Assessment of the efficacy of a cosmetic ingredient claiming antiageing efficacy

KERAT'INNOV

CYNATINE® TOP

(batch no. K180021)

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STUDY DESIGN

1.1. Title

Assessment of the efficacy of a cosmetic ingredient claiming antiageing efficacy.

1.2. Aim of the study

The study is aimed to assess the efficacy of a cosmetic ingredient claiming antiageing efficacy. In order to reach this goal a clinical study is carried out on 40 (n=20 active group, n=20 placebo group) healthy female subjects showing the clinical signs of skin ageing on the face. The ingredient is tested in a base cosmetic formulation. Product efficacy is assessed both objectively and subjectively (self-assessment).

1.3. Tested products

1.3.1. Information provided by the Customer

☒ Products identification: **CYNATINE® TOP** (batch no. K180021)

☒ Way of use: the product was used twice per day (in the morning and in the evening) on clean skin.

☒ The tested cosmetic products conform to Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products (recast) (Text with EEA relevance) and to its annexes.

☒ The cosmetic product to be tested is safe under normal or reasonably foreseeable conditions of use.

☒ Qualitative EU INCI formula. The ingredient was formulated at 0.5% concentration in a leave on formulation. The ingredient INCI name is "*Hydrolyzed Keratin Peptide Powder*". The placebo formulation is the same of the active formulation except for the active ingredient.

Ingredients. AQUA (WATER), COCO CAPRYLATE/CAPRATE, PRUNUS AMYGDALUS DULCIS OIL, GLYCERYL STEARATE, CETYL ALCOHOL, CETEARYL ALCOHOL, STEARIC ACID, SODIUM LAUROYL GLUTAMATE, HYDROLYZED KERATIN PEPTIDE POWDER (0.5%), TOCOPHERYL ACETATE, PHENOXYETHANOL, SODIUM BENZOATE, POTASSIUM SORBATE, SODIUM DEHYDROACETATE, LACTIC ACID, PARFUM (FRAGRANCE).

1.4. Ethical requirements

The study is carried out according the ethical requirements listed here below.

1.4.1. All participants in the study are healthy volunteers, aged over 18 years old.

1.4.2. All participants in the study are screened and enrolled under the supervision of an experimenter, according to specific inclusion/non-inclusion criteria.

1.4.3. Volunteers participation in the study is free.

1.4.4. All participants in the study are informed of the aim and the nature of the study.

1.4.5. All participants in the study are informed of the possible risks involved in the study.

1.4.6. All participants in the study sign a written consent form before the study begins.

1.4.7. Before volunteers are exposed to the tested product, all safety information regarding the product and its individual ingredients are assessed.

1.4.7. All the study procedures are carried out in compliance with the ethical principles for medical research (Ethical Principles for Medical Research Involving Human Subjects, Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and its amendment).

1.4.9 All the precautions are taken in order to avoid adverse reactions occurrence.

1.4.10 In case of non-expected/adverse reaction occurrence the medical investigating specialist evaluate the severity of the reaction (reporting it in the data collecting sheet of the volunteer) and as a consequence start the appropriate therapy.

1.5. Subjects participating in the study

1.5.1. Subjects enrolment

The subjects participating in the study are screened and enrolled in the study under the supervision of a board certified dermatologist from a panel of healthy female subjects, in accordance with the inclusion and non-inclusion criteria reported in the sections here below.

1.5.1.1. Inclusion criteria

☑ Healthy female subjects

☑ Caucasian ethnicity

☑ Age between 40 and 65 years old

☑ Mild to moderate ageing signs (both chronoageing and photoageing)

☑ Subjects who have not been recently involved in any other similar study

☑ Willingness to not use during all the study period topic products with similar effect to that one of the product to be tested

☑ Willingness to not vary the normal daily routine

☑ Subject is under effective contraception (oral/not oral) therapy

1.5.1.2. Non-inclusion criteria

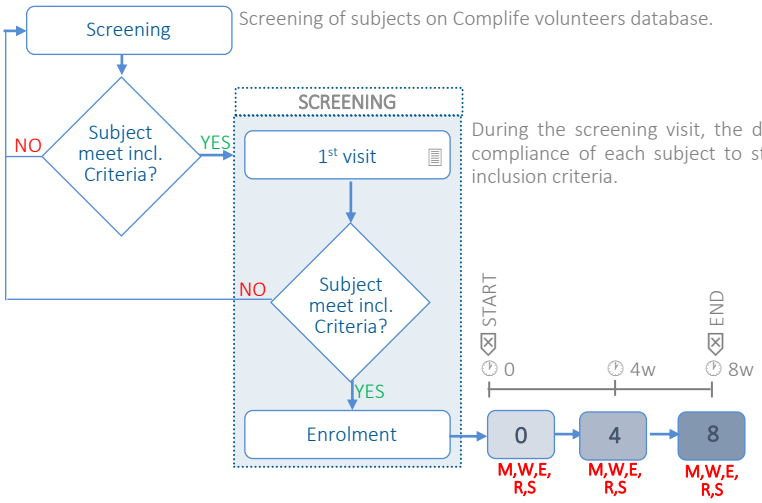
✘ Subject does not meet the inclusion criteria

- ✘ Positive history for atopy or hypersensitive skin
- ✘ Past history of allergy or sensitivity to cosmetics, toiletries, to solar and/or topical medications
- ✘ Any skin condition that the principal investigator deems inappropriate for participation
- ✘ Pregnancy or nursing women
- ✘ Impaired immune system due to immunosuppressive diseases such as AIDS and HIV, or use of immunosuppressive medications
- ✘ Pharmacological treatments (topic or systemic) known to interfere with skin metabolism/physiology
- ✘ Severe concurrent diseases
- ✘ Adult protected by the law (under guardianship, or hospitalized in a public or private institution, for a reason other than the research, or incarcerated)
- ✘ Subject is unable to communicate or cooperate with the Investigator due to language problems, poor mental development, or impaired cerebral function

1.6. Study development

The study flow and the schedule of assessments chart is reported in figure 1.6.1.

Figure 1.6.1 Study flow and schedule of assessments chart



Legend. **M** Skin moisturization | **W** Wrinkle depth | **E** Skin elasticity | **R** Skin radiance | **S** Self-assessment questionnaire

1.7. MATERIALS AND METHODS

In the sections here below are reported the materials and the methods employed in the study.

1.7.1. Method of assigning subjects to treatment (randomization)

Subjects are assigned to treatment groups using a computer-generated restricted randomization list (PASS 11, version 11.0.8; PASS, LLC. Kaysville, UT, USA). The study adheres to establish procedures to maintain separation between the investigator and her collaborators and the staff that will deliver the intervention. Investigator and her collaborators who will obtain outcome measurements are not informed on the product group assignment. Staff who deliver the intervention does not take outcome measurements. Subjects, investigator and her collaborators are kept masked to products assignment.

1.7.2. Skin moisturization

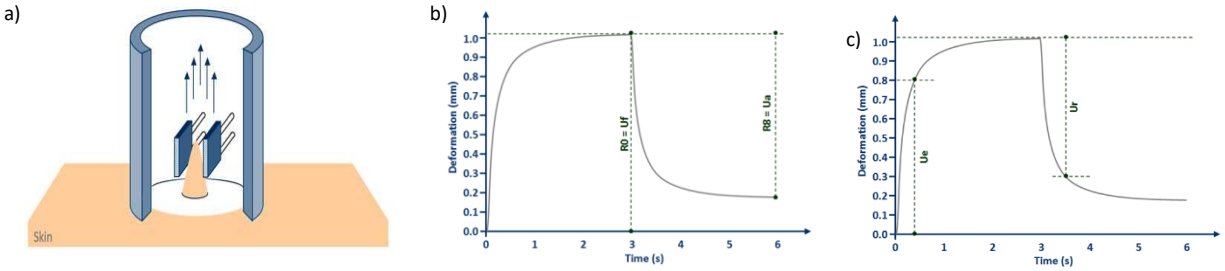
The measurement of skin moisturization is based on the Corneometer® method. The corneometer® method is based on the dielectric constant of water. The probe shows changes of capacitance according to the moisture content of the skin. An electric scatter field penetrates the very first layers of the skin (10-20 µm) and determines the dielectricity. The used device is the Corneometer® CM 825 (Courage+Khazaka, electronic GmbH). Skin moisturization is measured in the cheek.

1.7.3. Skin elasticity

The measurement of skin elasticity is based on the suction method using a negative pressure mechanically deforming the skin (Cutometer® method). A Negative pressure (450 mbar) is created in the device and the skin is drawn into the aperture of the probe for 2 seconds and after a defined time (2 seconds) released again. Inside the probe, the penetration depth is determined by a non-contact optical measuring system. The optical measuring system consists of a light source and a light receptor, as well as two prisms facing each other, which project the light from transmitter to receptor. The light intensity varies due to the penetration depth of the skin. The resistance of the skin to the negative pressure and its ability to return into its original position are displayed

as curves (penetration depth in mm/time) in real time during the measurement. The used device is the Cutometer® MPA 580 (Courage+Khazaka, electronic GmbH). Skin elasticity is measured in the cheek. R2 and R5 parameters are measured (Fig. 1.7.3.1).

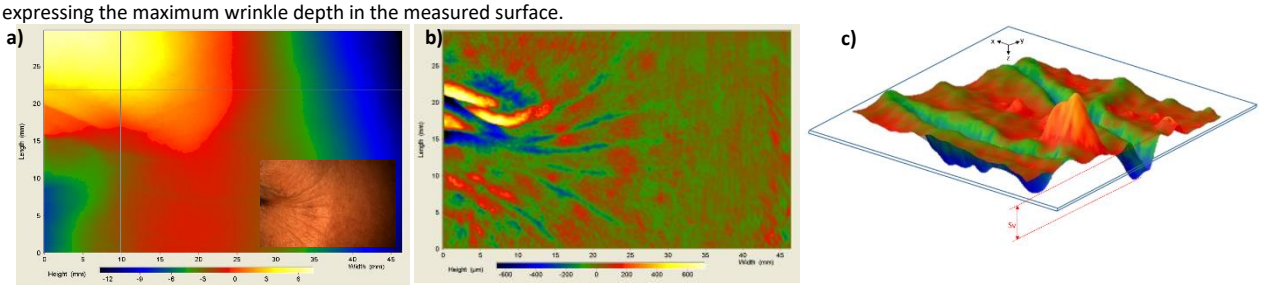
Figure 1.7.3.1. (a) Skin elasticity measurement process. (b) R2 (Ua/Uf, overall elasticity) represents the ability of the skin to return to its basal state. (c) R5 (Ur/Ue, net elasticity) represent the elastic recovery of the skin to its basal state due to its elastic component after deformation. The parameter decays with ageing and it is independent of the skin thickness.)



1.7.4. Wrinkle depth

Wrinkle depth, in the "crow's feet" area, is measured using a real 3D microtopography imaging system (Primos[lite] GFMesstechnik GmbH). Skin surface is reconstructed using an algorithm to generate 3D images (Fig. 1.7.4.1). Subjects repositioning is ensured by a repositioning device (Canfield Scientific); while before/after images matching is ensured by an overlapping feature of the image analysis software

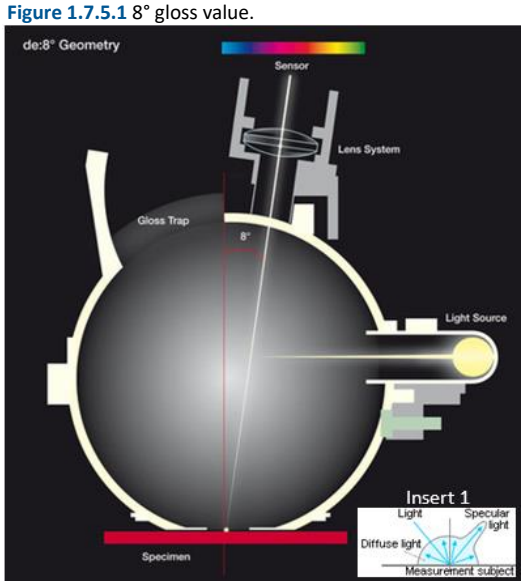
Figure 1.7.4.1 Wrinkle depth measurement using Primos 3D lite. (a) Point cloud image (data point defined by x, y, and z coordinates intended to represent the external surface of the skin). In the insert is shown the original 2D picture of the area to be measured. (b) Skin microtopography reconstruction by temporal phase shift algorithm. (c) Sv parameter (maximum wrinkle depth). Sv is a 3D parameter expressing the maximum wrinkle depth in the measured surface.



1.7.5. Skin radiance

Skin radiance is measured using a spectrophotometer/colorimeter CM 700D (Konica Minolta). The measured parameter is the 8° gloss value (Fig. 1.7.5.1).

Figure 1.7.5.1 8° gloss value.



When light reach a surface it is reflected at the equal but opposite angle from the light source; this is called specularly reflected light. This specular component is reflected as if reflected by a mirror. The light that is not specularly reflected, but scattered in many directions, is called diffuse reflectance (insert 1). The sum of the specular reflectance plus the diffuse reflectance is called the total reflectance. For objects with shiny surfaces, the specularly reflected light is relatively strong and the diffused light is weaker. On rough surfaces with a low gloss, the specular component is weak and the diffused light is stronger.

The measuring geometry d:8° features an optical device which provides diffuse illumination (Ulbricht sphere). The light (Xenon lamp) is projected into a sphere. The interior of the sphere is coated with a white highly reflecting substance (barium sulphate, ceramic, special plastic) which reflects the light manifold. A shutter, an optical element inside the sphere, prevents the directional rays from reaching the measuring sample directly. The sample is positioned at an opening of the sphere and is illuminated from all directions with a close to perfect diffuse light. Through an opening at the top of the sphere the sensor is viewing the surface being measured with an angle of 8° to the vertical. In order to prevent reflection of specular light from the sample surface, the instrument feature a gloss trap. When the trap which is arranged with an angle of -8° to the viewing opening, is open, the light which would otherwise be reflected from the interior wall of the sphere, will be eliminated and can therefore not illuminate the sample. The relation between directional and diffuse reflection allows calculating the gloss component. The measuring system including gloss is named di:8° whilst the measuring system excluding gloss is described as de:8°.

1.7.3. Self-assessment

Subjects are asked to give their opinion on the tested product by means of a self-assessment questionnaire.

1.8. Results and statistic

1.8.1. Results

Results are reported in tables in their respective units.

1) Mean values are calculated as:

$$m = \frac{\sum_{1}^{n} p}{n}$$

where: p is the value of the parameter under analysis; n is the number of subjects participating in the study

2) Percentages are calculates as follows:

$$\%var.vs.T0 = \left(\sum_{1}^{n} \frac{p_t - p_0}{p_0} \right) x100$$

or

$$\%of\ subjects = \left(\frac{\sum_{1}^{n} answers}{n} \right) x100$$

where: p_t is the value of the parameter under analysis after product application; p_0 is the value of the parameter under analysis before product application; n is the number of subjects participating in the study

3) The mean standard error of data is calculated as:

$$SEM. = \frac{\sqrt{\frac{\sum_{1}^{n}(p_i^2) - \frac{\sum_{1}^{n} p_i^2}{n}}{(n-1)}}}{\sqrt{n}}$$

where: p is the value of the parameter under; n is the number of subjects participating in the study

All the calculations are done using a Microsoft® Excel 2013 (vers. 15.0.4997.1000; Microsoft, USA) worksheet running on Microsoft® Windows 10 Professional (Microsoft, USA).

1.8.2. Statistical analysis

Data are submitted to two-way t test of Student statistical test. Statistical analysis is carried out using a Microsoft® Excel 2013 (vers. 15.0.4997.1000; Microsoft, USA worksheet running on Microsoft® Windows 10 Professional (Microsoft, USA).

1.9 Interpretation of results

The study here above reported was designed to demonstrate the test product claim(s) in the current framework proposed by Commission Regulation (EU) No 655/2013. Endpoints are measured using techniques currently accepted in the cosmetic field while biases are minimized by procedure(s) standardization according to ISO 9001 Quality Management System. Data are analyzed and interpreted by skilled technician according to both descriptive and inferential statistical analysis procedures. Due to the lack of reference values in the cosmetic field, statistical significance (for instrumental analysis) and percentage of subjects showing an effect (for clinical/sensorial endpoints) are the primary criterion to evaluate the correspondence between the proposed claim(s) and the study output(s). In particular Intragroup (vs. T0) or intergroup (e.g. active vs. placebo, treated vs. non-treated) statistical analysis criterion to reject the null hypothesis (no product effect) is set at $p<0.05$. For clinical evaluations, the positive effect of the product on the measured parameter is confirmed if more than 50% of the subjects register an improvement. Finally, for the self-assessment questionnaires, the performance and the pleasantness of the product must be perceived by at least 60% of the subjects. Whenever reference values or threshold values exists that values are used to validate product claim(s).

1.10. Report change record

The table here below reports the change log of all approved changes made to the document that make up the course after initial approval.

Rev. no	Date	Description
00	12/04/2019	First release
01	18/04/2019	Minor modification
02	18/04/2019	Minor modification

RESULTS: SKIN MOISTURIZATION

Table 1 The table here below reports the data obtained for each subject participating in the study. Data are reported as corneometric units (cu).

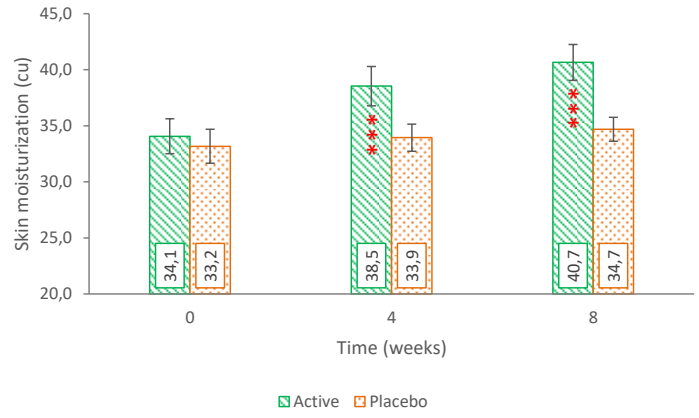
ACTIVE GROUP

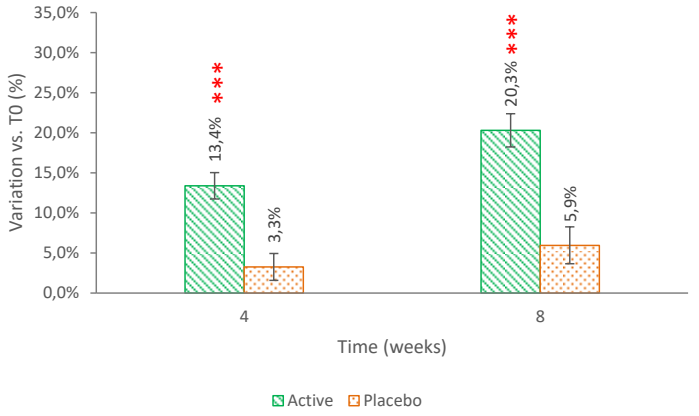
no.	Vol. ID	0	4w	8w	Variation vs. T0	4w	8w
01	A3893A	29,8	34,2	37,6		14,8%	26,2%
02	G0656C	39,4	45,3	46,4		15,0%	17,8%
03	M3265G	51,0	55,3	61,4		8,4%	20,4%
04	M0196D	47,1	53,3	48,4		13,2%	2,8%
05	G0147G	36,1	41,9	44,7		16,1%	23,8%
06	M3715F	29,7	31,7	34,7		6,7%	16,8%
07	C0052P	23,7	30,1	32,8		27,0%	38,4%
08	L2065A	28,1	37,1	39,8		32,0%	41,6%
09	B1572C	41,5	51,3	51,8		23,6%	24,8%
10	S0379S	40,8	46,6	45,4		14,2%	11,3%
11	C0771F	39,0	40,8	41,8		4,6%	7,2%
12	P0402S	30,4	35,2	38,2		15,8%	25,7%
13	C3983L	34,7	36,4	39,0		4,9%	12,4%
14	F1334T	29,0	30,4	34,8		4,8%	20,0%
15	S0872M	30,4	34,3	36,7		12,8%	20,7%
16	R0855P	31,9	34,4	35,8		7,8%	12,2%
17	C0768G	29,2	31,8	35,0		8,9%	19,9%
18	C4074A	30,2	34,3	36,3		13,6%	20,2%
19	P1433E	29,1	31,3	34,1		7,6%	17,2%
20	A0486S	30,2	35,0	38,3		15,9%	26,8%
	Mean	**34,1**	**38,5**	**40,7**		**13,4%**	**20,3%**
	SE	1,6	1,8	1,6	Min	4,6%	2,8%
	t test vs. T0	---	0,0000	0,0000	Max	32,0%	41,6%

PLACEBO GROUP

no.	Vol. ID	0	4w	8w	Variation vs. T0	4w	8w
01	R0333S	24,7	31,0	31,2		25,5%	26,3%
02	B1495M	32,2	34,9	36,2		8,4%	12,4%
03	D0097E	39,3	41,5	39,4		5,6%	0,3%
04	V3024C	54,4	51,6	49,8		-5,1%	-8,5%
05	G0165F	34,4	32,9	36,2		-4,4%	5,2%
06	Z3554A	27,2	29,3	27,0		7,7%	-0,7%
07	M1721L	36,9	38,9	38,0		5,4%	3,0%
08	G0166R	44,8	38,3	39,3		-14,5%	-12,3%
09	M2006A	26,5	27,8	34,4		4,9%	29,8%
10	L4007M	29,3	30,1	35,8		2,7%	22,2%
11	M4075E	28,1	30,2	30,2		7,5%	7,5%
12	G4078S	31,0	30,9	31,0		-0,3%	0,0%
13	B4079M	31,3	32,2	32,2		2,9%	2,9%
14	F4076F	30,8	30,9	31,6		0,3%	2,6%
15	M1950M	34,2	35,0	35,1		2,3%	2,6%
16	S4073L	34,1	35,4	35,7		3,8%	4,7%
17	C3711A	30,3	30,2	32,1		-0,3%	5,9%
18	01603G	29,8	32,2	32,3		8,1%	8,4%
19	M4081A	32,1	33,2	33,7		3,4%	5,0%
20	M1591D	32,0	32,4	32,5		1,3%	1,6%
	Mean	**33,2**	**33,9**	**34,7**		**3,3%**	**5,9%**
	SE	1,5	1,2	1,1	Min	-14,5%	-12,3%
	t test vs. T0	---	0,1797	0,0476	Max	25,5%	29,8%

Figure 1 a) The graph shows the product effect on the measured parameter (raw data) reported here above. b) The graph shows the product effect on the measured parameter (% variation vs. T0) reported here above. Data are reported as mean ± SE. Inside the bars is reported the intragroup (vs. T0) statistical analysis. Upon the bars is reported the intergroup (active(s) vs. placebo) statistical analysis. Statistical significance is reported as follows: * p<0.05, ** p<0.01, *** p<0.001.





Comment. The active ingredient is effective in improving skin moisturization. The percentage variation of the parameter improvement is statistically significant when compared to the placebo product.

Table 1a. Intergroup statistical analysis output

	4w	8w
Active vs. Placebo	0.000	0.000

RESULTS: SKIN ELASTICITY, R2 PARAMETER, OVERALL ELASTICITY

Table 2 The table here below reports the data obtained for each subject participating in the study. Data are reported as Ua/Uf ratio.

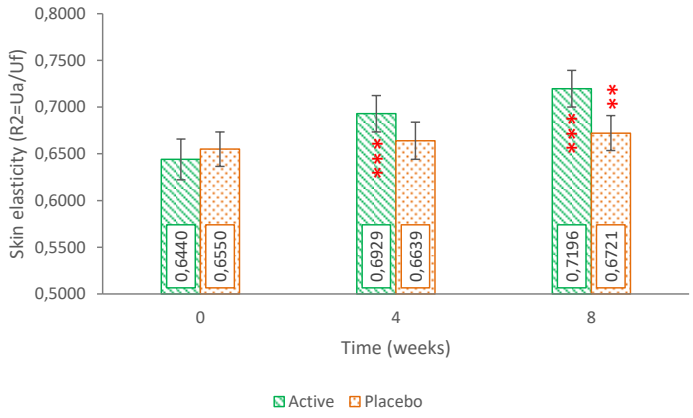
ACTIVE GROUP

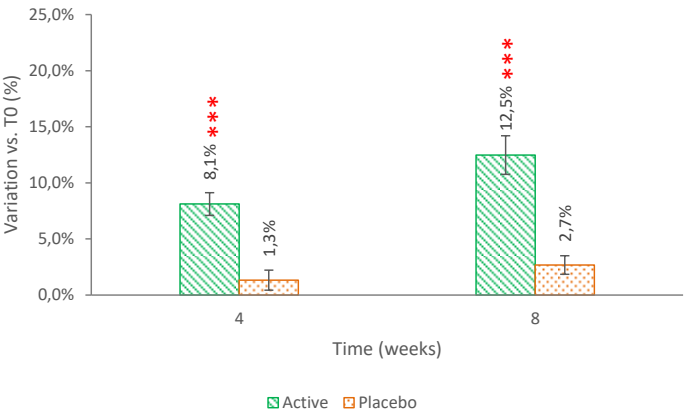
no.	Vol. ID	0	4w	8w	Variation vs. T0	4w	8w
01	A3893A	0,6193	0,6450	0,6623		4,1%	6,9%
02	G0656C	0,7612	0,7806	0,8514		2,5%	11,8%
03	M3265G	0,5905	0,6511	0,6855		10,3%	16,1%
04	M0196D	0,6117	0,6453	0,6335		5,5%	3,6%
05	G0147G	0,6678	0,7401	0,7847		10,8%	17,5%
06	M3715F	0,6768	0,7234	0,7517		6,9%	11,1%
07	C0052P	0,6327	0,6525	0,6660		3,1%	5,3%
08	L2065A	0,6055	0,6682	0,6613		10,4%	9,2%
09	B1572C	0,6955	0,7724	0,8124		11,1%	16,8%
10	S0379S	0,5817	0,6212	0,7151		6,8%	22,9%
11	C0771F	0,4597	0,5378	0,5539		17,0%	20,5%
12	P0402S	0,8221	0,8531	0,8536		3,8%	3,8%
13	C3983L	0,6360	0,7054	0,7480		10,9%	17,6%
14	F1334T	0,7199	0,7508	0,7511		4,3%	4,3%
15	S0872M	0,4241	0,5058	0,5690		19,3%	34,2%
16	R0855P	0,5722	0,6304	0,6388		10,2%	11,6%
17	C0768G	0,7655	0,7907	0,7980		3,3%	4,2%
18	C4074A	0,7500	0,7944	0,8246		5,9%	9,9%
19	P1433E	0,6124	0,6692	0,6738		9,3%	10,0%
20	A0486S	0,6749	0,7212	0,7567		6,9%	12,1%
	Mean	**0,6440**	**0,6929**	**0,7196**		**8,1%**	**12,5%**
	SE	0,0218	0,0195	0,0196	Min	2,5%	3,6%
	t test vs. T0	---	0,0000	0,0000	Max	19,3%	34,2%

PLACEBO GROUP

no.	Vol. ID	0	4w	8w	Variation vs. T0	4w	8w
01	R0333S	0,6181	0,6163	0,6424		-0,3%	3,9%
02	B1495M	0,6172	0,6935	0,6941		12,4%	12,5%
03	D0097E	0,6422	0,6411	0,6902		-0,2%	7,5%
04	V3024C	0,6545	0,6996	0,6683		6,9%	2,1%
05	G0165F	0,7348	0,7147	0,7415		-2,7%	0,9%
06	Z3554A	0,6954	0,7176	0,7023		3,2%	1,0%
07	M1721L	0,5680	0,5507	0,6143		-3,0%	8,2%
08	G0166R	0,7370	0,7372	0,7168		0,0%	-2,7%
09	M2006A	0,6254	0,6570	0,6508		5,1%	4,1%
10	L4007M	0,6102	0,5754	0,5970		-5,7%	-2,2%
11	M4075E	0,7349	0,7391	0,7455		0,6%	1,4%
12	G4078S	0,8243	0,8599	0,8560		4,3%	3,8%
13	B4079M	0,5000	0,5051	0,5096		1,0%	1,9%
14	F4076F	0,7657	0,7700	0,7701		0,6%	0,6%
15	M1950M	0,5722	0,5506	0,5565		-3,8%	-2,7%
16	S4073L	0,5416	0,5575	0,5548		2,9%	2,4%
17	C3711A	0,6124	0,6241	0,6247		1,9%	2,0%
18	01603G	0,6749	0,6832	0,7059		1,2%	4,6%
19	M4081A	0,6360	0,6383	0,6411		0,4%	0,8%
20	M1591D	0,7349	0,7479	0,7601		1,8%	3,4%
	Mean	**0,6550**	**0,6639**	**0,6721**		**1,3%**	**2,7%**
	SE	0,0184	0,0199	0,0187	Min	-5,7%	-2,7%
	t test vs. T0	---	0,1289	0,0035	Max	12,4%	12,5%

Figure 2 a) The graph shows the product effect on the measured parameter (raw data) reported here above. b) The graph shows the product effect on the measured parameter (% variation vs. T0) reported here above. Data are reported as mean ± SE. Inside the bars is reported the intragroup (vs. T0) statistical analysis. Upon the bars is reported the intergroup (active(s) vs. placebo) statistical analysis. Statistical significance is reported as follows: * p<0.05, ** p<0.01, *** p<0.001.





Comment. The active ingredient is effective in improving skin overall elasticity. The percentage variation of the parameter improvement is statistically significant when compared to the placebo product.

Table 1a. Intergroup statistical analysis output

	4w	8w
Active vs. Placebo	0.000	0.000

RESULTS: SKIN ELASTICITY, R5 PARAMETER, NET ELASTICITY

Table 3 The table here below reports the data obtained for each subject participating in the study. Data are reported as Ur/Ue ratio.

ACTIVE GROUP

no.	Vol. ID	0	4w	8w		4w	8w
01	A3893A	0,3090	0,3640	0,3760		17,8%	21,7%
02	G0656C	0,4514	0,4550	0,4730		0,8%	4,8%
03	M3265G	0,2832	0,3010	0,3108		6,3%	9,7%
04	M0196D	0,3344	0,3490	0,3336		4,4%	-0,2%
05	G0147G	0,2269	0,3096	0,3147		36,4%	38,7%
06	M3715F	0,2150	0,2791	0,2535		29,8%	17,9%
07	C0052P	0,2391	0,2540	0,2674		6,2%	11,8%
08	L2065A	0,2148	0,2821	0,3037		31,3%	41,4%
09	B1572C	0,3281	0,3643	0,3816		11,0%	16,3%
10	S0379S	0,2429	0,2708	0,2947		11,5%	21,3%
11	C0771F	0,2056	0,2437	0,2415		18,5%	17,5%
12	P0402S	0,4889	0,4905	0,5011		0,3%	2,5%
13	C3983L	0,3622	0,3748	0,6578		3,5%	81,6%
14	F1334T	0,2864	0,2924	0,3456		2,1%	20,7%
15	S0872M	0,1534	0,1946	0,2686		26,9%	75,1%
16	R0855P	0,3394	0,3663	0,4122		7,9%	21,4%
17	C0768G	0,5404	0,6174	0,6203		14,2%	14,8%
18	C4074A	0,3238	0,3863	0,4089		19,3%	26,3%
19	P1433E	0,3022	0,3500	0,3896		15,8%	28,9%
20	A0486S	0,3483	0,3640	0,6265		4,5%	79,9%
	Mean	**0,3098**	**0,3454**	**0,3891**		**13,4%**	**27,6%**
	SE	0,0219	0,0213	0,0283	Min	0,3%	-0,2%
	t test vs. T0	---	0,0000	0,0002	Max	36,4%	81,6%

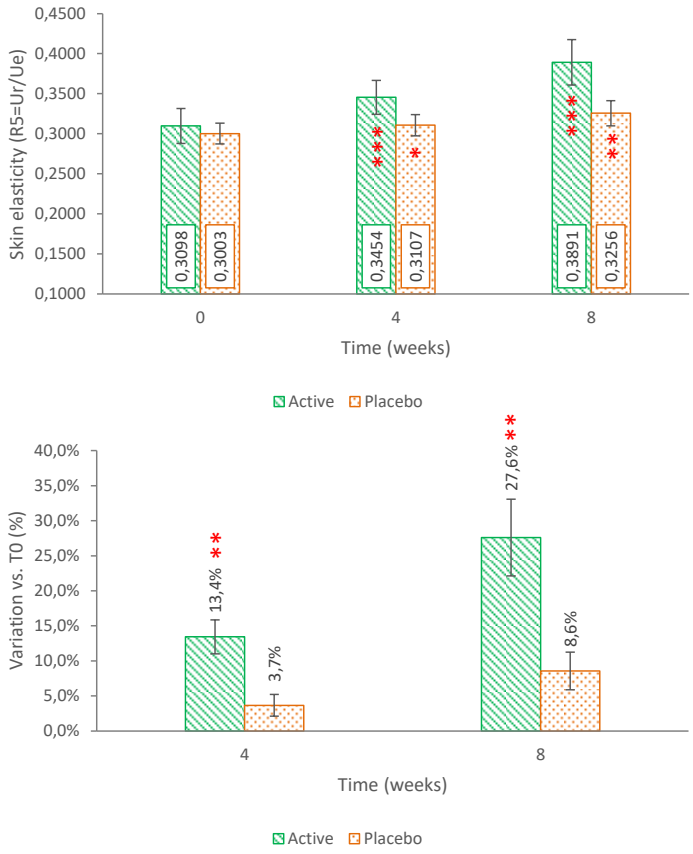
Variation vs. T0

PLACEBO GROUP

no.	Vol. ID	0	4w	8w		4w	8w
01	R0333S	0,2418	0,2582	0,2956		6,8%	22,2%
02	B1495M	0,3327	0,3438	0,3036		3,3%	-8,7%
03	D0097E	0,2770	0,2792	0,3160		0,8%	14,1%
04	V3024C	0,2376	0,2728	0,2418		14,8%	1,8%
05	G0165F	0,3628	0,3645	0,3939		0,5%	8,6%
06	Z3554A	0,2551	0,2482	0,2516		-2,7%	-1,4%
07	M1721L	0,2178	0,2008	0,2213		-7,8%	1,6%
08	G0166R	0,3633	0,3977	0,3660		9,5%	0,7%
09	M2006A	0,2571	0,3226	0,3025		25,5%	17,7%
10	L4007M	0,2714	0,2711	0,2333		-0,1%	-14,0%
11	M4075E	0,3793	0,3868	0,3915		2,0%	3,2%
12	G4078S	0,3239	0,3308	0,3522		2,1%	8,7%
13	B4079M	0,2941	0,3003	0,3148		2,1%	7,0%
14	F4076F	0,2723	0,2887	0,3033		6,0%	11,4%
15	M1950M	0,3394	0,3320	0,4496		-2,2%	32,5%
16	S4073L	0,1875	0,1953	0,2101		4,2%	12,1%
17	C3711A	0,3022	0,3075	0,4033		1,8%	33,5%
18	01603G	0,3483	0,3625	0,4011		4,1%	15,2%
19	M4081A	0,3622	0,3619	0,3698		-0,1%	2,1%
20	M1591D	0,3793	0,3899	0,3915		2,8%	3,2%
	Mean	**0,3003**	**0,3107**	**0,3256**		**3,7%**	**8,6%**
	SE	0,0128	0,0132	0,0156	Min	-7,8%	-14,0%
	t test vs. T0	---	0,0172	0,0056	Max	25,5%	33,5%

Variation vs. T0

Figure 3 a) The graph shows the product effect on the measured parameter (raw data) reported here above. b) The graph shows the product effect on the measured parameter (% variation vs. T0) reported here above. Data are reported as mean ± SE. Inside the bars is reported the intragroup (vs. T0) statistical analysis. Upon the bars is reported the intergroup (active(s) vs. placebo) statistical analysis. Statistical significance is reported as follows: * p<0.05, ** p<0.01, *** p<0.001.



Comment. The active ingredient is effective in improving skin net elasticity. The percentage variation of the parameter improvement is statistically significant when compared to the placebo product.

Table 1a. Intergroup statistical analysis output

	4w	8w
Active vs. Placebo	0.002	0.003

RESULTS: SKIN RADIANCE

Table 4 The table here below reports the data obtained for each subject participating in the study. Data are reported as arbitrary units (au).

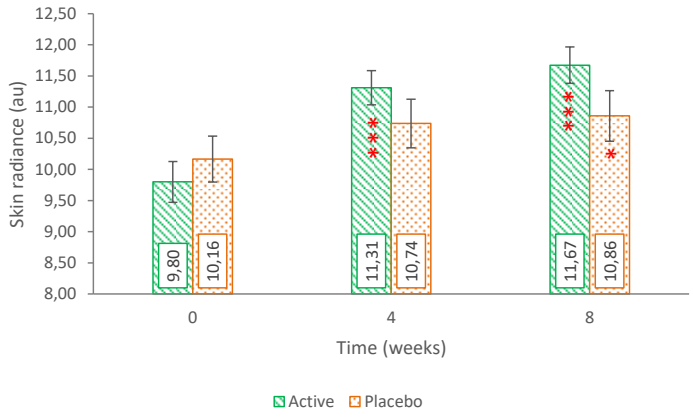
ACTIVE GROUP

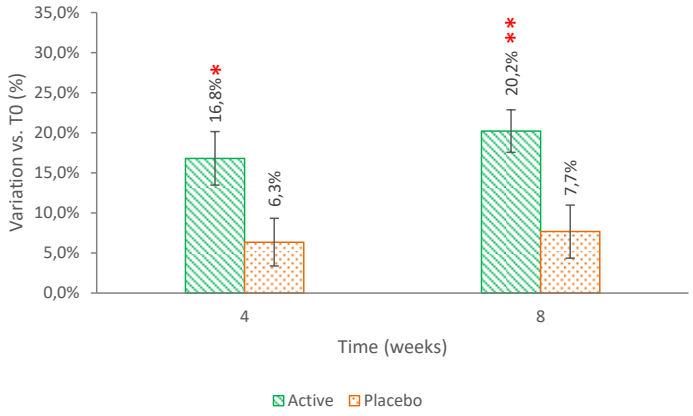
no.	Vol. ID	0	4w	8w	Variation vs. T0	4w	8w
01	A3893A	10,75	11,23	12,14		4,5%	12,9%
02	G0656C	8,34	10,94	9,22		31,2%	10,6%
03	M3265G	7,10	8,35	9,56		17,6%	34,6%
04	M0196D	8,29	9,37	9,24		13,0%	11,5%
05	G0147G	8,89	10,40	11,12		17,0%	25,1%
06	M3715F	8,38	11,51	11,53		37,4%	37,6%
07	C0052P	11,73	12,04	12,26		2,6%	4,5%
08	L2065A	11,05	12,49	12,18		13,0%	10,2%
09	B1572C	9,99	10,41	11,37		4,2%	13,8%
10	S0379S	7,30	12,30	11,23		68,5%	53,8%
11	C0771F	11,15	13,01	13,66		16,7%	22,5%
12	P0402S	10,12	10,66	12,18		5,3%	20,4%
13	C3983L	10,66	12,01	13,21		12,7%	23,9%
14	F1334T	12,05	13,38	13,75		11,0%	14,1%
15	S0872M	10,69	12,05	12,15		12,7%	13,7%
16	R0855P	10,88	11,67	11,88		7,3%	9,2%
17	C0768G	11,06	12,38	13,28		11,9%	20,1%
18	C4074A	9,30	10,69	11,05		14,9%	18,8%
19	P1433E	9,95	11,05	11,48		11,1%	15,4%
20	A0486S	8,33	10,28	10,96		23,4%	31,6%
	Mean	**9,80**	**11,31**	**11,67**		**16,8%**	**20,2%**
	SE	0,33	0,27	0,29	Min	2,6%	4,5%
	t test vs. T0	---	0,0000	0,0000	Max	68,5%	53,8%

PLACEBO GROUP

no.	Vol. ID	0	4w	8w	Variation vs. T0	4w	8w
01	R0333S	9,65	10,03	9,61		3,9%	-0,4%
02	B1495M	8,66	12,96	13,34		49,7%	54,0%
03	D0097E	8,17	9,47	9,77		15,9%	19,6%
04	V3024C	8,91	9,74	8,33		9,3%	-6,5%
05	G0165F	6,27	6,80	7,41		8,5%	18,2%
06	Z3554A	12,34	13,05	10,59		5,8%	-14,2%
07	M1721L	12,80	11,16	11,61		-12,8%	-9,3%
08	G0166R	9,42	7,43	8,42		-21,1%	-10,6%
09	M2006A	8,01	9,02	8,16		12,6%	1,9%
10	L4007M	11,04	12,82	12,44		16,1%	12,7%
11	M4075E	11,38	11,98	12,05		5,3%	5,9%
12	G4078S	10,66	11,11	12,56		4,2%	17,8%
13	B4079M	11,03	11,97	13,01		8,5%	18,0%
14	F4076F	12,05	12,11	12,65		0,5%	5,0%
15	M1950M	10,15	10,18	10,31		0,3%	1,6%
16	S4073L	10,12	10,56	10,78		4,3%	6,5%
17	C3711A	9,57	10,04	11,02		4,9%	15,2%
18	01603G	10,66	10,73	10,89		0,7%	2,2%
19	M4081A	12,21	12,92	13,31		5,8%	9,0%
20	M1591D	10,18	10,65	10,89		4,6%	7,0%
	Mean	**10,16**	**10,74**	**10,86**		**6,3%**	**7,7%**
	SE	0,37	0,39	0,40	Min	-21,1%	-14,2%
	t test vs. T0	---	0,0509	0,0377	Max	49,7%	54,0%

Figure 4 a) The graph shows the product effect on the measured parameter (raw data) reported here above. b) The graph shows the product effect on the measured parameter (% variation vs. T0) reported here above. Data are reported as mean ± SE. Inside the bars is reported the intragroup (vs. T0) statistical analysis. Upon the bars is reported the intergroup (active(s) vs. placebo) statistical analysis. Statistical significance is reported as follows: * p<0.05, ** p<0.01, *** p<0.001.





Comment. The active ingredient is effective in improving skin radiance. The percentage variation of the parameter improvement is statistically significant when compared to the placebo product.

Table 1a. Intergroup statistical analysis output

	4w	8w
Active vs. Placebo	0.025	0.005

RESULTS: WRINKLE DEPTH

Table 5 The table here below reports the data obtained for each subject participating in the study. Data are reported as microns (µm).

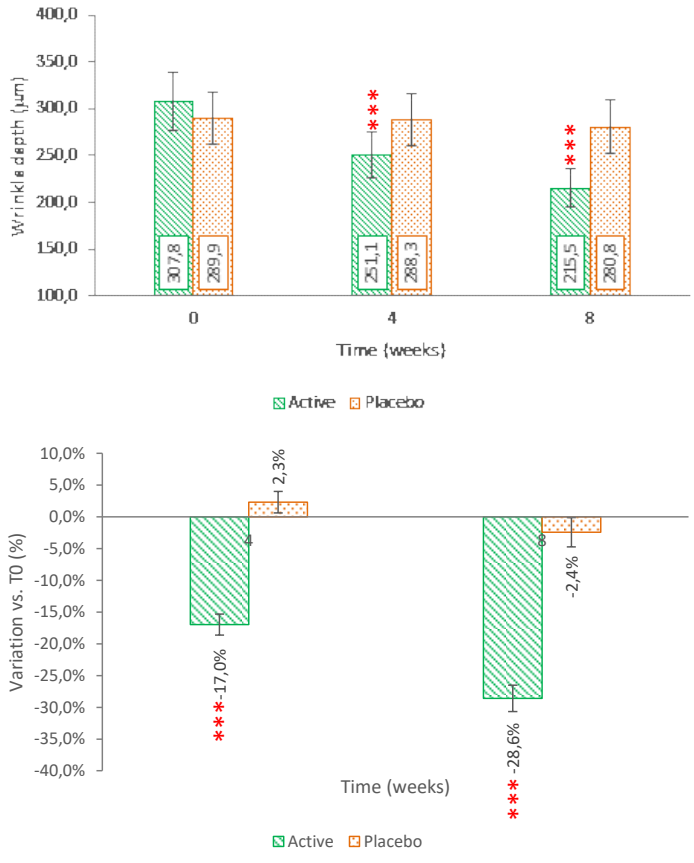
ACTIVE GROUP

no.	Vol. ID	0	4w	8w	Variation vs. T0	4w	8w
01	A3893A	213,0	177,0	146,5		-16,9%	-31,2%
02	G0656C	196,0	196,0	157,0		0,0%	-19,9%
03	M3265G	331,0	274,2	212,5		-17,2%	-35,8%
04	M0196D	342,5	298,5	255,3		-12,8%	-25,5%
05	G0147G	170,0	161,0	112,5		-5,3%	-33,8%
06	M3715F	177,5	136,5	127,5		-23,1%	-28,2%
07	C0052P	351,0	322,5	308,5		-8,1%	-12,1%
08	L2065A	241,5	220,0	199,0		-8,9%	-17,6%
09	B1572C	244,5	175,0	149,0		-28,4%	-39,1%
10	S0379S	495,0	456,0	363,0		-7,9%	-26,7%
11	C0771F	552,0	444,0	450,0		-19,6%	-18,5%
12	P0402S	425,5	386,5	288,5		-9,2%	-32,2%
13	C3983L	321,5	169,0	201,0		-47,4%	-37,5%
14	F1334T	202,5	197,0	179,5		-2,7%	-11,4%
15	S0872M	468,0	351,0	274,0		-25,0%	-41,5%
16	R0855P	256,0	221,0	197,5		-13,7%	-22,9%
17	C0768G	631,5	403,5	302,0		-36,1%	-52,2%
18	C4074A	192,0	144,5	128,5		-24,7%	-33,1%
19	P1433E	185,5	159,0	165,0		-14,3%	-11,1%
20	A0486S	159,5	130,5	93,0		-18,2%	-41,7%
	Mean	**307,8**	**251,1**	**215,5**		**-17,0%**	**-28,6%**
	SE	31,3	24,1	20,6	Min	-47,4%	-52,2%
	t test vs. T0	---	0,0002	0,0000	Max	0,0%	-11,1%

PLACEBO GROUP

no.	Vol. ID	0	4w	8w	Variation vs. T0	4w	8w
01	R0333S	154,00	191,00	135,00		24,0%	-12,3%
02	B1495M	264,50	203,50	228,50		-23,1%	-13,6%
03	D0097E	419,50	402,50	442,00		-4,1%	5,4%
04	V3024C	420,00	489,50	418,00		16,5%	-0,5%
05	G0165F	218,00	254,00	272,00		16,5%	24,8%
06	Z3554A	139,00	175,00	155,00		25,9%	11,5%
07	M1721L	199,50	225,50	198,50		13,0%	-0,5%
08	G0166R	234,50	215,00	220,50		-8,3%	-6,0%
09	M2006A	154,00	164,00	136,00		6,5%	-11,7%
10	L4007M	427,00	272,50	251,50		-36,2%	-41,1%
11	M4075E	191,00	182,50	215,50		-4,5%	12,8%
12	G4078S	121,50	134,00	112,00		10,3%	-7,8%
13	B4079M	222,00	337,50	190,50		52,0%	-14,2%
14	F4076F	233,50	152,50	201,50		-34,7%	-13,7%
15	M1950M	317,50	275,50	435,00		-13,2%	37,0%
16	S4073L	502,00	522,50	489,30		4,1%	-2,5%
17	C3711A	283,00	302,50	278,00		6,9%	-1,8%
18	01603G	384,50	375,00	324,00		-2,5%	-15,7%
19	M4081A	356,20	365,50	370,00		2,6%	3,9%
20	M1591D	556,30	525,50	542,40		-5,5%	-2,5%
	Mean	**289,88**	**288,28**	**280,76**		**2,3%**	**-2,4%**
	SE	28,35	27,63	28,55	Min	-36,2%	-41,1%
	t test vs. T0	---	0,9013	0,4609	Max	52,0%	37,0%

Figure 5 a) The graph shows the product effect on the measured parameter (raw data) reported here above. b) The graph shows the product effect on the measured parameter (% variation vs. T0) reported here above. Data are reported as mean ± SE. Inside the bars is reported the intragroup (vs. T0) statistical analysis. Upon the bars is reported the intergroup (active(s) vs. placebo) statistical analysis. Statistical significance is reported as follows: * p<0.05, ** p<0.01, *** p<0.001.



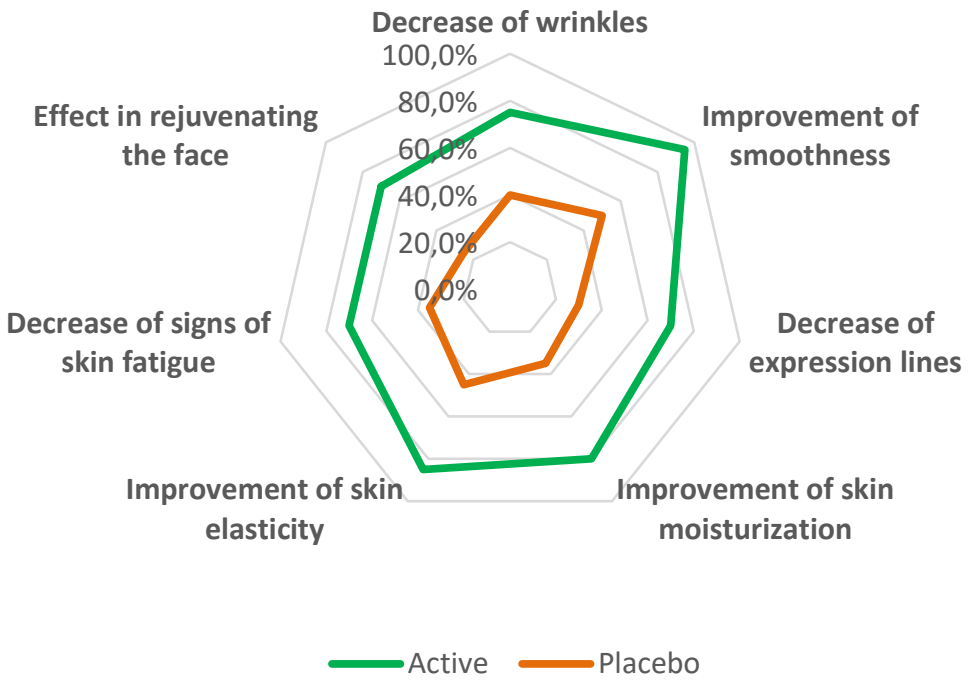
Comment. The active ingredient is effective in reducing wrinkle depth. The percentage variation of the parameter improvement is statistically significant when compared to the placebo product.

Table 1a. Intergroup statistical analysis output

	4w	8w
Active vs. Placebo	0.000	0.000

RESULTS: SELF-ASSESSMENT QUESTIONNAIRE AFTER 8 WEEKS USE

Figure 6 The graph here below reports the self-assessment questionnaire output. Data are reported as % of subjects giving a positive response.



	Active	Placebo	Intergroup statistics
Decrease of wrinkles	75.0%	40.0%	* (p=0.0145)
Improvement of smoothness	95.0%	50.0%	** (p=0.0037)
Decrease of expression lines	70.0%	30.0%	** (p=0.0032)
Improvement of skin moisturization	80.0%	35.0%	** (p=0.0062)
Improvement of skin elasticity	85.0%	45.0%	** (p=0.0039)
Decrease of signs of skin fatigue	70.0%	35.0%	** (p=0.0015)
Effect in rejuvenating the face	70.0%	25.0%	** (p=0.0065)

CONCLUSION

According to the obtained results, elsewhere reported in this document, it is possible to conclude that the ingredient **CYNATINE® TOP** formulated in a cosmetic product is effective in improving the clinical signs of ageing skin. The following results were obtained:

	Active		Placebo	
	4w	8w	4w	8w
Skin moisturization	+13.4% [a,p]	+20.3% [a,p]	+3.3%	+5.9%
Wrinkle depth	-17.0% [a,p]	-28.6% [a,p]	+2.3%	-2.4%
Skin elasticity				
R2 parameter*	+8.1% [a,p]	+12.5% [a,p]	+1.3%	+2.7% [a]
R5 parameter**	+13.4% [a,p]	+27.6% [a,p]	+3.7% [a]	+8.6% [a]
Skin radiance	+16.8% [a,p]	+20.2% [a,p]	+6.3%	+7.7% [a]

Legend. [a] statistically significant vs. T0 | [p] statistically significant vs. placebo | Overall elasticity | ** net elasticity*

The effects of the product were noted by the subjects participating in the study. Both the active and the placebo products were well tolerated. No significant adverse reactions were reported during the study period.

Investigator

Dr Enza Cestone

DOTT.SSA ENZA CESTONE

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Date: 2019.04.18 18:02:22 +02'00'

Study Director & Quality control

Dr Vincenzo Nobile

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Date: 2019.04.18 18:02:46 +02'00'

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