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Study number 2202218970

Muenster, 12.05.2022

Expert report by dermatological specialists about a clinical-dermatological application study

on 51 subjects with application of test product once daily on the eye area over a period of four weeks

Examination for dermal tolerability and determination of single wrinkle depth

Vitayes Instant Ageback

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Table of content

1 General information

Title

Clinical application study under dermatological control

Testing body

Dermatest GmbH
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D-48143 Münster

Specialists in dermatology

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Venereology, Allergology,
Phlebology and Environmental Medicine

Dr. med. Gerrit Schlippe
Specialist in Dermatology and Venereology

Study coordinator

PhD Tanja Emmler
Biologist

1.1 Synopsis

Study title	Clinical application study under dermatological control
Test product	**Vitayes Instant Ageback**
Product type	eye cream
Study design	Single-centre
Testing body	Dermatest GmbH Engelstr. 37 D-48143 Münster
Expert report version and date	Version 1, 12.05.2022 Version 2, 13.05.2022
Test period	March - May 2022
Primary study objectives	Assessment of skin tolerability From the time of start of the study to the end of the study and 30 days beyond, all skin reactions and any other adverse reactions are recorded in the reaction file.
Secondary study objectives	Assessment of efficacy - Depth of single wrinkle (PRIMOS CR)
Quantity of subjects	51
Application period	four weeks
Times of measurement	Depth of single wrinkle: T_0 and T_{28}
Test area	Eye area
Frequency of application	once daily
Inclusion criteria	- 35 years and older - Female and male healthy volunteers - All skin type - Subjects with crow´s feet - Written informed consent of the subjects or legal guardian is available
Exclusion criteria	- Severe or chronic skin inflammations - Severe internal or chronic diseases - Taking of drugs that may interfere with skin reactions (glucocorticoids, antiallergics, topical immune modulators, etc.) - Application of active substance-containing products and care products 7-10 days before the start of the test - Severe allergies or any serious side effects of cosmetic preparations ever occurred - Sun baths or solarium visits during the study

	- Known neoplastic disease - Pregnancy and breast-feeding

1.2 Schedule

Study day	Day 0	Day 28
Information of the subjects	✔	
Informed Consent Form Sheet	✔	
Medical history	✔	
Dermatological examination	✔	✔
Compliance with the inclusion and exclusion criteria	✔	✔
Measurement of depth of single wrinkle (PRIMOS CR)	✔	✔

2 Introduction

The human skin is the largest and functionally most versatile human organ. It delimits the organism against the outside world, protecting against dehydration and environmental influences. The skin consists of three layers: Epidermis (upper skin layer), dermis (true skin) and subcutis (hypoderm). The epidermis, in turn, is composed of five layers and consists of 90 % keratinocytes (horny cells). From outside to inside, the superimposed layers are: *Stratum corneum*, *Stratum lucidum*, *Stratum granulosum*, *Stratum spinosum* and *Stratum basale*.

These days a lot of products, in particular cosmetics, consumer goods and medical devices, are in contact with the skin daily and often over long periods. Good tolerability is a prerequisite for application of these products. Since alternative test methods such as animal testing are prohibited and results of cell culture experiments can be applied to humans only in limited extent, tests under medical supervision are currently required from an ethical and scientific point of view. For analysis of the skin tolerability of products, application studies, so-called home-in-use tests, can be carried out. The product to be tested is applied over a prolonged period on the intended application area. Inclusion and exclusion criteria of the subjects are adapted to the target group as far as possible. Before each testing the risk of all ingredients of the test product are assessed. All available information are systematically analysed in order to identify potential hazards and to avert risks.

3 Study objective

The objective of this study was to precisely investigate the skin tolerability and efficacy of the product **Vitayes Instant Ageback** according to clinical-dermatological test criteria.

Before inclusion the dermatological integument of all subjects was investigated regarding health and integrity. In case of necessary medical treatment the subjects were excluded. Furthermore, the conditions of the study were explained to all subjects as well as the rights and duties of the subjects in the context of the study by the attending study nurse or the attending dermatologist. All subjects were included into the study only, if they did not exhibit any pathological changes of the skin in the application area, signed the consent statement of their own free will or with agreement of their legal guardians and complied with all other inclusion and exclusion criteria. During the study all subjects could consult the attending study nurse or the attending dermatologist in case of any objective and subjective skin changes. According to the schedule, all dermatological examinations were done.

3.1 Primary outcomes

Assessment of skin tolerability, and possible sensitisation potential

- Application study

3.2 Secondary outcomes

Assessment of efficacy

- depth of single wrinkle (PRIMOS CR)

3.3 Study parameters

Monocentric clinical trial over a period of four weeks in total.

4 Selection of subjects

The study was carried out with 39 female and 12 male subjects in the age of 35 years and older according to the inclusion and exclusion criteria. All subjects were selected from the subject database or recruited by flyers, social networks and newspapers.

4.1 Information of the subjects

Before the study all subjects were informed about the course of the study by the attending study nurse or the attending dermatologist. Participation in the study was voluntary. All subjects could discontinue the study at any time and without giving any reason as well as without any negative consequences for the subjects.

4.2 Inclusion criteria

- 35 years and older
- Female and male healthy volunteers
- All skin type
- Subjects with crow´s feet
- Written informed consent is present

The subjects had to be able to communicate with the attending study nurse or the attending dermatologist and to understand and follow the requirements of this clinic-dermatological application study.

4.3 Exclusion criteria

- Severe or chronic skin inflammations
- Severe internal or chronic diseases
- Taking of drugs that may interfere with skin reactions (glucocorticoids, antiallergics, topical immune modulators, etc.)
- Application of active substance-containing products and care products 7-10 days before the start of the test
- Severe allergies or any serious side effects of cosmetic preparations ever occurred
- Sun baths or solarium visits during the study
- Known neoplastic disease
- Pregnancy and breast-feeding

4.4 Exclusion of subjects from the clinical-dermatological application study

The investigator could exclude a subject from the clinical-dermatological application study if any of the following conditions occurred:

- Revocation of the consent
- Occurrence of an undesirable event
- Deterioration of the clinical condition

If premature withdrawal of a subject happened, it was documented completely. Supervision of these and all subjects continues for reasonable time in order to control clinical condition and occurrence of adverse events.

4.5 List of subjects

Subject №	Initials	Sex [f/m]	Age
1	AcIl	f	70
2	AcNi	f	39
3	AcSa	m	48
4	AlIr	f	61
5	AlPe	f	59
6	AmEl	f	38
7	ArEw	f	52
8	BaBi	f	57
9	BaRü	m	58
10	BeSo	f	47
11	BöSa	f	39
12	DiMa	f	66
13	FrSi	f	53
14	GeCe	f	39
15	HaMa	f	42
16	HeMa	m	52
17	HoSa	f	47
18	HoAr	m	52
19	JüDa	f	63
20	KoAn	f	36
21	KrIn	f	72
22	KrUl	f	51
23	LaNi	f	50
24	LaSa	f	56
25	MaSe	f	60
26	MaMi	m	58
27	MaMi	f	57
28	MeSt	f	57
29	MeSa	f	51
30	MoMa	f	51
31	NeJö	m	45
32	NgSa	f	54
33	NiAn	f	65
34	OeMa	m	37
35	PiAl	f	49
36	PlGi	f	57
37	PoAs	f	62
38	ScNa	f	42
39	ScCh	m	60
40	ScMa	m	41
41	ScTa	f	47
42	ScMe	f	61
43	SoMi	f	54
44	SpBi	f	59

Subject №	Initials	Sex [f/m]	Age
45	StMa	f	62
46	ThHa	m	67
47	TsBe	f	58
48	VaBe	m	42
49	WiRe	m	43
50	WiKa	f	60
51	ZsMa	f	54

5 Test product

5.1 Application of the investigational product

The product was applied on the eye area once daily over the entire application period. The subjects were instructed not to use any equivalent product in the test area during the test period.

5.2 Interruptions / Discontinuation of the application

Application of the test product could be discontinued at any time by the subject or according to the decision of the investigator, if the clinical condition required so. Each discontinuation was documented completely. It was the responsibility of the investigator to assess, whether conditions for discontinuation were given.

6 Benefit-risk consideration and precautions

There was no known risk for use of the product. If a residual risk was recognised or if a change in acceptance of the product was evident, the sponsor was notified immediately.

If during the study 10 % or more of the test subjects experienced a product-related reaction, that was not acceptable for the corresponding product category, the study was terminated immediately and the sponsor was informed accordingly.

7 Methods

In order to minimise fluctuations caused by external influences such as room temperature and relative humidity, all measurements were always carried out at the same physical ambient conditions in rested status (≈20 °C, humidity 40–60 %).

7.1 Measurement of the individual wrinkle depth (PRIMOS CR)

In the course of life every human develops permanent wrinkles around the eyes. Due to the characteristic radiating structure, these wrinkles are colloquially also called crow's feet. The older and more stressed the skin is, the more intense expressed are these wrinkles. The depth of the wrinkles can be determined by the optical 3D in vivo skin measurement PRIMOS (***P**hase-shift **R**apid **I**n vivo **M**easurement **O**f **S**kin*), based on the digital strip projection technique (PRIMOS CR, Canfield Scientific, Inc.). To measure wrinkle depth, a parallel strips pattern is projected onto the skin and recorded by a CCD recording camera. Minute differences in skin topology respectively differences in heights of the skin distort the parallel projection strips and thus form a quantitative and qualitative measure of the skin surface to be analysed. The corresponding software enables exact retrieval of the analysed area by its overlay function, providing direct comparison of the reference data set (data before) with a measurement data set (data after). To quantify wrinkle depth, the profile of a cutting line was selected, and the absolute depth of the wrinkle was determined.

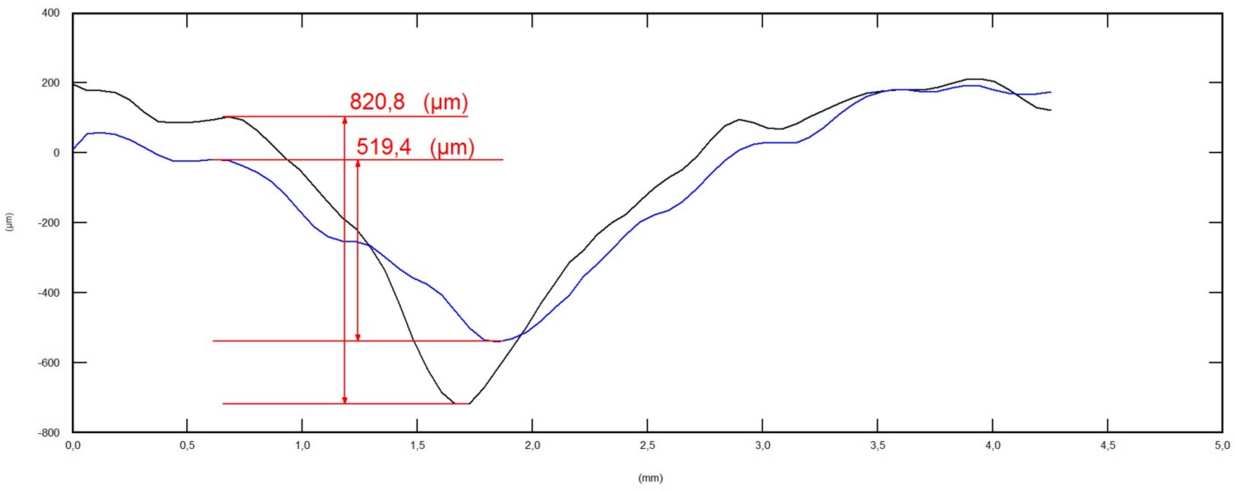

Figure: Graphical presentation of depth of a single wrinkle before (black line) and after (blue line) the application period. (Manual Optical 3D skin measuring device PRIMOS compact).

One quantification of depth of a single wrinkle was executed per time of analysis and per subject.

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- S. Jaspers, H. Hopermann, G. Sauermann, U. Hoppe, R. Lunderstädt, J. Ennen: "Rapid in vivo measurement of the topography of human skin by active image triangulation using a digital mircromirror device", Skin Research & Technology, Vol. 5, Issue 3, August 1999, pp. 195-207.
- R. Lunderstädt, U. Müller: "Laserprofilometrie zur quantitativen Analyse der menschlichen Haut", Technisches Messen tm 59 (1992), S. 448-453.

8 Results

8.1 Dermatological examination results

The examinations were carried out according to clinical-dermatological evaluation criteria. 50 out of 51 test persons showed healthy skin in the test area before, during and after the application study. No pathological skin lesions were found in any form. No test interruption, even less treatment by a specialist in dermatology was performed in any case. The product named was very well tolerated, and it did not lead to dermatologically relevant skin changes in any of these subject.

After the 3rd application of the product one Test person showed a light reaction, which was expressed as redness, burning and tightness sensation and stopped application.

Subject №	Findings before	Findings after	Type of reaction
1	–	–	
2	–	–	
3	–	–	
4	–	–	
5	–	–	
6	–	–	
7	–	–	
8	–	–	
9	–	–	
10	–	–	
11	–	–	
12	–	–	
13	–	–	
14	–	–	
15	–	–	
16	–	–	
17	–	–	
18	–	–	
19	–	–	
20	–	–	
21	–	–	
22	–	–	
23	–	–	
24	–	–	
25	–	–	
26	–	–	
27	–	–	
28	–	–	
29	–	–	
30	–	–	
31	–	–	
32	–	–	
33	–	–	
34	–	–	
35	–	1*	redness, burning and tightness sensation

Subject №	Findings before	Findings after	Type of reaction
36	–	–	
37	–	–	
38	–	–	
39	–	–	
40	–	–	
41	–	–	
42	–	–	
43	–	–	
44	–	–	
45	–	–	
46	–	–	
47	–	–	
48	–	–	
49	–	–	
50	–	–	
51	–	–	

If skin reactions occurred, the type of the reaction was assessed clinically dermatologically and documented according to following scale:

–	no pathological findings
1	mild reaction
2	moderate reaction
3	severe reaction

* Reaction occurred after three applications and lasted more than three days.

8.2 PRIMOS CR / individual wrinkle depth

Measurements of the depth of a single wrinkle were executed on the crow's feet area of every subject at indicated times. The results of corresponding quantitative evaluation as well as percentage change of wrinkle depth of all investigated 50 subjects are presented in following table.

Subject №	T_0 [µm]	T_{28} [µm]	Difference [µm]	Change [%]
1	1402,0	1195,7	-206,3	-14,71
2	366,0	324,0	-42,0	-11,48
3	589,5	532,0	-57,5	-9,75
4	415,3	403,5	-11,8	-2,84
5	488,6	207,0	-281,6	-57,63
6	542,9	516,0	-26,9	-4,95
7	710,7	756,0	45,3	6,37
8	679,7	655,0	-24,7	-3,63
9	1314,4	1143,9	-170,5	-12,97
10	892,3	674,4	-217,9	-24,42
11	447,0	500,0	53,0	11,86
12	333,6	362,0	28,4	8,51
13	577,3	431,0	-146,3	-25,34
14	466,1	237,4	-228,7	-49,07
15	554,0	301,0	-253,0	-45,67
16	370,0	348,0	-22,0	-5,95
17	238,0	211,0	-27,0	-11,34
18	1659,0	1325,0	-334,0	-20,13
19	1173,7	665,0	-508,7	-43,34
20	362,7	211,0	-151,7	-41,83
21	964,3	609,6	-354,7	-36,78
22	749,5	597,0	-152,5	-20,35
23	1372,8	642,8	-730,0	-53,18
24	759,7	648,6	-111,1	-14,62
25	1390,0	1198,4	-191,6	-13,78
26	514,0	473,3	-40,7	-7,92
27	1302,0	619,0	-683,0	-52,46
28	595,3	515,5	-79,8	-13,41
29	626,7	614,0	-12,7	-2,03
30	516,6	230,0	-286,6	-55,48
31	405,0	211,1	-193,9	-47,88
32	776,0	703,0	-73,0	-9,41
33	783,0	421,7	-361,3	-46,14
34	245,0	206,0	-39,0	-15,92
35	717,0	530,6	-186,4	-26,00
36	644,0	505,6	-138,4	-21,49
37	465,0	287,0	-178,0	-38,28
38	595,0	544,3	-50,7	-8,52
39	233,6	227,0	-6,6	-2,83

40	1536,0	986,0	-550,0	-35,81
41	523,0	318,0	-205,0	-39,20
42	767,0	723,3	-43,7	-5,70
43	740,0	621,9	-118,1	-15,96
44	925,0	666,0	-259,0	-28,00
45	328,4	276,3	-52,1	-15,86
46	437,0	324,3	-112,7	-25,79
47	325,0	295,0	-30,0	-9,23
48	346,1	309,6	-36,5	-10,55
49	1016,5	806,0	-210,5	-20,71
50	670,0	505,0	-165,0	-24,63
Mean	**697,0**	**532,3**	**-164,7**	**-21,52**
Minimum	233,6	206,0	-730,0	-57,63
Maximum	1659,0	1325,0	53,0	11,86
Std.Dev.	363,0	276,0	172,2	17,80

9 Assessment of the study results

9.1 Skin tolerability

The test product **Vitayes Instant Ageback** was applied once a day onto the eye area over a period of four weeks by 50 out of 51 subjects. From the clinical-dermatological perspective no relevant skin reactions arose, the product was tolerated very well. Neither intolerance reactions in terms of skin irritation nor allergic reactions (contact dermatitis) were detected.

One subject showed a mild reaction after the 3rd application of the product, manifesting as redness, burning and tightness sensation and probably attributable to the product ingredients.

Accordingly, from a dermatological viewpoint the tested product **Vitayes Instant Ageback** might lead to skin irritations in particularly sensitive persons.

9.2 Efficacy

The efficacy of the test product **Vitayes Instant Ageback** with respect to individual wrinkle depth was determined by means of optical 3D in vivo skin measurement (PRIMOS CR, Canfield Scientific, Inc.). Improvement of individual wrinkle depth by 21,52 % in the test area could be shown.

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10 Addendum

10.1 Quality control, quality assurance and data protection

The quality of the study execution and of the data recording was ensured by ISO 9001 and checked in regular intervals internally as well as externally by monitoring through TÜV Rheinland.

The provisions of the applicable data privacy legislature were respected. All data of the subjects were handled confidentially and are disclosed to the sponsor only in a pseudonymised version. All data are stored for ten years.

10.2 Certificates

- Skin tolerability
- Efficacy

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DEUTSCHLAND

Study number 2202218970

Muenster, 12.05.022

Certificate

about the cosmetic product

Vitayes Instant Ageback

Clinical application study under dermatological control

The test product was applied over a period of four weeks by 50 out of 51 subjects once daily on the eye area. From the clinical-dermatological point of view no relevant skin reactions occurred in the test area. The product was tolerated

excellently.

Neither intolerance reactions suggestive of irritation nor allergic reactions (contact dermatitis) were detected. Neither intolerance reactions in terms of irritation nor allergic reactions (contact dermatitis) were detected. Accordingly, from the dermatological point of view there is no high potential for irritation and sensitisation by the tested product when used as intended.

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Study number 2202218970

Muenster, 12.05.2022

Certificate

about the cosmetic product

Vitayes Instant Ageback

Clinical application study under dermatological control and individual wrinkle depth

The test product was applied during a period of four weeks by 50 out of 51 subjects once a day onto the eye area. Determination of the individual wrinkle depth carried out under clinical-dermatological control showed

improvement of the individual wrinkle depth by 21,52 %

in the test area.

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