Bionos

Testing Efficacy

CLINICAL ANTIWRINKLES ASSESSMENT OF FACE SERUM MF-001-081 DURING 28 DAYS IN 42 VOLUNTEERS

Face Serum A MF-001-081

Face Serum B MF-001-081

Bionos
Testing Efficacy

FINAL REPORT

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CLINICAL ANTIWRINKLES ASSESSMENT OF FACE SERUM MF-001-081 DURING 28 DAYS IN 42 VOLUNTEERS

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Executive Summary

GOAL: Clinical antiwrinkles assessment of the topical treatment with "Face Serum A MF-001-081" (hereafter, "Serum A") or "Face Serum B MF-001-081" (hereafter, "Serum B") during 28 days in 42 volunteers, through quantification of wrinkles using Bio3D Structured-light Scanner.

METHODOLOGY: 2 independent groups of 21 volunteers (42 volunteers in total) were initially submitted to a 28-day topical treatment with Face Serum A MF-001-081 or Face Serum B MF-001-081 on the facial area (twice per day, morning and night). One group was submitted to Serum A and the other group was submitted to Serum B. Images were taken with Bio3D Structured-light Scanner from the forehead (glabellar lines) and crow's feet (periorbital) areas before (Day 0) and after 28 days of treatment (Day 28). Images were processed through specific software and 3 parameters (total area, length and depth of forehead and crow's feet wrinkles) were obtained from each of the volunteers. Additionally, each volunteer answered a self-assessment questionnaire at the end of the treatment. For all cases, values were normalized to the corresponding levels at Day 0 and subjected to a statistical analysis.

RESULTS: Results showed that treatment with Serum A during 28 days significantly decreased the area, length and depth of **crow´s feet wrinkles** by 8.8 ± 3.0 %, 10.6 ± 3.7 % and 4.5 ± 0.9 %, respectively, compared to the initial values (D0). In contrast, no significant reduction was observed after treatment with Serum B, neither for area, length or depth of crow's feet wrinkles. When comparing the effect of both treatments at Day 28, results indicated that Serum A significantly decreased the depth of wrinkles by 2.7 ± 1.3 %, compared to the results obtained after treatment with Serum B. In the same direction, the treatment with Serum A decreased area and length of crow's feet wrinkles by 4.8 ± 3.9 % and 8.0 ± 4.6 %, respectively, even though results were not statistically significant ($p > 0.05$), compared to the results obtained after treatment with Serum B.

With regard to **forehead wrinkles**, results indicated the treatment with Serum A for 28 days significantly decreased the depth of wrinkles by 4.5 ± 1.3 %, compared to basal values at Day 0; whereas no significant decrease was observed after treatment with Serum B. On the

other hand, results indicated the treatment with Serum A decreased area and length of forehead wrinkles by 10.0 ± 4.9 % and 9.1 ± 4.6 %, respectively; whereas the treatment with Serum B decreased area and length by 1.6 ± 6.9 % and 5.8 ± 5.0 %, respectively, even though results were not statistically significant ($p > 0.05$), compared to basal values at Day 0. When comparing the effects of both treatments at Day 28, no statistical significance ($p > 0.05$) was yielded, neither for area, length or depth.

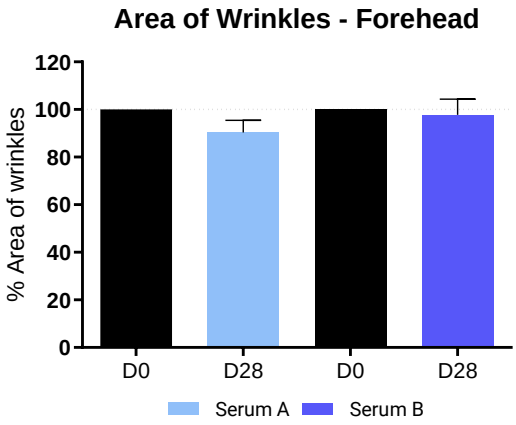
These results were subjectively confirmed through the **self-assessment questionnaire**, showing better results in the group submitted to Serum A, compared to the group submitted to Serum B treatment, including cosmetic attributes, cosmetic efficacy and consumer opinion.

Taken together, results indicated positive evaluations (overall acceptance over 80 %) for most of the assessed parameters and overall acceptance averages of 83% for Serum A and 81 % for Serum B, after 28 days of treatment. Specifically, a positive evaluation was obtained for 6 out of 6 parameters on the product's cosmetic attributes for Serum A and Serum B, 8 out of 13 parameters on the product's cosmetic effectiveness for Serum A and 7 out of 13 for Serum B, and 4 out of 4 parameters related to the consumer's opinion for Serum A and 2 out of 4 for Serum B.

With regard to skin compatibility and acceptability, none of the volunteers showed any skin acceptability problem, neither manifested any adverse symptom or cutaneous reaction during the period of treatment or the days after.

CONCLUSION: The ***in vivo*** **topical treatment** with **Face Serum A MF-001-081** during 28 days **displays antiwrinkles effects, substantiated in a significant reduction of wrinkles in forehead and crow´s feet areas,** compared to the basal values before the treatment. On the other hand, **no significant effects were observed after treatment with Face Serum B MF-001-081.** When comparing the effects of **Face Serum A MF-001-081 against Face Serum B MF-001-081**, statistically **significant results** were **only** observed for **depth of crow's feet wrinkles**.

Regarding dermatological surveillance, the **products Face Serum A MF-001-081** and **Face Serum B MF-001-081 show good skin compatibility** and may claim **"Dermatologically tested", "Clinically Tested" and "Tolerance Tested".**


Area of Wrinkles - Forehead
% Area of wrinkles
120
100
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60
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20
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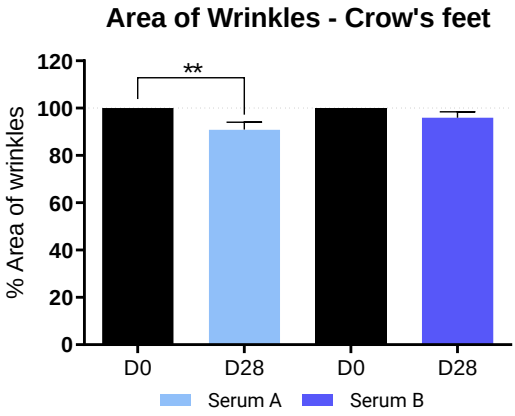
D0
D28
D0
D28
Serum A
Serum B


Area of Wrinkles - Crow's feet
**
% Area of wrinkles
120
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D0
D28
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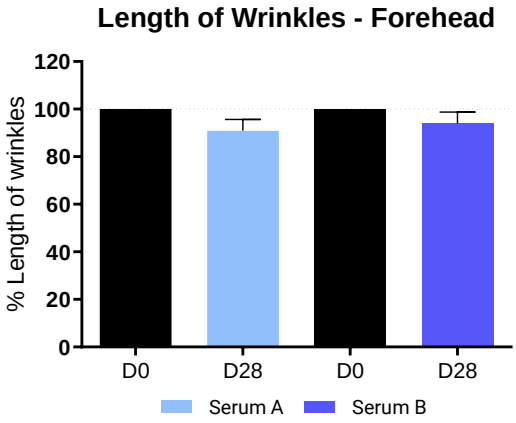
D28
Serum A
Serum B


Length of Wrinkles - Forehead
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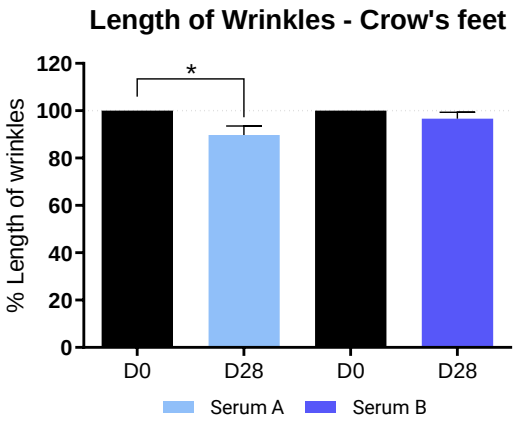
Serum A
Serum B


Length of Wrinkles - Crow's feet
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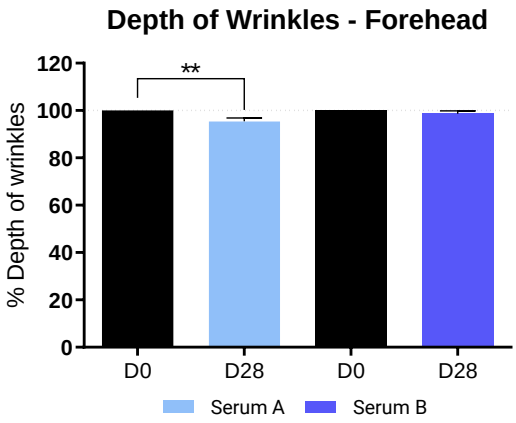
Serum A
Serum B


Depth of Wrinkles - Forehead
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% Depth of wrinkles
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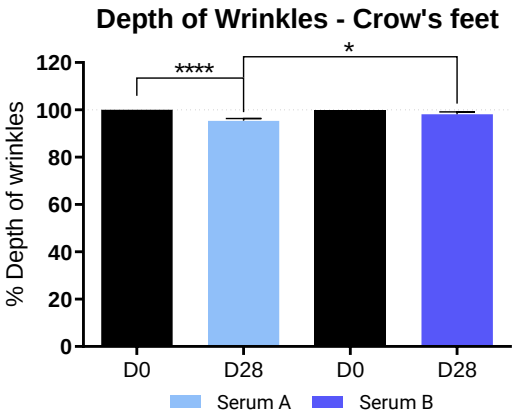
Serum A
Serum B


Depth of Wrinkles - Crow's feet
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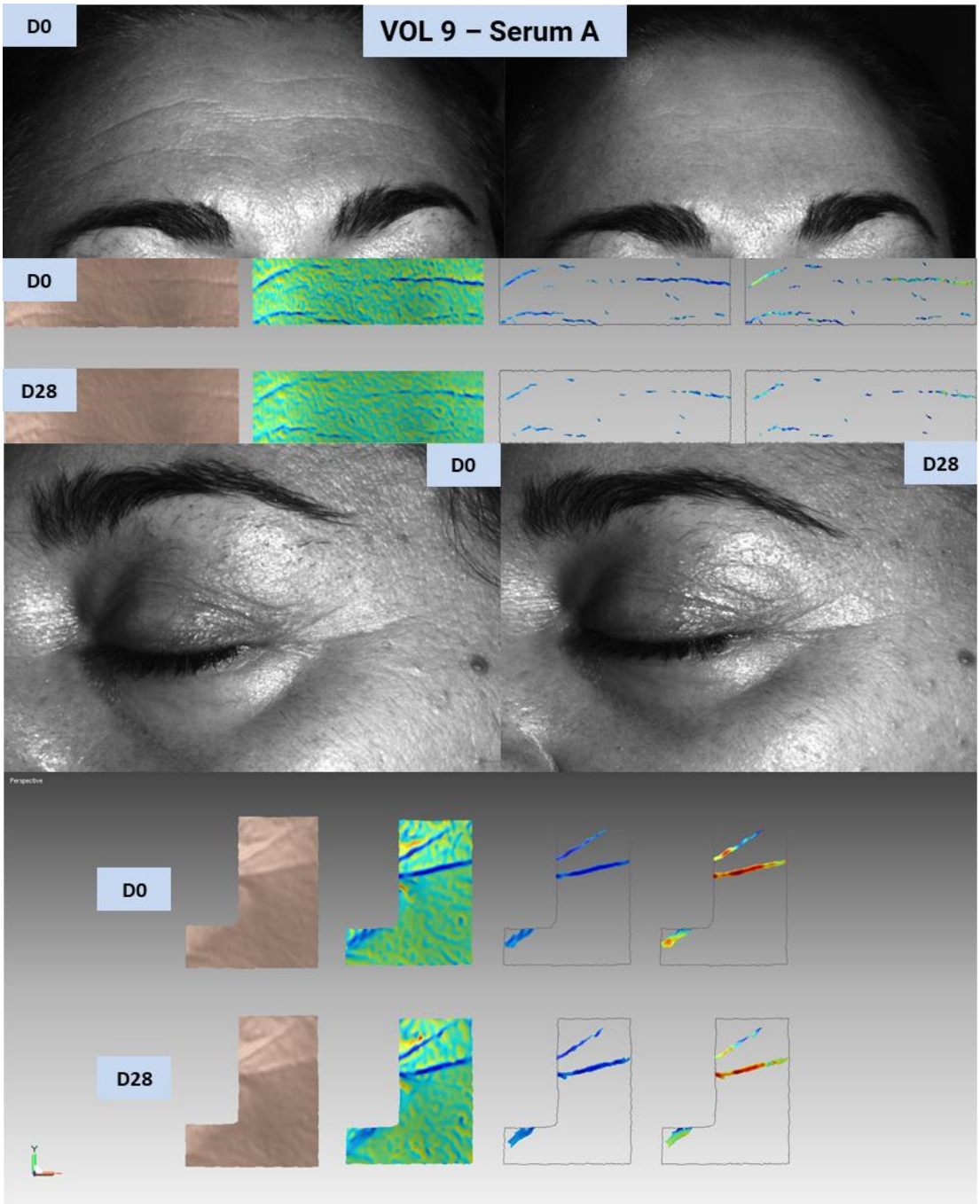
Serum A
Serum B


D0
VOL 9 – Serum A
D0
D28
D0
D28
D0
D28

1 Title

Clinical antiwrinkles assessment of Face Serum MF-001-081 during 28 days in 42 volunteers.

2 Product tested

The tested samples were received in Bionos on 23/10/2020 and labelled as indicated:

P.1787: Face Serum A MF-001-081

P.1788: Face Serum B MF-001-081

The samples were stored at room temperature in our facilities until they were delivered to the volunteers at the start of the treatment.

3 Registration dates

Study begins: 16/09/2020

Study ends: 09/12/2020

Experimental phase begins: 29/10/2020

Experimental phase ends: 04/12/2020

Dates of measurements: 1st 29/10/2020 - 30/10/2020

2nd 28/11/2020 - 29/11/2020

4 Platform

Human volunteers, self-applying the product during 28 days (twice per day, morning and night, according to client's instructions).

5 Material and methods

5.1 Analytical equipment and software used

A structured-light 3D scanner is a 3D scanning device measuring the three-dimensional shape of an object using projected light patterns and a camera system [*Borko Furht, 2008*]. Projecting a narrow band of light onto a three-dimensionally shaped surface produces a line of illumination that appears distorted from other perspectives than that of the project, and can be used for geometric reconstruction of the surface shape (light section).

The evaluation of three-dimensional (3D) shapes employing optical sensors has an increasing importance in several applications because of the intrinsic noncontact nature of the measurement and the possibility of reducing the measurement time concerning contact probes. Typical applications in the industrial field are production quality control, both in the microrange and the macrorange [*Docchio et al., 1999*], the digitalization of free-shape surfaces in the reverse engineering process [*El-Hakim and Pizzi, 1993*], and several 3D computer vision problems [*Poussart and Laurendeau, 1989*]. More recently, they have been successfully used in other fields, such as archeology, for measuring and preserving cultural heritage and in entertainment and 3D virtual reality frameworks [*Rioux et al., 1997*].

Many publications now exist on the optical techniques developed for 3D measurement, both of the passive and the active nature. In passive methods, no controlled source of light is necessary. Surface reflectance, stereo disparity, and camera motion are examples of techniques based on this passive approach. However, the main drawback is represented by the high computation effort needed to get deep information [*Jarvis, 1983*]. In active methods, the use of a pattern of radiation simplifies the problem of depth measurement. Interferometric and more techniques achieve very accurate measurements over small depth ranges [*Kuwamura and Yamaguchi, 1997*], time-of-flight methods are suitable for medium and long distances and triangulation-based methods match the short-distance interval. Within this frame, the systems based on the scanning of coherent light are widely used [*Rioux, 1984*], as well as whole-field profilometers, based on the projection of structured-light. Several pattern projection schemes belong to this last category and differ from each other in the coding used to express the light directions. It has been developed a technique that combines two methods for the projection and the demodulation of bidimensional patterns of light, known as the gray-

code and the phase-shift methods [*Sansoni et al., 1999*]. The resulting technique, hereafter called **GCPS (Gray-code and Phase-shift)** has been integrated into a prototype for 3D vision developed to achieve a system that performs at optimal accuracy and speed over a wide typology of objects.

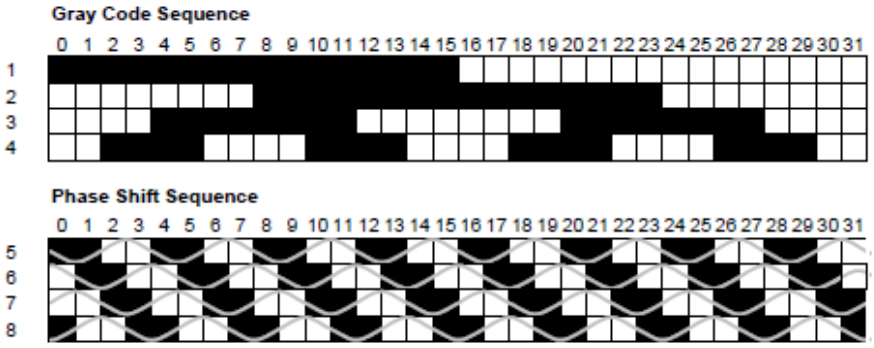


Figure 1. *Representation of Gray code and Phase shift patterns.*

The gray-code technique allows the unique description of 2 different directions of projection through the well-known one-distance gray code. The number of the directions of projection that can be unequivocally defined equals the number of the code words, thus, the larger this number, the wider the non-ambiguity height range. On the other hand, as each projection direction is associated with a code word, but not further decomposed, the measurement resolution is rather low [*Sansoni et al., 1997*]. With the phase-shift approach, the directions of projection are coded by phase values. Because the phase is continuously distributed within its range of non-ambiguity, a theoretically infinite height resolution can be obtained, actually limited only by the errors that are due to gray-level quantization and noise. On the other hand, the range of non-ambiguity is limited to the interval 0-2, and this fact strongly reduces the height range [*Sansoni et al., 1997*].

The combination of gray code and phase shift in GCPS has been proposed by several authors to exploit the positive features of each method and compensate for their drawbacks [*Krattenthaler et al., 1993*]. In principle, the latter is used to increase the information given by the former by adding a fractional contribution to the code words that identify each direction of projection. Consequently, the measurement performance is strongly improved as to the resolution and the range of the measurement.

Two major methods of stripe pattern generation have been established: Laser interference and projection. The laser interference method works with two wide planar laser beam fronts. Their interference results in regular, equidistant line patterns. Different pattern sizes can be obtained by changing the angle between these beams. The method allows for the exact and easy generation of very fine patterns with unlimited depth of field. Disadvantages are high cost of implementation, difficulties providing the ideal beam geometry, and laser typical effects like speckle noise and the possible self-interference with beam parts reflected from objects. Typically, there is no means of modulating individual stripes, such as with Gray codes.

On the other hand, the projection method uses incoherent light and conceptually works like a common video projector. Patterns are usually generated by passing light through a digital spatial light modulator, typically based on one of the three currently most widespread digital projection technologies, transmissive liquid crystal, reflective liquid crystal on silicon (LCOS) or digital light processing (DLP) modulators, which have various comparative advantages and disadvantages for this application.

A typical measuring assembly consists of one projector and at least one camera, as shown in Figure 2. For many applications, two cameras on opposite sides of the projector have been established as useful.

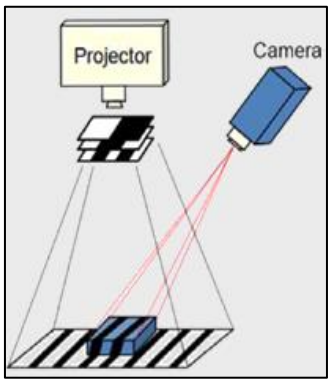


Figure 2*. Schematic representation of the Bio3D Structured-light Scanner set up.*

In Bionos Biotech, we have developed the **Bio3D Structured-light Scanner**, a 3D digitalization system based on structured-light fringe projection (gray code + phase shift method), which works at 290 images per second, reducing the effects of movement and getting a higher resolution than other systems currently available in the market. The 3D information obtained is analysed with specific software, developed internally to perform different quantifications of the skin surface and profile [*Groves et al., 2014*].

The projector used is a high-performance and high-reliability device, with a very small size that uses DLP technology and a high-power white LED light source with a frame rate of 290 fps. The camera used is based on a 1.3 Mpixels CMOS sensor with GigE Interface for high-speed optical metrology applications. The purpose of using these devices is to synchronize camera and projector to work at a frame rate of 290 fps, and in this way, be able to scan the scene in a time less than 0.15 sec. This scanning speed allows to maintain the precision of the method (> 0.1 mm) in the 3D reconstruction of *in vivo* objects.

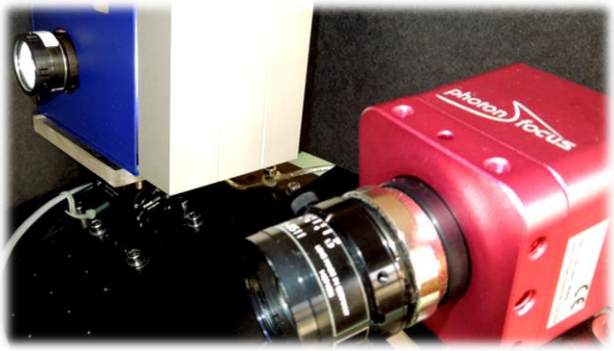


Figure 3*. Image from part of Bio3D Structured-light device used in this assay.*

2D images from the face (forehead and crow's feet areas) are processed in order to assess the effects of the treatment on total area, length, and depth. State comparatives can be performed before and after a cosmetic or clinical treatment, through specific software, in order to estimate the level of improvement in each of the volunteers. Raw data of measurements are shown in **Attachment 2 and 3.**

5.2 Procedure

5.2.1 Data register and treatment application

The experimental area was defined as the forehead (glabellar lines) and crow's feet areas, since these areas are the target of the specific treatment. Different 2D images were taken through Bio3D Structured-light Scanner from each of the volunteers before the start of the treatment (D0) and after 28 days (D28) of topical application with Serum A (P.1787) or Serum B (P.1788).

Images were processed to generate 3D reconstructions and 3 parameters (total area, length, and depth of wrinkles) were obtained for each of the volunteers. Raw data is shown in **Attachment 2 and 3**. Unprocessed (2D) and processed (3D) images for each of the volunteers are included in a digital file.

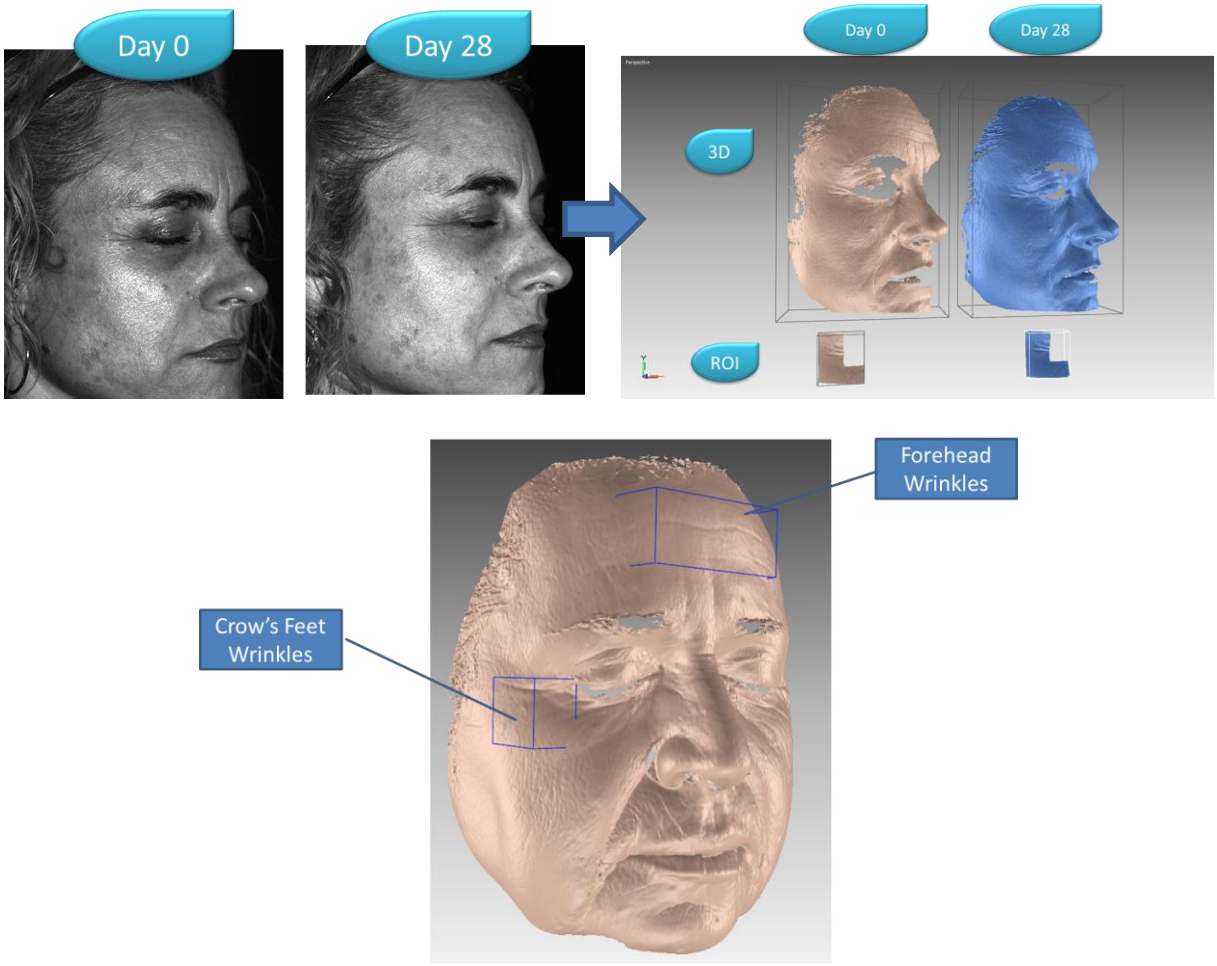


Figure 4*. 2D pictures were initially obtained from each of the volunteers (left, above) and 3D*

reconstructions from the face area (right, above) obtained after image processing through specific software. ROI selected for analysis is shown below the 3D reconstructions. The target areas (crow's feet and periorbital crow's feet wrinkles) are shown (below).

From the whole 3D reconstruction, a Region of Interest (ROI) is selected in which the wrinkles analysis will be carried out. The analysis performed is a curvature analysis. The curvature of a point belonging to a surface is a measurement directly related to the geometry of the surrounding area of that determined point. The curvature is the inverse of the sphere's radius that best fits with the surrounding area of that assessed point. In Figure 5, it is shown the concept of curvature.

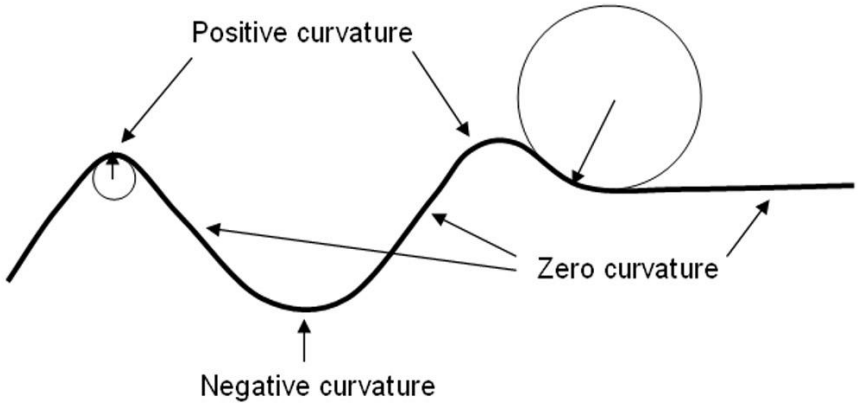


Figure 5. *Schematic representation about curvature, interpreted as the inverse of the sphere's radius that best fits with the surrounding area of the assessed point.*

Wrinkles correspond to the areas with minimum curvature. The total area, length, and depth are obtained from the 3D reconstructions (in pixels). In Figure 6, it is shown the 3D area assessed (ROI), the curvature analysis (Topography), the wrinkles detected from the analysis.

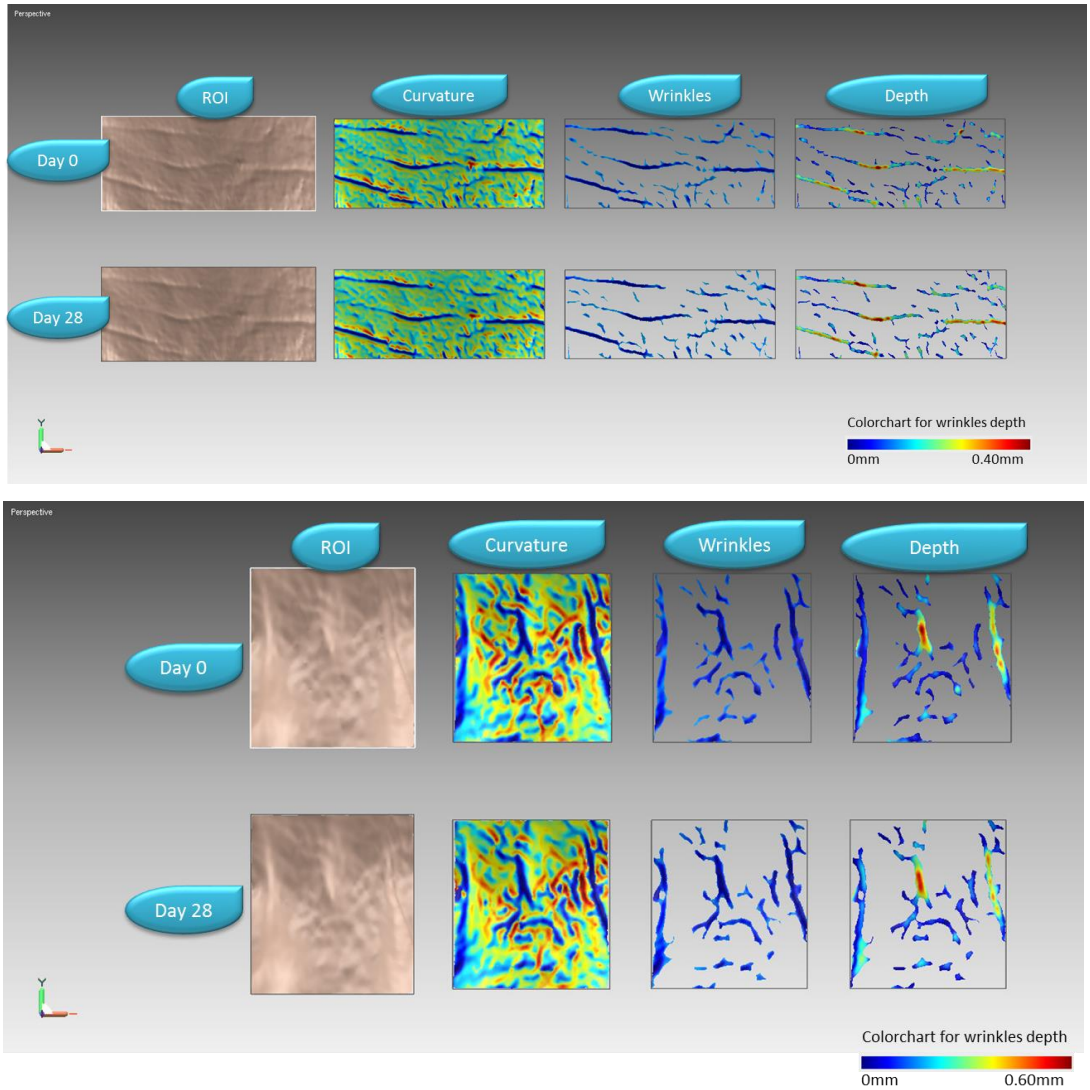


Figure 6*. Images showing 3D area selected (ROI), curvature analysis from that selected area (topography), the area of wrinkles detected from the analysis and the wrinkles including depth analysis, in forehead area.*

It is important to remark that 2D images, obtained from 3D information, are shown in the document, so dimensions tend to appear smaller than reality, as shown in Figure 7.

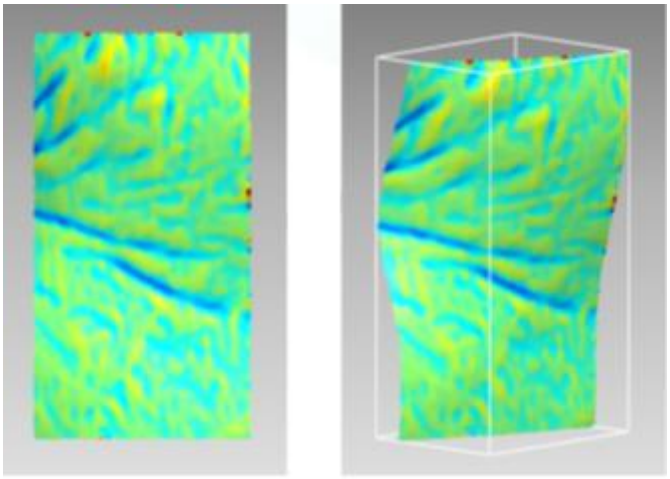


Figure 7*. Image comparison between 2D image processed and assessed (left) and real 3D information (right).*

USE CONDITIONS

Volunteers self-applying the product, twice per day (morning and night), according to client's instructions.

PANEL

Panel represents the susceptible population to use the product. **Inclusion criteria** were:

- Presence of wrinkles on the forehead and crow's feet areas.
- Relative frequency in the use of skin care cosmetic products.
- Age: Between 35 and 65 years.
- Gender: 100 % Female.
- Skin phototype (Fitzpatrick): II, III and IV.
- Skin type: Any.
- Last participation in a clinical study, at least one month before the start of this experiment.
- Understanding and signature of Informed Consent (copy of original Informed Consent is shown in **Attachment 7**).

On the other hand, the **exclusion criteria** were:

- Allergy or reactivity to some of the components of the product, or a product with a similar category than tested one.
- Surgery at the facial area.
- Relevant cutaneous marks in the experimental areas, which could interfere with the measurements (scars, sunburns, etc.).
- In-use relevant pharmacological or hormonal treatment.
- Presence of skin diseases or melanomas.
- Forecast of change of routine or relevant way of life, during the period of study.

STUDY OBLIGATIONS

Obligations imposed on volunteers were the following:

- Do not apply other similar treatments (cosmetic or nutricosmetic) from the tested one in the experimental area (face) during the period of study.
- Do not apply aesthetic treatments (exfoliating, botox, clinical peelings, hyaluronic acid, etc.) in the experimental area from 3 months before the start of the experiment.
- To respect the use conditions of the tested treatment.
- Do not apply self-tanning products in the experimental area.
- Do not take drugs or dietetic supplements containing carotene.
- Conservation of the hygiene and/or makeup habits.
- Do not receive any treatment based on Vit-A or its derivatives (in case of necessity, exclusion from the study) from 1 month before the start of the experiment.
- Do not use makeup in the experimental area (face) during control days in the research center.
- Do not perform Turkish baths or sauna during the study.
- To avoid intense sun exposure (directly to the sun or in tanning studio), during the study period.

VOLUNTEERS

The number of volunteers according to the client's need was 40, divided in 2 groups of 20 volunteers. In total, 42 volunteers were initially included in the study, 21 for each group. Volunteers were alphabetically ordered (1st surname) and randomized according to the following:

Volunteers 1 – 21	Face Serum A MF-001-081
Volunteers 22 – 42	Face Serum B MF-001-081

The Volunteer's data are found in **Attachment 1**.

Self-assessment questionnaire was filled up by the 42 volunteers who completed the treatment. Volunteer 29 was home isolated shortly before appointment at D28, due to

COVID19-imposed restrictions, and therefore unable to attend the measurements on that date. Raw data and additional comments from the volunteers are shown in **Attachment 5**. Original self-assessment questionnaires are attached in a digital file.

INFORMED CONSENT

An informed consent was obtained from each volunteer before initiating the study describing reasons for the study, possible adverse effects, associated risks and potential benefits of the treatment, and their limits of liability. The panelists signed and dated the informed consent document to indicate his authorization to proceed and acknowledge his understanding of the contents, before the start of the study. Informed consent model is shown in **Attachment 7**.

IMAGE AND PERSONALITY RIGHTS

The sponsor (Bio-Botanica Inc.) may use the pictures from all of the volunteers included in the study, for internal discussion of the results.

The sponsor (Bio-Botanica Inc.) can make commercial and marketing use of the pictures from the volunteers who gave the consent to transfer their image and personality rights (for this specific study), according to the information shown in the table of Attachment 1 (Volunteer's data).

The sponsor (Bio-Botanica Inc.) can make commercial and marketing use of the pictures from the volunteers who did NOT give the consent to transfer their image and personality rights (for this specific study), according to the information shown in the table of Attachment 1 (Volunteer's data), if they are able to assure the impossibility to recognise the person (e.g. using a black bar to completely cover the area of the eyes to avoid full personal recognition).

ETHICS

The study protocol is in accordance with the Scientific Committee on Consumer Safety (SCCS) guidance. It meets all international standards for research studies involving human subjects, the Good Clinical Practices (ICH-GCP), and the World Medical Association. It has been conducted pursuant to the Declaration of Helsinki (1864), with the amendments of Tokyo (1975), Venice (1983), Hong Kong (1989), and Seoul (2008).

CHECKING OF THE ACCEPTABILITY

The subjects were requested to note every day any reaction observed and sensation of discomfort felt. A skin examination of the experimental area under standard daylight source was performed by the responsible researcher or technician, the same days of the technical measurements.

Together with the clinical examinations performed during the treatment, each subject was questioned about possible disturbing sensations or other potential discomforts by the responsible technician at the end of the study.

CONSUMPTION CONTROL

Consumption control was carried out to verify that volunteers followed instructions and applied the treatment. Product containers were weighed before and after treatment. Results are shown in **Attachment 4**.

5.2.2 Statistical analysis

For the analysis of the effect of each treatment over the course of the study, data at each timepoint (D0 and D28) were statistically analysed applying **paired Student's t-test**, since each volunteer shows values that can be assessed in pairs (before and after the treatment) [*David et al., 1997*]. By comparing the same subject's numbers before and after treatment, we are effectively using each volunteer as their own control sample. That way, the correct rejection of the null hypothesis (no difference made by the treatment) can become much more likely, with statistical power increasing simply because the random between volunteers variation has now been eliminated [*Walpole et al., 2002; Gross and Watkins, 1999*]. Additionally, in order to compare the efficacy of Serum A vs Serum B after 28 days of treatment, an unpaired Student's t-test was applied.

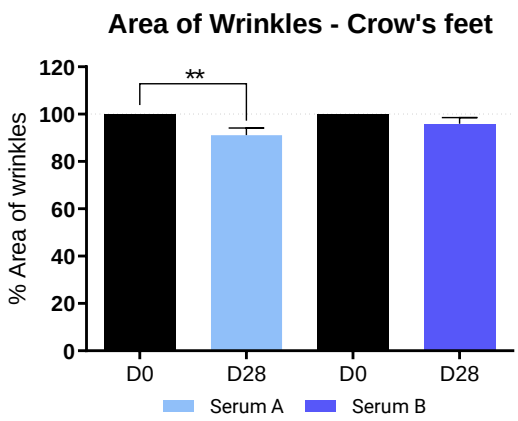
For the **self-assessment questionnaire**, opinions are given according to parameters from 0 to 3, (0 = completely disagree / 1 = disagree / 2 = agree / 3 = completely agree). For positive feelings, satisfaction is considered when volunteers select parameters from 2 to 3. A significant percentage of volunteers is considered above 80 %.

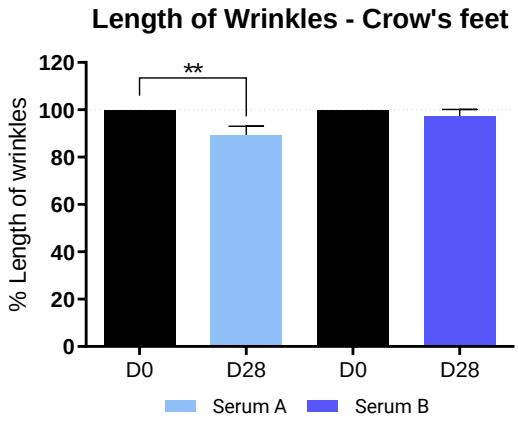
6 Efficacy results

6.1 Wrinkles

The results obtained before and after the treatment (Day 0 and Day 28) were analysed to assess the total area, depth, and length in every wrinkle the software recognised in the Region of Interest (ROI).

Results showed that treatment with Serum A during 28 days significantly decreased the area, length and depth of **crow´s feet wrinkles** by 8.8 ± 3.0 %, 10.6 ± 3.7 % and 4.5 ± 0.9 %, respectively, compared to the initial values (D0). In contrast, no significant reduction was observed after treatment with Serum B, neither for area, length or depth of crow's feet wrinkles. When comparing the effect of both treatments at Day 28, results indicated that Serum A significantly decreased the depth of wrinkles by 2.7 ± 1.3 %, compared to the results obtained after treatment with Serum B. In the same direction, the treatment with Serum A decreased area and length of crow's feet wrinkles by 4.8 ± 3.9 % and 8.0 ± 4.6 %, respectively, even though results were not statistically significant ($p > 0.05$), compared to the results obtained after treatment with Serum B; as shown in Figure 8 and Table 1.





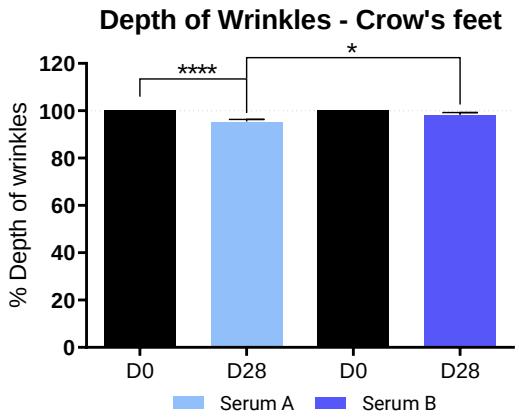


Figure 8. Crow's feet wrinkles*. Graphical representation of the total area, length, and depth of crow's feet wrinkles, before (Day 0) and after 28 (Day 28) with Serum A or Serum B in 2 independent groups of 42 volunteers (from V1 to V21 submitted to treatment with Serum A, and from V22 to V42 submitted to Serum B). For all cases, values were normalized to the corresponding levels at Day 0 and subjected to paired (for comparison between timepoints) or unpaired (for comparison between treatments at D28) Student's t-test for significance. Mean and Standard Error of the Median (SEM) are shown. * Represents statistical significance with p-value < 0.05. ** Represents statistical significance with p-value < 0.01. **** Represents statistical significance with p-value < 0.0001.*

Table Analyzed	**CROW´S FEET WRINKLES – LENGHT**			
	Serum A	**Serum B**	**Comparison**	
Column B	D28	D28	Column D	D28
vs.	vs,	vs,	vs.	vs,
Column A	D0	D0	Column B	D28
Paired t test			**Unpaired t test**	
P value	0,0076	0,1318	P value	0,2344
P value summary	**	ns	P value summary	ns
Significantly different? (P < 0.05)	**Yes**	No	**Significantly different (P < 0.05)?**	No
One- or two-tailed P value?	Two-tailed	Two-tailed	One- or two-tailed P value?	Two-tailed
t, df	t=2,970, df=20	t=1,575, df=19	t, df	t=1,208, df=39
Number of pairs	21	20		
How big is the difference?				
Mean of differences	**-8,810**	-4,049	Mean ± SEM of column B	91,19
SD of differences	13,59	11,50	Mean ± SEM of column D	95,95
SEM of differences	2,967	2,571	**Difference between means**	4,761 ± 3,942
95% confidence interval	-15,00 to -2,621	-9,429 to 1,332	95% confidence interval	-3,212 to 12,73
R square	0,3060	0,1155	R square	0,03606

Table Analyzed	CROW´S FEET WRINKLES AREA			
	Serum A	**Serum B**	**Comparison**	
Column B	D28	D28	Column D	D28
vs.	vs,	vs,	vs.	vs,
Column A	D0	D0	Column B	D28
Paired t test			**Unpaired t test**	
P value	0,0089	0,3483	P value	0,0932
P value summary	**	ns	P value summary	ns
Significantly different? (P < 0.05)	**Yes**	No	**Significantly different (P < 0.05)?**	No
One- or two-tailed P value?	Two-tailed	Two-tailed	One- or two-tailed P value?	Two-tailed
t, df	t=2,896, df=20	t=0,9631, df=18	t, df	t=1,722, df=38
Number of pairs	21	19		
How big is the difference?				
Mean of differences	**-10,61**	-2,618	Mean ± SEM of column B	89,39
SD of differences	16,78	11,85	Mean ± SEM of column D	97,38
SEM of differences	3,662	2,718	**Difference between means**	7,988 ± 4,639
95% confidence interval	-18,24 to -2,968	-8,329 to 3,093	95% confidence interval	-1,404 to 17,38
R square	0,2955	0,04901	R square	0,07237

Table Analyzed	CROW´S FEET WRINKLES – DEPTH			
	Serum A	**Serum B**	**Comparison**	
Column B	D28	D28	Column D	D28
vs.	vs,	vs,	vs.	vs,
Column A	D0	D0	Column B	D28
Paired t test			**Unpaired t test**	
P value	<0,0001	0,0933	P value	0,0426
P value summary	****	ns	P value summary	*
Significantly different? (P < 0.05)	**Yes**	No	**Significantly different (P < 0.05)?**	**Yes**
One- or two-tailed P value?	Two-tailed	Two-tailed	One- or two-tailed P value?	Two-tailed
t, df	t=5,288, df=20	t=1,767, df=19	t, df	t=2,096, df=39
Number of pairs	21	20		
How big is the difference?				
Mean of differences	**-4,502**	-1,763	Mean ± SEM of column B	95,50
SD of differences	3,902	4,461	Mean ± SEM of column D	98,24
SEM of differences	0,8514	0,9976	**Difference between means**	**2,740 ± 1,307**
95% confidence interval	-6,278 to -2,726	-3,851 to 0,3255	95% confidence interval	0,09591 to 5,384
R square	0,5830	0,1411	R square	0,1012

Table 1. *Statistical analysis of results shown in Figure 8.*

With regard to **forehead wrinkles**, results indicated the treatment with Serum A for 28 days significantly decreased the depth of wrinkles by 4.5 ± 1.3 %, compared to basal values at Day 0; whereas no significant decrease was observed after treatment with Serum B. On the other hand, results indicated the treatment with Serum A decreased area and length of forehead wrinkles by 10.0 ± 4.9 % and 9.1 ± 4.6 %, respectively; whereas the treatment with Serum B decreased area and length by 1.6 ± 6.9 % and 5.8 ± 5.0 %, respectively, even though results were not statistically significant ($p > 0.05$), compared to basal values at Day 0. When comparing the effects of both treatments at Day 28, no statistical significance ($p > 0.05$) was yielded, neither for area, length or depth; as shown in Figure 9 and Table 2.

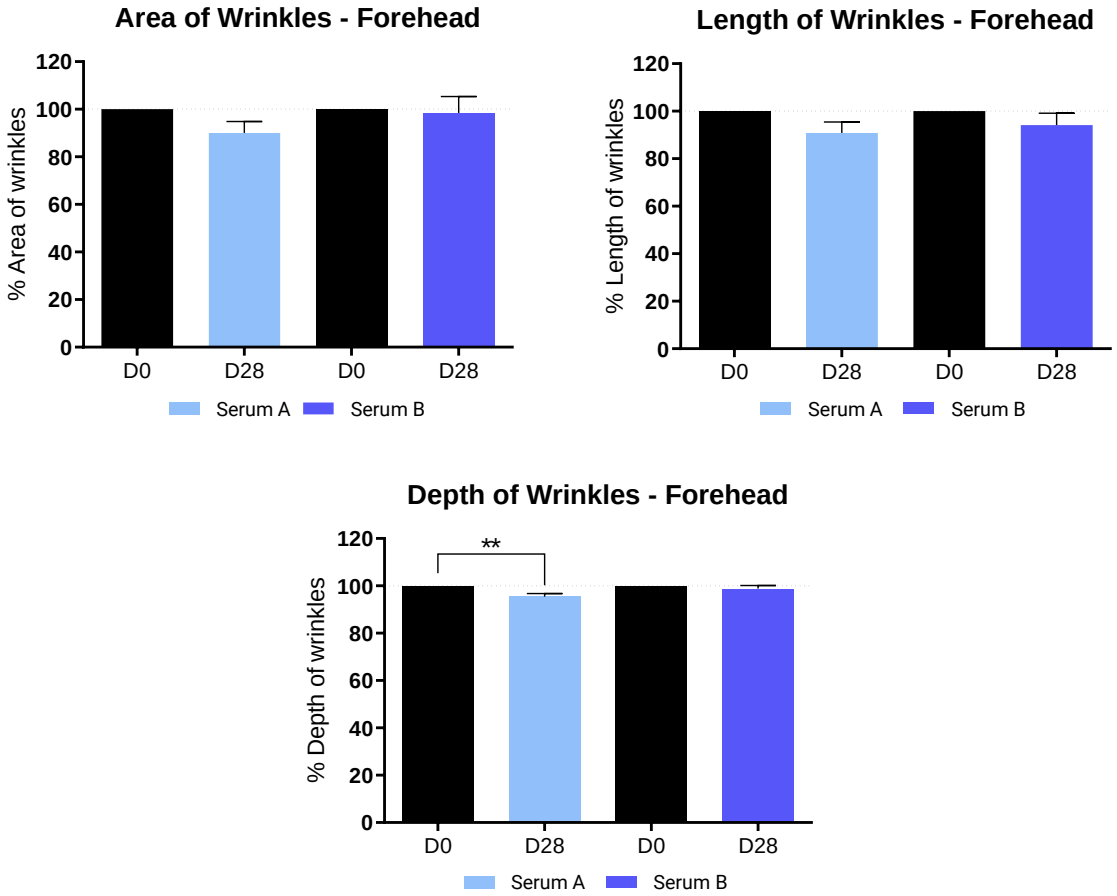


Figure 9. Forehead wrinkles*. Graphical representation of the total area, length, and depth of forehead wrinkles, before (Day 0) and after 28 (Day 28) with Serum A or Serum B in 2 independent groups of 42 volunteers (from V1 to V21 submitted to treatment with Serum A, and from V22 to V42 submitted to Serum B). For all cases, values were normalized to the corresponding levels at Day 0 and subjected to paired (for comparison between timepoints) or unpaired (for comparison between treatments at D28) Student's t-*

*test for significance. Mean and Standard Error of the Median (SEM) are shown. ** Represents statistical significance with p-value < 0.01.*

Table Analyzed	**FOREHEAD WRINKLES – AREA**			
	Serum A	**Serum B**	**Comparison**	
Column B	D28	D28	Column D	D28
vs.	vs,	vs,	vs.	vs,
Column A	D0	D0	Column B	D28
Paired t test			**Unpaired t test**	
P value	0,0540	0,8196	P value	0,3239
P value summary	ns	ns	P value summary	ns
Significantly different? (P < 0.05)	No	No	**Significantly different? (P < 0.05)**	No
One- or two-tailed P value?	Two-tailed	Two-tailed	One- or two-tailed P value?	Two-tailed
t, df	t=2,048, df=20	t=0,2312, df=19	t, df	t=0,9992, df=39
Number of pairs	21	20		
How big is the difference?				
Mean of differences	-9,971	-1,596	Mean ± SEM of column B	90,03
SD of differences	22,32	30,87	Mean ± SEM of column D	98,40
SEM of differences	4,870	6,903	**Difference between means**	8,375 ± 8,382
95% confidence interval	-20,13 to 0,1872	-16,04 to 12,85	95% confidence interval	-8,579 to 25,33
R square	0,1733	0,002805	R square	0,02496

Table Analyzed	FOREHEAD WRINKLES – LENGTH			
	Serum A	Serum B	Comparison	
Column B	D28	D28	Column D	D28
vs.	vs,	vs,	vs.	vs,
Column A	D0	D0	Column B	D28
Paired t test			Unpaired t test	
P value	0,0587	0,2581	P value	0,6255
P value summary	ns	ns	P value summary	ns
Significantly different? (P < 0.05)	No	No	**Significantly different? (P < 0.05)**	No
One- or two-tailed P value?	Two-tailed	Two-tailed	One- or two-tailed P value?	Two-tailed
t, df	t=2,005, df=20	t=1,166, df=19	t, df	t=0,4919, df=39
Number of pairs	21	20		
How big is the difference?				
Mean of differences	-9,128	-5,813	Mean ± SEM of column B	90,87
SD of differences	20,86	22,30	Mean ± SEM of column D	94,19
SEM of differences	4,552	4,986	**Difference between means**	3,316 ± 6,740
95% confidence interval	-18,62 to 0,3671	-16,25 to 4,623	95% confidence interval	-10,32 to 16,95
R square	0,1674	0,06676	R square	0,006167

Table Analyzed	FOREHEAD WRINKLES – DEPTH			
	Serum A	Serum B	Comparison	
Column B	D28	D28	Column D	D28
vs.	vs,	vs,	vs.	vs,
Column A	D0	D0	Column B	D28
Paired t test			Unpaired t test	
P value	0,0018	0,3882	P value	0,0595
P value summary	**	ns	P value summary	ns
Significantly different? (P < 0.05)	**Yes**	No	**Significantly different? (P < 0.05)**	No
One- or two-tailed P value?	Two-tailed	Two-tailed	One- or two-tailed P value?	Two-tailed
t, df	t=3,599, df=20	t=0,8831, df=19	t, df	t=1,941, df=39
Number of pairs	21	20		
How big is the difference?				
Mean of differences	-4,566	-1,105	Mean ± SEM of column B	95,43
SD of differences	5,814	5,593	Mean ± SEM of column D	98,90
SEM of differences	1,269	1,251	**Difference between means**	3,461 ± 1,783
95% confidence interval	-7,212 to -1,919	-3,722 to 1,513	95% confidence interval	-0,1457 to 7,068
R square	0,3931	0,03943	R square	0,08809

Table 2. *Statistical analysis of results shown in Figure 9.*

7 Self-Assessment questionnaire

The efficacy of the treatment with Serum A or Serum B during 28 days was subjectively evaluated by a use test (self-assessment questionnaire), answered at the end of the treatment (D28).

For each attribute, the number and percentage of satisfied volunteers according to the punctuation is shown. For positive impressions, satisfaction was considered when volunteers either scored parameters from 2 to 3. Complete results for each volunteer are shown in **Attachment 4**.

FACE SERUM A MF-001-081

COSMETIC ATTRIBUTES	0	1	2	3	% Satisfied
1. The application of the product is easy	0	0	0	1	**100**
2. The texture of the product is pleasant	0	0	1	2	**95**
3. Product absorption is fast	0	0	0	4	**100**
4. The perfume of the product is pleasant	0	0	2	14	**90**
5. The colour of the product is nice	0	0	1	9	**95**
6. The product oils the skin	0	0	20	0	**95**

For a significant percentage of volunteers, it is considered that:

- The application of the product is easy.
- The product has a pleasant texture.
- The product's absorption is fast.
- The product has a pleasant perfume.
- The product has a pleasant color.
- The product oils the skin.

COSMETIC EFFECTIVENESS	0	1	2	3	% Satisfied
7.The contour of my face appears smoothed	0	0	2	15	**90**
8.My neck jowl has been reduced	0	0	13	8	38
9.My skin is pulped	0	0	3	13	**86**
10.My skin looks younger	0	0	3	16	**86**
11.My skin is firmer	0	0	5	10	76
12.My wrinkles appear reduced	0	0	3	10	**86**
13.My skin is smoother	0	0	4	9	**81**
14.My skin seems more radiant	0	0	7	9	67
15.My skin seems more flexible (elastic)	0	0	2	13	**90**
16.The treatment unifies the skin tone.	0	0	8	10	62
17.The treatment reduces the presence of dark spots	0	0	11	8	48
18.The treatment brightness my skin	0	0	2	15	**90**
19.The treatment improves visually the quality of my skin	0	0	2	11	**90**

For a significant percentage of volunteers, it is considered that:

- The contour of my face appears smoothed.
- My skin is pulped.
- My skin looks younger.
- My wrinkles appear reduced.
- My skin is smoother.
- My skin seems more flexible.
- The treatment brightness my skin.
- The treatment improves visually the quality of my skin.

No significant results (≥ 80 %) were obtained for the rest of the assessed parameters. However, 76 % of the volunteers considered their skin is firmer.

CONSUMER OPINION	0	1	2	3	% Satisfied
20.I am satisfied with the treatment received	0	0	1	8	**95**
21.I would use the treatment again	0	0	3	6	**86**
22.I would recommend the treatment	0	0	3	6	**86**
23.I will buy the global treatment	0	0	3	12	**86**

A significant percentage of volunteers consider that:

- They are satisfied with the treatment.
- They would use the treatment again.
- They would recommend the treatment.
- They would buy the treatment.

Taken together, results indicated positive evaluations (overall acceptance over 80 %) for most of the assessed parameters and overall acceptance averages of 83% after 28 days of treatment. Specifically, a positive evaluation was obtained for 6 out of 6 parameters on the product's cosmetic attributes, 8 out of 13 parameters on the product's cosmetic effectiveness, and 4 out of 4 parameters related to the consumer's opinion.

FACE SERUM B MF-001-081

COSMETIC ATTRIBUTES	0	1	2	3	% Satisfied
1. The application of the product is easy	0	0	0	3	**100**
2. The texture of the product is pleasant	0	0	1	5	**95**
3. Product absorption is fast	0	0	0	6	**100**
4. The perfume of the product is pleasant	0	0	2	8	**90**
5. The colour of the product is nice	0	0	2	7	**90**
6. The product oils the skin	0	0	19	0	**90**

For a significant percentage of volunteers, it is considered that:

- The application of the product is easy.
- The product has a pleasant texture.
- The product's absorption is fast.
- The product has a pleasant perfume.
- The product has a pleasant color.
- The product oils the skin

COSMETIC EFFECTIVENESS	0	1	2	3	% Satisfied
7.The contour of my face appears smoothed	0	0	3	16	**86**
8.My neck jowl has been reduced	0	0	12	9	43
9.My skin is pulped	0	0	5	12	76
10.My skin looks younger	0	0	6	13	71
11.My skin is firmer	0	0	3	16	**86**
12.My wrinkles appear reduced	0	0	4	15	**81**
13.My skin is smoother	0	0	3	10	**86**
14.My skin seems more radiant	0	0	7	12	67
15.My skin seems more flexible (elastic)	0	0	4	15	**81**
16.The treatment unifies the skin tone.	0	0	3	14	**86**
17.The treatment reduces the presence of dark spots	0	0	9	10	57
18.The treatment brightness my skin	0	0	4	12	**81**
19.The treatment improves visually the quality of my skin	0	0	5	12	76

For a significant percentage of volunteers, it is considered that:

- The contour of my face appears smoothed
- My skin is pulped
- My skin is firmer
- My wrinkles appear reduced
- My skin is smoother
- My skin seems more flexible
- The treatment unifies the skin tone.
- The treatment brightness my skin

No significant results (≥ 80 %) were obtained for the rest of the assessed parameters. However, 76 % of the volunteers considered their skin is pulped and the treatment improves visually the quality of my skin.

CONSUMER OPINION	0	1	2	3	% Satisfied
20.I am satisfied with the treatment received	0	0	2	9	**90**
21.I would use the treatment again	0	0	2	8	**90**
22.I would recommend the treatment	0	0	5	7	76
23.I will buy the global treatment	0	0	5	11	76

A significant percentage of volunteers consider that:

- They are satisfied with the treatment.
- They would use the treatment again.

No significant results (≥ 80 %) were obtained for the rest of the assessed parameters.

Taken together, results indicated positive evaluations (overall acceptance over 80 %) for most of the assessed parameters and overall acceptance averages of 81% after 28 days of treatment. Specifically, a positive evaluation was obtained for 6 out of 6 parameters on the product's cosmetic attributes, 7 out of 13 parameters on the product's cosmetic effectiveness, and 2 out of 4 parameters related to the consumer's opinion.

8 Discussion and conclusions

In this assay, we assessed the clinical antiwrinkles effects of the topical treatment with "**Face Serum A MF-001-081**" or "**Face Serum B MF-001-081**" during 28 days in 42 volunteers, through quantification of wrinkles using Bio3D Structured-light Scanner.

For this, 2 independent groups of 21 volunteers (42 volunteers in total) were initially submitted to a 28-day topical treatment with Face Serum A MF-001-081 or Face Serum B MF-001-081 on the facial area (twice per day, morning and night). One group was submitted to Serum A and the other group was submitted to Serum B. Images were taken with Bio3D Structured-light Scanner from the forehead (glabellar lines) and crow's feet (periorbital) areas before (Day 0) and after 28 days of treatment (Day 28). Images were processed through specific software and 3 parameters (total area, length and depth of forehead and crow's feet wrinkles) were obtained from each of the volunteers. Additionally, each volunteer answered a self-assessment questionnaire at the end of the treatment. For all cases, values were normalized to the corresponding levels at Day 0 and subjected to a statistical analysis.

Results showed that **treatment with Serum A during 28 days significantly decreased the area, length and depth of crow´s feet wrinkles by 8.8 ± 3.0 %, 10.6 ± 3.7 % and 4.5 ± 0.9 %,** respectively, compared to the initial values (D0). In contrast, **no significant reduction was observed after treatment with Serum B**, neither for area, length or depth of crow's feet wrinkles. When **comparing the effect of both treatments at Day 28**, results indicated that **Serum A significantly decreased the depth of wrinkles by 2.7 ± 1.3 %**, compared to the results obtained after treatment with Serum B. In the same direction, the treatment with **Serum A decreased area and length of crow's feet wrinkles by 4.8 ± 3.9 % and 8.0 ± 4.6 %,** respectively, even though results were **not statistically significant (p > 0.05)**, compared to the results obtained after treatment with Serum B.

With regard to **forehead wrinkles**, results indicated the treatment with **Serum A for 28 days significantly decreased the depth of wrinkles by 4.5 ± 1.3 %**, compared to basal values at Day 0; whereas **no significant decrease was observed after treatment with Serum B**. On the other hand, results indicated the treatment with **Serum A decreased area and length of forehead wrinkles by 10.0 ± 4.9 % and 9.1 ± 4.6 %**, respectively; whereas the treatment with **Serum B decreased area and length by 1.6 ± 6.9 % and 5.8 ± 5.0 %**, respectively, even though

results were **not statistically significant (p > 0.05),** compared to basal values at Day 0. When comparing the effects of both treatments at Day 28, **no statistical significance (p > 0.05) was yielded, neither for area, length or depth.**

These results were subjectively confirmed through the **self-assessment questionnaire**, showing better results in the group submitted to Serum A, compared to the group submitted to Serum B treatment, including cosmetic attributes, cosmetic efficacy and consumer opinion.

Taken together, results indicated positive evaluations (overall acceptance over 80 %) for most of the assessed parameters and **overall acceptance averages of 83% for Serum A and 81 % for Serum B, after 28 days of treatment**. Specifically, a positive evaluation was obtained for 6 out of 6 parameters on the product's cosmetic attributes for Serum A and Serum B, 8 out of 13 parameters on the product's cosmetic effectiveness for Serum A and 7 out of 13 for Serum B, and 4 out of 4 parameters related to the consumer's opinion for Serum A and 2 out of 4 for Serum B.

With regard to skin compatibility and acceptability, none of the volunteers showed any skin acceptability problem, neither manifested any adverse symptom or cutaneous reaction during the period of treatment or the days after.

In conclusion, the ***in vivo*** **topical treatment** with **Face Serum A MF-001-081** during 28 days **displays antiwrinkles effects, substantiated in a significant reduction of wrinkles in forehead and crow´s feet areas,** compared to the basal values before the treatment. On the other hand, **no significant effects were observed after treatment with Face Serum B MF-001-081.** When comparing the effects of **Face Serum A MF-001-081 against Face Serum B MF-001-081**, statistically **significant results** were **only** observed for **depth of crow's feet wrinkles**.

Regarding dermatological surveillance, the **products Face Serum A MF-001-081** and **Face Serum B MF-001-081 show good skin compatibility** and may claim **"Dermatologically tested", "Clinically Tested" and "Tolerance Tested".**

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10 Registry and Regulation

The final report, the raw data, and the assay protocol have been saved in computer format and a copy on paper. All the information provided by the Client, volunteers, and generated by Bionos Biotech will be considered as *confidential*. The information about materials, reagents, and protocols adopted by Bionos Biotech SL during the assays is confidential and will not be shared with a third party.

This study was performed under the principle of Good Clinical Practices (International Recommendations ICH Topic E6, CPMP/ICH/135/95 of May 1st, 1996, European Parliament and Council Guideline 2001/20/CE – DOCE OF May 1st, 2001).

The whole process involving this assay was performed under **Quality Management System UNE-EN-ISO 9001/2015.**

Article 20 of the EC Cosmetic Products Regulation 1223/2009 (CPR) frames the requirements for cosmetic claims. Furthermore, cosmetic claims have to comply with **EU Regulation 655/2013** that provides the Common Criteria to ensure that the information conveyed to the end-users through claims is useful, understandable, and reliable so that consumers can make informed decisions.

The third Common Criterion, 'Evidential support', states that "claims for cosmetic products, whether explicit or implicit, shall be supported by adequate and verifiable evidence regardless of the types of evidential support used to substantiate them, including where appropriate expert assessments. Evidence for claim substantiation shall take into account the state of the art practices. Where studies are being used as evidence, they shall be relevant to the product and the benefit claimed, shall follow well-designed, well-conducted methodologies (valid, reliable, and reproducible) and shall respect ethical considerations."

Experimental studies include (but are not limited to) studies *in silico*, *in vitro*, *ex-vivo*, with instrumental or biochemical methods, studies conducted on volunteers, investigator evaluations, sensory evaluations, etc. Different types of experimental studies can be used to provide data on the performance of cosmetic products. Such studies should comprise methods that are reliable and reproducible. The studies should follow a well-designed and scientifically valid methodology according

to best practices. The criteria used for evaluation of product performance should be defined with accuracy and chosen in accordance with the aim of the test. The experimental aspect of studies calls for reliance on knowledge and awareness of statistical principles in the design and analysis of the study, e.g. in terms of the number of subjects, test samples, etc. This is necessary in order to ensure that the studies achieve scientifically and statistically valid conclusions.

Studies conducted on volunteers should follow ethical principles and products tested should have been assessed as safe. Human studies should be conducted on the target population where necessary, and be defined by strict inclusion/exclusion criteria.

Products may bear claims that relate to the nature of experimental studies. Consumer expectations regarding these claims may vary depending, in particular, upon the presentation of the claim and its specific context. However, in all circumstances, consumers will expect that such claims are made only when the effects tested are favorable:

- The claim "tolerance tested" means that the product underwent tests under the supervision of a scientifically qualified professional intended to study its tolerance on a target group and that the results of those tests show that the product was well tolerated by this group.
- The claim "tested under medical supervision" indicates that the product underwent tests conducted under the supervision of a medically qualified professional, such as a medical doctor or a dentist. Depending on the presentation of the claim, it may, for (example, refer to a specific efficacy of the product or skin tolerance.
- The claim "dermatologically tested" implies that the product was tested on humans under the supervision of a dermatologist. Depending on the presentation of the claim, it may refer to a specific efficacy or tolerance of the product. Consumer self-perceptions studies are not appropriate to support such claims. The same logic would apply to a claim referring to any other medical discipline.
- The claim "clinically tested" refers to the expertise, process, or conditions under which the tests were carried out. "Clinically tested" means that the product was tested on humans under the supervision of a medically qualified professional or another scientifically qualified professional according to a clinical protocol or in a clinical setting.

The treatments tested in this **study 822.20.10** may claim:

- **"Dermatologically Tested".**
- "**Tolerance tested**".
- "**Clinically tested**".

A critical point for the validity of consumer tests is the wording of the questionnaire. The questions and proposed answers should be clear enough to be unequivocally understood by participants. The answers scale should be well balanced (e.g. same number of positive and negative answers (a nominal, ordinal or visual analogical notation scale may be used)) and not capable of influencing the answer.

Special attention should be paid to the wording of questions for which responses will be used to substantiate the claim: the claim should be directly substantiated by the results related to the relevant question without any questionable interpretation.

Data processing and the interpretation of results should be fair and should not overstep the limits of the test's significance. Data recording, transformations, and representation in tabular or graphical form should be transparent or clearly explained if complex. It should not be designed to overstate the effect(s) measured. An appropriate statistical analysis of the data should be performed.

Attachments

Attachment 1: Volunteers data

	Nº Volunteer	ID Volunteer	Age	Gender	Type of skin	Transfer of image and personality rights
Serum A	1	417	47	Female	Combination	YES
	2	440	61	Female	Combination	YES
	3	1438	44	Female	Combination	YES
	4	1101	44	Female	Combination	YES
	5	1099	42	Female	Oily	YES
	6	1417	40	Female	Combination	YES
	7	11	53	Female	Combination	YES
	8	1156	45	Female	Combination	YES
	9	1288	49	Female	Combination	YES
	10	1291	40	Female	Combination	YES
	11	1455	61	Female	Dry	YES
	12	123	49	Female	Combination	YES
	13	996	46	Female	Combination	YES
	14	363	56	Female	Combination	YES
	15	373	38	Female	Combination	YES
	16	1448	42	Female	Combination	YES
	17	402	49	Female	Combination	YES
	18	1232	57	Female	Combination	YES
	19	408	48	Female	Combination	YES
	20	997	46	Female	Combination	YES
	41	1447	44	Female	Dry	YES
Serum B	21	1435	56	Female	Combination	YES
	22	437	60	Female	Dry	NO
	23	546	59	Female	Combination	YES
	24	1454	38	Female	Combination	YES
	25	738	60	Female	Dry	YES
	26	124	54	Female	Combination	YES
	27	632	54	Female	Dry	YES
	28	53	48	Female	Combination	YES
	29	1452	58	Female	Dry	YES
	30	1353	53	Female	Dry	YES
	31	763	53	Female	Oily	YES
	32	1102	59	Female	Combination	NO
	33	311	48	Female	Dry	YES
	34	1277	43	Female	Combination	YES
	35	1428	56	Female	Dry	YES
	36	1214	64	Female	Combination	YES
	37	359	50	Female	Combination	YES
	38	1441	54	Female	Dry	YES
	39	1415	48	Female	Combination	YES
	40	557	48	Female	Combination	YES
	42	1468	55	Female	Dry	YES

***Table 3**. Data (Number of subjects in the study, ID, age, gender, type of skin and transfer of image and*

personality rights) of the 42 volunteers initially included in the study. Volunteer 29 could not attend to the measurement at D28 due to COVID19-related restrictions and was excluded from the study by the researcher.

Attachment 2: Raw data Forehead wrinkles

	FORHEAD WRINKLES RAW DATA					
	Area (mm2)		Lenght (mm)		Depth (mm)	
	D0	D28	D0	D28	D0	D28
Vol.1	58,95	57,15	148,71	138,60	0,078	0,075
Vol.2	35,25	31,91	66,17	72,79	0,117	0,114
Vol.3	60,68	65,91	106,18	105,69	0,113	0,116
Vol.4	11,74	17,13	28,38	40,64	0,069	0,072
Vol.5	58,63	53,68	139,09	127,50	0,088	0,081
Vol.6	43,83	41,41	127,37	121,95	0,066	0,065
Vol.7	38,37	23,71	67,63	55,24	0,133	0,121
Vol.8	66,62	68,70	143,08	144,61	0,129	0,133
Vol.9	70,41	30,83	141,14	72,29	0,098	0,083
Vol.10	15,10	14,50	47,32	44,21	0,065	0,062
Vol.11	28,92	19,56	79,92	43,49	0,114	0,102
Vol.12	79,92	69,72	136,12	126,46	0,157	0,142
Vol.13	38,89	32,34	91,78	78,54	0,093	0,087
Vol.14	43,81	39,04	120,17	105,08	0,094	0,088
Vol.15	42,72	42,22	122,15	120,53	0,086	0,086
Vol.16	16,63	16,82	46,98	50,40	0,087	0,085
Vol.17	27,79	31,62	72,02	76,95	0,086	0,089
Vol.18	26,47	22,35	81,62	60,51	0,107	0,101
Vol.19	60,19	60,68	154,87	150,75	0,078	0,077
Vol.20	94,26	45,22	204,75	108,22	0,106	0,088
Vol.21	36,35	13,35	85,77	36,33	0,078	0,068
Vol.22	198,71	179,85	347,72	283,44	0,163	0,155
Vol.23	33,74	42,73	71,84	81,88	0,146	0,149
Vol.24	45,75	54,40	131,57	135,47	0,089	0,093
Vol.25	32,41	36,83	80,14	104,28	0,143	0,149
Vol.26	66,94	38,08	138,40	80,20	0,105	0,091
Vol.27	84,87	97,57	146,06	139,24	0,219	0,224
Vol.28	46,62	31,72	111,31	75,20	0,115	0,108
Vol.29						
Vol.30	38,19	40,55	89,18	98,12	0,084	0,086
Vol.31	23,60	15,80	62,96	48,33	0,079	0,074

Vol.32	93,45	93,17	231,58	231,50	0,108	0,107
Vol.33	30,76	32,27	90,51	91,55	0,095	0,097
Vol.34	49,44	50,91	144,19	143,68	0,071	0,072
Vol.35	21,24	13,10	61,06	44,70	0,096	0,089
Vol.36	48,83	53,65	95,18	95,30	0,153	0,154
Vol.37	13,05	23,55	29,60	38,24	0,082	0,086
Vol.38	32,86	35,01	82,72	86,25	0,112	0,116
Vol.39	18,14	15,12	51,92	44,62	0,086	0,083
Vol.40	79,13	85,73	180,19	187,26	0,108	0,111
Vol.41	37,42	31,33	93,74	84,46	0,126	0,119
Vol.42	42,20	46,76	122,50	132,02	0,087	0,089

	FORHEAD WRINKLES RELATIVE TO D0					
	Area (%)		**Lenght (%)**		**Depth (%)**	
	D0	**D28**	**D0**	**D28**	**D0**	**D28**
Vol.1	100,00	96,95	100,00	93,20	100,00	96,15
Vol.2	100,00	90,52	100,00	110,00	100,00	97,44
Vol.3	100,00	108,62	100,00	99,54	100,00	102,65
Vol.4	100,00	145,91	100,00	143,20	100,00	104,35
Vol.5	100,00	91,56	100,00	91,67	100,00	92,05
Vol.6	100,00	94,48	100,00	95,74	100,00	98,48
Vol.7	100,00	61,79	100,00	81,68	100,00	90,98
Vol.8	100,00	103,12	100,00	101,07	100,00	103,10
Vol.9	100,00	43,79	100,00	51,22	100,00	84,69
Vol.10	100,00	96,03	100,00	93,43	100,00	95,38
Vol.11	100,00	67,63	100,00	54,42	100,00	89,47
Vol.12	100,00	87,24	100,00	92,90	100,00	90,45
Vol.13	100,00	83,16	100,00	85,57	100,00	93,55
Vol.14	100,00	89,11	100,00	87,44	100,00	93,62
Vol.15	100,00	98,83	100,00	98,67	100,00	100,00
Vol.16	100,00	101,14	100,00	107,28	100,00	97,70
Vol.17	100,00	113,78	100,00	106,85	100,00	103,49
Vol.18	100,00	84,44	100,00	74,14	100,00	94,39
Vol.19	100,00	100,81	100,00	97,34	100,00	98,72
Vol.20	100,00	47,97	100,00	52,85	100,00	83,02
Vol.21	100,00	36,73	100,00	42,36	100,00	87,18
Vol.22	100,00	90,51	100,00	81,51	100,00	95,09
Vol.23	100,00	126,64	100,00	113,98	100,00	102,05

Vol.24	100,00	118,91	100,00	102,96	100,00	104,49
Vol.25	100,00	113,64	100,00	130,12	100,00	104,20
Vol.26	100,00	56,89	100,00	57,95	100,00	86,67
Vol.27	100,00	114,96	100,00	95,33	100,00	102,28
Vol.28	100,00	68,04	100,00	67,56	100,00	93,91
Vol.29						
Vol.30	100,00	106,18	100,00	110,02	100,00	102,38
Vol.31	100,00	66,95	100,00	76,76	100,00	93,67
Vol.32	100,00	99,70	100,00	99,97	100,00	99,07
Vol.33	100,00	104,91	100,00	101,15	100,00	102,11
Vol.34	100,00	102,97	100,00	99,65	100,00	101,41
Vol.35	100,00	61,68	100,00	73,21	100,00	92,71
Vol.36	100,00	109,87	100,00	100,13	100,00	100,65
Vol.37	100,00	180,46	100,00	129,19	100,00	104,88
Vol.38	100,00	106,54	100,00	104,27	100,00	103,57
Vol.39	100,00	83,35	100,00	85,94	100,00	96,51
Vol.40	100,00	108,34	100,00	103,92	100,00	102,78
Vol.41	100,00	83,73	100,00	90,10	100,00	94,44
Vol.42	100,00	110,81	100,00	107,77	100,00	102,30

Table 4. *Raw and relative (to Day 0, in %) data from forehead wrinkles, obtained for each of the volunteers included in the study, after treatment with Serum A or Serum B.*

Attachment 3: Raw data Crow´s feet wrinkles

	CROW´S FEET WRINKLES RAW DATA					
	Area (mm2)		Lenght (mm)		Depth (mm)	
	D0	D28	D0	D28	D0	D28
Vol.1	12,13	10,92	41,12	34,46	0,112	0,105
Vol.2	48,58	51,38	100,08	97,68	0,355	0,349
Vol.3	17,07	14,92	43,50	35,92	0,174	0,167
Vol.4	13,51	15,43	36,01	37,11	0,131	0,135
Vol.5	36,32	32,68	105,75	92,19	0,102	0,095
Vol.6	22,16	13,96	54,81	37,86	0,144	0,129
Vol.7	19,67	15,24	35,70	31,38	0,209	0,195
Vol.8	57,38	58,20	115,70	117,86	0,220	0,225
Vol.9	23,47	22,03	33,41	31,88	0,251	0,232
Vol.10	16,10	11,12	41,48	36,34	0,128	0,112
Vol.11	34,71	32,90	62,50	55,40	0,247	0,242
Vol.12	34,41	31,20	64,64	54,77	0,259	0,245
Vol.13	36,42	29,60	65,13	53,94	0,290	0,263
Vol.14	32,26	31,24	68,92	69,4	0,172	0,167
Vol.15	7,39	6,89	24,73	19,67	0,089	0,085
Vol.16	6,83	8,05	15,96	21,50	0,134	0,130
Vol.17	13,37	11,61	29,63	24,43	0,231	0,222
Vol.18	33,11	30,36	61,20	59,77	0,249	0,233
Vol.19	26,93	27,12	52,15	53,74	0,194	0,196
Vol.20	6,29	4,55	12,35	5,54	0,232	0,222
Vol.21	24,18	19,33	45,43	37,86	0,229	0,215
Vol.22	51,87	50,28	94,24	90,99	0,267	0,260
Vol.23	43,90	40,94	81,83	83,40	0,183	0,179
Vol.24	12,58	14,09	25,86	26,91	0,214	0,219
Vol.25	35,10	25,00	61,73	55,92	0,201	0,180
Vol.26	36,52	27,67	97,13	69,70	0,129	0,121
Vol.27	40,78	37,26	76,68	60,90	0,228	0,217
Vol.28	15,73	14,75	33,65	32,27	0,163	0,159
Vol.29						
Vol.30	33,07	35,98	52,54	53,29	0,291	0,310
Vol.31	37,75	35,01	71,22	65,01	0,237	0,223
Vol.32	44,35	47,75	82,36	87,47	0,222	0,232
Vol.33	12,21	13,84	23,81	28,24	0,225	0,219
Vol.34	6,67	6,32	16,73	16,42	0,133	0,130
Vol.35	23,10	24,73	41,34	45,21	0,266	0,248

Vol.36	37,63	38,09	68,52	67,12	0,223	0,228
Vol.37	11,58	9,99	19,43	15,64	0,328	0,313
Vol.38	21,22	21,20	53,08	49,69	0,154	0,156
Vol.39	27,28	27,44	35,90	36,92	0,251	0,262
Vol.40	6,02	6,08	17,86	20,80	0,100	0,102
Vol.41	24,65	23,80	50,02	41,04	0,224	0,217
Vol.42	49,63	45,36	113,25	106,08	0,197	0,194

	CROW´S FEET WRINKLES RELATIVE TO D0					
	Area (%)		**Lenght (%)**		**Depth (%)**	
	D0	**D28**	**D0**	**D28**	**D0**	**D28**
Vol.1	100,00	90,02	100,00	83,80	100,00	93,75
Vol.2	100,00	105,76	100,00	97,60	100,00	98,31
Vol.3	100,00	87,40	100,00	82,57	100,00	95,98
Vol.4	100,00	114,21	100,00	103,05	100,00	103,05
Vol.5	100,00	89,98	100,00	87,18	100,00	93,14
Vol.6	100,00	63,00	100,00	69,07	100,00	89,58
Vol.7	100,00	77,48	100,00	87,90	100,00	93,30
Vol.8	100,00	101,43	100,00	101,87	100,00	102,27
Vol.9	100,00	93,86	100,00	95,42	100,00	92,43
Vol.10	100,00	69,07	100,00	87,61	100,00	87,50
Vol.11	100,00	94,79	100,00	88,64	100,00	97,98
Vol.12	100,00	90,67	100,00	84,73	100,00	94,59
Vol.13	100,00	81,27	100,00	82,82	100,00	90,69
Vol.14	100,00	96,84	100,00	100,70	100,00	97,09
Vol.15	100,00	93,23	100,00	79,54	100,00	95,51
Vol.16	100,00	117,86	100,00	134,71	100,00	97,01
Vol.17	100,00	86,84	100,00	82,45	100,00	96,10
Vol.18	100,00	91,69	100,00	97,66	100,00	93,57
Vol.19	100,00	100,71	100,00	103,05	100,00	101,03
Vol.20	100,00	72,34	100,00	44,86	100,00	95,69
Vol.21	100,00	79,94	100,00	83,34	100,00	93,89
Vol.22	100,00	96,93	100,00	96,55	100,00	97,38
Vol.23	100,00	93,26	100,00	101,92	100,00	97,81
Vol.24	100,00	112,00	100,00	104,06	100,00	102,34
Vol.25	100,00	71,23	100,00	90,59	100,00	89,55
Vol.26	100,00	75,77	100,00	71,76	100,00	93,80
Vol.27	100,00	91,37	100,00	79,42	100,00	95,18

Vol.28	100,00	93,77	100,00	95,90	100,00	97,55
Vol.29						
Vol.30	100,00	108,80	100,00	101,43	100,00	106,53
Vol.31	100,00	92,74	100,00	91,28	100,00	94,09
Vol.32	100,00	107,67	100,00	106,20	100,00	104,50
Vol.33	100,00	113,35	100,00	118,61	100,00	97,33
Vol.34	100,00	94,75	100,00	98,15	100,00	97,74
Vol.35	100,00	107,06	100,00	109,36	100,00	93,23
Vol.36	100,00	101,22	100,00	97,96	100,00	102,24
Vol.37	100,00	86,27	100,00	80,49	100,00	95,43
Vol.38	100,00	99,91	100,00	93,61	100,00	101,30
Vol.39	100,00	100,59	100,00	102,84	100,00	104,38
Vol.40	100,00	101,00	100,00	116,46	100,00	102,00
Vol.41	100,00	96,55	100,00	82,05	100,00	96,88
Vol.42	100,00	91,40	100,00	93,67	100,00	98,48

Table 5. *Raw and relative (to Day 0, in %) data from crow´s feet wrinkles, obtained for each of the volunteers included in the study, after treatment with Serum A or Serum B.*

Attachment 4: Consumption control

	VOLUNTEER	BASAL WEIGHT (g)	WEIGHT AFTER 28 DAYS (g)	PRODUCT USED AFTER 28 DAYS (g)
Face Saerum A	1	147,8	122,2	25,6
	2	146,9	103,2	43,7
	3	148	104,1	43,9
	4	146,9	116,9	30
	5	149,1	122,3	26,8
	6	147,2	125,1	22,1
	7	148	129,8	18,2
	8	146,8	123,1	23,7
	9	149,2	130,3	18,9
	10	147,9	121,3	26,6
	11	149,2	132,6	16,6
	12	149,4	103,6	45,8
	13	147,2	134,8	12,4
	14	147,5	130,2	17,3
	15	148	130,7	17,3
	16	150,4	113,3	37,1
	17	149	133	16
	18	148,6	120,6	28
	19	148,7	136,2	12,5
	20	149	125,2	23,8
	41	149,2	133,1	16,1
Face Serum B	21	149	130,1	18,9
	22	150,4	124	26,4
	23	148,9	123	25,9
	24	147,3	97	50,3
	25	147,8	120,7	27,1
	26	149,6	122,5	27,1
	27	149,6	124,8	24,8
	28	147,2	117,7	29,5
	29	151,8		151,8
	30	147,3	134,1	13,2
	31	148,8	135,1	13,7
	32	145,4	120	25,4
	33	149	121,1	27,9
	34	147,3	133	14,3
	35	146	140,2	5,8
	36	147,7	127	20,7
	37	147,2	129,9	17,3
	38	148,8	127	21,8
	39	147,2	130,7	16,5
	40	147,9	121,6	26,3
	42	149,1	129,3	19,8

Attachment 5: Raw data from self-assessment questionnaires

Serum A																					
VOLUNTEER	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**41**
COSMETIC ATTRIBUTES																					
1.The application of the product is easy	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	2	3	3	3
2.The texture of the product is pleasant	2	3	3	3	3	3	3	3	2	3	3	3	3	3	3	3	3	3	3	1	3
3.Product absorption is fast	2	3	3	3	3	3	3	3	2	3	3	3	3	3	2	3	3	2	3	3	3
4.The perfume of the product is pleasant	2	2	3	2	1	2	2	2	2	2	3	2	2	2	2	2	3	2	3	1	3
5.The colour of the product is nice	1	2	3	2	2	3	2	3	2	2	3	3	2	2	3	2	3	3	3	3	3
6.The product oils the skin	1	1	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	1	1	1	1
COSMETIC EFFECTIVENESS																					
7.The contour of my face appears smoothed	3	2	2	2	2	2	2	2	2	2	2	3	1	2	2	2	1	2	3	3	2
8.My neck jowl has been reduced	1	2	2	2	1	1	2	1	1	2	1	1	1	2	1	1	1	1	2	2	1
9.My skin is pulped	3	3	2	2	1	2	2	2	2	2	2	3	1	3	2	2	1	2	3	2	2
10.My skin looks younger	2	2	2	2	1	2	2	2	2	2	2	3	1	2	2	2	1	2	3	2	2
11.My skin is firmer	2	2	3	1	1	2	2	2	1	2	3	3	1	2	3	3	2	1	3	2	2
12.My wrinkles appear reduced	3	2	3	2	1	2	2	3	2	3	2	2	1	3	3	2	1	2	3	3	2
13.My skin is smoother	3	3	3	2	1	2	2	3	2	2	3	2	2	3	1	3	1	1	3	2	2
14.My skin seems more radiant	2	2	3	2	1	1	2	2	1	3	2	3	1	2	1	3	1	1	3	2	2
15.My skin seems more flexible (elastic)	2	3	2	2	1	2	2	3	2	3	2	2	2	2	2	3	1	2	3	3	2
16.The treatment unifies the skin tone.	1	3	2	1	1	2	2	3	1	2	2	1	1	2	2	2	1	1	3	2	2
17.The treatment reduces the presence of dark spots	1	2	3	1	1	1	3	2	2	2	1	1	1	2	1	1	1	1	2	2	2
18.The treatment brightness my skin	2	3	2	2	1	2	2	3	2	3	2	2	2	2	2	3	1	2	2	2	2
19.The treatment improves visually the quality of my skin	3	3	3	2	1	2	2	3	2	3	2	3	2	2	2	3	1	2	2	3	2
CONSUMER OPINION																					
20.I am satisfied with the treatment received	2	3	3	2	2	3	2	3	2	3	3	3	1	3	2	3	2	2	3	3	3
21.I would use the treatment again	2	3	3	2	1	3	2	3	2	3	3	3	1	3	2	3	1	2	3	3	3
22.I would recommend the treatment	2	3	3	2	1	3	2	3	2	3	3	3	1	3	2	3	1	2	3	3	3
23. I will buy the global treatment	2	3	3	2	1	2	2	3	2	2	2	2	1	3	2	3	1	2	2	2	3

SERUM B																					
VOLUNTEER	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**42**
COSMETIC ATTRIBUTES																					
1.The application of the product is easy	3	3	2	3	3	2	3	3	2	3	3	3	3	3	3	3	3	3	3	3	3
2.The texture of the product is pleasant	3	3	3	3	3	2	3	3	2	2	3	3	2	1	3	3	3	3	3	3	2
3.Product absorption is fast	2	3	3	3	3	2	3	3	3	2	3	2	3	2	2	3	3	3	3	3	3
4.The perfume of the product is pleasant	3	3	2	2	1	2	3	3	1	3	2	3	2	3	3	3	3	3	2	2	2
5.The colour of the product is nice	3	3	3	1	2	1	3	3	2	2	3	3	2	2	3	3	3	3	2	2	3
6.The product oils the skin	1	1	1	1	3	1	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1
COSMETIC EFFECTIVENESS																					
7.The contour of my face appears smoothed	2	2	2	2	2	1	2	2	2	3	3	1	2	2	2	2	2	1	2	2	2
8.My neck jowl has been reduced	1	2	1	2	2	1	2	1	1	1	1	1	2	1	2	2	2	1	1	2	1
9.My skin is pulped	2	2	2	3	2	1	3	2	2	3	2	1	2	1	2	3	2	1	2	2	1
10.My skin looks younger	3	2	2	1	2	1	2	2	2	2	2	1	2	1	2	2	3	1	2	2	1
11.My skin is firmer	2	2	2	3	2	1	3	1	2	2	2	1	2	2	2	2	2	2	2	2	2
12.My wrinkles appear reduced	2	2	2	1	2	1	3	2	2	2	3	1	2	1	2	2	2	2	2	2	2
13.My skin is smoother	3	2	2	3	3	2	3	2	2	3	3	1	3	1	2	2	3	2	2	2	1
14.My skin seems more radiant	2	2	2	3	2	1	3	1	1	2	2	1	2	1	1	2	2	2	1	2	2
15.My skin seems more flexible (elastic)	2	2	2	3	2	1	2	2	1	2	2	1	2	1	2	3	2	2	2	2	2
16.The treatment unifies the skin tone.	2	3	2	3	2	1	2	2	2	2	2	1	2	1	2	3	3	2	2	2	2
17.The treatment reduces the presence of dark spots	1	3	1	2	1	1	2	1	3	2	2	1	2	1	1	2	2	2	2	2	1
18.The treatment brightness my skin	3	3	2	3	2	1	3	2	2	2	2	1	2	1	1	2	3	2	2	2	2
19.The treatment improves visually the quality of my skin	2	3	2	2	2	1	3	2	3	2	2	1	2	1	1	3	2	2	1	2	2
CONSUMER OPINION																					
20.I am satisfied with the treatment received	3	3	2	2	2	1	3	3	3	3	3	2	2	1	2	3	2	2	3	3	2
21.I would use the treatment again	3	3	2	3	2	1	3	3	3	3	3	1	2	2	2	3	2	2	3	3	2
22.I would recommend the treatment	3	3	2	3	2	1	2	3	2	3	3	1	2	1	1	3	1	2	3	3	2
23.I will buy the global treatment	2	3	2	3	2	1	3	2	2	3	3	1	2	1	1	2	1	2	2	2	2

Attachment 6: Images

All images are enclosed in a digital file, together with this report, with the following folder structure:

822.– Bio-Botanica – Antiwrinkles Test

- **Digital Pictures**
  - **V01**
    - V1 basal.jpg
    - V1 final.jpg

- **Wrinkles 3D Pictures**
  - **V01**
    - Frontal.tif
    - Lateral.tif
    - Frontal_0.jpg
    - Frontal_28.jpg
    - Lateral_0.jpg
    - Lateral_28.jpg

Explanation of Figures:

- Frontal_0.tif: Frontal 2D picture included in the set used for the 3D reconstruction (wrinkles topography in forehead) before the treatment (D0).
- Frontal_28.tif: Frontal 2D picture included in the set used for the 3D reconstruction (wrinkles topography in forehead) after the treatment (D28).
- Lateral_0.tif: Lateral 2D picture included in the set used for the 3D reconstruction (wrinkles topography in crow's feet) before the treatment (D0).
- Lateral_28.tif: Lateral 2D picture included in the set used for the 3D reconstruction (wrinkles topography in crow's feet) after the treatment (D28).
- Frontal.jpg: Region of Interest (ROI) selected from the crow's feet area, extraction of wrinkles in the ROI (the bluer, the deeper wrinkles, the greener, the smooth area), wrinkles without background and wrinkles without background including depth analysis; at each of the time points (D0, above / D28, below).

- Lateral.jpg: Region of Interest (ROI) selected from the crow's feet area, extraction of wrinkles in the ROI (the bluer, the deeper wrinkles, the greener, the smooth area), wrinkles without background and wrinkles without background including depth analysis; at each of the time points (D0, above / D28, below).

Attachment 7: Informed Consent

Nº VOLUNTARIO: ____

INFORMACIÓN Y AUTORIZACIÓN DE PARTICIPACIÓN EN EL ENSAYO	
Código de Protocolo: ESTUDIO *IN VIVO* 822.20.10	Promotor: BIO BOTANICA
Fecha de la versión: 19/10/2020	Investigador Principal: Dr. Jose Luis Mullor SanJosé Dr. Joan Castells Ballester
CENTRO: BIONOS BIOTECH S.L.	

CONSENTIMIENTO INFORMADO:

Yo, _____

- He comprendido la información que se me ha facilitado.
- He podido hacer preguntas sobre el estudio.
- He recibido suficiente información sobre el estudio.
- Comprendo que mi participación es voluntaria.

AUTORIZACIÓN DE CESIÓN DERECHOS DE IMAGEN:
Al amparo de lo dispuesto en la Ley Orgánica 1/ 1982, de 5 de Mayo, de protección civil del derecho al honor, a la intimidad personal y familiar y a la propia imagen, como parte del estudio citado y en la hipótesis de una futura explotación publicitaria de los productos testados:

El cedente autoriza la reproducción y difusión de las mencionadas imágenes, o partes de las mismas con las siguientes condiciones:

- La cesión se efectúa a título gratuito; el cedente no recibe contraprestación alguna a cambio de la cesión de sus derechos de imagen.
- El promotor únicamente podrá identificarme por mi código de voluntario y no tendrá acceso a mis datos personales.
- Para marketing / publicidad, con la única salvedad y limitación de aquellas utilizaciones o aplicaciones que puedan atentar al derecho al honor en términos previstos en la Ley orgánica 1/1982.

Autorizo al Promotor del estudio a usar mi imagen/registros audiovisuales

SI ☐ NO* ☐

Apruebo la presente autorización

Firmado en Valencia a _____/_____/2020

Autorizo al Promotor del estudio a usar mi imagen/registros audiovisuales