have been previously arranged.

18. QUALITY CONTROL

Each study centre will implement quality control procedures during the study to assure the data generated are accurate and the study was conducted correctly.

19. QUALITY ASSURANCE / INSPECTION

The Quality Assurance (QA) of Intertek may conduct audits during the study which may include review of protocol, amendments and study report and inspections of study conduct. In this case, an audit certificate will be produced. A copy of this document will be available in the study file and will be appended to the study report.

Representatives of the Sponsor and/or CA may also conduct audits and/or inspections of the testing facilities and/or the raw data and will have direct access to records of study participants held by each study centre. To facilitate such audits/inspections, appointments for visits will be requested by the Sponsor and/or CA in advance.

20. ARCHIVING OF STUDY DOCUMENTS

According to the current archiving SOP of each study centre, the investigator will retain originals of the study protocol, informed consent, original of the completed CRFs, relevant source documents and all other supporting documentation related to the study for a period of 10 years and each study centre should contact the Sponsor for authorisation prior to destroying any records relating to the study. The Sponsor should inform each study centre when these documents no longer need to be retained.

21. PUBLICATION

All information concerning the IP supplied by the Sponsor and not previously published is considered confidential and shall remain the sole property of the Sponsor. The investigator agrees to use this information only in the context of this study and not for any other purpose without written consent from the Sponsor.

It is understood that there is an obligation to provide the Sponsor with complete test results and all data generated during the study. It is understood by the Investigator that the results of the study will be used by the Sponsor in connection with the development of the IP and, therefore, may be disclosed as required to government agencies. It is understood that there is an obligation to provide the Sponsor with complete test results and all data generated during the study.



22. REFERENCE LIST

1. The World Medical Association Declaration of Helsinki.
2. Article R.1121-1 du code de la santé publique introduit par le décret du 9 mai 2017 précisant le champ d'application de la réglementation relative aux recherches impliquant la personne humaine et explicitant notamment la question des recherches portant sur les produits cosmétiques.

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24. APPENDICES

1. DECLARATION OF HELSINKI
2. GLOBAL ACNE EVALUATION
3. INFORMATIONS ABOUT HYDREANE LEGERE
4. SUMMARY OF EPIDUO® CHARCATERISTICS



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Appendix 1
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1. DECLARATION OF HELSINKI



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2. GLOBAL ACNE EVALUATION



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3. INFORMATIONS ABOUT HYDREANE LEGERE



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4. SUMMARY OF EPIDUO® CHARCATERISTICS