



**ASSESSMENT OF PRIMARY SKIN IRRITATION POTENTIAL OF A PRODUCT,
UNDER CONTROLLED AND MAXIMIZED CONDITIONS**

FINAL REPORT

INVESTIGATIONAL PRODUCT TYPE: Teeth Whitening

INVESTIGATIONAL PRODUCT NAME: Luminuex Oral Essentials Whitening Strip

INSTITUTE PRODUCT CODE: 097772-01

STUDY CODE: All-S-01/18/2022-GREEN-GROUP-IRRITATION-SENSITIZATION

REPORT CODE: All-S-IP-097772-01-01-22-RFV01-Rev01

REPORT DATE: 01/27/2022

SPONSOR: Oral Essentials Inc

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ASSESSMENT OF PRIMARY SKIN IRRITATION POTENTIAL OF A PRODUCT, UNDER CONTROLLED AND MAXIMIZED CONDITIONS

SUMMARY

Investigational Product Name	Luminuex Oral Essentials Whitening Strip
Product Code of the Institute	097772-01
Study Code	All-S-01/18/2022-GREEN-GROUP-IRRITATION-SENSITIZATION
Report Code	All-S-IP-097772-01-01-22-RFV01-Rev01
Sponsor	Oral Essentials Inc

OBJECTIVE OF THE STUDY

Proving the absence of primary skin irritation potential of a product under maximized conditions, with controlled product amount and application site, supervised by a dermatologist.

METHODOLOGY

Both the investigational product and control were applied to patch test filter paper discs and then applied to the right or left dorsum (scapular area) of the study subjects.

The application happened one single time. Forty-eight hours (48h) after application, the product was removed by expert technicians and the site was assessed in order to check the presence of possible clinical signs.

The dermatological clinical assessment was made and subjects were supervised by a dermatologist throughout the study.

INVESTIGATOR IN CHARGE

Mariane Martins Mosca

STUDY LENGTH

5 days.

APPLICATION SITE

Dorsum (Scapular area)

FREQUENCY OF APPLICATION

Single application.

INCLUDED STUDY POPULATION DESCRIPTION

Male and female subjects, aged between 18 and 60 years old (mean age: 39 years old), phototypes II to IV.

NUMBER OF SUBJECTS

A total of 80 study subjects were included in the study and a total of 70 subjects completed the study.

ETHICS

This study was conducted in conformity with the Declaration of Helsinki principles and according to the demands of applicable regulations, including CNS Resolution No. 466/12, and according to the Good Clinical Practices (Document of the Americas and ICH E6: Good Clinical Practices).

**RESULTS / CONCLUSION**

- The product did not induce a *primary skin irritation* process in the study group.
- The product was considered safe under the evaluated conditions.



QUALITY ASSURANCE

The study was conducted according to the Resolution CNS n° 466/12, based on the Good Clinical Practices and in compliance with the Standard Operating Procedures of the Institute.

Data quality is assured, considering that our personnel is trained according to the requirements of the study to be carried out, our equipment is always duly calibrated and the methods used are recognized and/or validated.

The Quality Assurance Department is responsible by the Management System auditory; and it is completely available for any specific study monitory performed by the Sponsor.

The signature representing the Quality Assurance System means that the study was conducted as described above.

A handwritten signature in blue ink, appearing to read 'M. Giroto', written over a horizontal line.

Quality Assurance Coordinator
Marcella Carla Giroto
01/27/2022



CONTENTS

1. ABBREVIATION LIST	6
2. INTRODUCTION	7
3. OBJECTIVE.....	7
4. STUDY DESIGN.....	7
5. TEST SITE.....	8
6. INVESTIGATIONAL PRODUCT	8
6.1. Identification	8
6.2. Investigational Product Application Directions	8
7. STUDY PERIOD.....	8
8. STUDY SUBJECTS.....	8
8.1. Study Subjects Recruitment	8
8.2. Selection and Admission of Study Subjects	9
8.3. Study Population	9
8.4. Inclusion Criteria.....	9
8.5. Non-Inclusion Criteria	9
8.6. Study requirements	10
8.7. Medications and Prohibited concomitant treatments	11
9. METHODOLOGY	12
9.1. Material and Equipment	12
9.2. Procedure Schedule	13
9.3. Methods and Criteria of Assessment	13
9.4. Criteria and Procedures for Study Subjects Withdrawal	14
10. ADVERSE EVENTS.....	15
11. APPLICABLE ETHICAL REMARKS	16
12. RESULTS... ..	17
12.1. Protocol Deviations	17
12.2. Study Population Description and Study Adherence	17
12.3. Dermatological Clinical Assessment	19
13. CONCLUSION.....	21
14. REFERENCES	22
APPENDIX 1 INFORMED CONSENT FORM	23
APPENDIX 2 STUDY GROUP	31
APPENDIX 3 INVESTIGATIONAL PRODUCT INFORMATION	34



1. ABBREVIATION LIST

Ave.	Avenue
cm	Centimeter
CNS	Conselho Nacional de Saúde (Brazilian Health Council)
CRM	Regional Council of Medicine
Dr	Doctor
h	Hour
i.e.	<i>Id Est</i>
ICDRG	International Contact Dermatitis Research Group
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
Inc.	Incorporated
LTDA	Limited
Min.	Minutes
No.	Number
SP	State of São Paulo
Tx	Study Assessment Time-Points



2. INTRODUCTION

Industry awareness and consumer's and regulatory agencies requirements caused personal hygiene, household, cosmetic and perfume products manufacturers to adopt procedures that lead them to know better their products: to conduct clinical tests on safety and efficacy, which are coordinated by expert physicians, before marketing a product. These procedures provide cosmetic companies with greater safety, credibility and reliability among their consumers.

Once the personal hygiene, household, cosmetic and perfume products become freely available for the consumer, it must be safe when applied under normal or reasonably foreseeable conditions of use. For this, the raw materials used in the product formulation must be raw materials with proved safety and with well-established use in the industry. In addition, the safety of the final formulation must be tested before it is marketed.

The contact of the skin with topical products, such as personal hygiene, cosmetic and perfumes products, may trigger different types of reactions. Among these adverse reactions, we can point out eczematous contact dermatitis, urticaria, acne and blemishes (SAMPAIO & RIVITTI, 2000). In general, the contact dermatitis results from two mechanisms: the primary irritation, through the action of irritant substances; or the sensitization, in the presence of an allergenic ingredient.

In order to evaluate the irritation and sensitization potential of a product, a series of variables must be taken into account: components used in the formulation, ingredient concentration, absorption, amount applied, skin condition, application directions and frequency, as well as the cumulative effect (DOOMS-GOOSSENS, 1993).

The objective of studies for safety assessment of personal hygiene, house cleaning, cosmetic and perfume products is to confirm the absence of risk associated with the product use.

Compatibility studies performed through patch test aim to prove the absence of adverse events during the contact of personal hygiene, household, cosmetic and perfume products for the first time on the skin, proving that they are safe for use. They consist of repeated applications of the product to the skin, assessing the non-occurrence of irritation or sensitization (KLIGMAN & WOODING, 1967; FISHER, 1995). The absence of photoirritant or photoallergy potential can also be proved.

3. OBJECTIVE

The objective of this study was to prove the absence of the primary skin irritation potential of a product, under maximized conditions, with controlled product quantity and application site, supervised by a dermatologist.

4. STUDY DESIGN

Comparative, single-blind, controlled clinical study.



5. TEST SITE

The product was applied to the study subjects' dorsum (scapular area).

6. INVESTIGATIONAL PRODUCT

Product information, as declared by the Sponsor, are described in APPENDIX 3. One sample of the product was cataloged and can be found in the Institute's archive, for a period of one month after the end of the study.

6.1. Identification

Table 1. Investigational product identification

Product Name	Product Type	Product Code
Luminuex Oral Essentials Whitening Strip	Teeth Whitening	097772-01

6.2. Investigational Product Application Directions

The investigational product (in the amount of 0.02ml) was applied in the concentration of 2%, diluted in distilled water.

The investigational product was distributed over the filter paper disc of the patch test, duly identified, with the alphabet letter corresponding to the product. Sterile saline solution (NaCl 0.9%) was used as the control, being distributed on another patch test filter paper disc.

The investigational product and control were applied always to the same alphabet letter and always attached to the same dorsum area of the subjects throughout the induction period of the study.

7. STUDY PERIOD

The total duration of the study was 5 days.

- **Clinical Assessment and Application:** 01/18/2022;
- **End Date:** 01/22/2022.

8. STUDY SUBJECTS

8.1. Study Subjects Recruitment

The study subjects were recruited by the recruitment department of the Study Site that has a computerized and updated register system. The subjects registered in this system are interested in taking



part of clinical trials. They were contacted and asked to take part in the screening process and if they met all required criteria, they would be included in the studies.

The study was performed in one of Allergisa's facilities and the subjects were informed about the address/site when they were contacted.

8.2. Selection and Admission of Study Subjects

During the subjects selection to this study, the physician in charge ensured that the subjects did not present pathologies that could interfere on the study results and the physician is also responsible for the information on the study subject evaluation form, verifying all the inclusion and non-inclusion criteria for the subjects admission.

8.3. Study Population

The sample size of the population to be recruited predicted by Protocol was up to 150 subjects, with the objective of completing the study with 50 responses.

8.4. Inclusion Criteria

- Healthy subjects;
- Intact skin on test site;
- Agreement to adhere to the procedures and requirements of the study and to report to the institute on the day(s) and at the time(s) scheduled for the assessments;
- Ability of giving consent for participation in the study;
- Aged from 18 to 70 years old;
- Phototype (Fitzpatrick): I to IV;
- Any gender.

8.5. Non-Inclusion Criteria

- Pregnancy or breastfeeding;
- Any skin marks on the test site that might interfere with the assessment of possible skin reactions (pigmentation disorders, vascular malformations, scars, increased pilosity, and great amounts of ephelides and nevus, sunburns);
- Active dermatosis (local or disseminated) that might interfere with the results of the study;
- Antecedents of allergic reactions or intense discomfort sensations to topical products: cosmetics, health products or medications;



- History of atopy (atopic dermatitis, allergic rhinitis, allergic bronchitis, allergic conjunctivitis, etc.);
- Discomfort sensation with temperature changes (too hot/too cold) and/or when you are in the air conditioner;
- Subjects with history of allergy to the materials used in the study;
- History of pathologies aggravated or triggered by ultraviolet radiation;
- Subjects suffering from immunodeficiencies;
- Intense exposure to sunlight or to sun tanning sessions up to 15 days before the initial assessment;
- Intention of being intensely exposed to sunlight or to sun tanning sessions during the study period;
- Forecast of sea bathing, of going to the pool or bathtub during the study;
- Subjects who practice water sports;
- Dermographism;
- Aesthetic and/or dermatological treatment performed in the body within 03 weeks before selection;
- Use of the following topical or systemic medications: immunosuppressant drugs, anti-histaminic drugs, non-hormonal anti-inflammatory drugs, and corticosteroids up to 2 weeks before selection; in case of deposit corticosteroids, up to 1 month before selection;
- Oral or topical treatment with vitamin A acid and/or its derivatives up to 01 month before the study started;
- Intention of vaccination during the study or up to 03 weeks before the study.
- Be currently taking part or have already participated in another clinical study which was concluded less than 07 days before selection, if the previous study is an in-use study;
- Be currently taking part or have already participated in another clinical study which was concluded less than 21 days if the previous study was a Compatibility study or an Adverse Reaction Investigation;
- Any conditions not mentioned above which the investigator finds compromising to the evaluation of the study;
- History of lack of adherence or unwillingness to adhere to the study protocol;
- Professionals who are directly involved in the performance of the current protocol as well as their relatives.

8.6. Study requirements

- Not to apply any other product to the test site (dorsum);
- Not to change any cosmetic habits, including personal hygiene;



- Not to have body aesthetic or dermatological treatments performed;
- Not to change food habits;
- Not to change hormone treatment;
- If female, not to change the contraception method;
- Not to wet the patches: during shower, in swimming pools on the sea, sauna or excessive sweat;
- Not to remove the plasters;
- Not to wear tight clothes which can remove the plaster through friction or cause redness;
- Not to expose yourself to prolonged intense sunlight and not to submit yourself to artificial tanning;
- Not to use the medication described below.

8.7. Medications and Prohibited concomitant treatments

Do not use any of these medications and/or perform any of the treatments prohibited during the study. (In case the therapeutic use of any medication mentioned below is necessary, the subject would be excluded from the study).

- Non-hormonal anti-inflammatory drugs of continuous use (the sporadic use should be evaluated by the investigator, concerning the non-inclusion in the study);
- Corticoids;
- Antihistamines;
- Immunosuppressant drugs;
- Acid vitamin A and oral and topical derivatives (e.g.: Isotretinoin);
- Antibiotics;
- Tetracyclines;
- Topical medications of acne treatments, such as benzoyl peroxide;
- Anti-androgenics;
- Halogens;
- Vitamins B12, B6, B1 and D2;
- Isoniazid, rifampicin, ethionamide (treatment for tuberculosis and leprosy);
- Phenobarbiturics, trimethadione, hydantoin, lithium, chloral hydrate (neurological and psychiatric treatment);
- Quinine;
- Disulfiram;
- Thiouracil;
- Thiourea;
- During the study, any aesthetic, cosmetic or dermatological treatment was also forbidden.



9. METHODOLOGY

9.1. Material and Equipment

- Semi-occlusive hypoallergenic adhesive tape for the patch test with paper filter discs with 1.0 cm², duly identified;
- 0.9% sterile saline solution (NaCl 0.9%);
- Distilled water;
- Mineral oil or petrolatum;
- Gloves, masks and caps;
- Beaker;
- Dropper bottle;
- Transparent bottle;
- Surgical marker pen;
- Cotton swab;
- Cotton;
- Alcohol.
- Repipettor;
- Weight Scale.



9.2. Procedure Schedule

Table 2. Study Schedule

		Visit 1	Visit 2	Visit 3
Phases	Signature of the Informed Consent Form	X	-	-
	Dermatological Clinical Assessment	X	-	-
	Product Application	X	-	-
	Product Removal	-	X	-
	Assessments (Readings)	-	X	X

9.3. Methods and Criteria of Assessment

9.3.1. Dermatological Clinical Assessment

The dermatological clinical assessment of the subjects was made in the initial visit, to check the inclusion and non-inclusion criteria of the study, and in the final visit to check possible adverse events and discomfort sensations. Subjects were supervised by a dermatologist throughout the study and assessed in case there were any symptoms or clinical signs.

9.3.2. Skin Primary Irritation Assessment

The patch test methodology (KLIGMAN & WOODING, 1967), also known as contact test or epicutaneous test, was used.

The investigational product was applied to the same area (right or left dorsum of the subjects). Product application was performed only once.

The product was removed after 48 hours of contact with the skin. The assessments (readings) were performed immediately and, approximately 48 hours after the product removal.

The subjects were instructed to contact the study coordinator at any time, in case they had any complaints. In these cases, they would be sent for evaluation and guidance by the dermatologist in charge, who would evaluate the subjects, then rate the reaction and follow the appropriate procedure (guidance and/or medication and photographic record, when necessary).

The reading (48h after the application) was made right after investigational product removal, for all cases when no clinical signs were observed. If it was observed, the readings would be carried after a minimum of 30 minutes and maximum of 60 minutes, so the sign, possibly caused by the act of investigational product removal, would not represent a false positive.



9.3.3. Assessment of Clinical Signs (Readings)

During the study, the areas of product application and control were assessed and, if any clinical signs were verified, they would be classified according to the standardized scale by the International Contact Dermatitis Research Group - ICDRG - (FISHER, 1995).

Table 3. Scale published by the International Contact Dermatitis Research Group - ICDRG

REACTION	RESULT
0 – Absent	Negative (-)
1 - Mild Erythema	Doubtful (?)
2 - Clear Erythema	Positive (+)
3 - Erythema + Edema + Papules	Positive (++)
4 - Erythema + Edema + Papules + Vesicles	Positive (+++)

The signs described in the table above are considered expected signs for this study, considering mainly the type of maximized exposure to the product, predicted by the methodology. Therefore, they are not considered adverse events.

Every sign observed during the study is supervised by the investigator. In the case of more intense signs (scores 3 and 4), there must be the need of interruption of product application, according to the assessment of the investigator.

9.4. Criteria and Procedures for Study Subjects Withdrawal

The removal of a study subject by the investigator could occur due to the following reasons:

- Study subjects not included: subjects who sign the ICF, but who do not meet the inclusion and non-inclusion criteria of the study;
- Subjects who present complications that affect their eligibility after the study consent;
- Subjects who present - at the Investigator's discretion - any problem that would prevent product applications from continuing, at any time during the study;
- Consent withdrawal by the study subject, regardless of the reason;
- Lack of adhesion of the study subject to the study. A significant lack of adhesion will be recorded if the subject does not visit the study center for assessments;
- Serious Adverse Event;
- Concurrent disorder or treatment: any pathological process or treatment that occurred during the study period and that might interfere with the study product, such as a medication interaction or masking of results.

Those subjects removed from the study by the investigator would be supervised in case they present any event possibly related to the study, even after their removal. Those subjects removed due to occurrence of adverse event were continually supervised until the case is completely resolved.



10. ADVERSE EVENTS

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the investigational product use (adapted from ICH, 2016).

According to the Good Clinical Practices (ICH, 2016), a Serious Adverse Event is any untoward medical occurrence that at any dose

- results in death;
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect.

Thus, any new sign, symptom or disease, or clinically significant worsening compared to the condition at the first visit, should be considered an Adverse Event. Lack of clinical or self-assessment efficacy of a cosmetic product or drug is not considered an Adverse Event.

Clinical signs and dermatological or systemic diseases observed during the selection process of the study subjects are not considered as Adverse Events. This information is recorded on the medical evaluation form as a reason for non-inclusion and the subjects are then not included in the study.

The adverse events occurred as a result of incorrect product use (either cosmetics or drug products) - such as inappropriate frequency or incorrect application - are considered as adverse events that do not interfere with the product evaluation, since the subject- in this situation - does not follow the correct use directions stated on the product label.

In case there is an adverse event with doubtful causal nexus, an investigation process is initiated in order to determine if such event is or is not related to the study or investigational product.

The procedures adopted during the event investigation are defined by the physician in charge, based on the nature of the reaction, the subject's medical history and on factors that may interfere with the occurrence of the event, such as medication or other concomitant disorders.

For the conclusion of the final diagnosis, the relation of an Adverse Event can be defined using the decision tree Colipa (2016), according to the following description:

- Very likely: Only cases in which the clinical condition is considered to be evocative are classified as a very likely nexus, the following conditions occurring together: (i) the temporality of the facts is compatible with an adverse reaction to cosmetics and (ii) there is a laboratory test that confirm the relationship with the investigational product (e.g. positive patch test for the investigational product).

- Likely: The cases in which the clinical condition is considered to be evocative are classified as likely causal nexus, occurring with the following conditions together: (i) the temporality of the facts is



compatible with an adverse reaction to cosmetics and (ii) there is no laboratory test to confirm the relationship with the investigational product (e.g. diagnosis of contact dermatitis, without patch test, cosmetic acne - there are no laboratory tests to confirm the relationship with the product).

- Not clearly attributable: Cases in which the clinical scenario is not considered to be evocative or the chronology is not clearly compatible or unknown, are classified as nexus not clearly attributable.

- Unlikely: The following two cases are associated with an unlikely nexus: the clinical scenario is not considered to be evocative; the chronology is not clearly compatible or unknown, and the result of the investigation with the investigational product is negative (patch test or re-exposure).

- Excluded: The cases in which the diagnosis corresponds to a dermatosis of well-known cause and / or known to be caused by the use of products are classified as excluded nexus (e.g. vitiligo, tineas, pityriasis rosea, pityriasis versicolor, psoriasis, folliculitis, solar melanosis, ephelides, among others), when there is no correlation between the subject's complaint and the use of a product (for example: muscle pain, lack of appetite, stomach pain, diarrhea, insect bites, among others) or the chronology is clearly incompatible with an adverse reaction to the product (for example: there is no improvement in the scenario, even with the interruption of the product; there is relapse of the scenario, without the reintroduction of the product; the signs and symptoms started before the start of the product use).

11. APPLICABLE ETHICAL REMARKS

Before the study starts, the subjects were informed about the study objective, its methodology and length, and about the possibly expected benefits and the constraints related to the study. Subjects who agreed to take part in the study signed an Informed Consent Form (ICF) (APPENDIX 1), elaborated according to the Declaration of Helsinki and Resolution No. 466/12. The process of obtaining the ICF confirmed the voluntary nature of subjects participation in the study.

In order to maintain confidentiality of subjects' data, all data collected were identified by a number given to them at the beginning of the study. No personal information was disclosed in all data analyses. If necessary, the investigator in charge must allow the study monitor to access all subjects related records. This includes all documents containing the subject's clinical history for checking suitability for the study, diagnoses and any other document concerning the subject in the study.

All data that were found or proved by the study results are considered as being confidential information and sponsor's property. No information - as well as all documents generated during the study - will be copied or disclosed without a previous written consent of the sponsor. All information was kept confidential until the results were published.

The study technical documentation is in the Institute's archives, where it will be stored for a 5 years period.



12. RESULTS

12.1. Protocol Deviations

It was verified, after the start of the study, that subject 009 does not have the inclusion criteria of intact skin on test area for having nevus on the dorsum area. It was a failure in screening (FS), the subject was excluded from the study and your data were not considered in the study.

It was verified, after the start of the study, that subject 024 does not have the inclusion criteria of intact skin on test area for having a tattoo on dorsal area. It was a failure in screening (FS), the subject was excluded from the study and your data were not considered in the study.

12.2. Study Population Description and Study Adherence

Eighty (80) subjects were included in the study, among them, 70 finished the study. The summarized description of the population and adherence to the study is available in the following table. The detailed description of the population can be found in APPENDIX 2.



Table 4. Population Included and Adherence to the Study

Population Included									Adherence		
Recruited ¹	Not Included ²	Withdrawn ³	Included ⁴	Gender (F)	Gender (M)	Minimum Age (years)	Maximum Age (years)	Mean Age (years)	Absences ⁵	Removed ⁶	Finished the Study ⁷
83	03	00	80	70	10	18	60	39	07	03	70
Subjects									(030, 031, 047, 065, 070, 072 and 076)	009, 024 and 045	

¹subjects who attended the Institute and signed the ICF.

²Subjects who did not meet the inclusion criteria or presented any of the non-inclusion criteria.

³subjects who withdrew from the study after the study consent for personal reasons and were not included.

⁴subjects who were approved in the study.

⁵subjects who were absent in the study for personal reasons unrelated to the study and to the investigational product.

⁶subjects removed from the study are characterized as protocol deviations or another reason recorded by the study investigator.

⁷subjects considered in the total who finished the study.

Caption: F=Female; M=Male

Subject 009 and 024 were removed from the study for characterizing as protocol deviation as described in the item 12.1

Subject 045 was removed from the study for presenting adverse event, according to item 12.3.

The study achieved its objective to obtain, at its end, a minimum of 50 answers.



12.3. Dermatological Clinical Assessment

Subject 045

The study subject presented irritation after the continuous exposure of the skin to the adhesive tape (adhesive plaster), probably due to individual predisposition, and for this reason the applications were interrupted and their data not used in the study. It was a cases of excluded nexus, i.e. unrelated to the product.

During the study, no subjects experienced clinical signs on the investigational product application area.

No subjects presented clinical signs in the control site.

The clinical signs observed on the product application site can be found described in Table 5.



Table 5. Assessment – Investigational Product

Subject	Application	Immediate Reading	48h Reading
001	0	0	0
003	0	0	0
004	0	0	0
005	0	0	0
006	0	0	0
007	0	0	0
008	0	0	0
009	0	FS/R	R
010	0	0	0
011	0	0	0
012	0	0	0
013	0	0	0
014	0	0	0
015	0	0	0
016	0	0	0
017	0	0	0
018	0	0	0
019	0	0	0
020	0	0	0
021	0	0	0
022	0	0	0
023	0	0	0
024	0	FS/R	R
025	0	0	0
026	0	0	0
027	0	0	0
028	0	0	0
029	0	0	0
030	0	0	F/R
031	0	F/R	R
032	0	0	0
033	0	0	0
034	0	0	0

Subject	Application	Immediate Reading	48h Reading
035	0	0	0
036	0	0	0
037	0	0	0
038	0	0	0
039	0	0	0
040	0	0	0
041	0	0	0
042	0	0	0
043	0	0	0
044	0	0	0
045	0	EA/R	R
046	0	0	0
047	0	0	F/R
048	0	0	0
049	0	0	0
050	0	0	0
051	0	0	0
052	0	0	0
053	0	0	0
054	0	0	0
055	0	0	0
056	0	0	0
057	0	0	0
058	0	0	0
059	0	0	0
060	0	0	0
062	0	0	0
063	0	0	0
064	0	0	0
065	0	F/R	R
066	0	0	0
067	0	0	0
068	0	0	0

Subject	Application	Immediate Reading	48h Reading
069	0	0	0
070	0	F/R	R
071	0	0	0
072	0	0	F/R
073	0	0	0
074	0	0	0
075	0	0	0
076	0	0	F/R
077	0	0	0
079	0	0	0
080	0	0	0
081	0	0	0
082	0	0	0
083	0	0	0

Caption:

X = Not Applied / Reading Not Performed

F= Absent

R = Removed from the Study

E = Darkening

D = Dryness

F/R = Absent / Removed from the study

EA = Adverse Event

FS = Screening Failure checked after study

0= No reaction

1 = Mild Erythema

2 = Clear Erythema

3 = Erythema + Edema + Papules

4 = Erythema + Edema + Papules + Vesicles



13. CONCLUSION

According to the methodology used to assess absence of primary skin irritation potential of the product **Luminuex Oral Essentials Whitening Strip**, submitted by the company **Oral Essentials Inc**, it could be concluded that:

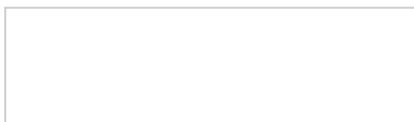
- The product did not induce a *primary skin irritation* process in the study group.
- The product was considered safe under the evaluated conditions.

Handwritten signature of Mariane Martins Mosca in blue ink.

Mariane Martins Mosca
Investigator in Charge
01/27/2022

Handwritten signature of Bruna Galusni Senna in blue ink.

Dr. Bruna Galusni Senna
Dermatologist (CRM 182754)
01/27/2022





14. REFERENCES

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APPENDIX 1 INFORMED CONSENT FORM

Due to sharing the study among different sponsors, the ICF attached concerns all studies on which the subject was clarified and included.



Sub No.: _____

INFORMED CONSENT FORM

ICF APC 0040 - VER_01 – 05/26/2021

page 1 of 8

Date: ____/____/____ Group: _____

TITLE OF THE STUDY PROJECT: ASSESSMENT OF THE PRIMARY AND CUMULATIVE SKIN IRRITATION AND SKIN SENSITIZATION POTENTIAL OF PRODUCTS TO BE APPLIED TO THE SKIN UNDER CONTROLLED AND MAXIMIZED CONDITIONS (HRIPT)

NAME OF THE INVESTIGATOR IN CHARGE: Mariane Martins Mosca

STUDY SITE: Allergisa Pesquisa Dermato-Cosmética Ltda.

You are being invited to join a study that will be carried out by Allergisa's staff together with the company that is sponsoring this study.

Before any decision, it is important that you read with attention all information presented, and if you decide to join, you will be requested to sign two originals of this informed consent form and one original will be given to you.

Your participation in this study is completely voluntary and it depends only on your will, and you are also free to withdraw from the study at any time.

Any doubts you might have before, during or after the study will be promptly solved.

This study is being done with all the safety measures necessary to avoid the contamination by coronavirus, which causes the disease COVID-19. If you agree in taking part of this study, please follow the instructions below to keep your own safety.

What are the objectives of this study?

The objective of the study is to prove the absence of skin irritation and/or skin sensitization of cosmetic products (examples: soaps, shampoos, deodorants, powders, bath oils, moisturizers, lotions, perfumes, colognes, sunscreens, insect repellent among others), health care products (examples: dressing, adhesive plasters, hospital-medical use products), topical medications (examples: ointments, gels, for use on the skin), sanitizing products (detergents, soaps, softeners, multipurpose products among others) and/or raw materials (examples: individual ingredients that compose a cosmetic product).

You may take part in one or more panels (groups of subjects) with up to **150** subjects each, being that these panels may be with subjects who have sensitive skin or not.

Skin Irritation and Sensitization are irritation and allergic reactions, which may occur eventually in your skin, after these products application.

Can I join the study?

To participate in the study, firstly you must present good health and meet other requirements called inclusion and non-inclusion criteria, that will be assessed and discussed by the specialist physician.

You can even be dismissed by the expert physician(s), after signing the informed consent form, if you present any of the non-inclusion criteria of the study, also in case the total amount of subjects was already reached.

Subject's Initials: _____ Initials of the person in charge for applying the ICF: _____

Allergisa Pesquisa Dermato-Cosmética Ltda.

IRRITATION - SENSITIZATION

F-SOP_15.01_ CT Rev. 21 – 05/24/2021



INFORMED CONSENT FORM

ICF APC 0040 - VER_01 – 05/26/2021

page 2 of 8

Where will the study be conducted?

The study will be conducted in one of the facilities of ALLERGISA pesquisa dermato-cosmética Ltda, head office located at 452/466 Dr. Romeu Tórtima Avenue – Barão Geraldo – Campinas – SP, with all the necessary precautions for your safety.

What will I have to do?

Your participation in the study will last 06 weeks. During this period, about 13 visits will be made.

At the beginning of the study you will be previously clinically assessed by a dermatologist and you will be supervised all along the study.

You can also call at any time, to clarify any questions or to inform any discomfort sensation you might present during the study. If your discomfort creates the need of an on-site attention care, an appointment will be scheduled according to the urgency of the case, in which all the precautions recommended by experts will be taken to ensure your safety in the first place.

Your adherence to the visits schedule is important for the study results. In case you cannot attend the scheduled date, please, contact the investigator or the study team and check the possibility of returning as soon as possible for the visit.

You commit yourself not to join any other research during this study.

What are the study procedures?

The following procedures will be performed during the study:

- Before the beginning of the study, a technician will clean the counter and the chairs of the room using Gel Alcohol hand sanitizer 70%;
- Before entering or leaving the test room, the technician will put the hand sanitizer on your hands, so that you can sanitize them;
- You will be instructed to sit and get comfortable in the chair of the test room, respecting a minimum distance of 2 meters from other subjects;
- You will be instructed to avoid talking to other subjects to minimize the risk of contamination inside the test room;
- Upon arriving at the Institute, you will receive a mask of mandatory use during the whole time of permanence in the test room;
- You will be instructed to avoid touching your face and mask;
- You will be questioned if your mask is wet; if so, you will get another one for use;
- If you feel the need to go to the toilet, you must wash your hands with water and soap and, then, sanitize them again with the gel alcohol hand sanitizer provided.
- You will be informed about the study objective, its methodology and duration, and about the possibly expected benefits and the constraints related to the study and, if you agree, you will sign this Informed Consent Form;
- You will be clinically assessed by a dermatologist at the beginning and at the end of the study and you will be supervised all along the study;

Subject's Initials: _____ Initials of the person in charge for applying the ICF: _____

Allergisa Pesquisa Dermato-Cosmética Ltda.

IRRITATION - SENSITIZATION

F-SOP_15.01_ CT Rev. 21 – 05/24/2021



Sub No.: _____

INFORMED CONSENT FORM

ICF APC 0040 - VER_01 – 05/26/2021

page 3 of 8

Date: ____/____/____ Group: _____

- The "patch tests" (adhesive tape) containing the assessed products will be applied on the right and/or left dorsum (back), always to the same site, three times a week, for three consecutive weeks.
- After this period of "induction", you will remain in rest for, at least, 10 days and should return to apply again the "patch tests" containing the assessed products, which will be removed by the trained technician after 48 hours or by you, at home, after 24 hours. In this case, you will be previously informed. You must come to the Institute for the products application and performance of the readings after the applications.

IMPORTANT!!!

On these returns, all the precautions recommended by our health experts will be taken to ensure your safety and the safety of the study team. Masks will be provided by the Institute for use during your stay at the Institute and during the whole study, and there will be gel alcohol hand sanitizer available. The rooms will be cleaned and disinfected with alcohol 70%, there will be appropriate distancing between people, scheduled and individual appointments and a measurement of your temperature at a distance always when necessary.

We ask you to be at the Institute ONLY at the time informed to you, in order to avoid crowds.

Procedures summary:

PROCEDURES	VISIT	TIME SPENT AT THE INSTITUTE
Signature of the Informed Consent Form Dermatological Clinical Assessment Readings before the Application by the Trained Technician "Patch tests" application (adhesive tape)	1	15 to 30 minutes
"Patch tests" removal (adhesive tape) "Patch tests" application (adhesive tape) Readings by the trained technician	2-10	15 to 30 minutes
"Patch tests" removal (adhesive tape) Readings by the trained technician	11 and 13	15 to 30 minutes
Readings by the trained technician Dermatological Clinical Assessment	13	15 to 30 minutes
Diagnosis for COVID-19 (if applicable)	Any visit, as needed	15 to 30 minutes

What information will be obtained about me?

Personal information such as name, age, usual medications, etc., will be obtained.

For this study, information will be obtained about possible adverse reactions that the product might cause on your skin.

Subject's Initials: _____ Initials of the person in charge for applying the ICF: _____

Allergisa Pesquisa Dermato-Cosmética Ltda.

IRRITATION - SENSITIZATION

F-SOP_15.01_CT Rev. 21 – 05/24/2021



INFORMED CONSENT FORM

ICF APC 0040 - VER_01 – 05/26/2021

page 4 of 8

If you present an adverse reaction with clinical sign on the skin (reaction that is able to be observed to the naked eye: irritation, redness, swelling, etc.), photos will be taken with the single purpose of investigation of the reaction and record of these information. Your identity will be kept confidential during the photographic records performance.

The photographs that need to be sent will be received in a phone number exclusively for the use of the Institute physician and all the information and files sent will be confidential and kept in privacy.

If you present any flu symptoms (headache, fever, shortness of breath, etc.), do not come to the Institute. You must call use so we can schedule a teleconsultation with a physician, we will inform you about the procedures to be followed.

What is a teleconsultation?

The teleconsultation is a remote appointment done by a physician through a telephone call or video conference. During the teleconsultation, you will be ensured of the confidentiality of the medical attention, that is, that it was done in a place where only the physician and the authorized person of the technical department were present during the call.

How will the information be protected, in order to preserve my privacy?

All information obtained about you, from your participation in this study, will be treated confidentially, and your identity will be kept confidential, under all circumstances. The information collected about you will be used only with study purpose.

Your identity will be kept confidential throughout the process and only the study investigator in charge or people from the team delegated will have access to those records.

If the study results are published, your identity will remain confidential.

If it is necessary to perform the teleconsultation, it will be performed with a tool that presents data safety, ensuring confidentiality of the medical attention.

According to Law No. 13.709, of August, 2018, which concerns the General Data Protection Law, Allergisa Pesquisa Dermato-Cosmética LTDA, together with the sponsor, declares to be in compliance with all obligations applicable to the Personal Data Processing (including any and all obligations of information to the Data Subject). Allergisa Pesquisa Dermato-Cosmética LTDA guarantees the continuous monitoring of risks and failures of Information Security that may compromise your personal data (such as name, last name, ID, "CPF", address, etc.), and the sensitive personal data (personal information concerning health, ethnic group, racial origin, political party preferences, among others), through our platforms of digital information storage.

In case any of your register data change (e.g. telephone number, address, etc.), please ask the study organizers to have them updated.

What are my responsibilities in this study?

You should attend the Institute on the days and times determined for each visit. In addition, there are some restrictions that you will follow, such as:

- Wear a mask during the whole study procedure and commute to the Institute;
- Respect the social distancing;

Subject's Initials: _____ Initials of the person in charge for applying the ICF: _____

Allergisa Pesquisa Dermato-Cosmética Ltda.

IRRITATION - SENSITIZATION

F-SOP_15.01_ CT Rev. 21 – 05/24/2021

All-S-IP-097772-01-01-22-RFV01-Rev01



Sub No.: _____

INFORMED CONSENT FORM

ICF APC 0040 - VER_01 – 05/26/2021

page 5 of 8

Date: ____/____/____ Group: _____

- Frequent cleaning of the hands with soap and/or gel alcohol hand sanitizer;
- Attend only at the times scheduled to avoid crowds;
- Allow temperature measures performed by the technical team on all visits to the Institute, if necessary;
- Do not apply any other product to the test site (dorsum);
- Do not change any cosmetic habits, including personal hygiene;
- Do not have body aesthetic or dermatological treatments performed;
- Do not change food habits;
- Do not change hormone treatment;
- If female, do not change the contraception method;
- Do not wet the patch tests (adhesive tape): during shower, in pools or sea, sauna or excessive sweat;
- Do not remove the "patch tests" (adhesive tape);
- Do not wear tight clothes which can remove the "patch tests" (adhesive tape) through friction or cause redness;

• Do not expose yourself to prolonged intense sunlight and not to submit yourself to artificial tanning;
You cannot perform any dermatological treatment during the study. If the treatment is necessary, immediately inform the study site.

We also ask you to communicate the Institute about any type of medication or external/skin or oral use, tablets and liquids (solutions and syrups) or injections, such as cortisone, anti-allergic or any other and also vitamins.

The dates you must attend to the study procedure (return visits) are described in the schedule you will receive in the study start.

If you change any of your habits, we ask that you please keep us informed, so we can better interpret the results.

We ask you not to use of any products (e.g.: deodorants or antiperspirants, talcum powder, bath oil, creams, lotions, perfumes, colognes and topical medications) in areas close to the products application area. If you use any of these products or are taking any medication, please, let us know.

Can I withdraw from the study at any time?

Yes, you are completely free to withdraw from the study at any time, not having to worry with any negative consequences. You can also remove your data (information given) at any time, if you wish.

In case of new information available that can change your desire to continue your participation in the study, you will be timely communicated by the investigator and study team and you will be completely free to withdraw from the study. Just let us know about your willingness to give up.

What benefits will I have to join the study?

Clinical studies aim to prove the safety and efficacy of the products. By joining this study, you will be contributing that those products are used by the population with much lower risk of skin reactions proven. You will also

Subject's Initials: _____ Initials of the person in charge for applying the ICF: _____

Allergisa Pesquisa Dermato-Cosmética Ltda.

IRRITATION - SENSITIZATION

F-SOP_15.01_CT Rev. 21 – 05/24/2021

All-S-IP-097772-01-01-22-RFV01-Rev01



INFORMED CONSENT FORM

ICF APC 0040 - VER_01 – 05/26/2021

page 6 of 8

undergo free medical assessments.

Is there any risk related to the study participation?

In general, products topically applied products present a good risk/benefit relation; however, they may cause allergy and irritation - especially after long-term use. In case of any reactions occurs, you will undergo assessments and you will receive all necessary dermatological monitoring.

All raw materials used in the product are approved for topical use and are not toxic.

However, same as with any other products, they might cause unexpected reactions such as "redness", "swelling", "itching" and "burning" on the product application sites. The risks presented are already known, and if they occur, they will be as minimized as possible. You will be clinically supervised by the study site, until your health clinical conditions are reestablished, regardless of the time that it might take. Any health problems you might have during the study should be informed to the investigator or study team immediately. All immediate or late assistance will be provided.

The risk of contamination by the coronavirus exists independently of your participation in the study. There is a risk of contracting the coronavirus for people who use public collective transportation, due to gatherings of people without the necessary care.

As one more safety measure and risk reduction, the Institute will recruit subjects that do not need this type of transportation, and that live close to the Facility; however, if it is necessary to use this mean of transportation to attend the visits, it is important to follow the safety measures of hands sanitation with gel alcohol hand sanitizer provided and the use of masks, avoiding to the put the hands on the face. The transmission of the coronavirus happens from a sick person to another by close contact through: touch, cough, sneezing, mucus, objects or surfaces contaminated such as cell phones, tables, etc. If you feel sick, with Flu symptoms SUCH AS fever, cough, shortness of breath, loss of sense of smell and taste, among other indispositions, you must avoid physical contact with other people, especially elderly and people with chronic diseases and must stay at home for 14 days.

During the study conduction, a test for diagnosis of COVID-19 (disease caused by the new coronavirus) may be performed, as one more measure of safety taken by the Institute during this period. This test will be done with a manual device, through a small hole in your finger, to collect a small blood sample. The advantage of this test is to obtain a quick and practically painless result. In case of suspect or confirmation by COVID-19, follow the recommendations that the Institute will provide based on the health organs. All immediate or late assistance will be provided and, for cases of possible infections by Covid-19, all the instructions to perform a quarantine or seek hospital attention will be given according to the recommendations of the health organs. The subject will be supervised until his/her health is reestablished.

What if I am pregnant or breastfeeding?

Pregnant or breastfeeding women, or women who are planning to get pregnant are not allowed to take part in this study.

If, despite the orientations given by the physician and the study team, you get pregnant and find out during the study, your participation will be terminated for your safety and the safety of the baby. Please inform the study investigator or study team immediately. They will make sure you get advice on what to do during pregnancy, and you will be

Subject's Initials: _____ Initials of the person in charge for applying the ICF: _____
 Allergisa Pesquisa Dermato-Cosmética Ltda. IRRITATION - SENSITIZATION

F-SOP_15.01_CT Rev. 21 – 05/24/2021



Sub No.: _____

INFORMED CONSENT FORM

ICF APC 0040 - VER_01 – 05/26/2021

page 7 of 8

Date: ____/____/____ Group: _____

supervised during the pregnancy until the birth.

Will I have any type of reimbursement for the expenses for participating of this study?

As predicted by Brazilian laws, you will not have any type of financial compensation/payment for your participation in the study; however, you will receive a reimbursement in the end of the study due to expenses of your participation.

If you are removed from the study before its conclusion by the investigator in charge, for example, for safety reasons or non-compliance with the study requirements, you will receive the reimbursement for the expenses regarding the days in which you participated.

How can I know about the study results?

The study results will be assessed by the investigator in charge after it is completed. The results can be published, but your name will not be mentioned.

You can still ask to the investigator about the study results after the conclusion of the study.

If you perform the diagnosis test for COVID-19, you will be informed about the result immediately, in private.

Can I be removed from the study?

Yes, your participation in this study can finish earlier than predicted.

It is duty of the investigator, at any moment, to remove you from the study, if you present any reaction to the products or if your health has been affected for any reason and you are not in conditions to continue as a study subject. You can also be removed from the study in case you do not fulfill your responsibilities, according to the study protocol.

What if my participation in the study cause any harm to any other medication I am currently taking?

It is highly important that you inform the investigator in charge of the study about the use of usual medications, or use of any other different medication when you sign this document and during your participation.

In case you need to take a specific medication, non-mentioned previously, you should communicate the study investigator in charge immediately, because he/she will know how to give you instructions about the best conduct for your case.

With whom will I be able to contact if I do not feel well during the study or present any reactions to the products?

If you do not feel well or in case of any irritation skin signs, immediately communicate, attending to the study site or by telephone: 19-3517-6800 (working hours) or 19-99778-0204 (from 5 pm to 10 pm). In case of any doubts or problems, you can contact the investigator in charge (**Mariane Martins Mosca**) or the medical team by the same telephone numbers.

We assure that for any complications or damages caused by the study, a full assistance will be given to the study subjects together with the sponsors of this study.

Eventual indemnifications for damages caused by the study are assured.

Subject's Initials: _____ Initials of the person in charge for applying the ICF: _____

Allergisa Pesquisa Dermato-Cosmética Ltda.

IRRITATION - SENSITIZATION

F-SOP_15.01_CT Rev. 21 – 05/24/2021

All-S-IP-097772-01-01-22-RFV01-Rev01



INFORMED CONSENT FORM

ICF APC 0040 - VER_01 – 05/26/2021

page 8 of 8

We ask you to call the Institute at any moment if you feel symptoms such as cough, fever, coryza, sore throat or shortness of breath, or if you would like to cancel your participation in the study, through the telephones 19-3517-6800 (business hours) or 19-99778-0204 (from 5 p.m. to 10 p.m.). Subjects who present these symptoms will not be allowed to participate in the study and if you arrive at the Institute with the symptoms, you will not be allowed inside and will be instructed to go home.

If you have any complaints or any questions about your rights as a subject of this study, you might contact the Independent Ethics Committee INVESTIGA – Instituto de Pesquisas, located at 739, Dr. Romeu Tórtima Avenue – Cidade Universitária – Campinas-SP – Postal Code: 13084-791 by the telephones (19) 3517-6830 and (19) 99822-9083. The hours of operation are on Monday to Friday from 9am to 5pm. The Independent Ethics Committee (IEC) is an agency that has the objective to evaluate and supervise the ethical aspects of all studies involving human beings, aiming to assure the dignity, rights, safety and well-being of the study subject.

Important information!

If you have any questions about the study that was not answered yet, you should ask to the investigator or study team.

Please, keep this document for your information.

Signatures Page – ASSESSMENT OF THE PRIMARY AND CUMULATIVE SKIN IRRITATION AND SKIN SENSITIZATION POTENTIAL OF PRODUCTS TO BE APPLIED TO THE SKIN UNDER CONTROLLED AND MAXIMIZED CONDITIONS (HRIPT)

I read and understood the information provided in this Informed Consent Form. I have obtained the answers for all my questions and I freely decided to join this study. I offer my consent, freely, to join this study, as explained in this document.

I am aware that the photographs and/or videos obtained for the medical attention and investigation are part of the procedure of this study and I agree with the obtaining of these images.

By signing this document, I did not waive from any legal rights I have when I participate in a study, including the indemnification.

01		
	Signature of the Study Subject (as in the ID or Driver's License)	Date

02		
	Signature of the person in charge of explaining the ICF	Date

Subject's Initials: _____ Initials of the person in charge for applying the ICF: _____
 Allergisa Pesquisa Dermato-Cosmética Ltda. IRRITATION - SENSITIZATION

F-SOP_15.01_CT Rev. 21 – 05/24/2021



APPENDIX 2 STUDY GROUP

SUBJECT	AGE (YEARS)	GENDER	PHOTOTYPE	STATUS
001	40	F	III	I
002	37	F	IV	NI
003	32	F	III	I
004	38	F	IV	I
005	54	F	III	I
006	44	F	III	I
007	51	F	II	I
008	54	F	III	I
009	32	F	NA	FS
010	52	M	II	I
011	27	F	II	I
012	58	F	IV	I
013	43	F	III	I
014	34	M	III	I
015	38	F	IV	I
016	58	F	III	I
017	46	F	III	I
018	27	F	II	I
019	60	F	III	I
020	22	F	IV	I
021	42	F	IV	I
022	40	F	IV	I
023	34	F	III	I
024	33	F	NA	FS
025	34	F	IV	I
026	53	F	III	I
027	38	F	III	I
028	51	F	II	I
029	54	F	III	I
030	20	M	II	I

Caption:

F= Female;

M= Male;

I = Included;

NI = Not Included (present any non-inclusion criteria and/or not present some of the inclusion criteria);

FS = Failure in Selection (presented some of the exclusion criteria and/or did not present some of the inclusion criteria, verified throughout the study or immediately after subject inclusion in the study);

NA = Not applicable (subjects *Failure of Selection (FS)* and *Withdrawn (DE)* may have their phototypes not assessed).



Study Group: Continuation

SUBJECT	AGE (YEARS)	GENDER	PHOTOTYPE	STATUS
031	26	M	III	I
032	41	F	III	I
033	36	F	II	I
034	39	F	III	I
035	23	F	IV	I
036	22	F	II	I
037	42	M	II	I
038	50	F	III	I
039	44	F	II	I
040	29	F	IV	I
041	38	F	III	I
042	23	F	II	I
043	54	F	III	I
044	25	M	III	I
045	43	M	II	I
046	29	M	IV	I
047	22	F	IV	I
048	37	F	IV	I
049	50	F	III	I
050	34	F	IV	I
051	56	F	III	I
052	51	F	III	I
053	59	F	IV	I
054	29	F	IV	I
055	33	F	II	I
056	32	F	III	I
057	58	F	III	I
058	49	F	III	I

Caption:

F= Female;

M= Male;

I = Included;

NI = Not Included (present any non-inclusion criteria and/or not present some of the inclusion criteria);

FS = Failure in Selection (presented some of the exclusion criteria and/or did not present some of the inclusion criteria, verified throughout the study or immediately after subject inclusion in the study);

NA = Not applicable (subjects *Failure of Selection (FS) and Withdrawn (DE)* may have their phototypes not assessed).



Study Group: Continuation

SUBJECT	AGE (YEARS)	GENDER	PHOTOTYPE	STATUS
059	48	F	III	I
060	48	F	III	I
061	41	F	IV	NI
062	20	F	III	I
063	41	F	III	I
064	29	F	IV	I
065	18	F	IV	I
066	35	F	IV	I
067	26	F	III	I
068	26	F	IV	I
069	43	F	IV	I
070	44	F	III	I
071	25	F	IV	I
072	43	F	IV	I
073	44	F	III	I
074	43	F	IV	I
075	25	F	IV	I
076	18	F	IV	I
077	39	M	III	I
078	32	F	IV	NI
079	34	F	IV	I
080	44	F	II	I
081	39	F	IV	I
082	30	F	IV	I
083	35	M	III	I

Caption:

F= Female;

M= Male;

I = Included;

NI = Not Included (present any non-inclusion criteria and/or not present some of the inclusion criteria);

FS = Failure in Selection (presented some of the exclusion criteria and/or did not present some of the inclusion criteria, verified throughout the study or immediately after subject inclusion in the study);

NA = Not applicable (subjects *Failure of Selection (FS)* and *Withdrawn (DE)* may have their phototypes not assessed).



APPENDIX 3 INVESTIGATIONAL PRODUCT INFORMATION
“FORMULA NOT RECEIVED”