Università "G. d'Annunzio" – Facoltà di Medicina e Chirurgia – Dipartimento di Oncologia e Neuroscienze
CLINICA DERMATOLOGICA
SCUOLA DI SPECIALIZZAZIONE IN DERMATOLOGIA E VENEREOLOGIA
(Direttore (Prof. A.Tulli)
Policlinico "SS. Annunziata" - Via dei Vestini, 66013 Chieti
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UNIVERSITY 'G. D'ANNUNZIO'
CHIETI - PESCARA

DEPARTMENT OF ONCOLOGY AND NEUROSCIENCES

SPECIALIZATION COURSE IN DERMATOLOGY AND VENEREOLOGY

HEAD OF DEPT.: Professor A. Tulli

Università "G. d'Annunzio" – Facoltà di Medicina e Chirurgia – Dipartimento di Oncologia e Neuroscienze
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A clinical trial was undertaken in the Dermatologic Clinic of the University óG. DôAnnunzioô in Chieti, to evaluate the performance and the safety of the intradermal use of an extemporaneous mixture of hyaluronic acid and amino acids as adjuvants in the reduction of skin blemishes of the face, using the product Jalu-Pro.

A total of 60 treatments was administered, each treatment including two implants, at T0 and at T7, as specified in the protocol. Clinical evaluations of the general health of the subjects and of the quality of the skin were carried out at T0, T1, T7 and T8. The thickness of the skin folds was assessed before starting the treatment and on the day following the second implant session. The thickness of the folds was evaluated both clinically and through skin replicas, later subjected to profilometric examination.
No adverse events occurred during the study period.
Preliminary data, derived from the clinical evaluation of the thickness of the skin folds before and after the treatment, show a satisfying reduction in depth of the wrinkles tested during the study, the severity score of the folds decreasing by an average of two degrees in the wrinkling of the examined area.
The above clinical data were confirmed by those deriving from the results of the profilometric examination carried out by:

Evic Italia Srl
00196 Rome (RM) ï Lungo Tevere Arnaldo da Brescia,11

Faithfully Yours,

Professor A. Tulli

CLINICAL PROTOCOL

Title :

STUDY PROJECT FOR THE EVALUATION OF THE PERFORMANCE ON SKIN BLEMISHES OF THE FACE AND OF THE SAFETY OF AN EXTEMPORANEOUS MIXTURE OF HYALURONIC ACID AND AMINO ACIDS AS ADJUVANTS WITH ACCESSORY ACTIVITY (JALU-PRO) FOR INTRADERMAL IMPLANTS

Protocol Number : PDI0103

Sponsor:
Professional Dietetics s.r.l.
Registered office: Via F. Petrarca 22, 20123 Milano
Operating office: Via Ciro Menotti, 1/A, 20122 Milano
Hereinafter called Professional Dietetics

Study center:
Clinica Dermatologica XII liv. Corpo B
Ospedale Clinicizzato S.S. Annunziata 66013 Chieti

Monitoring and examination of skin replicas:
Evic Italia Srl
00196 Roma (RM) ï Lungo Tevere Arnaldo da Brescia, 11
Tel. 06.36006629 ï 06.36006633 ï 06.36006671

Investigators:

Project Manager:	Professor Franco Conti Professional Dietetics
Responsible Investigator:	Professor A. Tulli
Appointed Investigator:	Dott.ssa P. Toto, Dott.ssa S. Caporale, Dott. P. Amerio
Monitor:	Dott.ssa M.G.Ingaldi
Responsible for Biometrics:	Professor Leonardo Celleno Specialist in Dermatology and Venereology

Product :

JALU-PRO
DESCRIPTION: Jalu-ProÊ is a medical device consisting of:
1) 100 mg of a lyophilized, sterile, apyrogenic mixture of: proline (37.6 mg), glycine (50 mg), lysine (7 mg), leucine (5.4 mg)
2) Hyaluronic acid: sodium hyaluronate, 2 ampoules x 30 mg

Mode of preparation: reconstitute the lyophilized amino acids at 1) with a 30 mg ampoule of sodium hyaluronate. Aspirate and bring to volume with the second 30 mg ampoule of hyaluronic acid.
The product, locally administered via injection, is intended for the reduction of skin blemishes.

INVESTIGATORSô APPROVAL

I hereby declare to have examined and approved the present protocol

Responsible Investigator: Prof. A. Tulli

Signature: Date:

Project Manager: Prof. Franco Conti

Signature: Date:

Appointed Investigator: Dott.ssa P. Toto, Dott.ssa S. Caporale, Dott. P Amerio

Signature: Date:

Monitor: Dott.ssa M.G. Ingaldi

Signature: Date:

Responsible for Biometrics: Prof. Leonardo Celleno

Signature: Date:

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  Helsinki Declaration

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TITLE:

STUDY PROJECT FOR THE EVALUATION OF THE PERFORMANCE ON SKIN BLEMISHES OF THE FACE AND OF THE SAFETY OF AN EXTEMPORANEOUS MIXTURE OF HYALURONIC ACID AND AMINO ACIDS AS ADJUVANTS WITH ACCESSORY ACTIVITY (JALU-PRO) FOR INTRADERMAL IMPLANT

I. INTRODUCTION

Aim of the present study is to evaluate the performance and the safety related to the intradermal use of an extemporaneous mixture of hyaluronic acid and amino acids as adjuvants in the reduction of skin blemishes of the face, using the product Jalu-Pro.
The safety of such products is ensured by studies guaranteed for by Professional Dietetics.
Should the Investigator, at any time during the study, notice a lack of safety related to the study products (e.g. a number of severe adverse events), the study shall be discontinued.

II. ETHICS

A. Ethic Committee approval

A final version of the study protocol, including the appendices, shall be submitted for examination to an Ethic Committee, with no relation to the Sponsor; copy of the decision taken by the committee shall be sent to Professional Dietetics to be introduced in the study file. Furthermore, copy of such approvals should be attached to the study documentation, while the consent forms (as they include the subjectsô names) should be kept separate from the other study records to ensure subjectsô confidentiality. The Sponsor and the Investigator agree not to include any subject in the study before having obtained his/her consent and the approval by the Ethic Committee. The Sponsor and the Investigator also agree to inform the Ethic Committee about all subsequent corrections to the protocol and about all possible severe or unexpected adverse events that might compromise the safety of the subjects or the conduct of the study. The present study shall be conducted in accordance with the ethical principles contained in the óHelsinki Declarationô (see appendix). A list of the members of the Ethic Committee examining the protocol shall also be recorded in the Sponsorôs and Investigatorôs files.

The approval letter shall include the following information:

- Protocol title, issue date, study Sponsor and Investigator.
- Statement declaring that both the protocol and the consent form have been approved, indicating any modification needed.
- List of members of Ethic Committee.
- Signature of the Ethic Committeeôs Chairman.
- Ethic Committeeôs address.

B. Informed consent

The Investigator shall ensure that the subjects be adequately informed, both verbally and in writing, about the study details (see appendix).
Finally, before being considered eligible to enter the study, all subjects shall be asked to sign an informed Consent Form (see appendix), to show their understanding of the study and their agreement to participate in it. The contents of the information document / consent form shall be agreed upon by

Sponsor, Project Manager and Investigator and shall include the basic elements of the Informed Consent, as drafted in the ôHelsinki Declarationô (see appendix).

III. STUDY OBJECTIVE

To evaluate the safety and the performance of the use of a mixture of hyaluronic acid and amino acids for intradermal implant on skin blemishes of the face in subjects with medium / moderate facial rhytidosis.

IV. METHODS

A. Study design

The present study is designed as open-label and it is expected that a number of at least 25 participating subjects complete the study. The product to be tested is óJALU-PROô, based on hyaluronic acid and amino acids, for intradermal injection. The subjects shall be men and women, aged between 35 and 60, with medium / moderate rhytidosis but otherwise healthy.
The visit at baseline shall include an accurate medical history and an objective examination of the skin of the face to assess whether the subjects meet the criteria needed for the inclusion in the study. In case of a positive evaluation, the subjects shall be included in the study that implies two intradermal implants of a mixture of hyaluronic acid and amino acids at the level of both nasolabial folds, with a 7-day interval. The control visit shall take place on the day following the last implant. Clinical evaluation at the level of the implant sites shall be carried out during the visits. During the baseline visit, at baseline and one day after the second implant, photographs of the skin areas being studied and skin replicas of the fold regarded as deepest by the Investigator at baseline shall also be taken.

Times	T0	T7	T8
Visit	*	*	*
Photograph	*		*
Replica	*		*
1st implant	*		
2nd implant		*	

In order to obtain significant supporting evidence as to the safety and the performance of the medical device under examination, the study is designed as to:

1. Assess whether or not the subjects have exhibited any adverse event.
In case of a suspected adverse event being exhibited by a subject, the Investigator shall record it in the form regarding adverse events included in the Case Report Form (CRF). For each adverse event, the Investigator shall also act to find out:

(a) whether the adverse event is severe or non-severe (serious or non serious)
(b) the relationship between adverse event and study product

The Investigator shall then decide whether:

(a) to withdraw the subject from the study
(b) to continue to use the product according to the protocol

(c) to include the subject in a subsequent follow-up phase
(d) to end the study

Objective examination (wrinkle grading): the evaluation of deep and superficial wrinkles shall be done at the level of nasolabial folds. The evaluation shall always be carried out for both sides of the face. Each side shall be lighted by a reading lamp with a 45° incident light with respect to the face of the subject being examined (see scheme).

Degree 0 (null) *No wrinkles*	Total absence of skin ridges with specific direction	
Degree 1 (light) *Very light wrinkles*	Presence of some light lines, few in number	
Degree 2 (weak) *Light wrinkles*	Presence of more marked and longer lines	
Degree 3 (quite evident) *Rather visible*	Wrinklesô formation: the lines exhibit more defined contours	
Degree 4 (evident) *Visible*	Quite deep and longer wrinkles	
Degree 5 (very evident) *visible*	Deep and numerous wrinkles (skin retains good tonicity around the wrinkles)	*Very*
Degree 6 (marked)	Deeper wrinkles, lack of skin tonicity (the number of wrinkles may be quite small)	*Pronounced*
Degree 7 (very marked) *Pronounced*	Particularly ócheppedô wrinkles, very large, surrounded by skin pads (due to lack of skin tonicity)	*Very*

2. Objective symptoms (their presence at baseline shall be an exclusion criterion):

Erythema	score:	0 = absent 1 = mild 2 = moderate 3 = marked 4 = very marked
Edema	score:	0 = absent 1 = mild 2 = moderate 3 = marked 4 = very marked
Papules	score:	0 = absent 1 = mild 2 = moderate 3 = marked 4 = very marked
Pustoles	score:	0 = absent 1 = mild 2 = moderate 3 = marked 4 = very marked

Other _____

These evaluations shall be carried out by the Investigator at baseline, and following treatment.

The objective tolerance of the volunteerôs shall also be recorded and evaluated at all time points considered:
itching (VAS score)
pain (VAS score)
other
The presence of objective symptomatology at baseline shall be a criterion for the exclusion of the subject from the study.

As regards the subject not presenting any kind of problems, the study shall be completed 14 days after the last implant, upon evaluation by the Investigator. These subjects shall not be required to do anything else. The subjects presenting any adverse event shall be followed until the resolution thereof.

B. Sample population

The subjects shall be enrolled locally, mainly from a pre-existing subjectsô panel. Staff working in the study centre and all staff involved in the conduction of the study may not be enrolled. Based upon the inclusion criteria, the Investigator shall confirm whether a subject is eligible to enter the study. The Investigator shall be responsible for keeping detailed records on all the subjects presenting themselves to be included in the study, and shall provide the reasons behind the exclusion of the non eligible subjects.

C. Inclusion criteria, prohibitions and limitations

Inclusion criteria:

In order to be included in the study, the subjects shall meet the following criteria.
The subjects shall:
1. Give their written informed consent
2. Be between 35 and 60 years old
3. Suffer from medium / moderate face rhytidosis (that is, exhibit degree 2-6 wrinkles at the level of nasolabial folds)
4. Agree to undergo the two planned JALU-PRO implants and to follow the indications given by the Investigator during the entire study period
5. Be willing and able to go back to the study centre at the defined times
6. Assure they will not take any medication / undergo any treatment that might modify their skin characteristics during the entire study period
7. Present them wearing no make-up at all visits (including initial visit)
8. Assure they will not participate in other clinical trials and that they have not taken part in a clinical trial in the 3 months preceding the initial visit
9. Assure to avoid using any sun lamp during the entire study period and to avoid undergoing other skin treatment procedures (chemical peeling, implants of other biomaterials, etc.)
10. Generally be in good health, according to the opinion of the Investigator.

Exclusion criteria:

The subjects shall be excluded if:
1. In the course of the baseline dermatological examination they have exhibited significant clinical conditions of the skin (active eczema, dermatitis, psoriasis, dermatitis on the face area, etc.)
2. They exhibit wrinkles at the level of nasolabial folds, the degree of which was 0,1 or 7
3. They exhibit single but very deep lines, due to sagging of the skin
4. They are taking anti-inflammatory drugs, antihistamines, steroids for topical or systemic use, tranquilizers, antidepressants, drugs acting on the CNS, immunosuppressants (with the exception of oral contraceptives and hormonal replacement therapy) or other drugs which might impair the study, according to the opinion of the investigator
5. They have exhibited, in their medical past history, a significant hepatic, renal, cardiac, pulmonary, digestive, hematological, neurological, locomotorial or psychological adverse event
6. They have a history of drug allergies
7. They suffer from insulin-dependent diabetes
8. They have been shown to be sensitive to the product to be tested or to one or more of its ingredients
9. They are pregnant, nursing or planning to become pregnant
10. They are about to be treated for any kind of cancer or have been treated for cancer during the preceding six months
11. They are part of the staff working in the study center or for Professional Dietetics
12. They are deemed by the Investigator as non eligible to enter the study

Subjects shall be excluded in case any of the above listed characteristics is noticed.

Prohibitions and restrictions

A list of prohibitions and restrictions shall be provided to the subjects as part of the subject information document. During the study subjects:

1. Shall not change their normal habits as regards moisturizing, personal cleanliness, use of make-up
2. Shall not participate in other clinical trials
3. Shall not undergo any sun lamp nor other kinds of treatment (peeling, implants, etc.).
4. Shall present themselves to all evaluation visits wearing no make-up.

Early study discontinuation

Subjects shall be discontinued from the study if:

1. They withdraw their consent
2. They suffer from adverse events which, according to the opinion of the Investigator, justify their discontinuation
3. They significantly violate the protocol, according to the opinion of the Investigator
4. They develop some of the exclusion conditions specified in the study (at the discretion of the Investigator)
5. They are at any time deemed as non eligible to continue the study (at the discretion of the Investigator).

A Study End form shall be compiled for each subject excluded from the study.

D. Planning of study procedures

1. Inclusion visit

During the initial visit (time 0), subjects will be given exhaustive verbal explanations about study procedures and prohibitions. During the visit, each subject shall be assigned a progressive record number and shall be asked to give his/her consent to the participation in the study by signing the consent form. The Investigator shall then compile a Medical and Dermatological form and shall carry out a dermatological examination of the face. Using the recorded information, the Investigator shall confirm whether the subjects are eligible to enter the study, depending on their skin type. The baseline examination of all subjects included in the study shall be based upon their concise medical history and their usual habits and customs. Subjects meeting all inclusion criteria listed in part IV(C) shall be accepted for the study.
Each subject shall be notified in writing about the date on which he/she shall have to go back to the study center for the following visits.

2. Study conduct

Once a subject has been deemed as eligible to participate in the study, the treatment shall begin, involving the intradermal implant, with an injection of óJALU-PROô, based on hyaluronic acid and

amino acids. Two implants at the level of both nasolabial folds are planned, with a 7-day interval (T0, T7).

3. Methods for performing the implant

The needle is inserted along the fold and then gradually withdrawn, at the same delivering the product. After injecting the product, if necessary, a light massage is done to model the treated area. The amount of material needed for the treatment varies depending on the numbers of areas to be treated and on the depth of the fold or wrinkle. The most suitable point where to inject the material for the correction of thin wrinkles is the papillary dermis. In order to completely correct the defect, it is important to inject an adequate amount of material. But is also necessary to avoid overcorrecting.
To obtain a good result in case of deeper wrinkles and folds, it is usually necessary to inject the implant material from the central part to the deep part of the reticular dermis. If appropriate, this procedure may be followed by a more superficial injection at papillary level to complete the treatment. Once again, the area should be treated only to cancel the wrinkle or the fold, without overcorrecting.
To avoid potential redness and swelling, as well as to minimize pain, it is advisable to avoid to insert excessive amounts of the product and to inject slowly.

4. Methods for taking the photographs

The photographic documentation is obtained with a digital camera, set in the macro mode and kept perpendicular to the test skin area and at a fixed distance.
The area to be photographed is the nasolabial fold regarded as deepest by the Investigator at baseline. The lighting source and light incidence and angle should be the same for each photograph taken: side of the face lighted by a reading lamp with a 45° incident light with respect to the face of the subject being examined. While the photograph is being taken, the subject should not contract his/her face. Only the treated area should be photographed.

5. Control visits

In case of occurrence of any adverse event on the skin, the subjects shall immediately get in touch with the Investigator, and shall present themselves for a control on a working day. All subjects presenting adverse events on the skin shall be visited by the Investigator, and their conditions shall be monitored until resolved according to the clinical opinion of the Investigator.
The subjects shall go back to the study center on the day following the last treatment (T8).
During the control visit, the subjects shall undergo a dermatological examination carried out by the Investigator. He/she shall evaluate the rhytidosis degree according to a predefined scale (attachment 1) and assess whether the subjects have presented any adverse events and, if so, whether these are related or not to the study product and if the protocol has been followed. Photographs and replicas of the skin fold examined by the trial shall be taken during the control visit.

6. Execution of skin replicas

Skin replicas are taken at times T0 and T8 at the level of the nasolabial fold considered as deepest by the Investigator at baseline. They are taken with a silicone material for ósecond impressionsô. The material is first prepared for the replica by mixing the silicone with the catalyst in the proportions indicated by the manufacturer. Once a homogeneous compound has been obtained , it is applied to the selected skin area using a spatula. The subject shall be seated and keep his/her face as still as possible. The material is left to stand for about 5 minutes, until completely dry, and the replica thus obtained is removed.

7. Image acquisition

When studying replicas of skin surfaces, the image is usually acquired with a telecamera. To ensure the acquisition of reproducible and comparable data, standardized methods are needed for image acquisition, particularly as regards:

- model of telecamera
- setting of telecamera
- distance and intensity of lighting source
- incident angle of illumination (using a 45° angle, shaded areas are created, that allow to highlight wrinkles and furrows)
- absence of room lighting, thanks to a darkened room.

8. Image analysis of the replicas

The replicas, corresponding to the negative of the skin surface, are photographed and analysed with computerised image analysis. The processing of the acquired image is conducted through a computerised image elaboration. Skin replicas, photographed with a 45° incident light, show shadows at the level of the crests (that is, negative image of the wrinkles). The shadows are transformed into a grey scale the intensities of which are directly proportional to shadow intensities and therefore to wrinkle depth. Once the image has been displayed and the area to be examined identified, a series of lines perpendicularly crossing the area is defined, pixel by pixel (scan). The grey average intensity for each pixel in the detected area is thus obtained. Particular care should obviously be taken in executing and orienting a replica, which allows to always obtaining well reproducible scans (uncertainty level < 13; uncertainty calculated according to EN45001 norms). It is possible to calculate the following parameters: Ra (average roughness), representing the arithmetic mean, as absolute value, of all deviations from the mean value; Rt (maximum depth) representing the distance between tangent to crest peak (negative of the wrinkle) and tangent to fold, within the considered area; Rz (average depth); Rmax, maximum roughness; Rmin, minimum roughness (in accordance with DIN 4768, page 1).
The above profilometric parameters are calculated for primary wrinkles (deeper, wider and longer wrinkles) and for secondary wrinkles (less marked, thinner and shorter wrinkles).
Image acquisition of the replicas and their computerised image analysis are performed by Evic Italia.

9. Post-treatment period

For all subjects not presenting any adverse event, the study shall be completed at T8. Nothing else will be required from these subjects.

10. Post- adverse events period

For all subjects presenting adverse events, further follow-up visits shall be documented on the adverse event form until the resolution thereof.

V. STUDY MATERIALS

A. Formulation of the product tested and packaging

Refer to the Appendix for the formulation of the product.
Packaging: the study sample consists of a glass vial containing 100mg of lyophilized mixture and 2 glass ampoules containing 30 mg of hyaluronic acid each.

The packages shall be labelled specifying the essential trial data. Batch number and expiration date shall be included in the certificate of analysis.

B. Control of clinical supplies

All products to be tested shall be delivered to "Clinica Dermatologica XII liv. Corpo B Ospedale Clinicizzato SS. Annunziata 66013 Chieti" by land under the supervision of a carrier appointed by PROFESSIONAL DIETETICS.

All products to be tested shall remain in the study center for the duration of the clinical trial and shall be stored in an appropriate location, according to the indications provided by the manufacturer.

At the end of the study, all empty, unused or partially used packages shall be accounted for and sent back to PROFESSIONAL DIETETICS.

VI. STUDY CONDUCT

A. Monitoring

The study shall be regularly monitored by the Sponsor in accordance with the guidelines of the European Community Good Clinical Practice. The monitoring frequency shall be as required during the treatment / evaluation period and, if necessary, during the study follow-up phase.
These procedures shall be documented in the Monitoring Strategy. The director of the Dermatological Clinic of the Hospital "SS. Annunziata" in Chieti and the Investigator shall allow proper access to the documentation in order for the Monitor, Sponsor and Regulatory Authorities to be able to verify and examine the study documentation.

During the control visits, the following elements shall be verified by the Monitor and/or Sponsor:

a) Instrumental compliance and availability of equipment required for conducting the study
b) Protocol compliance
c) Adequate data collection
d) Appropriate study conduction
e) Notification of adverse events to Sponsor, Ethic Committee and competent organs
f) Product usage.

B. Adverse events

1. Definition and classification of adverse events

Any undesirable clinical event occurring during a clinical trial, whether related or non related to the study product is considered as an adverse event. This definition includes any alteration in the conditions of a subject or in the results of laboratory tests that has or may have damaging effects on the health of the subject or on his/her wellbeing.

All Adverse Events should be recorded in the data collection file.
Adverse events should be accurately monitored during the entire study conduction period.

A Serious Adverse Event is any undesirable clinical event that meets at least one of the following criteria:
- it proves to be lethal
- it threatens the life of the subject
- it requires the hospitalization of the subject or prolongs the hospitalization period
- it causes a persistent or significant inability / incapacity
- it requires an intervention to prevent a permanent damage to or worsening of the conditions of the subject
- it causes a congenital abnormality or a birth defect
- it induce the onset of a tumour
- it is an overdose

The data to be recorded in the Adverse Event form included in the Data collection File are at least: event type, duration of adverse event (onset and end date), dose, intensity, severity, actions undertaken, development, and causal relationship between event and product.
Adverse events should be notified to the Sponsor even after the end of the study is, according to the Investigator, there might be a relationship between event and study product.
Any Serious Adverse Event should be notified to the Monitor and to the Sponsor within 1 working day from the time when the Investigator is aware of it.
An event does not need to be notified as serious if it only consists of a relapse or an expected change, or a worsening of the conditions that caused the treatment with the study product, any other symptom and sign apart from those present before the treatment being absent.

2. Conduct after the onset of an adverse event

If the product causes adverse events after the first implant, the Investigator may discharge the subject from the study. The Investigator might also reintroduce the study product only if the subject is willing and if the adverse events have been classified as mild/moderate and unlikely/likely as regards their relationship to the study product. In this conduction phase of the study, the use of the product is at the discretion of the Investigator and all further visits shall be documented in the adverse event form. During the study end visit, the Investigator shall assess whether the adverse event is still ongoing or resolved. This phase following the onset of the adverse event is expected to help to assess whether the event is due or not to the study product. Once the subject has been discharged from the study, it is understood that data to be used in the final analyses shall no longer be collected.

Addresses:

Sponsor:	PROFESSIONAL DIETETICS Via Ciro Menotti, 1/A 20122 Milano Tel. 02/744020 Fax 02/70008791
Investigator:	Professor A. Tulli Clinica Dermatologica Policlinico SS. Annunziata Via dei Vestini 66013 Chieti (CH) Tel. 0871/358032-8 Fax 0871/551057
Monitor:	Dott.ssa M.G. Ingaldi

Analysis of the replicas: Evic Italia Srl
00196 Roma (RM) ï Lungo Tevere Arnaldo da Brescia, 11
Tel. 06/36006629-33-71

C. References

1. Documentation

The procedures regarding the documentation to be followed for the present study are described as follows and refer to the European Community Good Clinical Practice Guidelines. A list of forms and documents provided by PROFESSIONAL DIETETICS regarding the subjectôs Case Record Form follows here below. Each page shall be available in triplicate. The Information Document and the Informed Consent Form shall be in duplicate (one copy to be kept by the Investigator, one by the subject)

The following pages contain a list of items included in the subject information document and in the Case Record Form.

Case Record Form (CRF)
Subject Information and Consent Form
Demographics
Medical and Dermatological History Form
Baseline Dermatological Examination form
Verification of subjectôs eligibility
Form for the execution of 1st implant
Clinical report for visit after 1st implant: dermatological evaluation
Form for the execution of 2nd implant
Study End form (T8)
Adverse Event form
Concomitant Medications form
Investigatorôs statement

All documents regarding the study shall be compiled in black ink. Wherever an answer is required, no spaces shall be left blank and óNAô (not applicable) shall be written in the appropriate area.
Each change to the documentation shall be dealt with as follows:
If a correction is required, one single straight line shall be drawn on the words to be corrected, as not to completely cover the original information.
The correct information shall be inserted along with the reason for the correction, the date and the initials of the investigator. Only the Investigator and authorized staff may correct the recorded clinical data.
A code will be assigned, where appropriate, to the reasons behind the corrections: TE = Transcription Error; M = Missing data; IL = Illegible
No correction tape or fluid may be used , nor may the recorded data be fully erased.

The Investigator shall be responsible for the adequacy, completeness, accuracy and quality assurance of the information contained in the subjectôs Case Record Form. The Investigator shall make available the Case Record Forms for control, when required, during one of the periodic visits pre-scheduled by PROFESSIONAL DIETETICS or other relevant personnel.

All original copies of subjectsô Case Record Forms plus one copy shall be collected from the study center by a monitor authorized by PROFESSIONAL DIETETICS and given to PROFESSIONAL DIETETICS to be filed. At the end of the study, one copy of subjectsô Case Record Forms shall be filed by the Dermatological Clinic of the Hospital ôSS. Annunziataô of Chieti.

2. Filing of collected data and record maintenance

All documents pertaining to the study (e.g. copies of subjectsô Case Record Forms, correspondence, acts/proceedings of the Ethic Committee, etc.) shall be filed in a safe place for a minimum period of 15 years following the completion or the interruption of the clinical trial and by The Sponsor for the shelf-life of the product. The filed data should be kept in the form of an electronic record, provided a backup copy exits thereof from which a copy on floppy disk or CD-ROM may be obtainable.

3. Clinical Report

The preliminary Clinical Report shall be written by the Monitor and given to the Investigator and to the Sponsor to be checked. Following the control and the endorsement by the Hospital ôSS. Annunziataô, Professional Dietetics shall write the final Clinical Report.

D. Changes to the protocol

Neither the Project Manager, nor the Investigator or the Monitor shall change the protocol without having first obtained approval from the others through a correction dated and signed by Project Manager, Investigator and Monitor. In case of emergency, the Investigator may change the Protocol to ensure the safety of the subject(s); all possible efforts should anyhow be made to inform Professional Dietetics as soon as possible. Every correction made to the protocol shall be submitted as soon as possible for approval to the relevant ethic committee.

VII. STATISTICAL ANALYSIS PLAN

STATISTICAL METHODS

A. Sample size

No statistical considerations are taken into account when calculating the sample size to be included in the study since its purpose is exploratory.

B. Subject evaluation

All observations regarding the subjects enrolled in the present study and included in the CRF shall be statistically analysed. In case of violations to the protocol, they shall be pointed out and individually discussed, and their impact on the results of the study shall also be discussed.

C. Performance analysis of medical device

The efficacy of the treatment shall be assessed comparing baseline with post-treatment. To summarize the data, descriptive statistics shall be used, as well as inferential statistics (parametric tests, Studentôs t test, and non parametric tests, Wilcoxon, depending on data distribution) and result charts.

D. Safety analysis

The occurrence on any kind of adverse events shall be described in the study clinical report discussion individual cases and, if appropriate, through their aggregate analysis. Their frequency shall be discussed in relation to the number of patients enrolled. The relevant statistical analysis shall be descriptive.

VIII. CLINICAL REPORT PLAN

A. Preliminary Clinical Report

The Investigator shall prepare a brief overview report on safety during treatment with the study product within a week from the end of the study.

B. Final Clinical Report

The final Clinical Report shall be written by Professional Dietetics in collaboration with Hospital óSS. Annunziataô. The report shall describe study objectives and methods, shall contain a thorough analysis of all evaluations and shall include a discussion on adverse events. The report shall be written following the guidelines of the European Community Good Clinical Practice.

IX. SPECIFIC SPONSORôS RESPONSIBILITIES

a) Select the Investigator taking into account the adequacy and availability of the study center and of its equipment and verify Investigatorôs qualifications and availability for the entire study period; make sure the Investigator agrees to conduct the study as per the protocol and in accordance with current G.C.P. guidelines, including the acceptance of verification procedures, audit and inspection.

b) Provide the Investigator, as a basis for the planning of the study, with all chemical, toxicological and clinical information (including previous or ongoing clinical trials) apt to justify the nature, scope and duration of the study, and inform the Investigator about any new relevant data emerging during the study.
All relevant information shall be included in the Investigator Brochure, to be supplemented and/or updated by the Sponsor whenever new important information become available.

c) Forward to the competent authorities (when required) notifications and/or requests of authorization and make sure that all necessary documents are forwarded to the Ethic Committee and that all changes, amendments or violations to the protocol are communicated if they may affect subject safety, as well as notify the Investigator and competent authorities should the study be discontinued, specifying the reasons thereof.

d) Provide the medical device under study as fully characterized, prepared in accordance with G.M.P., properly packaged and labelled.
An adequate number of samples from each batch and documentation regarding static characteristics and specifications shall be kept as reference, as to allow an independent laboratory to control the study products, for instance as regards their bioequivalence.
The quantities of the medical device under study and their batch numbers should be recorded. The Sponsor shall make sure that the Investigator, in his/her department, sets up a system for the safe handling, storage and use of the experimental products supplied.

e) Appoint suitable and properly trained monitors, verifying their being constantly trained, as well as their co-workers.

f) Appoint suitable persons and/or committees to coordinate and supervise the study, to manage and statistically process the data and write clinical reports.

g) Promptly assess, together with the Investigator, all serious adverse events and adopt all adequate measures necessary to safeguard the subjects involved in the study, reporting the adverse events to the competent authorities according to current regulations.

h) Promptly inform the Investigator about any news of immediate importance that may become available during the study and make sure the Ethic Committee is informed by the Investigator when required.

i) Make sure an exhaustive clinical report is prepared, adequate to regulatory purposes regardless of whether the study has been completed or not. Updates on safety may be requested.

j) Arrange that subjects are properly indemnified / treated in case of damages or death related to the study and guarantee to the Investigator a legal and financial coverage, except in case of indemnity requirements due to negligence and/or incapacity.

k) Agree with the Investigator on how to share the responsibilities as regards data management, statistical processing, reporting of the results and publication criteria.

X. MONITORôS RESPONSIBILITIES

a) Work in accordance with predefined Standard Operating Procedures, audit the Investigator before, during and after the study to verify protocol compliance and ensure that all data are correctly and fully recorded and reported and that informed consent is obtained and recorded from all subjects before they participate in the study.

b) Make sure that the study center has adequate space, facilities (including labs), equipment and personnel and that it is possible to enrol an adequate number of subjects for the duration of the study.

c) Make sure that the personnel assisting the Investigator during the Study has been properly informed and operates according to study details.

d) Make sure that Investigator and Sponsor may promptly communicate at any given time.

e) Compare the C.R.F. data with source data and inform the Investigator about any mistakes or omissions.

f) Verify that the storage, distribution, return and documentation regarding the experimental medical devices are safe, appropriate and complying with local regulations.

g) Assist the Investigator in any necessary notification / request procedure.

h) Assist the Investigator in reporting study data and results to the Sponsor.

i) Forward to the Sponsor and to the Steering Committee, if present, a written report after each audit (monitoring report) and, after each important telephone conversation, letters and other documents attesting the contact with Investigator (audit paper trail).

XI. INVESTIGATORôS RESPONSIBILITIES

a) Be fully aware of the properties of the medical device under study described in the Investigator Brochure.

b) Make sure to have enough time to conduct and complete the study, to have personnel and facilities (including labs) that are adequate and available for the entire study period and make sure that other studies do not divert essential personnel or facilities from the object study.

c) Acquire retrospective data on the number of subjects who would have met the inclusion criteria proposed in periods preceding the study, in order to ensure an adequate enrolment rate.

d) Forward an updated curriculum vitae and other credentials to the Sponsor and, when required, to competent authorities.
e) Together with the Sponsor, accept and sign the protocol, confirming in writing to have read and understood it, as well as to be willing to operate in accordance with the protocol and G.C.P. accepting the supervision by the monitor and the control procedures, and agree upon publication criteria with the Sponsor.

f) If appropriate, appoint a local coordinator for assistance in the conduction of the study.

g) When required and together with the Sponsor, submit notifications and/or requests of authorizations to the appointed bodies, including hospital management, and to the Ethic Committee.

h) Inform all staff involved in the study or in other aspects of the treatment of the subject.

i) Obtain subjectsô informed consent before their enrolment in the study.

j) Define a procedure regarding the medical devices under study that ensures a person in charge (e.g. a pharmacist) correctly receives the products supplied by the Sponsor; make sure the receipt of such products is recorded; that the products are properly and safely stored and handled; that the study products are administered only to subjects enrolled in the study according to the protocol; that unused amounts of product are returned to the Sponsor.
At the end of the study, it should be possible to verify the correspondence between delivery notes and documents proving product utilization and the return of unused product quantities. Eventual discrepancies should be explained. Delivery and return notes shall be signed.

k) Pay particular attention to the management of coding procedures and documentation.

l) Correctly collect, record and report data.

m) Promptly notify (attaching documentation) the Sponsor and, if appropriate, the Ethic Committee (and competent authorities when necessary) about the occurrence of serious adverse events, and undertake measures necessary to safeguard the safety of the subjects.

n) Make available all data to Sponsor, monitor and/or appointed body (when required) for verification, audit or inspection purposes.

o) When required, sign and forward to the Sponsor and authorities the data (C.R.F.s), the results and the conclusions (analyses and reports) regarding the study.
Collaborating investigators and staff in charge of the analyses (including statistics) and of the interpretation of the results should also sign the above documents.

p) Approve and sign the Clinical Report.

q) Guarantee that the information regarding the subjects and the data provided by the Sponsor are treated as confidential by all staff involved in the study.

r) Observe the following points, particularly related patientsô care:
- if appropriate, a fully functioning intensive care unit shall be promptly available in case of emergency
- from the medical point of view, the Investigator is responsible for during the study and shall ensure that adequate medical care will be provided to them also after the end of the study
- clinically significant alterations in laboratory tests or significant clinical observations should be followed for the sake of the subject also after the completion of the study
- if appropriate, the subjects involved in a study should be given a document indicating that they are participating in the study. An address and a telephone number should be provided; to which one may refer should it be necessary to intervene regarding the subject in another place
- The case record form should clearly indicate that the subject is participating in a clinical trial.

Important notice: all study materials will be supplied free of charge to the university facility and operators, according to their specifications.
No expense shall be incurred by the above facilities, or by the patient, for the present study the results of which may be freely published by the Institute in which the study takes place.
The results may be used by the Sponsor, for the purposes legally allowed.

APPENDICES

ETHIC COMMITTEE APPROVAL

ETHIC COMMITTEE FOR BIOMEDICAL RESEARCH
UNIVERSITY G. DôANNUNZIO
LOCAL HOSPITAL AUTHORITY ï CHIETI
Tel: +39 0871 3554060 Fax: +39 0871 3554061
E-mail: comitatodietetica@unich.it

On the 27th of May 2003, at 11 a.m., the Ethic Committee for Biomedical Research of the University / Local Hospital Authority (ASL) met in the office of the Head of the Faculty of Medicine and Surgery of the University óG. DôAnnunzioô in Chieti, as per letter of convocation attached to the present minutes. Attending members, absentees with leave and absentees are:

	Nominativo/Name	Pres.	Abs/leave	Abs.
I	BALLONE Enzo	x		
2	BRUNETTI Luigi	x		
3	CACIAGLI Francesco			x
4	CARABELLA Mauro	x		
5	CARNEVALE Aldo			x
6	CARULL0 Giuseppe	x		
7	CASCAVILLA Michele		x	
8	CICCARELLI Renata	x		
9	COLAGRECO Armando		x	
10	COLLEVECCHIUO Giorgio			x
11	CONSOLI Agostino			x
12	D'ALONZO Luigi			
13	DE BENEDETTO Fernando		x	
14	DELLI PIZZI Camillo			x
15	DE ROSA Pier Luigi	x		
16	Di ILI0 Carmine			
17	*DI LISA Rosina*		*x*	
18	*DI MASCIO Rocco*	*x*		
19	FARAONE Gabriele	x		
20	FLACCO Pasquale			
21	GALLENGA Pier Enrico		x	
22	MARINUCCI Riccardo	x		
23	MELENA Ennio	x		
24	MEZZETTI Andrea	x		
25	NARDONE Ginevra	x		
26	NATOLI Clara			
27	NERI Matteo			
28	PETACCIA Susanna	x		
29	ROMANO Ferdinando			
30	SALVATI Filippo			
31	SAVINO Carlo			x
32	SCIARRA Ezia			x
33	STANISCIA Tommaso			

Having verified the quorum has been reached and while waiting for the arrival of Professor Gallenga, at 11.15 a.m. Professor Ballone declares the session open.

TEXT LEFT OUT

1. Review of the protocols:

1.1 Protocol by Prof. A. Tulli ñ Study project for the evaluation of the performance on skin blemishes of the face and of the safety of an extemporaneous mixture of hyaluronic acid and amino acids as adjuvants with accessory activity (Jalu-Pro), for intradermal implantò Comm. 161;
Professor Tulli is then asked to answer the questions formulated by the Committee about the two protocols.
As for the object protocol, Professor Ballone invites the speaker to address the questions to the Investigator, and in particular:
the insurance does not seem to fully cover the potential risks related to the trial;
the Investigatorôs Brochure referring to the drug is missing, as well as the Ministry of Health approval of the drug itself;
the evaluation criteria regarding the efficacy and the safety of the treatment should be better defined;
in the protocol, also the Ospedale Maggiore is referred to as study centre. Why ?
appendix 2 is missing;
the therapeutical methods should be better defined, in particular on which area of the face the trial is conducted;
the letter to the family doctor is missing (non compiled).

The investigators answers and explains all above listed points, hands out the missing appendices and undertakes to promptly provide the letter to the family doctor.

The investigator leaves.

The protocol is approved.

TEXT LEFT OUT

Nothing remaining to be decided the meeting is closed at 3.30 p.m..

The investigators answers and explains all above listed points, hands out the missing appendices and undertakes to promptly provide the letter to the family doctor.

The investigator leaves.

The protocol is approved.

TEXT LEFT OUT

Nothing remaining to be decided the meeting is closed at 3.30 p.m..

F.to Il Coordinatore Sottocommissione B

(Prof. Enzo Ballone)

CRF

CLINICAL TRIAL

EVALUATION OF THE PERFORMANCE OF SKIN BLEMISHES OF THE FACE AND OF THE SAFETY OF AN EXTEMPORANEOUS MIXTURE OF HYALURONIC ACID AND AMINO ACIDS AS ADJUVANTS WITH ACCESSORY ACTIVITY (JALU-PRO), FOR INTRADERMAL IMPLANTS

CASE RECORD FORM

APPOINTED INVESTIGATORS

NAMES: Dott.ssa P. Toto, Dott.ssa S. Caporale, Dott. P. Amerio

ADDRESS: Clinica Dermatologica XII livello corpo B
Ospedale SS. Annunziata, 66013 Chieti

TELEPHONE: 0871.358032 FAX: 0871.551057

SPONSOR

PROFESSIONAL DIETETICS S.r.l.
ADDRESS: Via Ciro Menotti, 1/A
20122 Milano
TEL.: 02.744020 FAX 02.70008791

MONITOR

NAME: Dott.ssa G. Ingaldi

TEL.: 349.3430369

INVESTIGATORS

Project Manager: Prof. Franco Conti (Professional Dietetics)
Responsible Investigator: Prof. A. Tulli
Appointed Investigators: Dott.ssa P. Toto, Dott.ssa S. Caporale, Dott. P. Amerio
Monitor: Dott.ssa G. Ingaldi

Give a copy of this form to subjects

APPOINTED INVESTIGATORS AUTHORIZED TO SIGN THE CRF:

Prof. A. Tulli, Dott.ssa P. Toto, Dott.ssa S. Caporale, Dott. P. Amerio

STUDY PRODUCT:

EXTEMPORANEOUS MIXTURE OF HYALURONIC ACID AND AMINO ACIDS AS ADJUVANTS WITH ACCESSORY ACTIVITY (JALU-PRO), FOR INTRADERMAL IMPLANTS

STUDY PROTOCOL NO.: PDI0103

CENTRE: Clinica Dermatologica XII livello corpo B Ospedale SS. Annunziata, 66013 Chieti

RESPONSIBLE INVESTIGATOR: Prof./Dott. A. Tulli

Case Record Forms (CRFs) may be compiled and signed by the following
APPOINTED INVESTIGATORS:

Prof./Dott._____
block letters signature in full initials

Prof./Dott._____
block letters signature in full initials

Prof./Dott._____
block letters signature in full initials

RESPONSIBLE INVESTIGATOR

Prof./Dott._____
block letters signature in full initials

INSTRUCTIONS FOR THE USE OF THE CASE RECORD FORM

1. The case record form should be prepared, assembled and stapled before the beginning of the study. The dossier number should be quoted on each page.

2. The case record form should be compiled using a black-ink pen.

3. In case of mistakes, do not erase, apply correcting tape or scrape off; put a cross over the mistake and write the correct information, including investigatorôs initials and date on which the correction is made.

4. All indications given in the case record form should be clearly legible, properly filled in and respected.

INFORMATION DOCUMENT

To be read to the subject participating in the study

STUDY PURPOSE

To evaluate the activity (performance) on skin blemishes of the face as well and the safety of an extemporaneous mixture of hyaluronic acid and amino acids as adjuvants with accessory activity (JALU-PRO) for intradermal implants. Since the implant is not permanent, the corrective effect obtained shall not be definitive.

PROTOCOL SYNOPSIS

Day 0 (T0):	- Enrolment of the subject by study doctor - Clinical evaluation of deep and superficial wrinkles - Execution of a skin replica - Photograph of the trial skin area (the photograph does not permit to identify the subject) - First intradermal implant in nasolabial folds
Day seven (T7):	- Clinical examination - Second intradermal implant in nasolabial folds
Day eight (T8):	- Clinical examination - Execution of a skin replica - Photograph of the trial skin area (the photograph does not permit to identify the subject)

PROHIBITIONS / LIMITATIONS AND OBLIGATIONS

- Do not change normal habits as regards moisturizing, personal cleanliness, use of make-up
- Do not participate in other clinical trials
- Do not undergo any sun lamp treatment
- Do not undergo any other procedure of cutaneous treatment (e.g. peeling, other implants, etc.)
- Present oneself to evaluation visits wearing no make-up

FORESEEABLE RISKS

All precautions have been taken in order to minimize risks. The trial is also covered by insurance policies warranting the civil liability of the sponsor.

Depending on individual sensitivity, some local cutaneous inflammation events may occur, such as erythema, skin swelling, itching and stinging.

Give one copy of the present document to the subject

FREE CONSENT FORM

To be signed by the participant

The Investigator has proposed me to participate in a study for the evaluation of the performance on skin blemishes of the face as well as of the safety of a product for intradermal implants based on hyaluronic acid and amino acids. Since the implant is not permanent, the corrective effect will not be definitive.

The Investigator has given me an Information Document regarding the study and has told me that I am free to accept or to refuse. Even in case of acceptance, I remain free to discontinue the study at any time, without giving an explanation; I only undertake to communicate my decision to the study doctor.

I was able to ask all the questions I wanted regarding the study, to which questions the study doctor has given clear and precise answers.

I therefore give my free and informed consent to the execution of the study.

I declare I have been informed about the objectives, the conditions and the duration of the trial and about the possible occurrence of events of intolerance to the treatment. I explicitly authorize the Investigator to process my study data and to anonymously communicate them to the Monitor and to the Sponsor, in compliance with the provisions of Law 675/96 regarding Privacy, paragraphs 10, 12, 13. I shall be able to access, modify or delete such data (if I deem it necessary) at the Institute of Dermatological Sciences of the Milan University, Via Pace, 9.

For the entire study period, I undertake to immediately inform the Investigator about any change to my state of health (even if unrelated to the ongoing treatment).

I realize that the Investigator or the Sponsor cannot be held responsible for eventual consequences deriving from procedures of cutaneous treatment outside the scope and conditions of the present study.

I declare that I am of age, that I am not currently participating in another clinical trial and that I am not pregnant.

Compiled iné é é é é é ., in duplicate

_____ _____

Mr./Mrsé é é é é é é .. Received by Doctor é é é é é é é é .

Signature (signature and stamp)

Give one copy of the present form to the subject

IDENTIFICATION OF PARTICIPATING SUBJECT

CASE RECORD FORM
No_____

SUBJECT NUMBER_____

SURNAME_____

NAME_____

DATE OF BIRTH_____

ADDRESS:

Street and number_____

ZIP Code_____

Town_____

Telephone_____

Form in one copy only, to be filed by the Institute of Dermatological Sciences

IDENTIFICATION OF PARTICIPATING SUBJECT

CASE RECORD FORM
No_____

SUBJECT NUMBER_____

SURNAME_____

NAME_____

DATE OF BIRTH_____

ADDRESS:

Street and number_____

ZIP Code_____

Town_____

Telephone_____

Form in one copy only, to be filed by the Institute of Dermatological Sciences

CLINICAL AND DERMATOLOGICAL HISTORY

Is the subject now suffering, or has he/she previously been suffering, from one of the following pathologies, in severe form: **Select x Σ**

	Yes	No		Yes	No
Neurological disorders	Σ	Σ	**Hepatic disorders**	Σ	Σ
Infarction	Σ	Σ	**Hepatitis**	Σ	Σ
Epilepsy	Σ	Σ	**Renal disorders**	Σ	Σ
Cardiac disorders	Σ	Σ	**Endocrinological disorders**	Σ	Σ
Abnormal blood pressure	Σ	Σ	**Diabetes**	Σ	Σ
Vascular disorders	Σ	Σ	**Psoriasis**	Σ	Σ
Hematological disorders	Σ	Σ	**Eczema**	Σ	Σ
Pulmonary disorders	Σ	Σ	**Dermatitis seborrheica**	Σ	Σ
Emphysema	Σ	Σ	**Allergic rhinitis**	Σ	Σ
Asthma	Σ	Σ	**Acne**	Σ	Σ
Gastrointestinal disorders	Σ	Σ	**Herpes**	Σ	Σ
Food allergies	Σ	Σ	**Skin ulcers**	Σ	Σ
Drug allergies	Σ	Σ	**Tumour or cancer**	Σ	Σ
Arthritis	Σ	Σ	**Psychological disorders**	Σ	Σ
Disorders of the immune system	Σ	Σ	**Generalized dermatitis**	Σ	Σ

If **Yes**, exclude the subject from the study

Form in triplicate

CLINICAL AND DERMATOLOGICAL HISTORY

The subject is allergic or intolerant to:

	Select x Σ	
	Yes	**No**
Wool	**Σ**	**Σ**
Pollen / plants	**Σ**	**Σ**
Dust	**Σ**	**Σ**
Antibiotics	**Σ**	**Σ**
Food	**Σ**	**Σ**

Does the subject have a family history of eczema, psoriasis, or allergies ?

Select	**x**
Yes	**No**

Is the subject ectopic ?

Select	**x**
Yes	**No**

Has the subject previously suffered from allergic reactions caused by skin treatments or by the ingredients contained therein ?

Select	**x**
Yes	**No**

If Yes, the subject should be excluded from the study

Form in triplicate

CLINICAL AND DERMATOLOGICAL HISTORY

Which of the following conditions better describes the pigmentation properties of the subjectôs skin ?

Select x Σ

Always burnt, never tanned Σ
Always burnt, at times tanned Σ
At times burnt, at times tanned Σ
At times burnt, always tanned Σ
Never burnt, always tanned Σ

Which of the following better describes the subjectôs skin type ?

Select x Σ

Fair Σ
Medium Σ
Dark Σ

Other, specify: _____

Form in triplicate

DERMATOLOGICAL EVALUATION FOR STUDY ENROLLMENT (T0)

Clinical evaluation of the state of subjectôs face upon dermatological examination

Select

ERYTHEMA

Ω Ω Ω Ω Ω

0 1 2 3 4

EDEMA

Ω Ω Ω Ω Ω

0 1 2 3 4

PAPULES

Ω Ω Ω Ω Ω

0 1 2 3 4

PUSTULES

Ω Ω Ω Ω Ω

0 1 2 3 4

OTHER _____

_____

Select x Σ

Is the subject currently taking concomitant medications ? Yes Ω **No** Ω

If **Yes**, specify the details in the form regarding the use of Concomitant therapies.

Subjectôs cutaneous sensibility		**Select x** Σ	
Dry skin	Ω	Sensitive skin	Ω
Greasy skin	Ω	Medium sensitive skin	Ω
Mixed skin	Ω	Non sensitive skin	Ω

Eventual remarks _____

Form in triplicate

INCLUSION CRITERIA

	Select x	Yes	No
1.	Has the subject given his / her written informed consent?	Ω	Ω
2.	Is the subject between 35 and 60 years old?	Ω	Ω
3.	Presence of wrinkles at the level of nasolabial folds 2 ÒI Ò6	Ω	Ω
4.	Does the subject agree to undergo the two planned JALU-PRO implants and to follow the investigatorôs indications during the entire study period?	Ω	Ω
5.	Is the patient willing and able to go back to the study centre at the defined times? Ω	Ω	
6.	The subjects assures that he / she will not take any medication that might modify his / her skin characteristics during the study period.	Ω	Ω
7.	Does the subject agree to present himself / herself wearing no make-up?	Ω	Ω
8.	Does the subject agree not to participate in other studies and does he/she assure that he/she has not participated in a clinical trial in the preceding three months ?	Ω	Ω
9.	Does the subject agree to avoid to use any sun lamps during the study period ?	Ω	Ω
10.	Is the subject globally in good health according to the investigatorôs opinion ?	Ω	Ω

IF ONE OF THE ABOVE LISTED QUESTIONS HAS BEEN ANSWERED WITH ôNOô, THE SUBJECT SHOULD BE EXCLUDED

Form in triplicate

EXCLUSION CRITERIA

Select x	Yes	No	
11. Upon dermatological examination, does the subject exhibit significant clinical conditions of the skin (active eczema, dermatitis, psoriasis, dermatitis on the face area, etc.)?	Ω	Ω	
12. Does the subject exhibit one single deep wrinkle due to skin sagging?	Ω	Ω	
13. Is the subject taking anti-inflammatory drugs, antihistamines, steroids for topical or systemic use, tranquilizers, antidepressants, drugs acting on the CNS, immunosuppressants (with the exception of oral contraceptives and hormonal replacement therapy) or other drugs which might impair the study, according to the opinion of the investigator?	Ω	Ω	
14. In his/her medical past history, has the subject suffered from a significant hepatic, renal, cardiac, pulmonary, digestive, hematological, neurological, locomotorial or psychological disorder ?	Ω	Ω	
15. Does the subject have a history of drug allergies ?	Ω	Ω	
16. Does the subject suffer from insulin-dependent diabetes ?	Ω	Ω	
17. Has the subject been shown sensitive to the product to be tested or to one or more of its ingredients ?	Ω	Ω	
18. If female, is the subject pregnant, nursing or planning to become pregnant?	Ω	Ω	
19. Is the subject about to be treated for any kind of cancer, or has the subject been treated for cancer during the past 6 months ?	Ω	Ω	
20. Is the subject an Investigator, Monitor or Sponsor staff member ?	Ω	Ω	
21. Is the subject deemed by the investigator as not eligible to enter the study ?		Ω	Ω

IF ONE OF THE ABOVE LISTED QUESTIONS HAS BEEN ANSWERED WITH ôYESô, THE SUBJECT SHOULD BE EXCLUDED

	Select x	
Is the subject eligible to enter the study ?	**Yes**	**No**

Form in triplicate

DERMATOLOGICAL EVALUATION AT BASELINE (T0)

The evaluation of deep and superficial wrinkles should be carried out at the level of nasolabial folds

The evaluation should always be carried out on the same side of the face: the left side, lighted by a reading lamp with a 45° incident light with respect to the face of the subject being examined (see scheme, attachment 1).

During the evaluation, the subject should not contract his/her face and should stare.

1) Wrinklesô degree at the level of nasolabial folds:
Evaluation of different wrinkle marks on a scale from 0 to 7

No wrinkles	Ω	0	Exclusion
Very light wrinkles	Ω	1	Exclusion
Light wrinkles	Ω	2	
Quite evident	Ω	3	
Evident	Ω	4	
Very evident	Ω	5	
Marked	Ω	6	
Very marked	Ω	7	

2) Evaluation of skin tone:

Very poor	Ω	0
Poor	Ω	1
Medium	Ω	2
Good	Ω	3
Very good	Ω	4

Form in triplicate

EXECUTI ON OF THE IMPLANT (T0)

DATE:_____

Skin replica

NASOLABIAL FOLD (chosen side)

Side **Replica no.:_ _ _**

Photographic documentation

NASOLABIAL FOLD (chosen side)

Side **Replica no.:_ _ _**

QUANTITY OF IMPLANTED MATERIAL (ML)

NASOLABIAL FOLD

LEFT:_____ RIGHT:_____

Evaluation of cutaneous resistance to trauma:

Very poor	Ω	0
Poor	Ω	1
Medium	Ω	2
Good	Ω	3
Very good	Ω	4

Eventual remarks

Form in triplicate

VISIT ON DAY SEVEN (T7)

FOLLOW-UP QUESTIONNAIRE

Select x

Has the subject exhibited any Adverse Event since the previous visit? **Yes** Σ **No** Ω

If **Yes**, specify the details in the Adverse Event form.

Select x

Has the subject taken any concomitant medication since the previous visit? **Yes** Σ **No** Ω

If **Yes**, specify the details in the Concomitant Pharmacological Treatments form and fill in an Adverse Event form (when appropriate).

Select x

Does the subject still meet the study inclusion criteria ? **Yes** Σ **No** Ω

If **No**, the subject should be discontinued from the study and a Study Termination form should be filled in.

Select x

Is the subject eligible to continue the study ? **Yes** Σ **No** Ω

If **No**, fill in the Study Termination form.

Form in triplicate

VISIT ON DAY SEVEN (T7)

Clinical evaluation of the state of subjectôs face upon dermatological examination

Select
ERYTHEMA

ΩΩΩΩΩ

0 1 2 3 4

EDEMA

ΩΩΩΩΩ

0 1 2 3 4

PAPULES

ΩΩΩΩΩ

0 1 2 3 4

PUSTULES

ΩΩΩΩΩ

0 1 2 3 4

OTHER

Evaluation of cutaneous resistance to trauma:

Very poor	Ω	0
Poor	Ω	1
Medium	Ω	2
Good	Ω	3
Very good	Ω	4

Form in triplicate

VISIT ON DAY SEVEN (T7)

EVALUATION OF WRINKLES

The evaluation of deep and superficial wrinkles should be carried out at the level of nasolabial folds

The evaluation should always be carried out on the same side of the face: the left side, lighted by a reading lamp with a 45° incident light with respect to the face of the subject being examined (see scheme, attachment 1).

During the evaluation, the subject should not contract his/her face and should stare.

1) **Wrinklesô degree at the level of nasolabial folds:**
Evaluation of different wrinkle marks on a scale from 0 to 7
(see scores in Attachment)

No wrinkles	Ω	0
Very light wrinkles	Ω	1
Light wrinkles	Ω	2
Quite evident	Ω	3
Evident	Ω	4
Very evident	Ω	5
Marked	Ω	6
Very marked	Ω	7

2) **Evaluation of skin tone:**

Very poor	Ω	0
Poor	Ω	1
Medium	Ω	2
Good	Ω	3
Very good	Ω	4

3) **Global efficacy evaluation:**

Very poor	Ω
Poor	Ω
Medium	Ω
Good	Ω
Very good	Ω

4) **Events that may have affected the results**

_____
_____
_____

Form in triplicate

EXECUTION OF THE IMPLANT (T7)

DATE:_____

QUANTITY OF IMPLANTED MATERIAL (ML)

NASOLABIAL FOLD

LEFT:_____ RIGHT:_____

Evaluation of cutaneous resistance to trauma:

Very poor	Ω	0
Poor	Ω	1
Medium	Ω	2
Good	Ω	3
Very good	Ω	4

Eventual remarks

Form in triplicate

VISIT ON DAY EIGHT (T8)

FOLLOW-UP QUESTIONNAIRE

Select x

Has the subject exhibited any Adverse Event since the previous visit ? **Yes** Σ **No** Ω

If **Yes**, specify the details in the Adverse Event form.

Select x

Has the subject taken any concomitant medication since the previous visit ? **Yes** Σ **No** Ω

If **Yes**, specify the details in the Concomitant Pharmacological Treatments report and fill in an Adverse Event form (when appropriate).

Select x

Does the subject still meet the study inclusion criteria ? **Yes** Σ **No** Ω

If **No**, the subject should be discontinued from the study and a Study Termination form should be filled in.

Select x

Is the subject eligible to continue the study ? **Yes** Σ **No** Ω

If **No**, fill in the Study Termination form.

Form in triplicate

VISIT ON DAY EIGHT (T8)

Clinical evaluation of the state of subjectôs face upon dermatological examination

Select
ERYTHEMA
ΩΩΩΩΩ

0 1 2 3 4
EDEMA

0 1 2 3 4
PAPULES

0 1 2 3 4
PUSTULES

0 1 2 3 4

OTHER

Form in triplicate

VISIT ON DAY EIGHT (T8)

EVALUATION OF WRINKLES

The evaluation of deep and superficial wrinkles should be carried out at the level of nasolabial folds

The evaluation should always be carried out on the same side of the face: the left side, lighted by a reading lamp with a 45° incident light with respect to the face of the subject being examined (see scheme, attachment 1).

During the evaluation, the subject should not contract his/her face and should stare.

1) Wrinklesô degree at the level of nasolabial folds:
Evaluation of different wrinkle marks on a scale from 0 to 7
(see scores in Attachment)

No wrinkles Ω 0

	Very light wrinkles	Ω	1
	Light wrinkles	Ω	2
	Quite evident	Ω	3
	Evident	Ω	4
	Very evident	Ω	5
	Marked	Ω	6
	Very marked	Ω	7

2) **Evaluation of skin tone:**

Very poor	Ω	0
Poor	Ω	1
Medium	Ω	2
Good	Ω	3
Very good	Ω	4

3) **Global efficacy evaluation:**

Very poor	Ω
Poor	Ω
Medium	Ω
Good	Ω
Very good	Ω

4) **Events that may have affected the results**

_____
_____
_____ _____

Form in triplicate

EXECUTION OF PHOTOGRAPH AND REPLICA (T8)

DATE:_____

Skin replica

NASOLABIAL FOLD (chosen side)

Side **Replica no.:**_ _ _

Photographic documentation

NASOLABIAL FOLD (chosen side)

Side **Replica no.:_ _ _**

Eventual remarks

Form in triplicate

END OF STUDY (T8)

Which is the subject status as regards the study ? **Select x**

Σ **Study completion**

Σ **Study discontinued**

If the subject has been **discontinued**, specify date of last implant:_____

If the subject has been **discontinued**, select with x only the MAIN reason:

Ω **Adverse events** (fill in the relevant Adverse Event form)

Σ **Non-compliance with protocol**

Σ **Withdrawal of Consent, with no Adverse events**

Σ **Lost to Follow-up**

Σ **Discontinuation required by Investigator**

Σ **Other, specify _____**

Please provide any other additional information regarding the reason why the subject has not completed the study:

Form in triplicate

ADVERSE EVENT REPORT

Has an adverse event occurred or is an adverse event reported in the previous visit still ongoing ?

Φ NO Φ YES - If yes, please specify:

DIAGNOSIS: (if impossible to give a diagnosis, indicate signs and/or symptoms)

Date of onset (or estimate):_____ Put a cross over Φ in case of serious adverse event

Severity:		Frequency:		Relationship to:	
Φ	Mild	Φ	Single episode	Φ	Study drug
Ω	Moderate	Σ	Intermittent	Φ	Basal clinical conditions
Σ	Severe	Φ	Persistent	Ω	Concomitant medications
		Σ	Recurrent	Φ	Other_____

Ω Resolved Φ Unresolved at visit Ω Severe or permanent disability
Σ Unknown
Φ Death Ω Date of death_____ Autopsy: Φ Yes Ω No

ACTIONS UNDERTAKEN:

In relation with Study drug:

Σ None Φ Study drug discontinued

Ω Study drug reduced: New dose:_____ For how long:_____

Σ Study drug interrupted: For how long:_____

Φ Resolution Ω No resolution

In relation with the event:

Σ Medications (specify in Concomitant Medications form)

Φ Concomitant medications interrupted (specify in Concomitant Medications form)

Ω Hospitalization, new or prolonged

INVESTIGATORôS ASSESSMENT OF THE RELATIONSHIP BETWEEN STUDY PRODUCT AND ADVERSE EVENT

INVESTIGATORôS STATEMENT

I have examined the data contained in this Case Record Form.

At the best of my knowledge, the data are both accurate and complete.

I therefore allow their release to the Sponsor.

Signature _____

HELSINKI DECLARATION

Università "G. d'Annunzio" – Facoltà di Medicina e Chirurgia – Dipartimento di Oncologia e Neuroscienze
CLINICA DERMATOLOGICA
SCUOLA DI SPECIALIZZAZIONE IN DERMATOLOGIA E VENEREOLOGIA
(Direttore (Prof. A.Tulli)
Policlinico "SS. Annunziata" - Via dei Vestini, 66013 Chieti
☎ +39-0871358032/8 fax +39-0871 551057 dermo@unich.it www.unich.it/apre/clinica.htm

The trial will be conducted in accordance with the Helsinki Declaration (1964) and subsequent modifications.

The Investigator and the Sponsor are further responsible for ensuring that the trial is conducted in accordance with the guidelines for Good Clinical Practice (Ministerial Decree 15.07.97 and subsequent modifications).

Yours faithfully
Prof. A. Tulli

PRODUCT CERTIFICATE OF ANALYSIS

monte research
PHARMACEUTICAL DEVELOPMENT SERVICE

CERTIFICATE OF ANALYSIS N° 020717/4

PRODUCT:	JALU-PRO® INTRA-ARTICULAR INJECTIONS		
	BATCH N°:	MANUFACT. DATE:	EXPIRY DATE:
LYOPHILISED POWDER	112/02	03/2002	03/2005
SODIUM HYALURONATE SOLUTION	P02/02	07/2002	07/2005

TESTS ON *Lyophilised powder*	RESULTS	SPECIFICATION
APPEARANCE	COMPLIES	HOMOGENEOUS WHITE POWDER
AVERAGE WEIGHT	99.3 mg	100 mg ± 5%
LOD	0.1%	MEETS THE EP REQUIREMENT
Assay of: - Glycine - L-Proline - Lysine monohydrochloride - L-Leucine	 100.0% 97.7% 99.3% 101.8%	95.0 – 105.0% (OF DECLARED CONTENT)
STERILITY (EP)	COMPLIES	MEETS THE EP REQUIREMENT
BACTERIAL ENDOTOXINS (EP)	COMPLIES	MEETS THE EP REQUIREMENT

monte research
PHARMACEUTICAL DEVELOPMENT SERVICE

(CERTIFICATE OF ANALYSIS N° 020717/4)

TESTS ON *SODIUM HYALURONATE SOLUTION*	RESULTS	SPECIFICATION
APPEARANCE	COMPLIES	HOMOGENEOUS TRANSPARENT COLOURLESS SOLUTION
FILLING VOLUME	3.1 ml	3.0 – 3.2 ml /VIAL
MINIMUM FILL	COMPLIES	MEETS THE USP REQUIREMENT
IDENTIFICATION TEST FOR: -SODIUM HYALURONATE	POSITIVE	POSITIVE
ASSAY (%) OF: -SODIUM HYALURONATE	99.8%	95.0 – 105.0% (OF DECLARED CONTENT)
STERILITY	COMPLIES	MEETS THE EP REQUIREMENT
BACTERIAL ENDOTOXINS	COMPLIES	MEETS THE EP REQUIREMENT

TESTS ON *RECONSTITUTED SOLUTION*	RESULTS	SPECIFICATION
APPEARANCE	COMPLIES	HOMOGENEOUS TRANSPARENT COLOURLESS SOLUTION
pH	6.4	5.5 – 7.5

STATUS: APPROVED ☑ REJECTED ☐ PROVISIONAL ☐

DATE	JULY. 17TH 2002	ANALYST	Nicolola	QC RESPONSIBLE	

STUDY OBJECTIVE

While the use of biomaterials for the correction of skin blemishes is very common, the concepts of bio-revitalization and bio-stimulation with synthetic materials have only recently become known.

While representing the safest option, autologous tissues such as fat do however require more invasive applications; in that respect, the use of biomaterials of animal or synthetic origin is significantly advantageous. Among these, hyaluronic acid is the key molecule for cutaneous bio-stimulation.

Hyaluronic acid is a glycoaminoglycan, common to all animal species, which consists of disaccharide units containing alternating d-glucoronic acid and N-acetyl-d-glucosammine.

Glycoaminoglycans are present in great numbers in fetal skin, numbers which progressively decrease in adults. They contribute to the forming of part of the extracellular matrix of the dermis. Hyaluronic acid plays a fundamental role in providing turgor and compactness to the skin since, binding to collagen, fibronectin and proteoglycans, it forms macromolecular complexes which provide a sort of support scaffold. The hyaluronic acid molecule further exhibits high hygroscopic power, thus ensuring higher skin hydration.

The lack of antigenicity of this substance and, consequently, the very small risk of allergic reactions make it a widely usable implant material.

The degradation of hyaluronic acid is isovolumic; the substance thus maintains most of its initial volume despite the degradation process. In addition to using hyaluronic acid to physically fill a blemish, its capacity to stimulate fibroblast proliferation thus promoting the synthesis of new collagen and other components of the extracellular matrix, as well as its action as scavenger of free radicals, have been exploited.

Natural, non chemically modified, hyaluronic acid is able to counteract the ageing of the skin, inducing an effect of fibroblast stimulation which leads to the synthesis of new collagen and other components of the dermis. This action has been defined as "Long Lasting Bio-revitalization". Its use thus allows an immediate corrective action related to the volume and the viscous-elastic characteristics of the product, as well as a delayed effect related to fibroblast stimulation.

A number of experimental evidences suggest that the bio-revitalizing action is realized through the role played by hyaluronic acid in the modulation of the intracellular fibroblast gap junctions, thus promoting the assembling and the organization of collagen fibres[1,2].

Although the role played by hyaluronic acid in skin bio-stimulation is proven by a number of both clinical and experimental evidences, scientific literature data suggest how the bioavailability of collagen-forming amino acids (Glycine, L-Proline, L-Lysine) may induce the synthesis of new fibres[3, 4, 5].

The present study aims to evaluate the performance and the safety related to the intradermal use of an extemporaneous mixture of hyaluronic acid and amino acids as adjuvants to attenuate skin blemishes of the face, using the product Jalu-Pro.

The efficacy will be evaluated through a profilometric examination of the skin surface.

The morphological examination of the skin through techniques replicating the skin surface has recently been applied to dermatology.

Such non invasive technique has its main advantage in allowing a detailed examination of the skin surface for the study of processes that are physiological to skin ageing and pathological such as inflammation, as well as in allowing to monitor the effects of drugs and topical products.

For such a reason, the method also finds valid application in cosmetology.

The cosmetic industry has employed such a technique to document the effects of cosmetic products on the skin surface and these evaluation methods are still essential to document the efficacy of products introduced in the market.

Morphological studies with image analysis allow a descriptive analysis of the skin surface. Until the past decade, replicas for optical microscopy were taken with plastic materials greatly affected by limitations related to the preparation of the skin to be replicated, which induced modifications and adulterations on the structure of the surface to be analysed.

The materials currently most widely used for morphological studies in the biomedical field are the impression materials used in odontology and silicone plastic materials which allow a detailed reproduction of the superficial characteristics of the skin.

Thanks to its penetration capacity in the incisions of the corneous surface, a quick setting silicone resin allows to obtain a replica on which lines are reproduced forming a characteristic pattern for human skin, which varies depending on the skin area considered, the age of the patient and the sex.

Optical profilometry of the skin replicas is a valid, non invasive study method for the efficacy evaluation of topical products and filling materials adjuvant in the treatment of skin ageing. Optical profilometry, while not being able to provide a direct reference numerical value, gives the possibility to detect changes in the depth and width of skin lines on a specific skin area.

It is further possible to assign reference scores according to an arbitrary scale for the parameters examined.

As regards photo-ageing, it is obvious that the parameters object of the study are represented by skin wrinkles. In accordance with Monti (Caputo R., Monti M., Manuale di Dermocosmetologia medica, Raffaello Cortina Editore, Milano 1996 (Handbook of medical dermo-cosmetology, published by Raffaello Cortina, Milan, 1996) these may be classified as:

- Expression lines or mimetic muscle lines or linear wrinkle

- Sagging creases
- Cutaneous texture
- Lines due to sleeping postures

A score may be assigned to each of these identification types, varying from 0 to 6, which progressively and increasingly indicates the kind of wrinkle present:

0 : absent

1 : light

4: moderate

6 : marked

For the *in vivo* analysis and to assign such score, it is fundamental that the analysis be conducted by investigators trained to the purpose and that the measurements be always made by the same operators. Should the Investigator, at any time during the study, notice a lack of safety related to the products used in the study (e.g. in case of a number of severe adverse events), the study shall be discontinued.

REFERENCES

[1] Moyer KE, Ehrlich HP. Modulation of human fibroblast gap junction intercellular communication by hyaluronan. J Cell Physiol. 2003 Jul;196(1):165-70.

[2] Wang TW, Huang YC, Sun JS, Lin FH. Organotypic keratinocyte-fibroblast cocultures on a bilayr gelating scaffold as a model of skin equivalent. Biomed Sci Instrum. 2003;39:523-8.

[3] Pearson D, Hamby D, Gehlsen G, Hazen N, Roush M and Harris T. Human Performance Laboratory, Ball State University, Muncie, IN. The effect og gelatin supplementation on anterior knee pain in collegiate-level athletes. 2000;14:368.

[4] Vinciguerra P, Camesasca FI, Ponzin D. Use of amino acids in refractive surgery. Journal of Refractive Surgery 2002; 18 (suppl): S374-S377.

[5] Vinciguerra P, Torres Munoz MI, Camesasca FI.The role of amino acids in corneal stromal healing: a method for evaluting cellular density and extracellular matrix distribution. Journal of Refractive Surgery 2003; 19 (suppl).

MATERIALS AND METHODS

We carried out the clinical evaluation of the patients and the infiltration therapy, as per attached protocol, in our dermatological clinic.

We entrusted the biometric study to Evic Italia.

We carried out a study on 30 participating subjects (see attached table), of female sex, aged 39 ï 59, in good health, with medium / moderate rhytidosis. Replicas of the nasolabial fold skin area of each volunteer were taken with the silicone resin Silfo (Flexico); the replicas were examined with optical profilometry using a VIDEOCAP instrument, magnification 20x, for the evaluation and the study of the depth of the skin wrinkles treated with infiltration materials based on a mixture of hyaluronic acid and amino acids at times T0 and T7 as per the protocol.

A skin replica at the level of the nasolabial fold was taken for each group upon inclusion (T0) and on the day following the second and final treatment (T8), and an optical profilometry analysis was carried out with a VIDEOCAP instrument, magnification 20x, to evaluate the changes visible on the skin after the injection treatment.

Give the area of application, wrinkles due to cutaneous texture and expression lines were taken into consideration, both present on the surface of the replica taken at the level of the nasolabial fold.

DEMOGRAPHICS

No. **Subject initials** **Sex** **Date of birth**

DATI DEMOGRAFICI			
N.	**Iniziali sog.**	**Sesso**	**Data di nascita**
1	T.M	F	12/08/1950
2	M.M.	F	09/06/1959
3	F.B.	F	19/09/1964
4	R.L.	F	26/11/1950
5	S.R.	F	24/04/1960
6	C.D.C	F	19/11/1948
7	A.B.	F	10/11/1956
8	A.P.	F	24/03/1945
9	M.G	F	17/04/1952
10	F.D.M	F	11/02/1957
11	D.M.	F	12/02/1960
12	G.G	F	11/02/1962
13	L.D.B.	F	08/01/1957
14	S.A.	F	18/04/1950
15	M.V.A	F	16/09/1946
16	G.E.	F	19/11/1948
17	R.T.	F	16/06/1945
18	M.S	F	02/01/1952
19	G.S	F	10/10/1950
20	C.D.F.	F	01/01/1958
21	L.B	F	03/10/1950
22	S.D.F.	F	03/08/1963
23	R.M.	F	13/06/1938
24	S.S.	F	01/02/1948
25	A.G.	F	22/11/1947
26	F.G.	F	17/08/1943
27	C.M.	F	14/03/1954
28	C.P.	F	20/07/1950
29	P.C.	F	09/11/1958
30	R.D.A.	F	25/11/1950

RESULTS AND CONCLUSIONS

The total mean scores at T8 has shown a significant reduction versus the scores given to the same parameters at T0.

The mean score at T0 was 4.50 for cutaneous texture and 4.33 for expression lines, while at T8 a reduction of the average of 2.27 and 2.17 was recorded.

A reduction equal to 50% of the initial score both for cutaneous texture and expression lines was noticed following analysis of the mean percent variations.

The variations noticed in the global mean scores also correspond to the decrease in the parameters seen in all subjects examined in the study.

The results obtained at the end of the study have highlighted the fact that the product under evaluation has induced a reduction in the wrinkle degree at the level of nasolabial folds for both parameters analysed : expression lines and cutaneous texture.

Such data are no doubt significant as one can easily see by merely looking at the attached graphs and photographs.

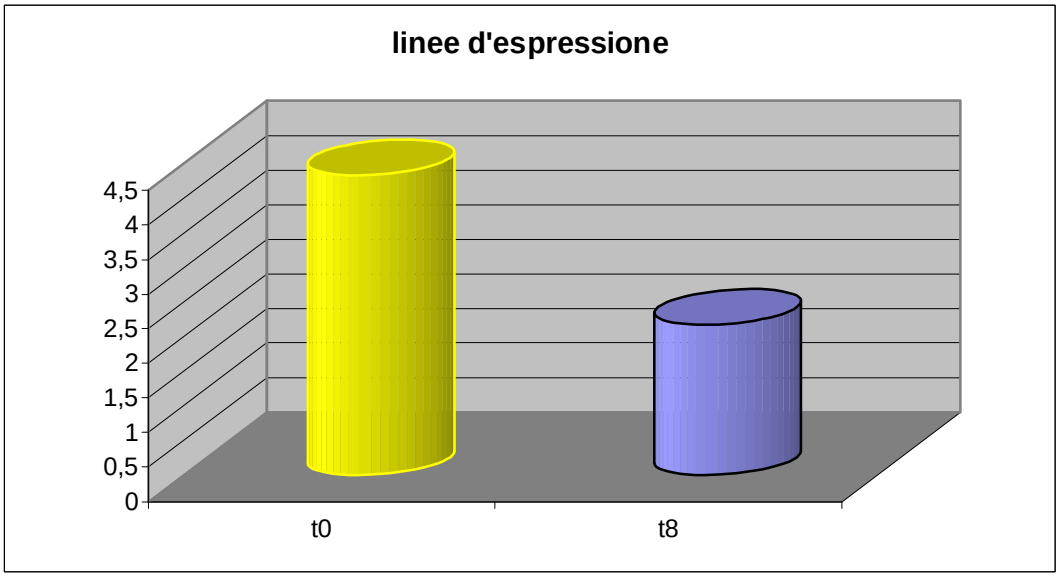
TABLE OF INDIVIDUAL RESULTS OF OPTICAL PROFILOMETRY EXPRESSION LINES

VOL./VOLUNTEER	**T0**	**T8**
1	5	2
2	6	2
3	4	2
4	6	2
5	4	2
6	5	2
7	5	2
8	4	2
9	4	2
10	4	2
11	3	2
12	3	1
13	2	1
14	4	2
15	4	3
16	6	4
17	3	2
18	5	2
19	5	2
20	4	1
21	5	3
22	4	3
23	4	3
24	5	3
25	5	3
26	5	2
27	4	1
28	4	3
29	4	2
30	4	2
Media/Mean	**4,33**	**2,17**

According to and evaluation scale from 0 to 6 (0 = absent, 2 = light, 4 = moderate, 6 = marked)

Percent Variation
T8-T0
-50,00%

Expression lines



t0	t8
4,33	2,17

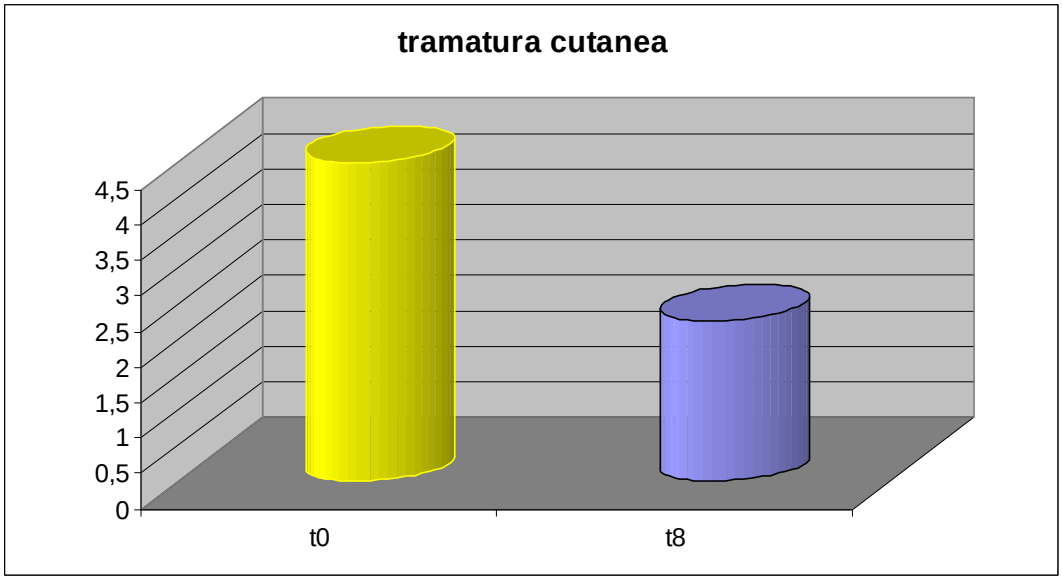
TABLE OF INDIVIDUAL RESULTS OF OPTICAL PROFILOMETRY
CUTANEOUS TEXTURE

VOL./Volunteer	**T0**	**T8**
1	5	2
2	6	2
3	4	2
4	4	2
5	6	2
6	5	3
7	4	2
8	6	3
9	4	2
10	4	2
11	4	2
12	3	1
13	2	1
14	4	2
15	5	3
16	5	4
17	4	2
18	4	2
19	4	2
20	4	2
21	5	3
22	4	3
23	5	2
24	5	3
25	5	2
26	6	3
27	5	1
28	5	4
29	4	2
30	4	2
Media/Mean	**4,50**	**2,27**

According to and evaluation scale from 0 to 6 (0 = absent, 2 = light, 4 = moderate, 6 = marked)

Percent Variation
T8-T0
-40,63%

Cutaneous texture



t0	t8
4,5	2,27

1 Volunteer T.M. Age 54 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	**5**	**2**
Expression line	**5**	**2**

2 Volunteer M.M. Age 45 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	**6**	**2**
Expression line	**6**	**2**

3 Volunteer F.B. Age 40 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	**4**	**2**
Expression line	**4**	**2**

4 Volunteer R.L. Age 54 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	**4**	**2**
Expression line	**6**	**2**

5 Volunteer S.R. Age 44 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	**6**	**2**
Expression line	**4**	**2**

6 Volunteer C.D. Age 56 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	5	3
Expression line	5	2

7 Volunteer A.B. Age 48 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	4	2
Expression line	5	2

8 Volunteer A.P. Age 59 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	6	3
Expression line	4	2

9 Volunteer M.G. Age 52 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	4	2
Expression line	4	2

10 Volunteer F.D. Age 47 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	4	2
Expression line	4	2

11 Volunteer D.M. Age 44 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	**4**	**2**
Expression line	**3**	**2**

12 Volunteer G.G. Age 42 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	**3**	**1**
Expression line	**3**	**1**

13 Volunteer L.D. Age 47 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	**2**	**1**
Expression line	**2**	**1**

14 Volunteer S.A. Age 54 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	**4**	**2**
Expression line	**4**	**2**

15 Volunteer R.L. Age 54 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	**5**	**3**
Expression line	**4**	**3**

16 Volunteer G.E. Age 56 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	**5**	**4**
Expression line	**6**	**4**

17 Volunteer R.T. Age 59 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	**4**	**2**
Expression line	**3**	**2**

18 Volunteer M.S. Age 52 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	**4**	**2**
Expression line	**5**	**2**

19 Volunteer G.S. Age 54 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	**4**	**2**
Expression line	**5**	**2**

20 Volunteer C.D. Age 46 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	**4**	**2**
Expression line	**4**	**1**

21 Volunteer L.B. Age 54 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	**5**	**3**
Expression line	**5**	**3**

22 Volunteer S.D. Age 39 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	**4**	**3**
Expression line	**4**	**3**

23 Volunteer R.M. Age 56 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	**5**	**2**
Expression line	**4**	**3**

24 Volunteer S.S. Age 56 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	**5**	**3**
Expression line	**5**	**3**

25 Volunteer A.G. Age 57 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	**5**	**2**
Expression line	**5**	**3**

26 Volunteer F.G. Age 59 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	**6**	**3**
Expression line	**5**	**2**

27 Volunteer C.M. Age 50 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	**5**	**1**
Expression line	**4**	**1**

28 Volunteer C.P. Age 54 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	**5**	**4**
Expression line	**4**	**3**

29 Volunteer P.C. Age 46 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	**4**	**2**
Expression line	**4**	**2**

30 Volunteer R.D. Age 54 NASOLABIAL FOLD

	T0	T8
Cutaneous texture	**4**	**2**
Expression line	**4**	**2**

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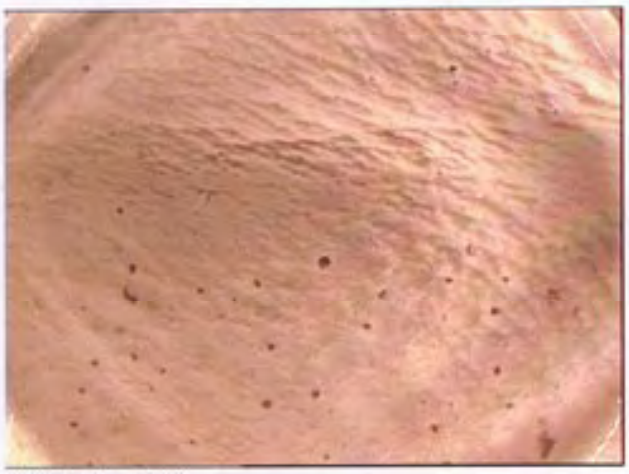
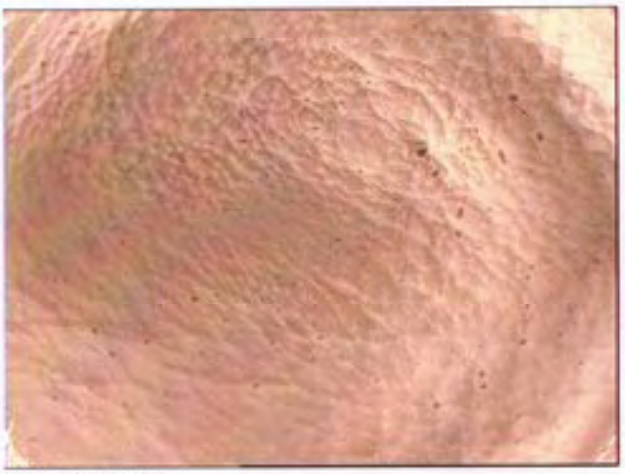


29/01/2004 - tulli 01



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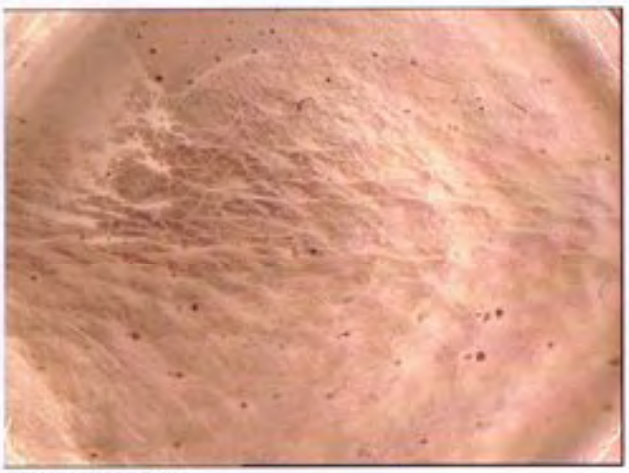

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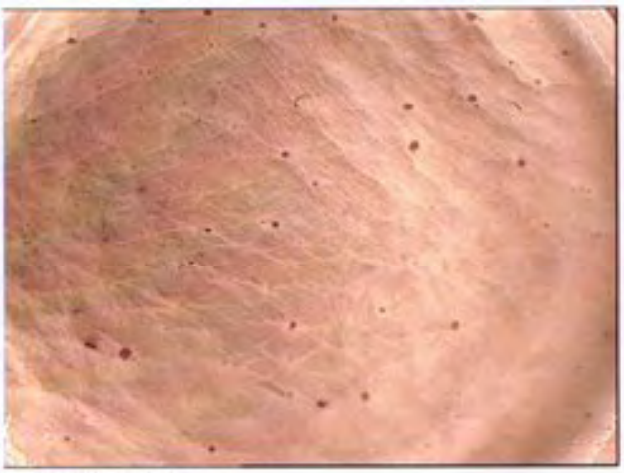

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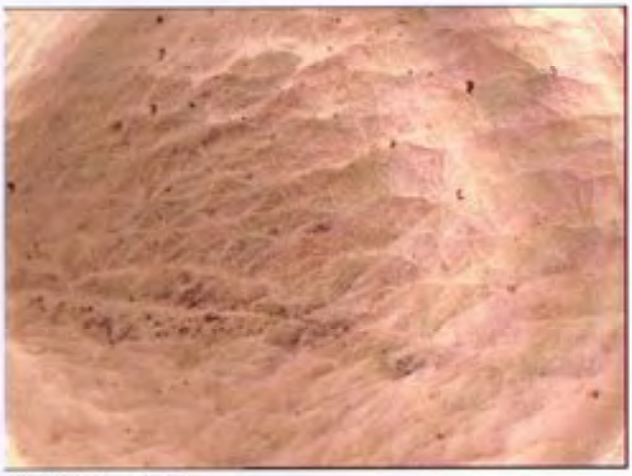

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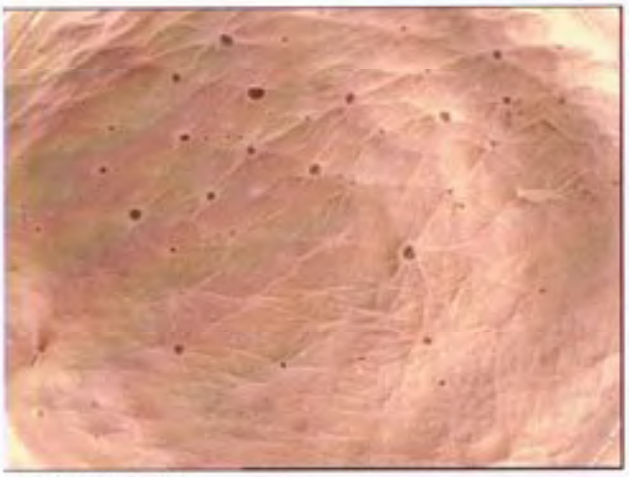

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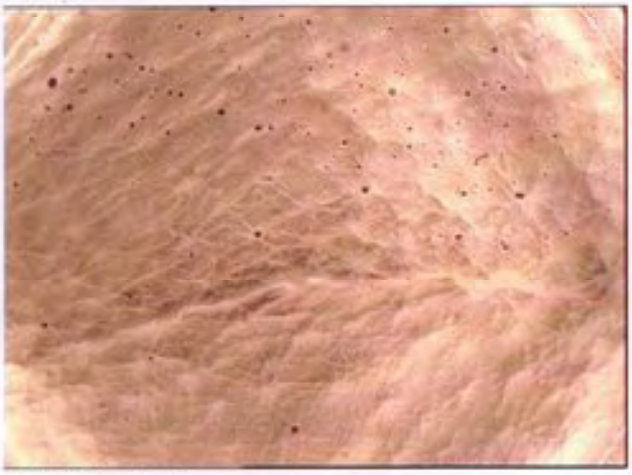

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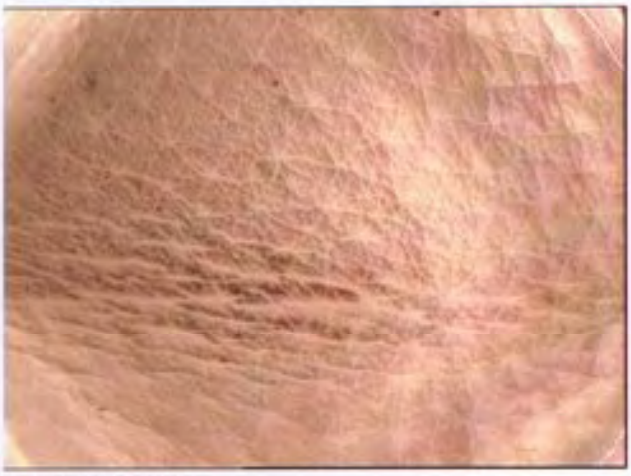

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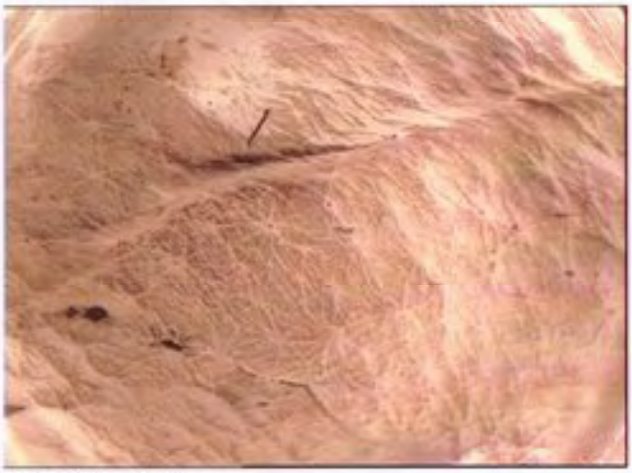

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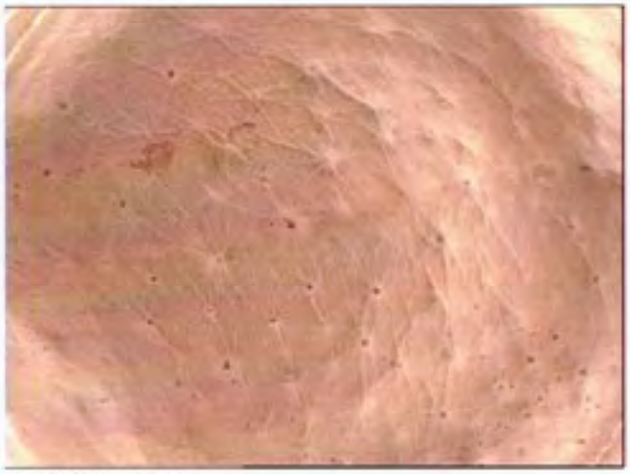

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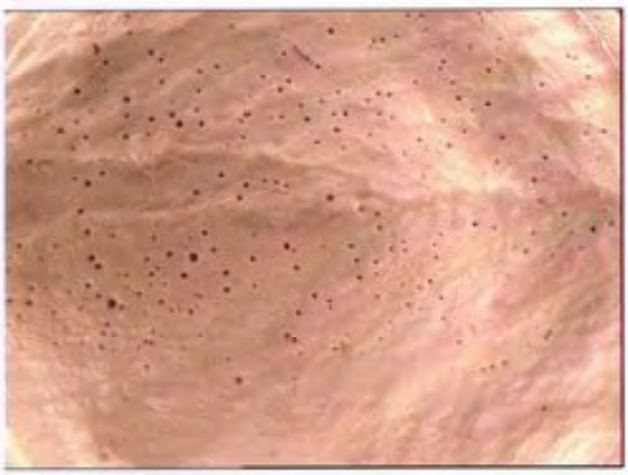

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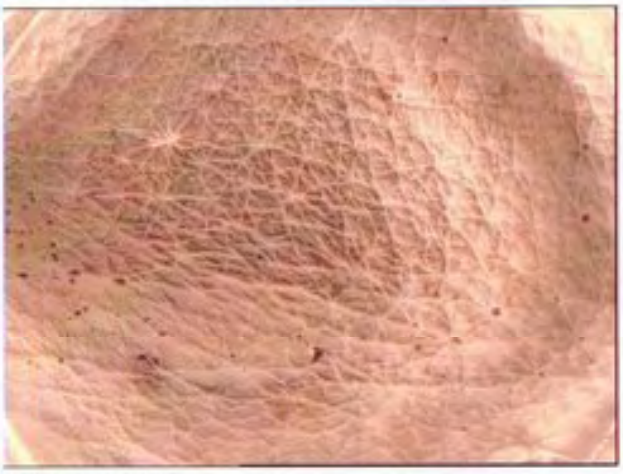

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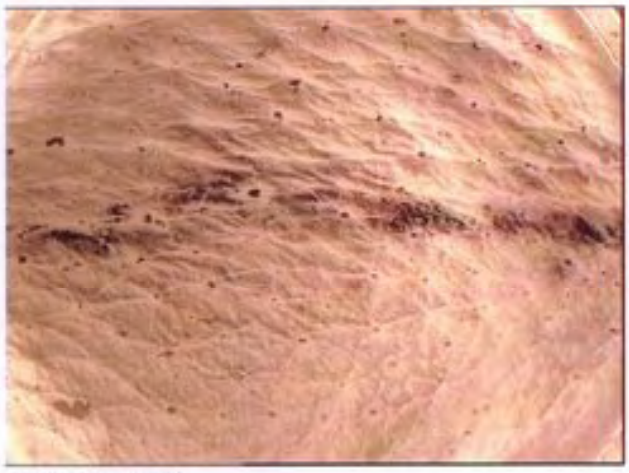

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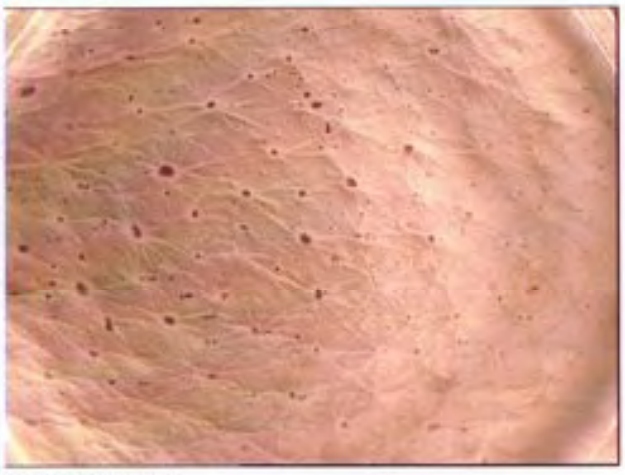

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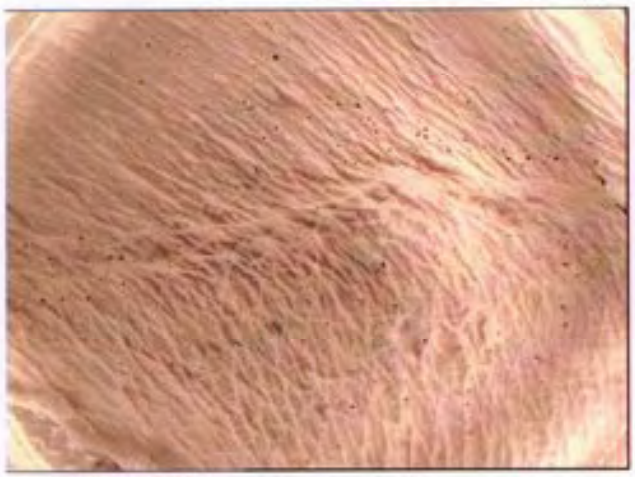

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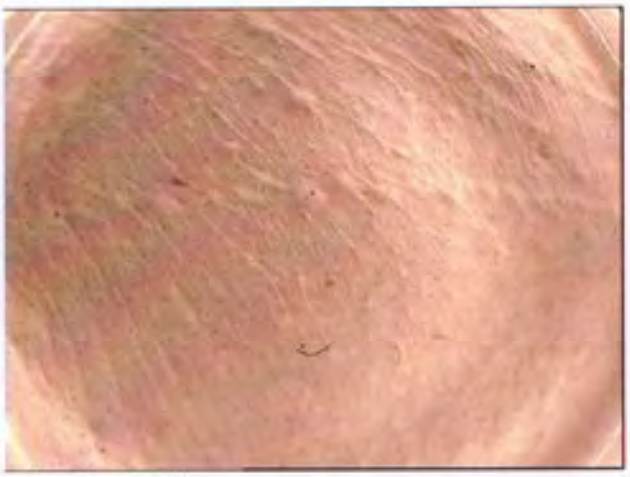

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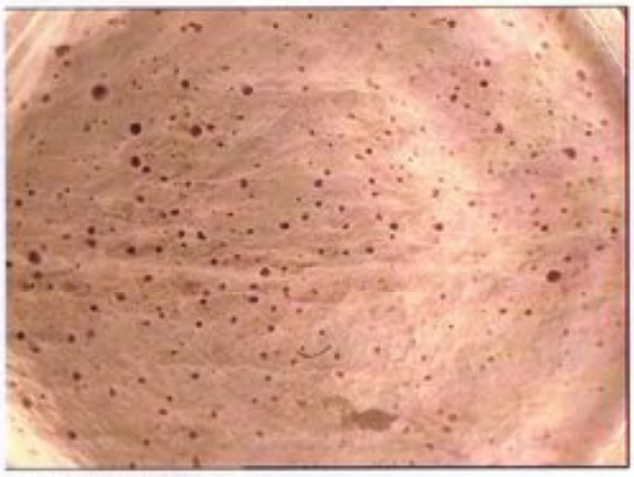

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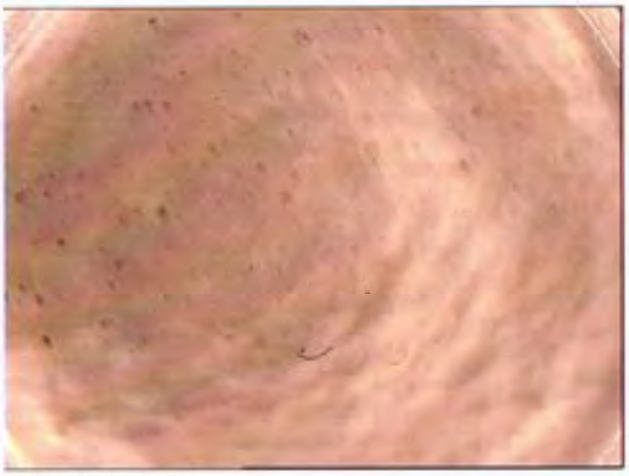

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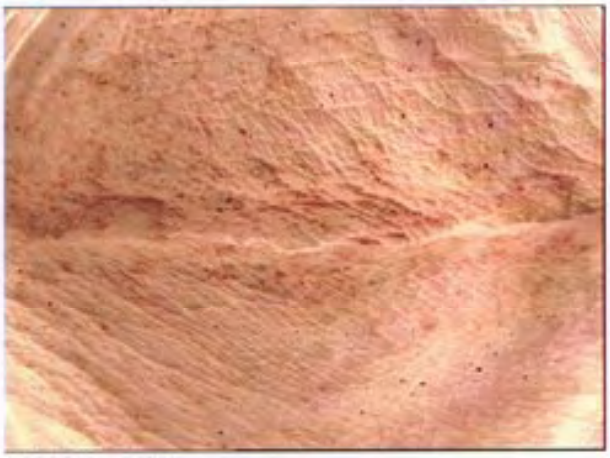

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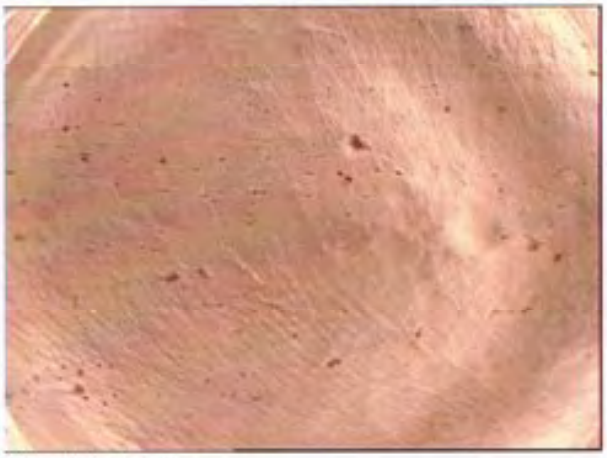

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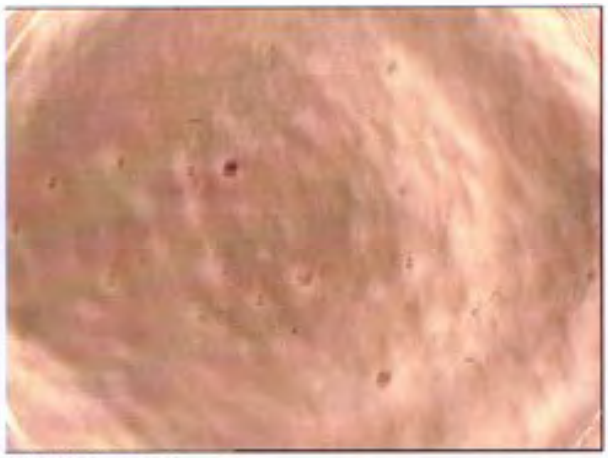

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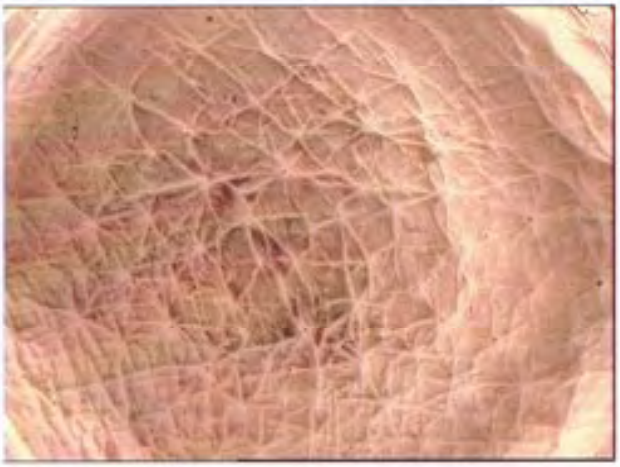

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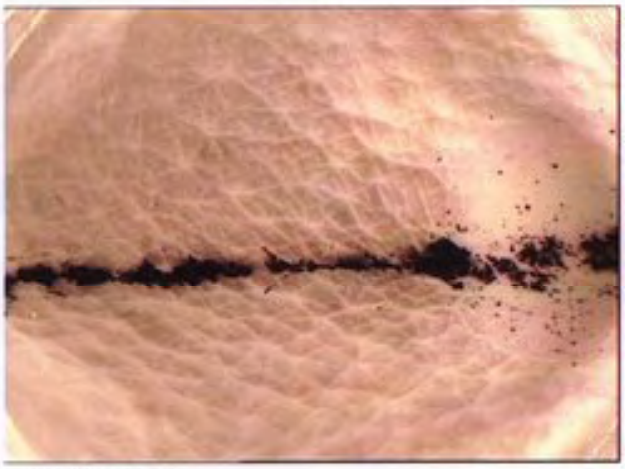

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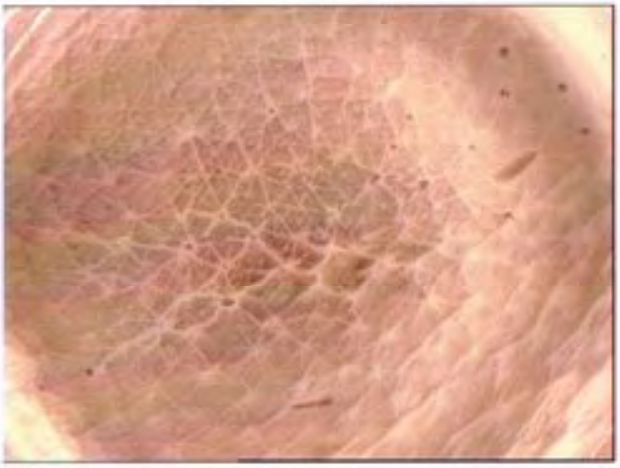

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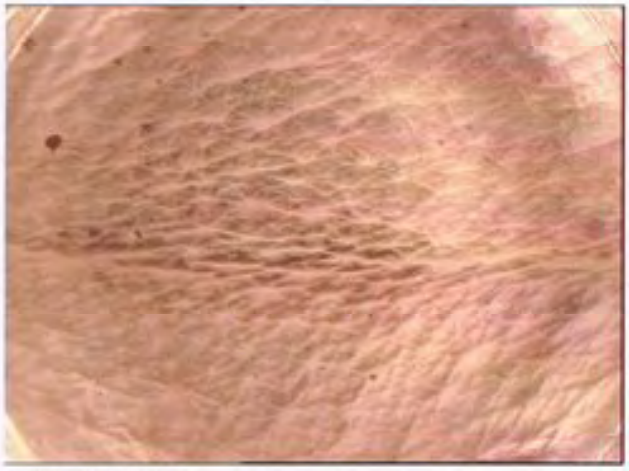

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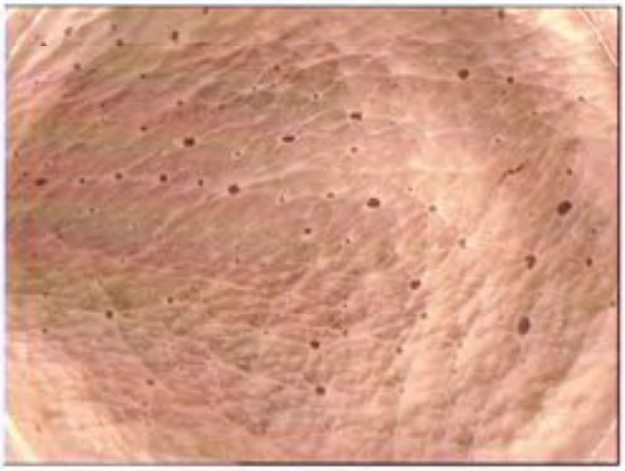

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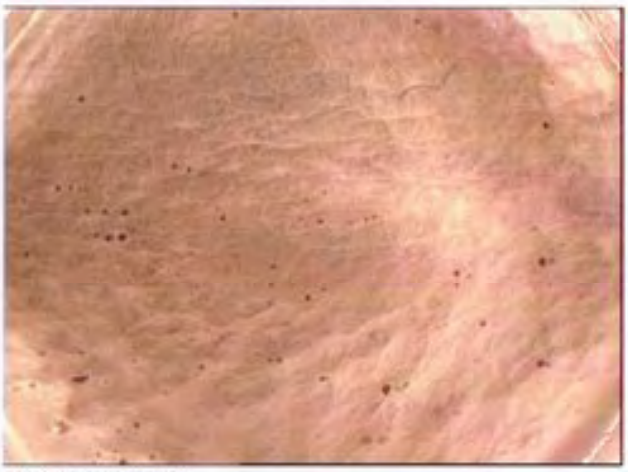

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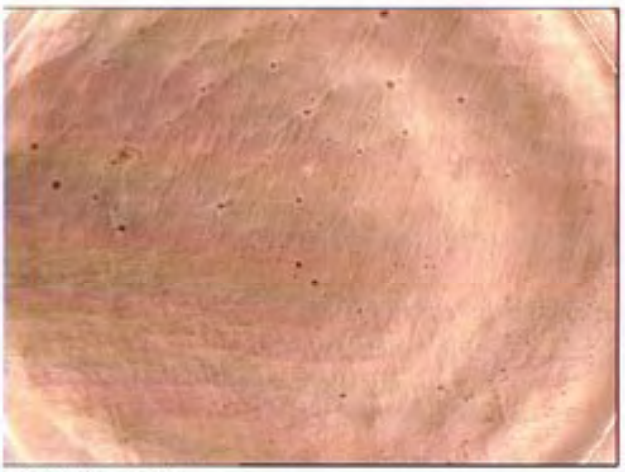

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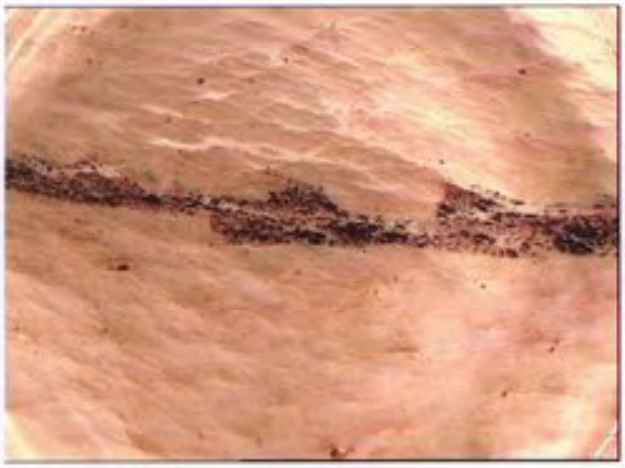

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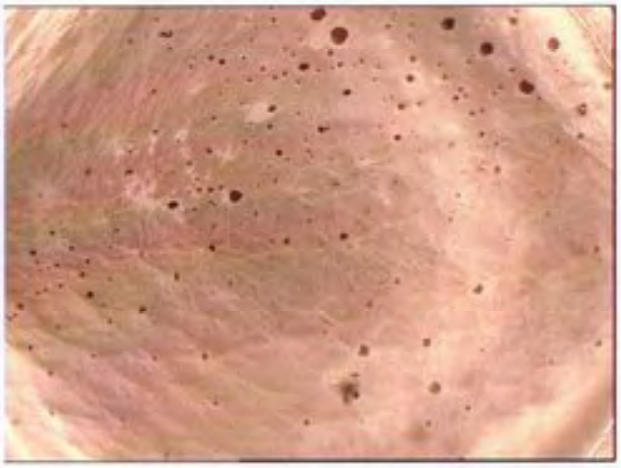

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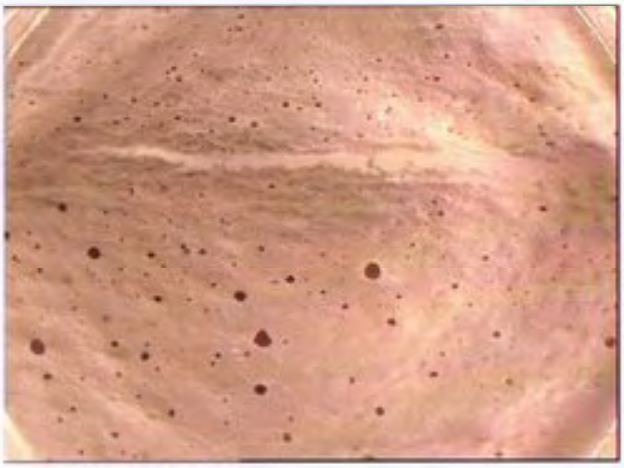

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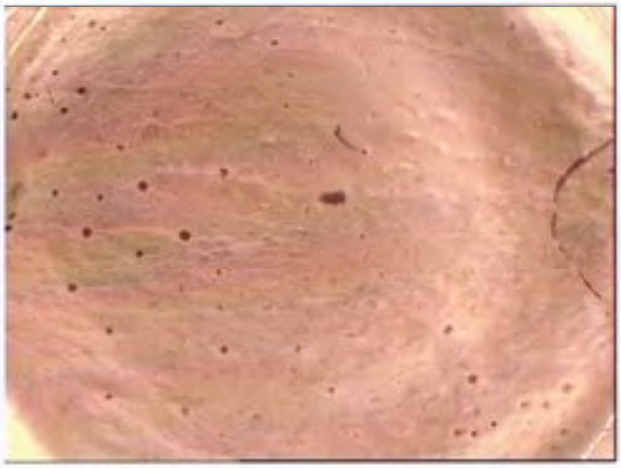

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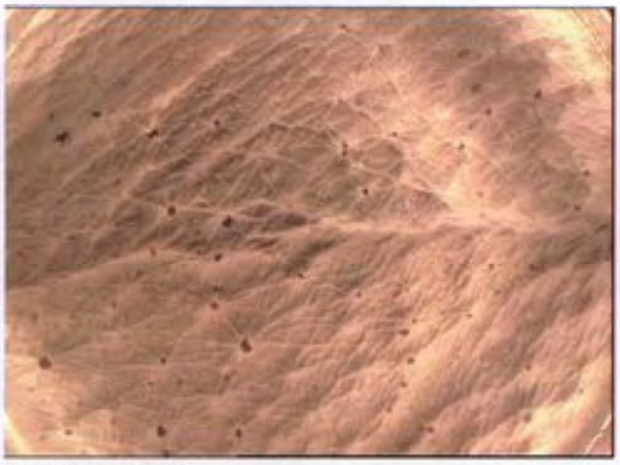

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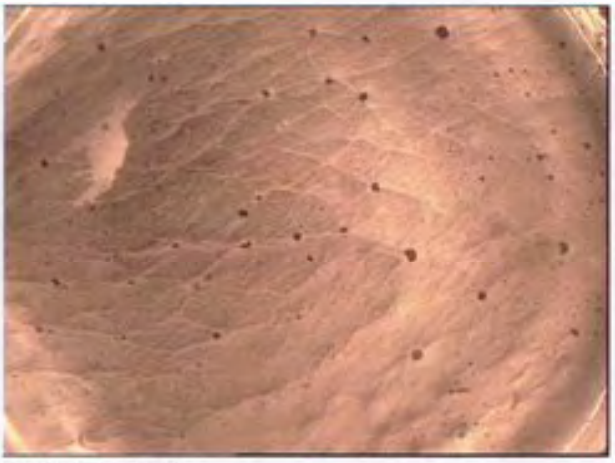

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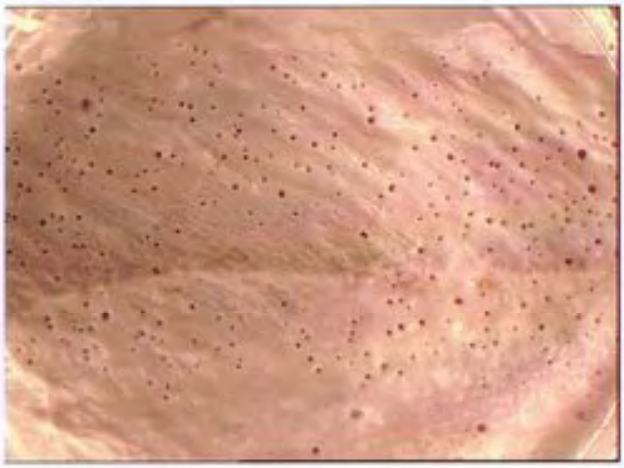

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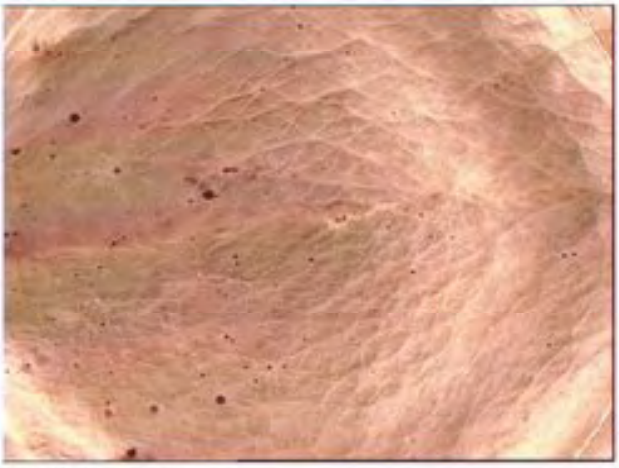

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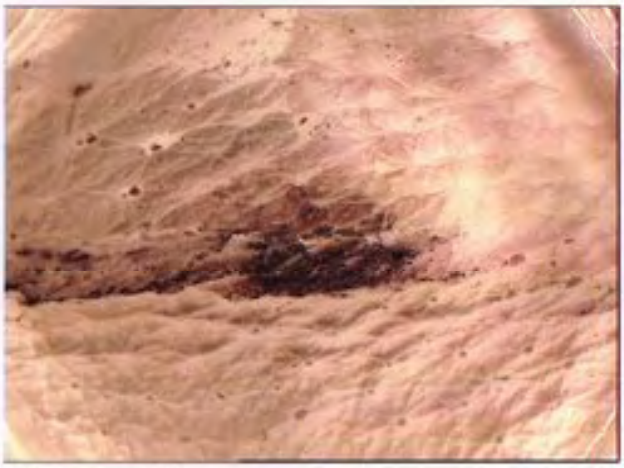

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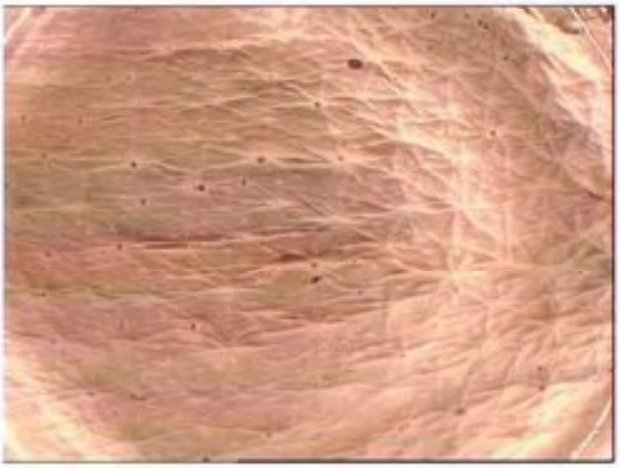

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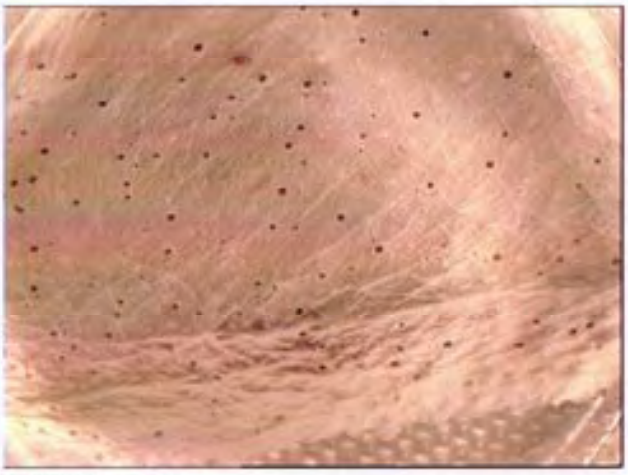

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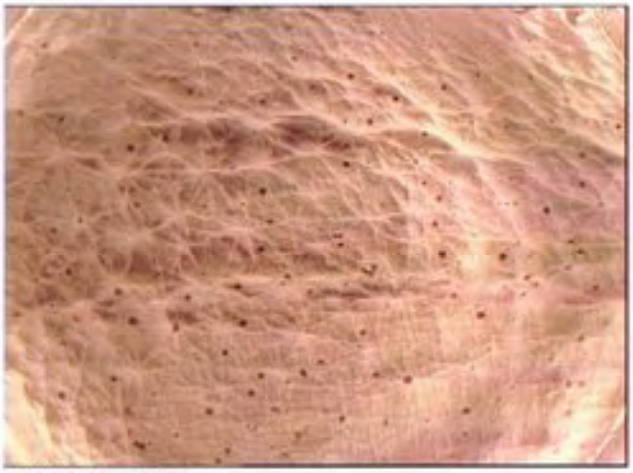

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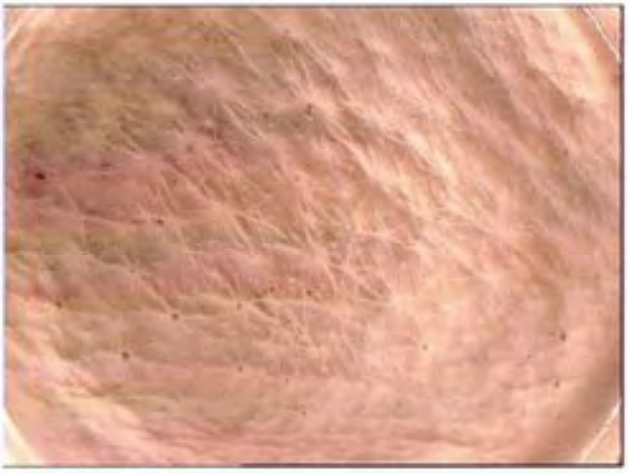

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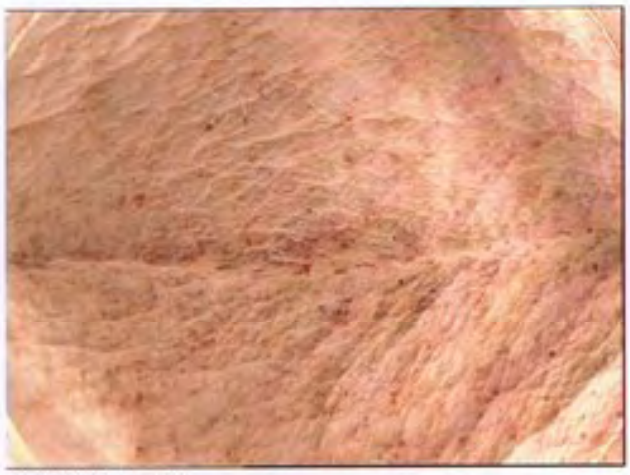

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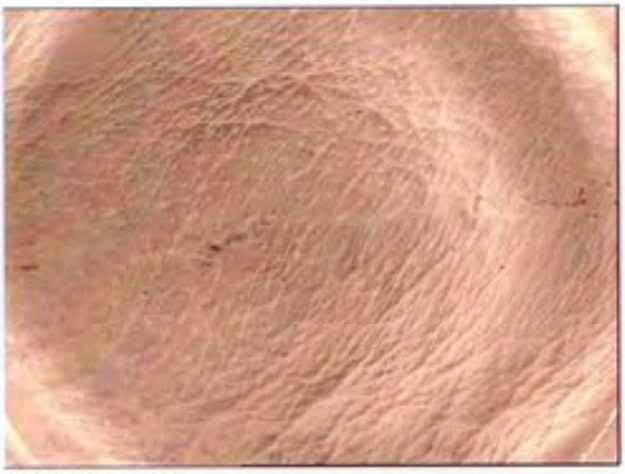

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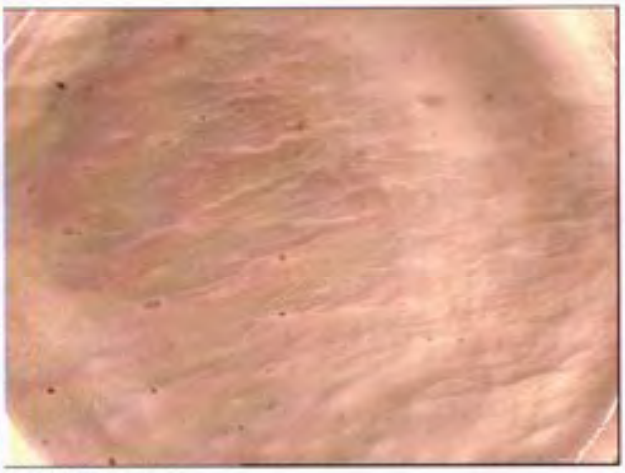

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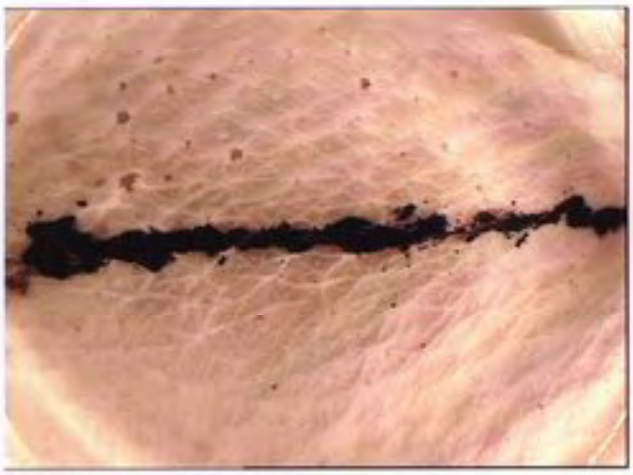

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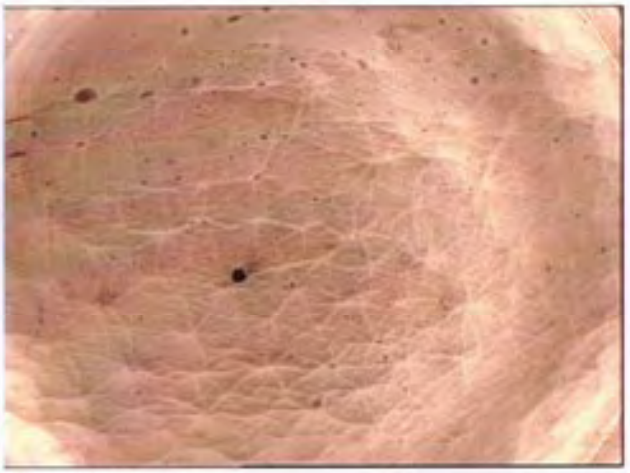

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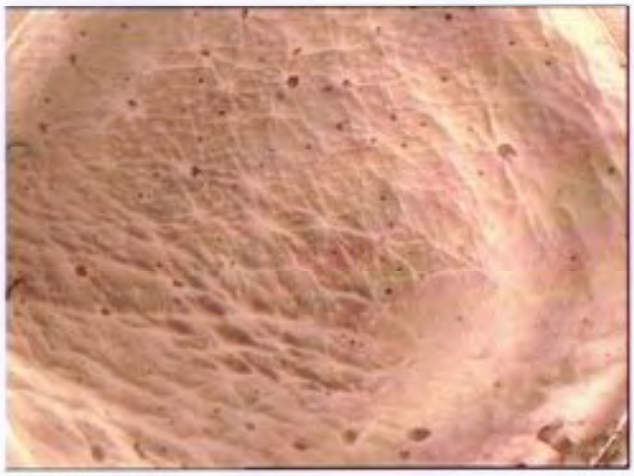

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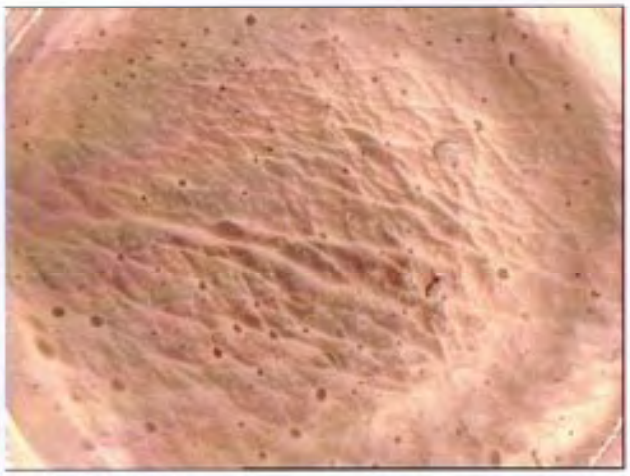

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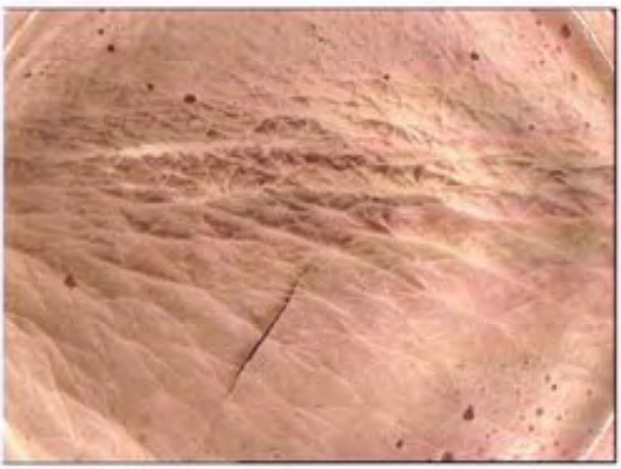

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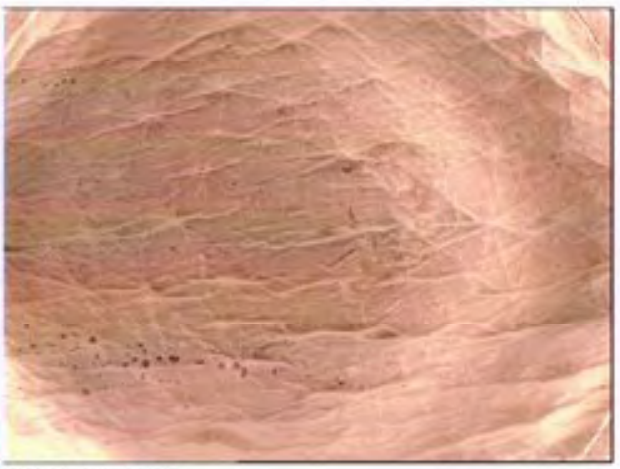

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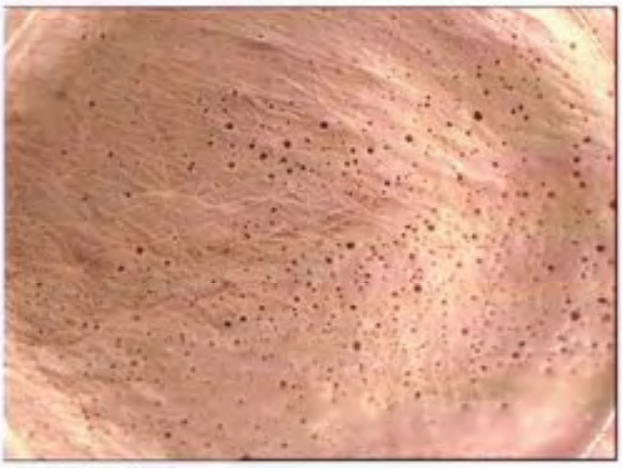

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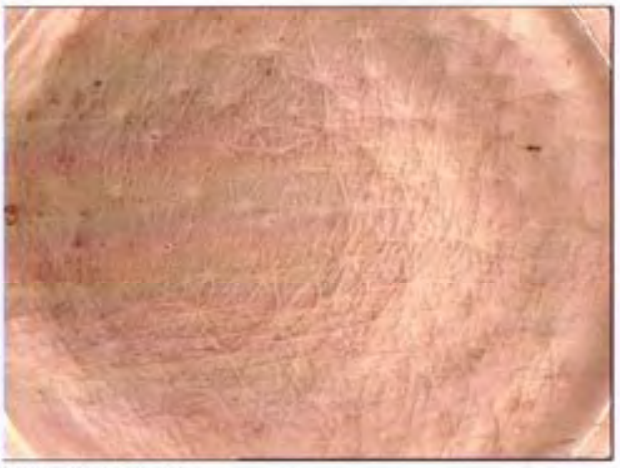

29/01/2004 - tulli 30

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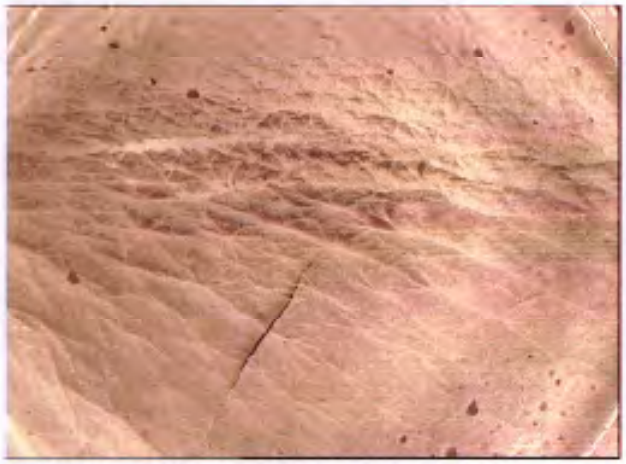

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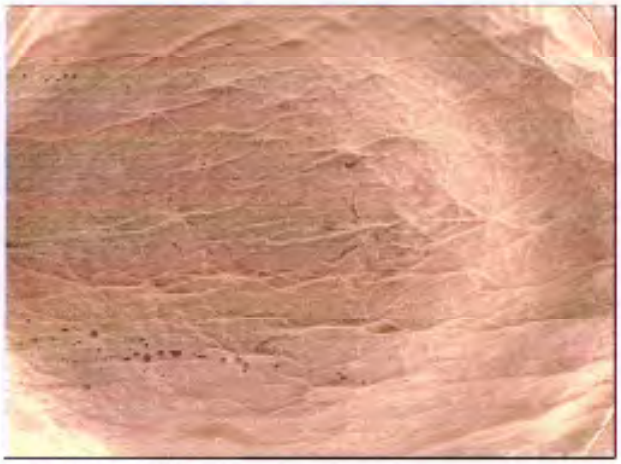

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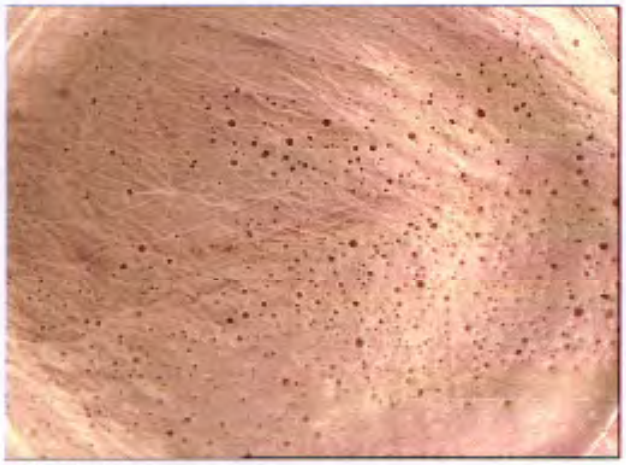

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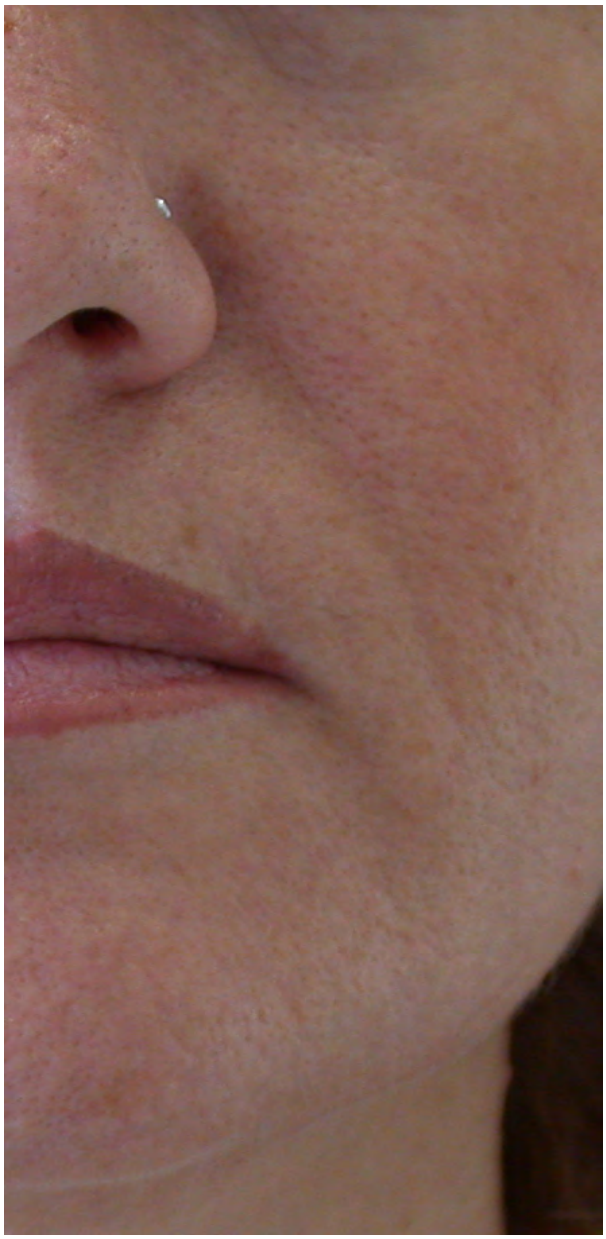
29/01/2004 - tulli 30

JALU-PRO STUDY: SELECTION OF THE REPRESENTATIVE PICTURES

SUBJECT 2 M.M.

A: BEFORE



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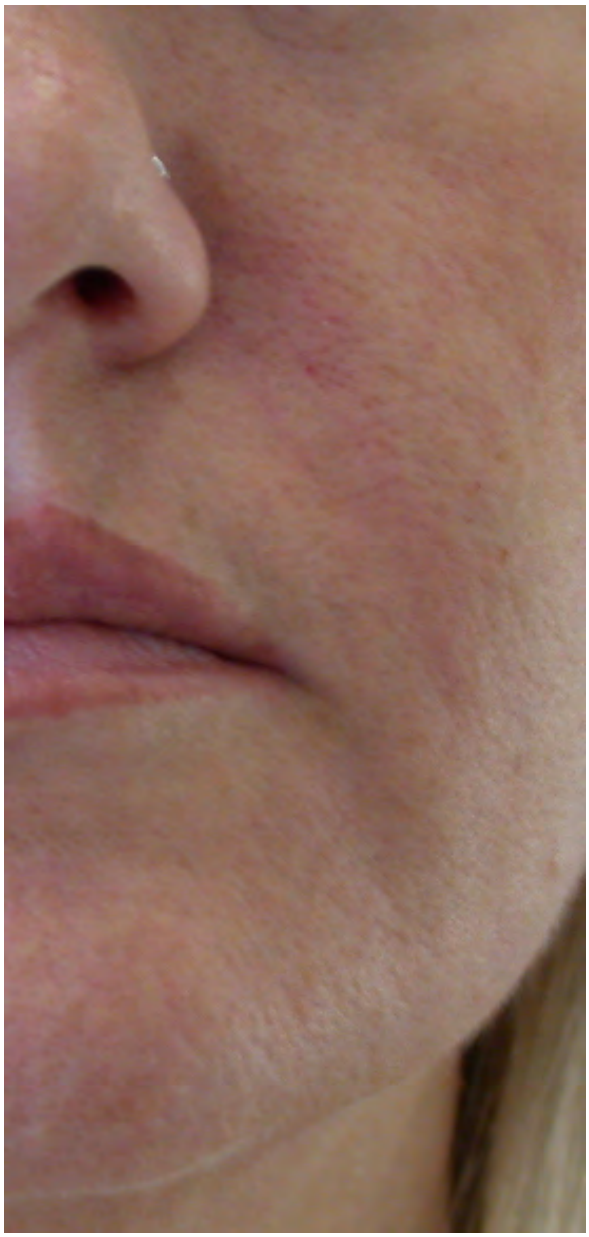

SUBJECT 9 M.G.

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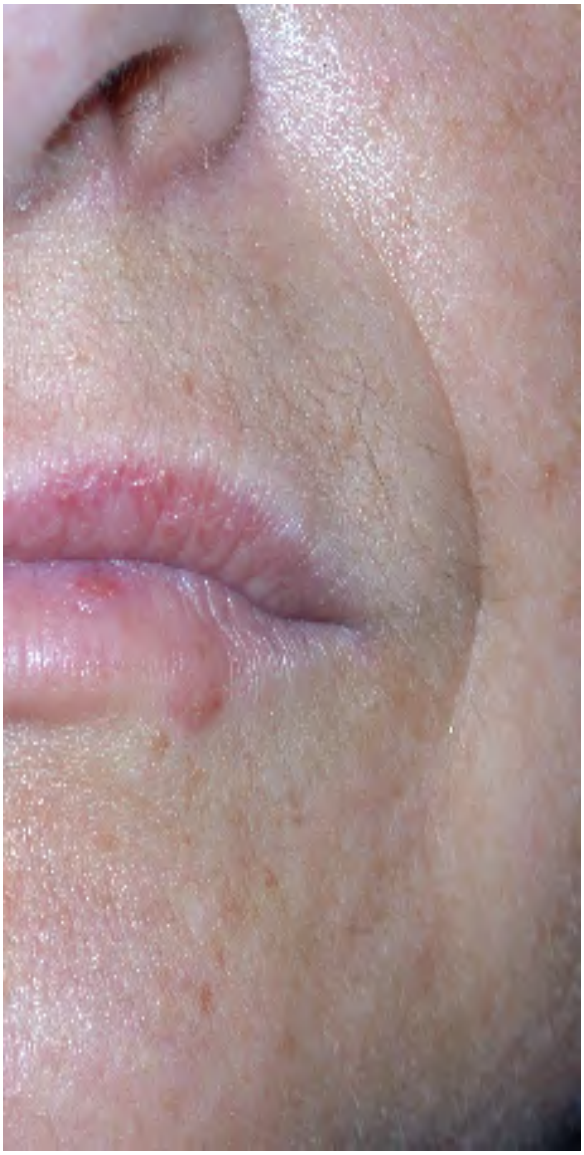

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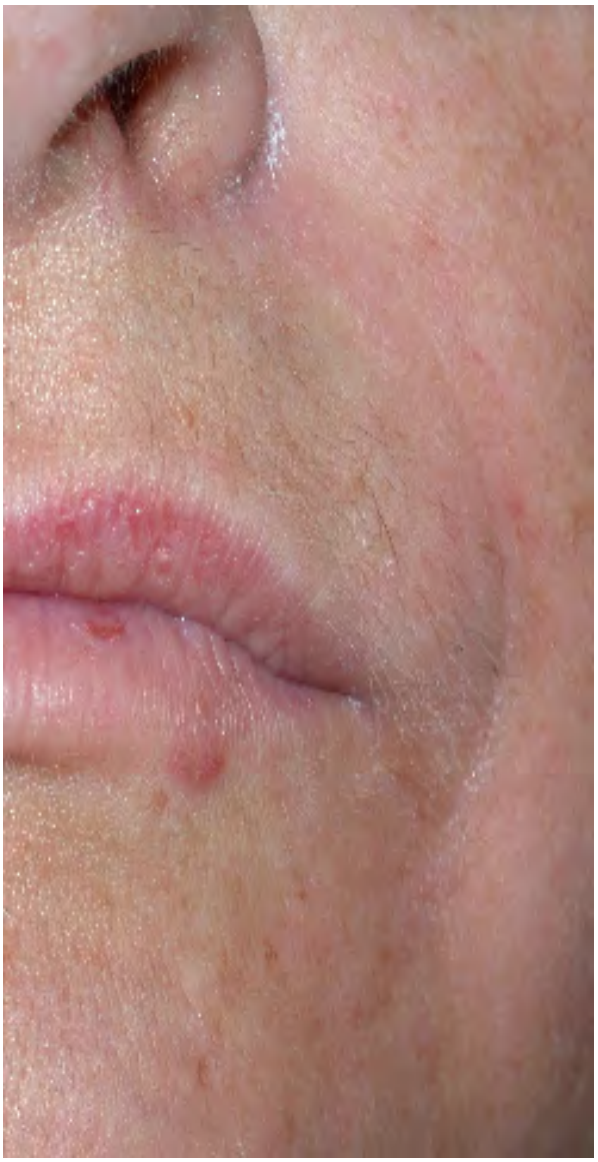
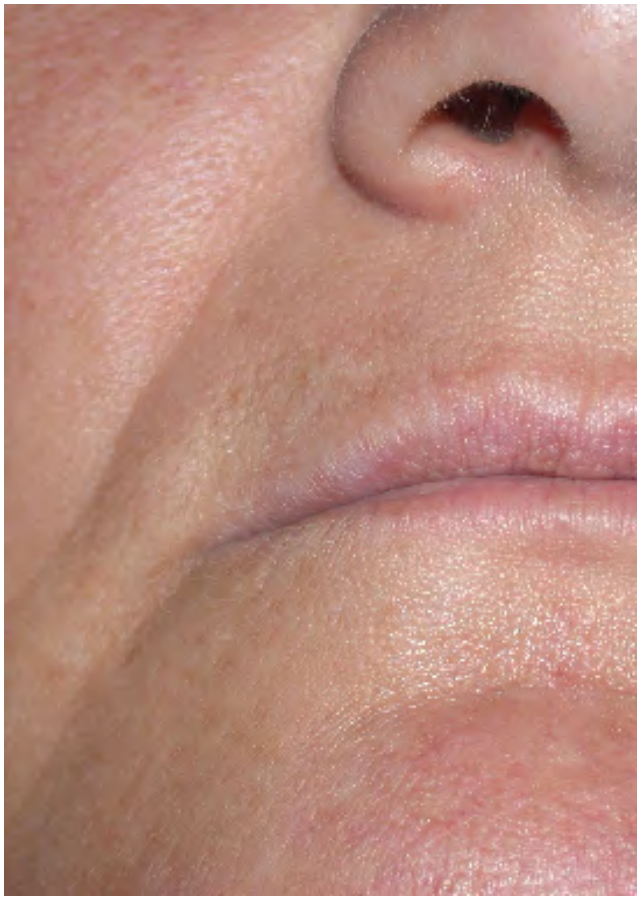


SUBJECT 15 M.V.A.

A: BEFORE



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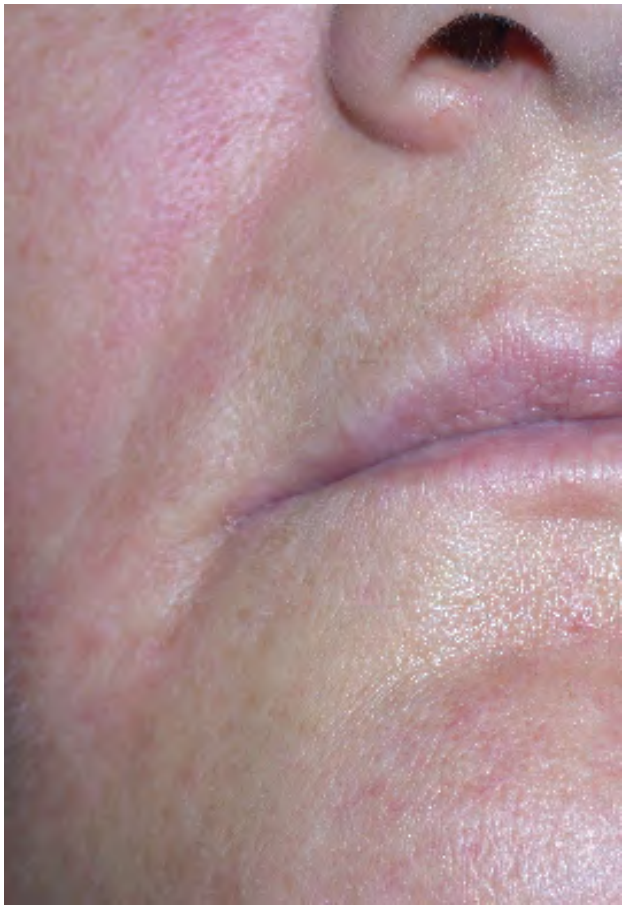
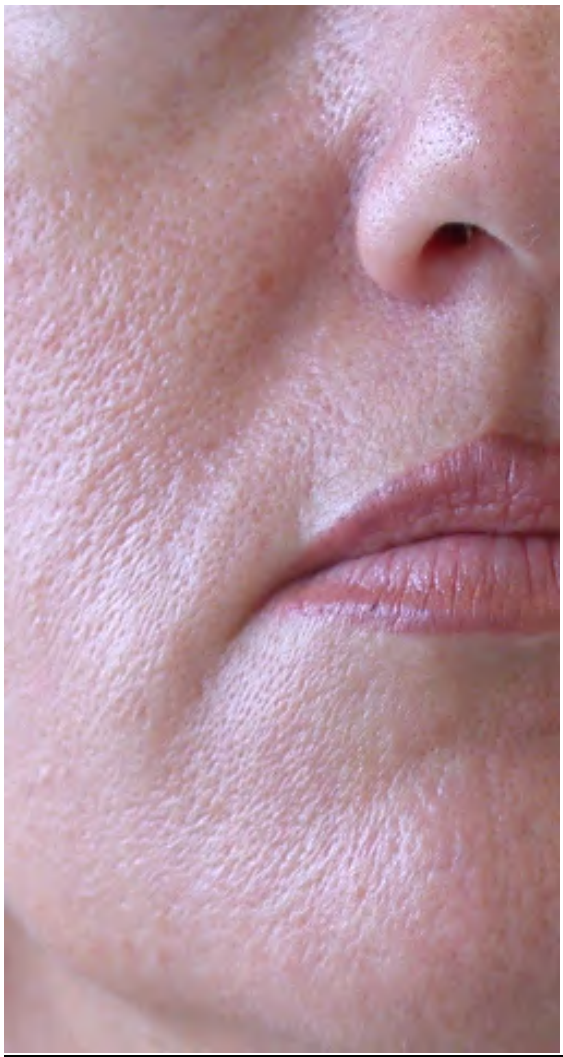
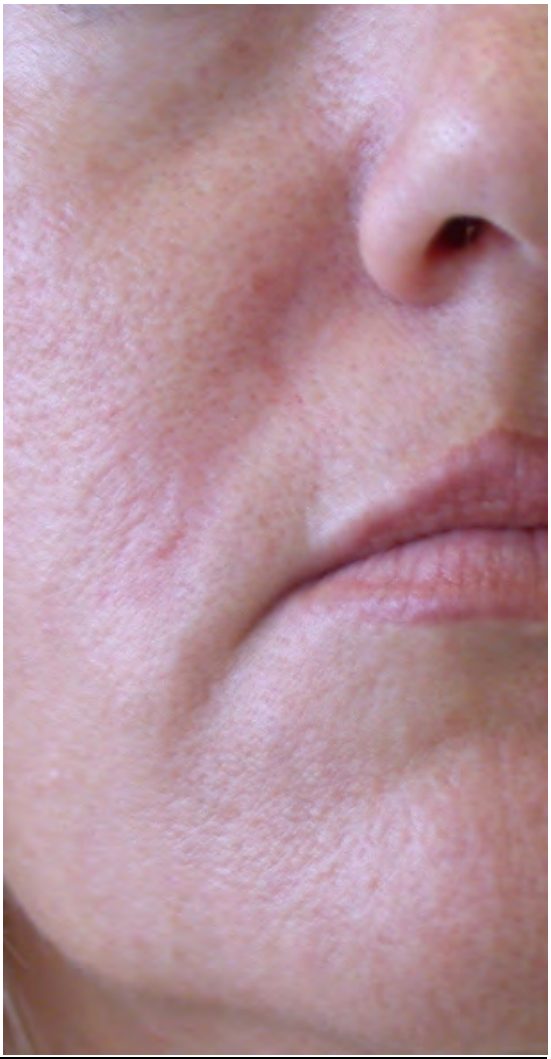


SUBJECT 16 G.E.

A: BEFORE

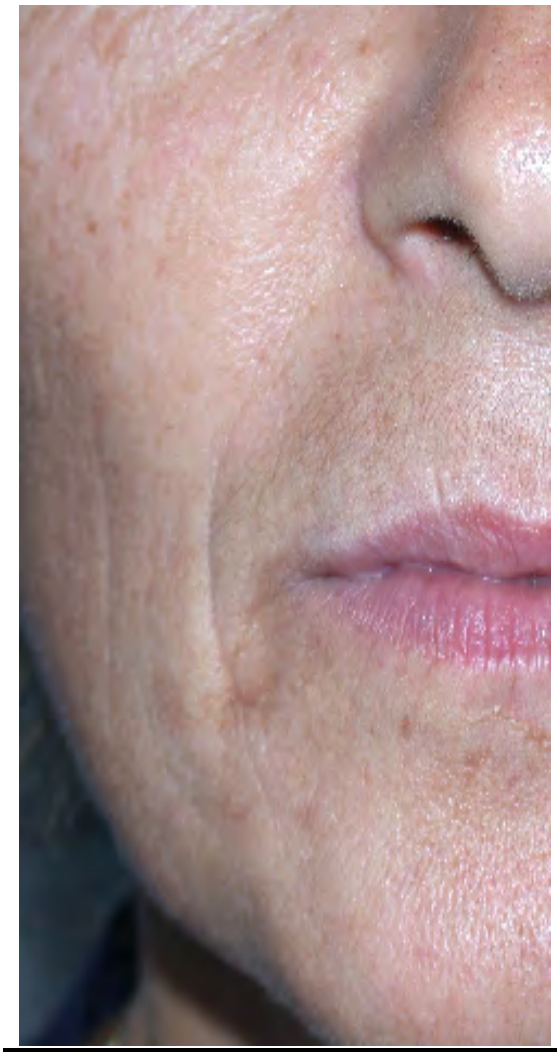


B: AFTER



SUBJECT 6 C.D.C.

A:BEFORE



B: AFTER