Study Protocol: Liftactiv B3 in Post Inflammatory Hyperpigmentation (PIHP)

Evaluation of the depigmenting effect of Liftactiv B3 serum (split face) in patients with mild to moderate facial post-acne PIHP for 3 months.

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SPONSOR:

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SIGNATURES

Principal Investigator*:*

Leigh Nattkemper, PhD

_____ _____

Date *Signature*

SPONSOR: VICHY LABORATOIRES

_____ _____

Date *Signature*

SYNOPSIS – PROTOCOL

Study title	Evaluation of the depigmenting effect of Liftactiv B3 serum (split face) in patients with mild to moderate facial post-acne PIHP for 3 months.
Sponsor	VICHY LABORATOIRES
Sponsor's contact	Margot NIORE
Investigator	Dr. Leigh Nattkemper, PhD
Study rational	This study is a split face study which aims is to show the depigmenting effect of Liftactiv B3 in patients with mild to moderate facial PHIP.
Products	Liftactiv B3 serum- 3 months - application twice a day (B3 5%, GA 1.5%, Hepes 5%, urea 5%, TXA 1%, VitCG 0.2%, VF 0.1%, Peptides)
Study objective	• **<u>Primary endpoint</u>:** Improvement of PAHPI score (J Am Acad Dermatol 2014;70:108-14) • **<u>Secondary endpoints</u>:** Improvement of IGA for hyperpigmentation Improvement of other clinical and instrumental parameters related to skin condition Global efficacy assessment Global tolerance assessment Safety Assessment Cosmetic acceptability
Evaluation criteria	• **Primary criterion:** PAHPI score assessment • **Secondary criteria:** Physician global assessment IGA (0 clear – 5 severe) Number of PIH lesions right vs left Number of acne lesions (inflammatory and non-inflammatory) Improvements in skin radiance, fine lines, roughness Patient global appearance assessment right vs left Patient assessment of intensity of PIHP right vs left Patient satisfaction right versus left Investigator assessment of wrinkles, fine lines, skin tone, skin complexion and pores right vs left Patient assessment of shiny skin right vs left Patient satisfaction right vs left Safety Global efficacy Global Tolerability Cosmetic acceptability questionnaire Exposome questionnaire • **Instrumental evaluations:** Clinical pictures (Visia Imaging, Canfield Corp, USA) Chromameter Mexameter (Courage and Khazaka, Germany) Skin Color Evaluation (Dark spots) TEWL (Courage and Khazaka, Germany), barrier function measurement

	Corneometry (Courage and Khazaka, Germany), hydration measurement Reflectance confocal microscopy (RCM, Vivascope 1500, USA)
Study design	The study duration will be 14 weeks after inclusion. The patients have: 5 visits on clinical site: D-14, D0, M1, M2, M3
Number of patients	30 subjects

Selection of volunteers	***Inclusion criteria***: • Multiethnic subjects • 18 to 50 YO • Phototype III-VI • All skin types • 50% with sensitive skin (declarative) • Symmetrical mild to moderate facial post-acne PIHP lesions with IGA scale • Mild active acne (less than 10 retentional and 5 inflammatory lesions) • Agreeing not to change their lifestyle during the study period. • Capable of reading the documents presented to them, of adhering to the study regulations and accepting the limitations. • Available to follow the study • Agreeing to participate and having signed the informed consent ***Non-inclusion criteria***: • Moderate to severe active acne • Patients under topical or systemic retinoids • Patients under systemic immunosuppressants • Patients under active treatment of PIHP (including topicals or procedures) within the last 3 months • Patients treated with facial procedures within the last 3 months • Pregnancy • Patient with a recent change in contraception (since less than 6 months) • Known allergy to any component of tested product • Not presenting with the conditions needed to comply with the protocol. • Unable to give their informed consent • Not available to follow the study in its entirety
Safety evaluation	• ***Adverse event and serious adverse event report*** An adverse event is defined as any untoward medical occurrence (sign, symptom or laboratory finding), regardless of severity and whether or not attributed to the study product. The investigator must report all adverse events (AEs) that occur throughout the study. All AEs must be recorded in the appropriate AE log. The report must include: date of onset, a description of the AE, severity, seriousness, action taken, relationship to the study drug,

	outcome of the event, and date of resolution. The sponsor must be notified of AE's within 5 business days
Study Timelines	Duration of the study will be 14 weeks after inclusion. • Wash out phase: 2 weeks with Hydreane legere and sunscreen • Treatment phase: 12 weeks Number of visits will be 5 visits; screening (D-14), baseline (D0) , M1, M2, M3.

Recruitment Methods

Patients with mild active acne seen for their routine care at the Dermatology Outpatient Clinics at the University of Miami Hospital, South Miami satellite site, or Lennar Medical Foundation satellite site will be identified for possible study eligibility by any of the dermatologists in our practice. If the treating dermatologist is a study team member, they will ask the potential subject if they would be interested in being contacted by the study team to learn more about a research study for mild active acne. A partial HIPAA waiver is needed, so that if the patient gives permission to be contacted, they will then be approached by a member of the study team while they are in clinic or if that is not feasible then the treating dermatologist will ask if the patient would like to be contacted by telephone. If the treating dermatologist is not a study team member, they will ask the potential subject to contact the study team for more information by providing the study team's contact information and/or the study flyer. If the potential subject agrees to be contacted by the study team, the treating physician will ask the patient to sign a PHI release authorization form, so that the physician can provide the study team the patient's contact information. If it is then determined that they are interested in participating, they will be scheduled for a visit with the PI at our University of Miami Hospital dermatology clinic site where informed consent and all other study procedures will take place. The risks/benefits of the study will be presented to the subjects, as well as the disclaimer that refusal to participate in the study will in no way, shape, or form alter the type or quality of their care.
A partial HIPAA waiver is also needed as patients diagnosed with mild active acne who signed the University of Miami's Consent to Contact consent during their routine medical care will be identified using research IT and URIDE. Each of those individuals with then be contacted by the phone by a study team member and asked if they would be interested in learning more about a research study on mild active acne. If it is then determined that they are interested in participating, they will be scheduled for a visit with the PI at our University of Miami Hospital dermatology clinic site where informed consent and all other study procedures will take place. The risks/benefits of the study will be presented to the subjects, as well as the disclaimer that refusal to participate in the study will in no way, shape, or form alter the type or quality of their care.

Data Management*

The collected, deidentified data will be arrayed in a spreadsheet within a project file located within a password protected server on Microsoft Teams. Only the PI

and approved study staff will have access to this file. Subject identities as participants in this study will be kept confidential for the remainder of the study and in any publication, and no identifiable patient information will be attributed to the dataset, thereby keeping them anonymous.

Provisions to Monitor the Data to Ensure the Safety of Subjects*

Adverse events will be collected each study visit and will followed until resolution.

Withdrawal of Subjects*

A subject may withdraw from the study at any time for any reason.

A subject will be withdrawn from the study if his/her safety or well-being is determined to be at risk. Withdrawal will be made at the discretion of the investigator or at the subject's request.

A subject must withdraw from the study for any of the following reasons:

- The subject withdraws consent
- There is a significant protocol violation as determined by the Sponsor or medical monitor.

A subject may be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Investigator discretion

Withdrawal is permanent; after a subject has been withdrawn, he/she will not be allowed to enroll again.

If a subject is withdrawn from the study for any reason, relevant information including the date and primary reason for withdrawal, must be documented on the source document.

If a subject withdraws from the study at any time due to an AE, the reason for withdrawal, the nature of the AE, and its clinical course must be fully documented. The investigator must strive to follow the subject until the AE has resolved, become clinically insignificant, is stabilized, or the subject is lost to follow-up.

Risks to Subjects*

This study is a minimal risk study. As such, skin measurement, photos and patient information will be collected. Although every measure will be taken to prevent any possible compromise of patient data (safe storage, password encryption, limited access, etc), the risks associated with possible disclosure of patient data are present. The risks include attainment of patient information by some third party – how they could use this information even if it were compromised, is not easily foreseen. Identifying variables (name, MRN, etc) will not be stored to minimize the risks, simply the variables that we are interested in. Although disclosure of patient information is conceptually possible, it is highly unlikely seeing as how we will take every possible precaution and not store any identifying information.

Potential Benefits to Subjects*

Subjects may benefit from the study by having a reduction in post inflammatory hyperpigmentation.

Vulnerable Populations*

This research study does not include vulnerable populations. Specifically, we will not enroll minors, pregnant women, prisoners, or cognitively impaired people.

Sharing of Results with Subjects*

There are no results to share with subjects.

Setting

Study procedures will take place at the following location:

- University of Miami
  Dr. Philip Frost Department of Dermatology and Cutaneous Surgery
  Skin Testing Unit, 1600 NW 10th Ave, RMSB 7104
  Miami, FL 33136

Confidentiality

Check all that apply:

☐ Data obtained or created for this research will be stored on an encrypted electronic device or system owned by the University of Miami or on a cloud storage system that has been approved by the University of Miami for storage or research data.

☐ The Investigator (or research staff) will record (e.g. write down, abstract) data collected in a manner that **does not include** any indirect or direct identifiers and the recorded data **will not be linked to the individual's' identity.**

☒ The investigator (or research staff) will record (e.g. write down, abstract) the data collected in a manner that does not include any direct identifiers of the subject. The investigator **will assign a code to each subject and link the code to the subject's identity**. The research team will maintain the link to the subject's identity on a document separate from the research data. Both documents will be stored in separate files on a University of Miami encrypted device or on a University of Miami approved cloud storage system. The research team will destroy the identifiers at the earliest opportunity.

☐ The research team will maintain the research data for at least three years.

☐ *Bio*-Specimens obtained for this research will be stored without any direct or indirect identifiers.

☐ *Bio*-Specimens obtained for this research will be stored in a de-identified coded manner.

☐ When required to transport data or bio-specimens for this research, the research team will transport the data and bio-specimens in a de-identified (or anonymous) manner with a link to the individual subject's identity maintain separately from the data and/or bio-specimen.

Provisions to Protect the Privacy Interests of Subjects

Throughout the duration of the entire study, the privacy interests of participants will be maintained by ensuring the presence of members approved to be involved in the study and maintaining absence of those who are not.

Compensation for Research-Related Injury

Treatment will be available if enrolled subjects get sick or injured. However, the subject or the subject's insurance will be responsible for these costs. Funds to compensate for pain, expenses, lost wages, and other damages caused by injury are not available.

Economic Burden to Subjects

The study subjects will not have to pay for any procedure involved in the research study.

Consent Process

Once patients are identified and consent to be contacted, they will be approached by a member of the study team during their outpatient visit OR will be contacted by a member of the study team by phone. Participants will be given ample time to consider their agreement. The study team will be available to answer any question in the method the participant prefers to communicate. No one in a perceived coercive position in relation to the participant will engage in the consenting process. Consent will be obtained voluntarily prior to initiating any study procedures.

Process to Document Consent in Writing

The study personnel will review ICF with each subject and give the subject an opportunity to have all questions answered before proceeding with any study procedures. A copy of the signed ICF will be given to every subject and the original will be maintained with the subject's records.

Authorization for Use and Disclosure of Protected Health Information (HIPAA)

If the research team will access patient medical records or other identifiable health information for this research, you must obtain a waiver of the requirement for written authorization from the patients to access their medical records.

Type of Request:

☒ Waiver of Authorization for access to medical record for subject identification/recruitment.

☐ Waiver of Authorization for access to medical record to obtain data for the research.

Confirm that you will destroy or de-identify the information you collect at the earliest opportunity.

☒ ***I confirm***

Confirm that the information you collect will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study or for other research for which the use or disclosure of PHI is permissible.

☒ ***I confirm***

Drugs or Devices

All cosmetic products and devices used in the study will be used in a manner consistent with routine clinical practice and “per label”.

SUMMARY TABLE

Visits	Screening D-14	D0 Baseline	D28 (1M)	D56 (2M)	D84 (3M)
Informed Consent	X				
Demographics	X				
Medical History	X				
Prior and current products, medications, therapies, and procedures	X	X	X	X	X
Eligibility assessment	X				
PAHPI Score	X	X	X	X	X
IGA Score for PIHP	X	X	X	X	X
Counting PIH lesions number	X	X	X	X	X
Counting acne lesions number	X	X	X	X	X
Evaluation of clinical parameters like fine lines, skin tone, radiance, global appearance		X	X	X	X
Standardized photographs (photos of lesions)		X	X	X	X
TEWL, barrier function measurement		X	X	X	X
Mexameter, Skin Color Evaluation (Dark spots)		X	X	X	X
Corneometry, hydration measurement		X	X	X	X
Chromameter					
Reflectance confocal microscopy		X			X
Global tolerance			X	X	X
Global efficacy			X	X	X
Cosmetic acceptability questionnaire			X	X	X
Exposome questionnaire (Annex 1)	X				X

OBJECTIVE OF THE STUDY:

The aim of the study is to show the depigmenting effect of Liftactiv B3 in patients with mild to moderate facial PHIP.

ENDPOINTS:

- ***Primary endpoint*:** improvement of PAHPI score
- ***Secondary endpoints*:** improvement of IGA for hyperpigmentation and other clinical and instrumental parameters related to skin condition

STUDY DESIGN:

This is randomized and monocentric study.

This study is a Split face study, each subject is used as her own control.
30 subjects affected by post inflammatory hyperpigmentation (PIHP) on the face will enter the study. The subjects will apply the active treatment (Liftactiv B3 serum) and a sunscreen on the half face. The other half face will be only treated with a sunscreen.
Left/Right randomization will be on a consecutive basis.
Subjects will be asked to sign an informed consent.

INCLUSION CRITERIA:

- Multiethnic subjects
- 18 to 50 years of age
- Phototype III-VI
- All skin types
- 50% with sensitive skin (declarative)
- Symmetrical mild to moderate facial post-acne PIHP lesions
- Mild active acne (less than 10 retentional and 5 inflammatory lesions)
- Agreeing not to change their lifestyle during the study period.
- Capable of reading the documents presented to them, of adhering to the study regulations and accepting the limitations.
- Available to follow the study
- Agreeing to participate and having signed the informed consent

EXCLUSION CRITERIA:

- Moderate to severe active acne
- Patients under topical or systemic retinoids
- Patients under systemic immunosuppressants
- Patients under active treatment of melasma (including topicals or procedures) within the last 3 months
- Patients treated with facial procedures within the last 3 months
- Pregnant women
- Patient with a recent change in contraception (since less than 6 months)
- Known allergy to any component of tested product
- Not presenting with the conditions needed to comply with the protocol.
- Unable to give their informed consent

- Not available to follow the study in its entirety

PRODUCTS TESTED:

- **Active treatment:** Liftactiv B3 (B3 5%, GA 1.5%, Hepes 5%, urea 5%, TXA 1%, VitCG 0.2%, VF 0.1%, Peptides)

For the wash-out period (2 weeks):

- Hydréane légère: La Roche-Posay Moisturizer
- Dry Touch 50+: Vichy Sunscreen

STUDY PROCEDURES:

The study will enroll 30 subjects affected by post-acne PIHP.

***Wash out phase*:** after selection and enrollment, all subjects will undergo a wash out phase of two weeks where they regularly apply a moisturizer (Hydreane legere) in the morning and a sunscreen in the morning and at the beginning of the afternoon provided by the Sponsor.

Treatment phase: on the 3rd week, subjects will apply Liftactiv B3 serum daily in the morning before sunscreen and in the evening (two applications daily) on half face for 3 months.

On the other half face, they will apply only the sunscreen in the morning and at the beginning of the afternoon for 3 months.

Left and right half faces will be randomized on a consecutive basis.

Duration of the study: 14 weeks

- **Wash out phase**: 2 weeks with Hydreane legere and sunscreen
- **Treatment phase**: 12 weeks for Liftactiv B3 serum and sunscreen on half face

STUDY SCHEDULE:

- **INCLUSION VISIT/ D-14** (START OF WASH-OUT PERIOD)

During this visit, **the investigator will**:

- Give the patient a consent form for participation, give the patient enough time to read and fill in the consent form if he/she agrees to be included in the study
- Indicate in which half face the patient applies the investigational product according to randomization
- Check the inclusion and exclusion criteria
- Collect the patient's identification
- Record the medical history and concomitant treatments
- Distribute study products of the wash-out period and explain the mode of application
- Give the patient the information letter

- Counting the PIH lesions
- Counting the acne lesions (inflammatory and non-inflammatory)
- Evaluate the PIHP of the patient using the PAHPI score

Evaluate the PIHP of the patient using the IGA score

The patient will:

- Complete the Exposome questionnaire

- **D0/ BASELINE** (START OF TREATMENT PERIOD)

During this visit, **the investigator will**:

- Distribute study products and explain the mode of application
- Counting the PIH lesions
- Counting the acne lesions (inflammatory and non-inflammatory)
- Take standardized photographs of the PIHP lesions
- Evaluate the PIHP of the patient using the PAHPI score
- Evaluate the PIHP of the patient using the IGA score
- Evaluate the clinical parameters of the patient like fine lines, skin tone, radiance, skin texture.
- Mesure the TEWL of the skin
- Assess the skin color (dark spot) with the mexameter
- Assess the hydratation of the skin with Corneometry
- Assess the skin color and luminescence with chromameter
- Assess the distribution of melanin in the skin with Reflectance confocal microscopy

The patient will:

- Evaluate the global efficacy of the investigational product right vs left
- Evaluate the global tolerance of the investigational product right vs left
- Evaluate the cosmeticity and acceptability of the investigational product

- **VISITS M1(D28), M2(D56)**

During this visit, **the investigator will**:

- Collect AEs
- Counting the PIH lesions
- Counting the acne lesions (inflammatory and non-inflammatory)
- Take standardized photographs of the PIHP lesions
- Evaluate the PIHP of the patient using the PAHPI score
- Evaluate the PIHP of the patient using the IGA score
- Evaluate the clinical parameters of the patient like fine lines, skin tone, radiance, skin texture.
- Mesure the TEWL of the skin
- Assess the skin color (dark spot) with the mexameter
- Assess the hydratation of the skin with Corneometry
- Assess the skin color and luminescence with chromameter

The patient will:

- Evaluate the global efficacy of the investigational product right vs left
- Evaluate the global tolerance of the investigational product right vs left
- Evaluate the cosmeticity and acceptability of the investigational product

VISIT M3(D84) : END OF TREATMENT

During this visit, **the investigator will**:

- Collect AEs

- Counting the PIH lesions
- Counting the acne lesions (inflammatory and non-inflammatory)
- Take standardized photographs of the PIHP lesions
- Evaluate the PIHP of the patient using the PAHPI score
- Evaluate the PIHP of the patient using the IGA score
- Evaluate the clinical parameters of the patient like fine lines, skin tone, radiance, skin texture.
- Mesure the TEWL of the skin
- Assess the skin color (dark spot) with the mexameter
- Assess the hydratation of the skin with Corneometry
- Assess the skin color and luminescence with chromameter
- Assess the distribution of melanin in the skin with Reflectance confocal microscopy
- Recover the investigational products

The patient will:

- Evaluate the global tolerance of the investigational product
- Evaluate the global efficacy of the investigational product
- Evaluate the cosmeticity and acceptability of the investigational product
- Complete the exposome questionnaire

CLINICAL EVALUATIONS:

- Counting the PIH lesions
- Counting the acne lesions

PIHP will be evaluated using the **post acne hyperpigmentation scale** (1).

PAHPI: The Post-acne Hyperpigmentation Index

Weighted Scores (S)	**Median lesion size**
2	<3 mm
4	3-6 mm
6	7-10 mm
8	>10 mm
Weighted Scores (I)	**Median lesion intensity**
3	Slightly darker than surrounding skin
6	Moderately darker than surrounding skin
9	Significantly darker than surrounding skin
Weighted score (N)	**Number of lesions**
1	01-15
2	16-30
3	31-45
4	46-60
5	>60

The Total Post-acne Hyperpigmentation Index (PAHPI) was equal to = S + I + N
The score range was: 6-22.Put the reference of the paper on PAHPI here?

Pigmentation will be also evaluated clinically using the Physician global assessment IGA (2).

IGA Scale	Hyperpigmentation	Erythema
0	Clear of hyperpigmentation	Clear of erythema
1	Almost clear of hyperpigmentation	Almost clear of erythema
2	Mild, but noticeable hyperpigmentation	Mild, but noticeable erythema
3	Moderate hyperpigmentation (medium brown in quality)	Moderate erythema (pink in quality)
4	Severe hyperpigmentation (dark brown in quality)	Severe erythema (dark pink in quality)
5	Very severe hyperpigmentation (very dark brown, almost black in quality)	Very severe erythema (very dark pink, almost red in quality)

Other clinical parameters like fine lines, skin tone, radiance, global appearance will be evaluated (left vs right) at each time point:

The study team member will perform clinical evaluation grading of characteristics of subject's skin through 0 to 9 point-scales in order to assess the improvement of these parameters. The skin parameters will be assessed globally on each subject's face using the scales according to the following definitions (scoring will be based on a full-point scale):

Attributes	**Definition**	**Type of Assessment**	**Points of the scale**
Deep wrinkles	Depth of visible wrinkles	Visual	0=none, skin is uniform without wrinkles, 1-3= slight to mildly observable skin wrinkles, with no deep wrinkles, 4–6= moderate to pronounced observable deep wrinkles, and 7–9=severe, skin with deep wrinkles
Fine lines	Number of fine lines	Visual	0 = none, without fine lines, 1-3 = slight to mildly observable fine lines, 4–6 = moderate observable fine lines, and 7–9 = severe, skin with numerous fine lines
Skin tone	Regularity of skin evenness. How much the skin tone is uniform	Visual	0=none, skin is uniform in skin color with perfect evenness, 1-3=mild, 4–6= moderate, and 7–9=severe, skin is uneven and blotchy in tone
Skin roughness / Skin texture	Regularity of Skin Surface. How much the skin is rough, looking like dehydrated skin	Visual	0=none, no observable skin roughness or surface bumps/depressions, 1–3=slight to mildly observable skin roughness or bumps/depressions, 4–6= moderate to pronounced observable skin roughness or surface bumps/depressions, and 7–9=severe, pronounced observable skin roughness or surface bumps/depressions
Radiance	Natural skin radiance, unrelated to oiliness	Visual	0= very radiant/luminous or glowing skin, 1–3= slightly glowing and radiant, 4–6=moderately dull, 7–9= dull/matte and or/sallow skin appearance

Skin elasticity	Viscoelastic properties of the skin	Visual	0 = none, skin is firm, 1-3 = mild, 4–6 = moderately elastic, and 7–9 = severe, very elastic, flabby skin

GLOBAL EFFICACY

Global efficacy of the treatment evaluated at each visit by the patient.
The measure of the global efficacy will be realized according to the following scale:

- o Nil
- o Moderate
- o Good
- o Excellent

GLOBAL TOLERANCE

Clinical tolerance global score will be assessed, on the treated area, at each visit using first a 4-point skin reaction scale which ranges from 0 which indicates no evidence of local intolerance and 4 indicates very severe signs or symptoms of intolerance:

0	None	No evidence of local intolerance
1	Mild	**Minimal signs or symptoms of intolerance** (May be present : minimal erythema and/or oedema and/or slight glazed appearance and/or pruritus and/or burning/stinging)
2	Moderate	**Definite signs or symptoms of intolerance** (May be present : definite erythema and/or oedema with peeling and/or cracking, moderate pruritus and/or burning/stinging)
3	Severe	**Severe signs or symptoms of intolerance** (May be present : severe erythema and/or oedema glazing with fissures and/or vesicles or papules, and/or severe pruritus and/or burning/stinging)
4	Very severe	**Very severe signs or symptoms of intolerance** (Usually : strong reaction spreading beyond the treated area, bullous reaction, erosions)

COSMETICITY QUESTIONNAIRE AND ACCEPTABILITY

Subjects will be questioned about their perceived effects of the investigational product on their skin.
The cosmeticity questionnaire is a five point scale (1-fully disagree; 2-disagree partly; 3-no opinion; 4-agree partly; 5-fully agree).

EFFICACY	
1	Skin feels moisturized
2	Skin feels smoother
3	Skin feels softer
4	Number of? Dark spots look minimized
5	Spots looks less dark
6	Color of spots look reduced
7	Skin looks more even
8	Skin looks more homogenous
9	Complexion looks more even
10	Complexion looks more homogenous
11	Complexion looks brighter
12	Skin looks more radiant
13	Skin looks healthier

14	Overall appearance looks improved
15	Overall appearance looks healthier
16	Skin looks improved
17	Skin feels renewed
18	Skin looks younger
19	Fine lines look reduced
20	Wrinkles looks reduced
21	Product feels safe to use

COSMETICITY	
1	The product has a light texture
2	The product does not leave the skin oily after application
3	The product does not leave the skin sticky after application
4	The product doesn't leave the skin shiny after application
5	The texture of the product is pleasant
6	The product does not go noodles on my skin
7	The product is suitable for my skin type
8	Product gives the skin a feeling of well being
9	The product texture is quickly absorbed
10	The product is easy to apply

APPRECIATION	
1	Globally, the product is pleasant
2	Would you like to continue using the product yes/no/
3	At the end of the test, would you buy the product (regardless of its price) yes/no

EXPOSOME QUESTIONNAIRE

Subjects will be questioned about their perceived effects of the investigational product on their skin. Five different answers will be proposed: (0) Fully disagree, disagree partly, no opinion, agree partly, (5) fully agree.

INSTRUMENTAL EVALUATION:

Will include at each time point:

- **Clinical pictures and UV pictures** (Visia Imaging, Canfield Corp, USA)
  VISIA® Skin Analysis System is computerized device for photography in Visible and UV light and image analysis of the skin. A newly designed capture module rotates smoothly around the subject, greatly simplifying the imaging process while providing greater comfort for the patient. Updated software allows faster image capture with automatic skin type classification, refined facial feature detection and more. The system is contactless.

- **Mexameter** (Courage and Khazaka, Germany) Skin Color Evaluation (Dark spots)
  Mexameter is a noninvasive device measuring light adsorbed and reflected by the skin allowing the quantification of erythema and skin color in general. Readings are done in few ms after placing the probe on the skin.

- **TEWL** (Courage and Khazaka, Germany), barrier function measurement
  TEWL is used to evaluate water loss that is not attributed to active sweating from the body, through the epidermis, to the environment. So, it is widely used to characterize the stratum corneum barrier function, both in physiological and pathological conditions, to perform predictive irritancy tests, and to evaluate the efficacy of therapeutic treatments on diseased skin. The measurements of TEWL is based on the estimation of water pressure gradient above the skin surface. The evaporative TEWL, is approximately proportional to the difference between the vapour pressures measured at 2 different fixed heights situated perpendicularly above the skin surface and within the zone of diffusion. These open chamber instruments, consists of a detachable measuring probe connected by a cable to a portable main signal processing unit. The teflon capsule of the probe head has a cylindrical measuring chamber, open at both ends where relative humidity sensors (hygrosensors) are paired with temperature sensors (thermistors). From this gradient, the evaporative TEWL value, in g/m2/h, is calculated by the signal processing units in the probe handle and main unit, and digitally displayed. The instrument is extremely sensitive to any disturbances in the microclimate, whether due to environment, instrument or individual related variables. The measurement is totally non invasive since the probe is only applied gently on top of measuring area.

- **Corneometry** (Courage and Khazaka, Germany), hydration measurement
  CORNEOMETRY is a method for measuring Stratum Corneum water content (capacitance measurement) . The importance of water to the proper functioning of the SC is well recognized. The reliable quantification of water in the corneum and its interaction with topically applied products is, infect, essential for understanding skin physiology and developing efficient skin care formulation. This instrument is described as being a „capacitance“ measuring device operating at low frequency (40-75 Mhz), which is sensitive to the relative dielectric constant (or permittivity) of material placed in contact with the electrode surface. Because increasing the water content of the stratum corneum will in general increase its relative permittivity (although by a very complex and variable relationship), the device can therefore estimate the stratum corneum water content in arbitrary (relative) units. The measurement is totally non invasive since the probe is only applied gently on top of measuring area for 20 ms.

- Chromameter

- Reflectance confocal microscopy (RCM, Vivascope 1500, USA) will be performed at baseline and end of the study on selected cases. (This is because the technique shows distribution of melanin in the skin but doesn’t provide a quantification)

The study will be submitted to clinicaltrial.gov

STATISTICS:

Skin parameters will be compared at each time point (active vs ~~placebo~~) using paired Student's t test. Differences between baseline and month 3 and end of the treatment for each treatment will be done using ANOVA for repeated measures.

Sample size determination:

To detect small effects of the treatments with a given α of 0.5 and an error probability of 0.05, with a power of 0.95, the total number of participants needed is 26. We will recruit a total of 30 subject to ensure the sample size reaches proper power after any dropouts or missing data.

PATIENT INFORMATION AND CONSENT

It is responsibility of the investigator to give each patient, before inclusion in the study, full and adequate verbal and written information regarding the objective and procedures of the study and the possible risks involved. The patient must be informed about their right to withdraw from the study at any time. Written patient information will be provided to the investigator and must be given to each patient before enrollment.

ADVERSE EVENTS

AEs are to be monitored throughout the course of the clinical trial. All AEs are to be reported on the Adverse Event Form of the CRF with complete information as required. If AEs occur, the main concern will be the safety of the subjects. At the time of the ICF signature, each subject must be provided with the name and phone number of clinical trial center personnel for reporting AEs and medical emergency.

Definition of Adverse Events:

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects taking part in the clinical study, and which does not necessarily require a causal relationship with the investigational product and/or a clinical trial procedure. An AE can be any unfavorable and unintended sign (including an abnormal laboratory value), symptom, or disease temporally associated with the use of the investigational product, whether or not related to this product. Reporting of Adverse Events.

Reporting of Adverse Events:

The records of AEs in the CRF describe the nature (diagnosis, signs and symptoms), severity, location, date of onset, date of end, outcome and actions taken, and relationship to the products (in the Investigator's opinion). It must be specified whether the event is serious or not. During the trial all Serious and non-Serious AEs should be followed up to determine the final outcome.

Undesirable effect/ related AE:

An undesirable effect is defined as any AE which the Investigator classifies as having a reasonable possibility for a causal relationship with the investigational product and/or a clinical trial procedure.

SERIOUS ADVERSE EVENTS

Definitions of (Serious) Adverse Event (Serious Adverse Event (SAE) Adverse event that:
a) led to a death, injury or permanent impairment to a body structure or a body function.
b) led to a serious deterioration in health of the subject, that either resulted in:
· a life-threatening illness or injury, or
· a permanent impairment of a body structure or a body function, or
· in-patient hospitalization or prolongation of existing hospitalization, or
· in medical or surgical intervention to prevent life threatening illness
c) led to foetal distress, foetal death or a congenital abnormality or birth defect.
NOTE 1: Planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a SAE.
Pregnancy: Any pregnancy which occurs during a clinical trial with an Investigational Product must be reported to Sponsor by use of the SAE Form - Clinical Trials and handled as an SAE with regard to reporting time frame. All pregnancies must be followed-up until conclusion.

Regulatory aspects:

Immediate notification to the Sponsor by the Investigator of serious adverse events is essential to comply with legal obligations and ethical responsibilities with respect to the Subjects treated (reporting to the National Agency for the Safety of Medicines and Health Products (ANSM), information of the coordinator by the Sponsor, information of the coordinator to the Ethics Committee).

Notification of serious adverse events:

The Investigator must inform the Sponsor, by fax and/or telephone within one working day of any serious AE that has occurred during the course of the trial, from the moment it is brought to his attention. Any SAE must be reported, whether or not it is considered to be related to the trial product, using the specific form "Report of suspected serious adverse reaction(s) or having required medical treatment or appearing to be of a serious nature observed during biomedical research on a cosmetic product" downloaded from the ANSM site, with all the information available at the time of discovery of the event. The Investigator must imperatively evaluate the imputability of each SAE to the products under test according to the classification defined above. This form must be sent by fax/email to the Sponsor representative.

CRO REQUIREMENT DUE TO COVID 19 SITUATION

The University of Miami commits to carry out the study in accordance with local Authorities recommendations to ensure the safety of employees and volunteers carrying out or participating in the studies.

QUALITY ASSURANCE / AUDIT / INSPECTION

The clinical trial is conducted under the sponsorship of Sponsor in compliance with the applicable international and local regulatory requirements as well as applicable ICH guidelines and in accordance with the SOPs for clinical trial conduct and monitoring from the assigned monitor. Audits of the clinical trial center may be conducted by the Sponsor/CRO representatives, and inspection may be performed by IECs before, during, or after the clinical trial. The Investigator will allow and assist the CRO/Sponsor's representatives, IECs and any regulatory agency to have direct access to all requested clinical trial-related records. For the audits performed by, or on behalf of, Sponsor auditors, audit certificate(s) will be provided by Quality Assurance.

ETHICAL CONDUCT OF THE STUDY

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later revisions.

References:

1. Savory SA, Agim NG, Mao R, Peter S, Wang C, Maldonado G, Bearden Dietert J, Lieu TJ, Wang C, Pretzlaff K, Das S, Vandergriff T, Lopez IE, Litzner BR, Hynan LS, Arellano-Mendoza MI, Bergstresser PR, Pandya AG. Reliability assessment and validation of the postacne hyperpigmentation index (PAHPI), a new instrument to measure postinflammatory hyperpigmentation from acne vulgaris. J Am Acad Dermatol. 2014 Jan;70(1):108-14. doi: 10.1016/j.jaad.2013.09.017. Epub 2013 Oct 28. PMID: 24176524.
2. Isedeh et al. Br J Dermatol 2015 1-6, DOI 10.1111/bjd.14184

ANNEX

Panelist Identification
EXPOSOME QUESTIONNAIRE

This questionnaire will be given on D0 to the volunteers, completed and given back to the study sponsor

Gender ..... ○ M ○ F

How old are you? ..... |___|___| years

Do you live alone? ..... ○ YES ○ NO

If NO, do you live with a partner? ..... ○ YES ○ NO

Do you have children? ..... ○ YES ○ NO

If YES, how many children? ..... |___|___|

How old are they? |___|___| |___|___| |___|___| |___|___| years

What is your profession? .....

1. ENVIRONMENT

Are you subject to pollution? ..... ○ YES ○ NO

Are you subject to environmental factors that cause nuisance other than pollution?

..... ○ YES ○ NO

If yes, which ones?

Noise? ..... ○ YES ○ NO

Temperature changes (air conditioning, cold, etc.)? ..... ○ YES ○ NO

Wind? ..... ○ YES ○ NO

Humidity? ..... ○ YES ○ NO

Other (which ones)? ..... ○ YES ○ NO

2. FATIGUE

Do you feel tired? ..... ○ YES ○ NO

Have you had a change in your lifestyle recently? ..... ○ YES ○ NO

If yes, which ones? .....

If yes, has the change accelerated the pace of your lifestyle? ..... ❍ YES ❍ NO

Do you feel stressed at the moment? (work, personal...) ..... ❍ YES ❍ NO

3. SLEEP

How many hours do you sleep on average per night?

During the week? ..... |___|___|Hours

During the weekend? ..... |___|___|Hours

Do you have sleep problems? ..... ❍ YES ❍ NO

If yes, which ones? ❍ Insomnia ❍ Short nights ❍ Night awakenings ❍ Sleep apnea

Are you taking naps? ..... ❍ YES ❍ NO

If yes clarify: When? .....

How many times per week? ..... |___|___|*per week*

How long in each time? ..... |___|___|Hours

4. WORK

Are you currently working? ..... ❍ YES ❍ NO

How many hours do you work per day? ..... |___|___|Hours

How many hours do you work per week? ..... |___|___|Hours

Do you work behind a computer screen most of the time? ..... ❍ YES ❍ NO

Do you have a fixed work schedules, daytime and regular? ..... ❍ YES ❍ NO

If yes: time slot? .....

For how long? ❍ <1 year ❍ 1 to 8 years ❍ >to 8 years

If not: clarify time slot? .....

Do you spend a lot of time (more than one hour per day) in transport?

..... ❍ YES ❍ NO

5. TOBACCO SMOKE

Do you currently smoke? ..... ❍ YES ❍ NO

➔If yes, since how many years: |___|___| years

➔If yes, how many cigarettes a day on average?

- ❍ *<5 cigarettes / day*
- ❍ *5 to 10 cigarettes / day*
- ❍ *10 to 20 cigarettes / day*
- ❍ *>20 cigarettes / day*

Do you smoke in the past? ..... ❍ YES ❍ NO

If yes, for how many years? ..... |___|___| years

How many cigarettes did you smoke a day on average? ..... |___|___|

6. FOOD HABITS

Have you a varied and well-balanced diet? ..... ❍ YES ❍ NO

Do you overeat one or more products? ..... ❍ YES ❍ NO

If yes, which one(s)? .....

Do you have an excessive consumption of sugar or snacks? ..... ❍ YES ❍ NO

Do you eat whey proteins? ..... ❍ YES ❍ NO

Do you drink alcohol? ..... ❍ YES ❍ NO

If YES, how often: ❍ *Occasionally* ❍ *Everyday*

How many times per day do you eat? ..... |___|___| Time/day

7. FEELINGS

How do you feel at this precise moment? 0= HAPPY, 10= DEPRESSED

❍ *0* ❍ *1* ❍ *2* ❍ *3* ❍ *4* ❍ *5* ❍ *6* ❍ *7* ❍ *8* ❍ *9* ❍ *10*

How do you feel at this precise moment? 0= ENERGETIC, 10= WITHOUT ENERGY

❍ *0* ❍ *1* ❍ *2* ❍ *3* ❍ *4* ❍ *5* ❍ *6* ❍ *7* ❍ *8* ❍ *9* ❍ *10*

How do you feel at this precise moment? 0= RELAXED, 10= TENSED

❍ *0* ❍ *1* ❍ *2* ❍ *3* ❍ *4* ❍ *5* ❍ *6* ❍ *7* ❍ *8* ❍ *9* ❍ *10*

8. SUN AND UV

Are you exposed to UV in your daily life? ..... ❍ YES ❍ NO

Currently, is your face frequently exposed to the sun? ..... ❍ YES ❍ NO

In the past, was your face frequently exposed to the sun? ..... ❍ YES ❍ NO

If yes, during how many years? ..... |___|___| years

If yes, did you regularly use sunscreen? ..... ❍ YES ❍ NO

Was it sunscreen with a SPF superior to 20? ..... ❍ YES ❍ NO

Do you practice outdoor activities (leisure, gardening, etc.) or professional activities where your face is unwillingly exposed to the sun? ..... ❍ YES ❍ NO

If yes, how do you protect yourself?

Sunscreen (Sunscreen with a SPF superior to 20) ..... ❍ YES ❍ NO

Clothes ..... ❍ YES ❍ NO

Hat ..... ❍ YES ❍ NO

Sunglasses ..... ❍ YES ❍ NO

How do you assess the efficiency of your protection against the sun?

❍ Very good ❍ Good ❍ Insufficient ❍ No protection

9. HORMONAL STATUS (women only)

Do you still have your menstruation? ..... ❍ YES ❍ NO

If no, are you in menopause? ..... ❍ YES ❍ NO

If yes, have you a regular menstrual cycle? ..... ❍ YES ❍ NO

Do you take any contraception? ..... ❍ YES ❍ NO

If yes, which one? ❍ Condom ❍ Estrogen-progestin pill ❍ Micro progestogen pill

❍ Hormonal IUD ❍ Copper IUD ❍ Implant ❍ Other: .....

PIHP PART:

Do you have a peak of acne at a specific time during your menstrual cycle?

..... ❍ YES ❍ NO

If yes, where is located your peak of acne on your face? .....