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Muenster, April 8th 2021

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

on 20 subjects with application once daily on hair and scalp over a period of 6 month

Examination of dermal tolerability
Quantification and differentiation of hair
Quantification of hair loss

CARON BIO C3 SHAMPOO

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1 General information

Title

Clinical application study under dermatological and dental control

Testing body

Dermatest GmbH
Engelstr. 37
D-48143 Münster

Specialists in dermatology

Dr. med. Werner Voss
Specialist in Dermatology
Venereology, Allergology,
Phlebology and Environmental Medicine

Dr. med. Gerrit Schlippe
Specialist in Dermatology and Venerology

Study coordinator

PhD Dominik Schmaltz
Biochemist

1.1 Synopsis

Study title	Clinical application study under dermatological control
Test product	**CARON BIO C3 SHAMPOO**
Product type	Shampoo
Study design	Single-centre
Testing body	Dermatest GmbH Engelstr. 37 D-48143 Münster
Expert report version, date	V1 08.04.2021
Test period	July 2020– March 2021
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	Quantification of hair loss by counting out fallen hair after combing Quantification of hair by TrichoScan concerning: Anagen and telogen hair Vellus and terminal hair Thickness of hair
Quantity of subjects	20
Application period	6 month
Test area	Hair and scalp
Frequency of application	once daily
Inclusion criteria	- 18 years and older - Female and male healthy volunteers - Skin type: any - Hair loss (alopecia), Norwood scale stadium at least III or beginning increased loss of hair - 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 91 (3 month)	Day 183 (6 month)
Information of the subjects	✔		
Informed Consent Form Sheet	✔		
Medical history	✔		
Dermatological examination	✔	✔	✔
Analysis of hair by TrichoScan	✔	✔	✔
Quantification of hair loss	✔	✔	✔
Compliance with the inclusion and exclusion criteria	✔	✔	✔

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 is 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 tolerability and efficacy of the product **CARON BIO C3 SHAMPOO** 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 and dental examinations were done.

3.1 Primary outcomes

Assessment of skin tolerability and possibly sensitisation potential

- Application study

3.2 Secondary outcomes

Control of efficacy

- Analysis of hair by TrichoScan
- Quantification of hair loss by counting out fallen hair after combing

3.3 Study parameters

Monocentric clinical trial over a period of 6 month in total including intermediate analysis after 3 month

4 Selection of subjects

The study was carried out with 6 female and 14 male subjects aged 19 up to 72 years, 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

- 18 years and older
- Female and male healthy volunteers
- Skin type: any
- Hair loss (alopecia), Norwood scale stadium at least III or beginning increased loss of hair
- Written informed consent is on hand

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 ever occurred serious side effects of cosmetic preparations
- Sun baths or solarium visits during the study
- Known neoplastic disease

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 [years]	Blood type (AB0, Rhesus)	Hair loss (alopecia) stadium [Norwood scale resp. Ludwig scheme]
1	BiSt	m	45	A, rh pos.	Norwood type VI
2	ErMi	m	51	0, rh pos.	Norwood type IV
3	ErPe	f	52	A, rh neg.	Ludwig scheme I
4	FeTo	m	34	0, rh neg.	Norwood type III
5	FuRe	f	61	0, rh pos.	Ludwig scheme II
6	GrBr	f	51	A, rh pos.	Ludwig scheme II
7	GrCh	f	19	A, rh pos.	Ludwig scheme I
8	HeCh	m	44	0, rh pos.	Norwood type VI
9	JqJa	m	63	AB, rh pos.	Norwood type VI
10	JuLo	m	71	A, rh pos.	Norwood type III vertex
11	JuMa	f	72	A, rh neg.	Ludwig scheme I
12	JuAn	m	47	A, rh pos.	Norwood type II
13	KlNi	f	40	A, rh pos.	Ludwig scheme II
14	MaWo	m	39	B, rh neg.	Ludwig scheme III
15	MaMi	m	57	A, rh pos.	Norwood type IV
16	ReJu	m	38	A, rh pos.	Norwood type IV
17	ScDe	m	26	A, rh neg.	Norwood type III vertex
18	TrSe	m	32	A, rh pos.	Norwood type IV
19	VoJo	m	27	A, rh pos.	Norwood type III
20	WiDe	m	31	A, rh pos.	Norwood type V

5 Test products

5.1 Application of the investigational products

The shampoo was applied on hair and scalp 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

7.1 Analysis of hair by TrichoScan

The special camera and software (version 4) of the TrichoScan HD system (DermoScan GmbH, Germany) were used to evaluate the density of hair (terminal and vellus hair) as well as the status of all analysed single hair concerning anagen or telogen stage. Further the thickness of hair was determined by the TrichoScan system and expressed as median value of all analysed hair beside expression as mean value of all analysed hair. The area on the scalp of a single measurement by the TrichoScan HD system was fixed to 0,59 cm^2, corresponding to a circle with 0,87 cm in diameter. The following pre-treatment of the analysed area on the scalp was carried out:

On the scalp of every subject one area with 2 cm in diameter was located by a dot mask in the transition zone between alopecia and regularly hirsute scalp. The hair was threaded through the hole of the mask and roughly shortened with a pair of scissors. Further the shortened hair was shaved to an even length of 0.8 mm by a Moser shaver (TrichoScan Edition). For this purpose the razor was moved in 90 ° angle to the scalp without pressure, resulting in a shaved area with 2 cm in diameter.

Two days after shaving the hair dye (Goldwell Topchic 2N) was applied by a wooden spatula on the shortened hair. In detail the same amount of the developer (creme oxide) was added to the hair dye (1:1 mixture). Hair dye and developer were mixed thoroughly until they reached a creamy consistency. The dye mixture was applied to the shaved area on scalp of the subject and remained there for 15 minutes. After this incubation time the dye mixture was removed coarsely with a swab and the area was cleaned very carefully with an alcoholic tincture (e.g. Kodan spray) and a soft swab.

The camera of the TrichoScan HD system was used to record the image files at scheduled times of analysis. The scalp was moistened thoroughly (Kodan spray) before recording of the images in the prepared area. Attention was paid to record the images without air bubbles and without surrounding hair. By this procedure the parameters density of terminal and of vellus hair [1/cm^2] as well as portion of anagen hair [%] and telogen hair [%] were quantified, using the TrichoScan HD software. Additionally portions of terminal and of vellus hair [%] as well as thickness of hair [µm] were determined.

7.2 Quantification of hair loss by counting of out fallen hair after combing

The quantity of out fallen hair was determined as following:

- After washing, the wet hair was combed intensively with a provided standardised comb by the subject, placed above a white DIN A4 paper sheet. This resulted in falling of hair on the paper sheet.
- The out fallen hair were counted by a qualified study nurse.

This procedure was executed at scheduled times of analysis.

8 Results

8.1 Dermatological examination results

The examinations were carried out according to clinical-dermatological evaluation criteria. All subjects exhibited healthy skin in the test area before, during and after the application period. No pathological skin lesions were found in any form. Neither interruption of test product application, nor reduced product application, decided by a dermatological specialist, occurred in any case. Not any treatment by a dermatological specialist was necessary. The product **CARON BIO C3 SHAMPOO** was very well tolerated and did not induce dermatological relevant skin changes on any subject.

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	–	–	

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

8.2 Quantity of out fallen hair

Hair loss of every subject was quantified at indicated times. Results are shown in following table.

	Quantity of out-fallen hair appl. of shampoo					Quantity of out-fallen hair shampoo		
Subject No.	**Start**	**After 3 months**	**Difference (After 3 month minus Start)**	**Difference [%] (After 3 month minus Start) Start = 100 %**		**After 6 month**	**Difference (After 6 month minus Start)**	**Difference [%] (After 6 month minus Start) Start = 100 %**
1	0	0	0	-		2	+2	+200
2	17	7	-10	-59		6	-11	-65
3	14	19	+5	+36		6	-8	-57
4	23	7	-16	-70		8	-15	-65
5	33	18	-15	-45		11	-22	-67
6	87	33	-54	-62		39	-48	-55
7	45	34	-11	-24		12	-33	-73
8	32	8	-24	-75		7	-25	-78
9	78	53	-25	-32		15	-63	-81
10	31	19	-12	-39		22	-9	-29
11	48	32	-16	-33		16	-32	-67
12	69	41	-28	-41		43	-26	-38
13	28	21	-7	-25		16	-12	-43
14	71	39	-32	-45		0	-71	-100
15	27	0	-27	-100		3	-24	-89
16	25	13	-12	-48		8	-17	-68
17	29	8	-21	-72		9	-20	-69
18	2	0	-2	-100		0	-2	-100
19	6	4	-2	-33		3	-3	-50
20	20	2	-18	-90		3	-17	-85
Mean	**34**	**18**	**-16**	**-50**		**11**	**-23**	**-54**
Median	**29**	**16**	**-16**	**-45**		**8**	**-19**	**-67**
Min	0	0	-54	-100		0	-71	-100
Max	87	53	+5	+36		43	+2	+200
Std.Dev.	24	15	13	31		11	19	61

Quantity of out fallen hair was determined reduced by 50 % in mean respectively by 45 % in median over analysed 20 subjects after 3 month applying the test product. The standard deviation of corresponding 20 change rates was 31 %.

After 6 month application of the test product quantity of out fallen hair was detected reduced by 54 % in mean respectively by 67 % in median over analysed 20 subjects. The standard deviation of corresponding 20 change rates was 61 %.

8.3 Percentage of anagen and telogen hair

Trichoscan analysis were carried out in the prepared area of every subject's scalp at indicated times. Percentages of anagen and telogen hair [%] were determined by nine repeated recordings in mean over all subjects, placing the camera head on nine different sites in the prepared scalp area and using the Trichoscan HD software for evaluation of recordings. The means of all nine fold repetition per subject and time of analysis are shown in the tables below.

	Anagen Hair [%] appl. of shampoo				**Anagen Hair [%] appl. of shampoo**	
Subject No.	**Start**	**After 3 month**	**Difference** (After 3 month minus Before)		**After 6 month**	**Difference** (After 6 month minus Before)
1	79	64	-15		76	-3
2	82	76	-5		74	-8
3	82	86	+4		89	+7
4	84	83	-1		91	+7
5	79	80	+1		82	+3
6	74	85	+11		78	+4
7	79	89	+10		80	+1
8	72	85	+13		85	+13
9	81	83	+2		84	+3
10	78	65	-13		74	-3
11	69	74	+4		86	+17
12	73	78	+5		89	+16
13	70	83	+13		81	+11
14	62	52	-10		83	+21
15	78	88	+9		88	+10
16	57	66	+9		81	+24
17	83	74	-9		75	-8
18	62	57	-5		77	+15
19	54	72	+18		89	+35
20	66	71	+6		80	+14
Mean	**73**	**75**	**+2**		**82**	**+9**
Median	**76**	**77**	**+4**		**82**	**+9**
Min	54	52	-15		74	-8
Max	84	89	+18		91	+35
Std.Dev.	9	10	9		5	11

The percentage of anagen hair was in mean by +2 %, in median by +4 % detected changed over all 20 subjects after 3 month application of the test product. After 6 month application an enhanced increase of anagen hair by 9 % in mean and median over all 20 subjects was determined. Corresponding 20 results about change of anagen hair after 6 month exhibit a standard deviation of 11 %.

	Telogen Hair [%] appl. of shampoo				Telogen Hair [%] appl. of shampoo	
Subject No.	**Start**	**After 3 month**	**Difference** (After 3 month minus Before)		**After 6 month**	**Difference** (After 6 month minus Before)
1	21	36	+15		24	+3
2	18	24	+5		26	+8
3	18	14	-4		11	-7
4	16	17	+1		9	-7
5	21	22	+0		18	-3
6	26	15	-11		22	-4
7	21	11	-10		20	-1
8	28	15	-13		15	-13
9	19	17	-2		16	-3
10	35	35	+0		26	-10
11	31	26	-4		14	-17
12	27	22	-5		11	-16
13	30	17	-13		19	-11
14	38	48	+10		17	-21
15	22	12	-9		12	-10
16	43	34	-9		19	-24
17	17	26	+9		25	+8
18	38	43	+5		23	-15
19	46	28	-18		11	-35
20	34	29	-6		20	-14
Mean	**27**	**25**	**-3**		**18**	**-10**
Median	**26**	**23**	**-4**		**18**	**-10**
Min	16	11	-18		9	-35
Max	46	48	+15		26	+8
Std.Dev.	9	10	8		5	10

The percentage of telogen hair was in mean by -3 %, in median by -4 % detected changed over all 20 subjects after 3 month application of the test product. After 6 month application an enhanced reduction of telogen hair by 10 % in mean and median over all 20 subjects was determined. Corresponding 20 results about change of telogen hair after 6 month exhibit a standard deviation of 10 %.

8.4 Thickness of hair

Trichoscan analysis were carried out in the prepared area of every subject's scalp at indicated times. Thickness of hair [µm] was determined by nine repeated recordings in mean over all subjects, placing the camera head on nine different sites in the prepared scalp area and using the Trichoscan HD software for evaluation of recordings. The means of all nine fold repetition per subject and time of analysis are shown in the tables below.

	Hair Thickness (Median) [µm] appl. of shampoo					Hair Thickness (Median) [µm] appl. of shampoo		
Subject No.	**Start**	**After 3 month**	**Difference** (After 3 month minus Before)	**Rel. Difference [%]** After 3 month minus Before) Start = 100 %		**After 6 month**	**Difference** (After 6 month minus Before)	**Rel. Difference [%]** After 6 month minus Before) Start = 100 %
1	42	39	-3	-7		37	-5	-13
2	63	63	0	0		60	-3	-4
3	68	72	+4	+6		73	+5	+8
4	59	57	-2	-3		62	+3	+5
5	56	53	-2	-4		64	+8	+15
6	60	56	-4	-6		57	-3	-4
7	49	55	+6	+11		53	+4	+8
8	45	50	+5	+12		52	+7	+15
9	54	60	+6	+11		60	+6	+11
10	39	36	-3	-7		44	+5	+14
11	42	52	+10	+24		49	+8	+19
12	50	46	-4	-8		48	-2	-4
13	45	44	-1	-2		46	+1	+3
14	48	46	-2	-4		60	+12	+25
15	78	88	+10	+13		95	+17	+22
16	56	51	-5	-9		56	+0	+0
17	36	44	+7	+21		40	+3	+9
18	39	38	-1	-2		48	+9	+24
19	31	37	+6	+18		55	+24	+77
20	45	41	-4	-9		44	-0	-1
Mean	**50**	**51**	**+1**	**+3**		**55**	**+5**	**+11**
Median	**49**	**51**	**-1**	**-2**		**54**	**+5**	**+8**
Min	31	36	-5	-9		37	-5	-13
Max	78	88	+10	+24		95	+24	+77
Std.Dev.	11	12	5	11		12	7	18

Expressed as median thickness of all analysed hair per measurement, the thickness of hair was detected in mean by +1 µm and median by -1 µm not changed meaningful over all 20 subjects after 3 month application of test product. After 6 month application a change of hair thickness by +5 µm in mean and median over all 20 subjects was determined. Corresponding 20 results about change of hair thickness after 6 month exhibit a standard deviation of 7 µm.

	Hair Thickness (Mean) [µm] appl. of shampoo					Hair Thickness (Mean) [µm] appl. of shampoo		
Subject No.	**Start**	**After 3 months**	**Difference** (After 3 months minus Before)	**Rel. Difference [%]** After 3 months minus Before) Start = 100 %		**After 6 months**	**Difference** (After 6 months minus Before)	**Rel. Difference [%]** After 6 months minus Before) Start = 100 %
1	51	47	-4	-8		42	-9	-17
2	64	61	-3	-5		60	-4	-6
3	64	69	+6	+9		69	+5	+8
4	59	60	+2	+3		65	+6	+10
5	57	56	-1	-2		63	+6	+11
6	58	56	-2	-4		60	+2	+3
7	53	58	+5	+10		60	+6	+11
8	49	53	+4	+8		57	+8	+16
9	58	63	+5	+9		62	+4	+6
10	51	46	-5	-10		55	+4	+7
11	48	56	+8	+17		54	+7	+14
12	55	54	-1	-2		56	+1	+2
13	50	51	+1	+2		52	+2	+4
14	54	54	-0	-1		62	+8	+15
15	74	80	+6	+8		87	+13	+18
16	61	56	-4	-7		60	-1	-1
17	46	52	+6	+14		48	+2	+4
18	47	45	-2	-4		58	+11	+24
19	44	47	+3	+7		59	+15	+35
20	53	47	-6	-11		50	-3	-5
Mean	**55**	**56**	**+1**	**+2**		**59**	**+4**	**+8**
Median	**54**	**55**	**+0**	**+1**		**59**	**+4**	**+8**
Min	44	45	-6	-11		42	-9	-17
Max	74	80	+8	+17		87	+15	+35
Std.Dev.	7	8	4	8		9	6	11

Expressed as mean thickness of all analysed hair per measurement, the thickness of hair was detected in mean by +1 µm and median by 0 µm not changed meaningful over all 20 subjects after 3 month application of test product. After 6 month application a change of hair thickness by +4 µm in mean and median over all 20 subjects was determined. Corresponding 20 results about change of hair thickness after 6 month exhibit a standard deviation of 6 µm.

8.5 Density of terminal and vellus hair

Trichoscan analysis were carried out in the prepared area of every subject's scalp at indicated times. Density of terminal and vellus hair [1/cm²] was determined by nine repeated recordings in mean over all subjects, placing the camera head on nine different sites in the prepared scalp area and using the Trichoscan HD software for evaluation of recordings. The means of all nine fold repetition per subject and time of analysis are shown in the tables below.

	Density Vellus Hair[1/cm²] appl. of shampoo					**Density Vellus Hair[1/cm²] shampoo+tonic**		
Subject No.	**Start**	**After 3 month**	**Difference** (After 3 month minus Before)	**Rel. Difference [%]** After 3 month minus Before) Start = 100 %		**After 6 month**	**Difference** (After 6 month minus Before)	**Rel. Difference [%]** After 6 month minus Before) Start = 100 %
1	51	54	+3	+7		76	+25	+49
2	35	34	-2	-5		41	+6	+17
3	28	14	-14	-50		24	-4	-14
4	33	48	+15	+44		50	+17	+51
5	46	42	-4	-9		47	+1	+3
6	34	39	+5	+15		20	-14	-41
7	41	53	+12	+28		48	+7	+17
8	36	34	-2	-6		32	-4	-12
9	25	23	-2	-7		29	+4	+17
10	146	128	-18	-12		86	-60	-41
11	64	46	-18	-29		60	-4	-7
12	46	70	+24	+53		63	+17	+37
13	8	69	+61	+730		54	+46	+554
14	31	25	-6	-19		29	-2	-6
15	21	21	+0	+0		27	+7	+33
16	31	41	+10	+32		39	+8	+24
17	59	32	-28	-47		57	-3	-5
18	78	80	+2	+3		56	-21	-28
19	80	92	+11	+14		65	-15	-19
20	70	58	-12	-17		64	-6	-8
Mean	**48**	**50**	**+2**	**+36**		**48**	**+0**	**+31**
Median	**39**	**44**	**-1**	**-3**		**49**	**-0**	**-1**
Min	8	14	-28	-50		20	-60	-41
Max	146	128	+61	+730		86	+46	+554
Std.Dev.	29	27	18	161		18	20	123

After 6 month application of the test product no change in density of vellus hair per cm² scalp was determined in mean and median over all 20 analysed subjects.

	Density Terminal Hair [1/cm²] appl. of shampoo					Density Terminal Hair [1/cm²] shampoo		
Subject No.	**Start**	**After 3 month**	**Difference** (After 3 month minus Before)	**Rel. Difference [%]** After 3 month minus Before) Start = 100 %		**After 6 month**	**Difference** (After 6 month minus Before)	**Rel. Difference [%]** After 6 month minus Before) Start = 100 %
1	83	64	-19	-23		75	-9	-11
2	134	114	-19	-14		110	-24	-18
3	80	77	-3	-4		87	+7	+9
4	100	134	+33	+33		154	+53	+53
5	91	85	-6	-6		126	+35	+38
6	114	116	+2	+2		115	+2	+2
7	202	219	+17	+9		223	+21	+10
8	86	96	+10	+11		99	+13	+16
9	52	67	+15	+28		70	+18	+35
10	150	110	-40	-26		133	-17	-11
11	89	126	+37	+41		132	+43	+48
12	115	149	+34	+30		155	+40	+35
13	19	99	+80	+412		83	+63	+326
14	63	32	-32	-50		94	+30	+48
15	74	85	+11	+16		118	+44	+60
16	131	136	+4	+3		151	+20	+15
17	50	41	-9	-17		62	+12	+24
18	86	83	-3	-3		125	+39	+45
19	51	78	+28	+54		117	+67	+131
20	125	79	-46	-37		117	-8	-7
Mean	**95**	**100**	**+5**	**+23**		**117**	**+22**	**+42**
Median	**88**	**91**	**+3**	**+3**		**117**	**+20**	**+29**
Min	19	32	-46	-50		62	-24	-18
Max	202	219	+80	+412		223	+67	+326
Std.Dev.	40	41	29	93		36	25	73

A change of +3 terminal hair per cm² in median over all 20 subjects was detected after 3 month applying the test product. Corresponding 20 results about change of terminal hair density exhibit a standard deviation of 29 terminal hair per cm². After 6 month an increase by 22 terminal hair in mean, respectively 20 terminal hair in median per cm² was determined over all 20 subjects, compared with density before starting application of test product. Corresponding standard deviation of the 20 change rates was 25 terminal hair per cm².

Sorting the results after 6 months concerning magnitude of change in terminal hair density per cm², reveals following table.

	Density Terminal Hair [1/cm²] appl. of shampoo				Density Terminal Hair [1/cm²] shampoo		
Subject No.	**Start**	**After 3 month**	**Difference** (After 3 month minus Before)	**Rel. Difference [%]** After 3 month minus Before) Start = 100 %	**After 6 month**	**Difference** (After 6 month minus Before)	**Rel. Difference [%]** After 6 month minus Before) Start = 100 %
19	51	78	+28	+54	117	**+67**	+131
13	19	99	+80	+412	83	**+63**	+326
4	100	134	+33	+33	154	**+53**	+53
15	74	85	+11	+16	118	**+44**	+60
11	89	126	+37	+41	132	**+43**	+48
12	115	149	+34	+30	155	**+40**	+35
18	86	83	-3	-3	125	**+39**	+45
5	91	85	-6	-6	126	**+35**	+38
14	63	32	-32	-50	94	**+30**	+48
7	202	219	+17	+9	223	**+21**	+10
16	131	136	+4	+3	151	**+20**	+15
9	52	67	+15	+28	70	**+18**	+35
8	86	96	+10	+11	99	**+13**	+16
17	50	41	-9	-17	62	**+12**	+24
3	80	77	-3	-4	87	**+7**	+9
6	114	116	+2	+2	115	**+2**	+2
20	125	79	-46	-37	117	**-8**	-7
1	83	64	-19	-23	75	**-9**	-11
10	150	110	-40	-26	133	**-17**	-11
2	134	114	-19	-14	110	**-24**	-18
Mean	**95**	**100**	**+5**	**+23**	**117**	**+22**	**+42**
Median	**88**	**91**	**+3**	**+3**	**117**	**+20**	**+29**
Min	19	32	-46	-50	62	-24	-18
Max	202	219	+80	+412	223	+67	+326
Std.Dev.	40	41	29	93	36	25	73

The results of 16 subjects indicate an increase of hair density by 2 – 67 terminal hair per cm² after 6 months applying the test product. The results of 4 subjects exhibit a decrease of terminal hair density by 8 – 24 terminal hair per cm² after 6 month.

8.6 Percentage of terminal and vellus hair

Trichoscan analysis were carried out in the prepared area of every subject's scalp at indicated times. Percentages of terminal and vellus hair [%] were determined by nine repeated recordings in mean over all subjects, placing the camera head on nine different sites in the prepared scalp area and using the Trichoscan HD software for evaluation of recordings. The means of all nine fold repetition per subject and time of analysis are shown in the tables below.

	Vellus Hair [%] appl. of shampoo					**Vellus Hair [%] shampoo**		
Subject No.	**Start**	**After 3 month**	**Difference** (After 3 month minus Before)	**Rel. Difference [%]** After 3 month minus Before) Start = 100 %		**After 6 month**	**Difference** (After 6 month minus Before)	**Rel. Difference [%]** After 6 month minus Before) Start = 100 %
1	38	46	+8	+21		54	+16	+43
2	21	23	+2	+9		63	+42	+200
3	26	15	-11	-41		63	+37	+143
4	25	26	+2	+7		25	-0	-0
5	33	33	-0	-1		27	-6	-18
6	23	25	+2	+10		15	-8	-36
7	17	19	+3	+16		18	+1	+6
8	30	26	-3	-11		24	-5	-18
9	33	26	-7	-21		29	-3	-10
10	49	54	+5	+10		40	-9	-18
11	43	27	-16	-38		31	-11	-27
12	28	32	+3	+12		29	+0	+1
13	31	41	+10	+32		39	+8	+27
14	33	45	+12	+36		24	-9	-27
15	21	20	-2	-9		19	-3	-12
16	19	23	+4	+23		20	+1	+7
17	54	43	-12	-21		48	-7	-13
18	47	49	+1	+3		31	-16	-35
19	62	54	-8	-12		36	-26	-42
20	36	42	+7	+19		35	-0	-1
Mean	**33**	**33**	**+0**	**+2**		**34**	**+0**	**+9**
Median	**32**	**29**	**+2**	**+8**		**30**	**-3**	**-11**
Min	17	15	-16	-41		15	-26	-42
Max	62	54	+12	+36		63	+42	+200
Std.Dev.	12	12	7	21		14	16	59

A change of vellus hair percentage in median by +2 % and mean by 0 % over all 20 subjects was detected after 3 month applying the test product. Corresponding 20 results about change of vellus hair percentage exhibit a standard deviation of 7 %. After 6 month a change of vellus hair percentage by -3 % was determined in median

over all 20 subjects, compared with percentage before starting application of test products, while corresponding standard deviation of the 20 change rates was 16 %.

	Terminal Hair [%] appl. of shampoo					Terminal Hair [%] appl. of shampoo		
Subject No.	**Start**	**After 3 month**	**Difference** (After 3 month minus Before)	**Rel. Difference [%]** After 3 month minus Before) Start = 100 %		**After 6 month**	**Difference** (After 6 month minus Before)	**Rel. Difference [%]** After 6 month minus Before) Start = 100 %
1	62	54	-8	-13		53	-9	-15
2	79	77	-2	-2		77	-2	-3
3	74	86	+11	+15		79	+4	+6
4	75	74	-2	-2		75	+0	+0
5	67	67	+0	+1		73	+6	+9
6	77	75	-2	-3		85	+8	+11
7	90	81	-9	-10		82	-7	-8
8	70	74	+3	+5		76	+5	+8
9	67	74	+7	+10		71	+3	+5
10	51	46	-5	-10		60	+9	+18
11	57	73	+16	+28		69	+11	+20
12	72	68	-3	-5		71	-0	-1
13	69	59	-10	-14		61	-8	-12
14	67	55	-12	-18		76	+9	+13
15	79	80	+2	+2		81	+3	+3
16	81	77	-4	-5		80	-1	-2
17	46	57	+12	+25		52	+7	+15
18	53	51	-1	-2		69	+16	+31
19	38	46	+8	+20		64	+26	+67
20	64	58	-7	-10		65	+0	+1
Mean	**67**	**67**	**-0**	**+1**		**71**	**+4**	**+8**
Median	**68**	**71**	**-2**	**-2**		**72**	**+4**	**+6**
Min	38	46	-12	-18		52	-9	-15
Max	90	86	+16	+28		85	+26	+67
Std.Dev.	12	12	8	13		9	8	17

No increase of terminal hair percentage was detected after 3 month applying the test product. After 6 month a change by +4 % in mean and median over all 20 subjects was determined. Corresponding standard deviation of the 20 change rates was 8 %.

9 Assessment of the study results

9.1 Skin tolerability

The test product **CARON BIO C3 SHAMPOO** was applied over a period of 6 month by 20 subjects once daily on the hair and scalp. From the clinical-dermatological perspective no relevant skin reactions arose in the test area; the product was tolerated very well. Neither intolerance reactions in terms of irritation nor allergic reactions (contact dermatitis) were detected.

Accordingly, from dermatological view, the tested product **CARON BIO C3** exhibits no high potential for irritation and sensitisation, when used as intended.

9.2 Efficacy

The efficacy of the test product **CARON BIO C3 SHAMPOO** to reduce hair loss was investigated by counting the out fallen hair after washing and combing by a standardised comb. In mean over the 20 subjects a decrease of out fallen hair by 50 %, in median by 45 % was determined after 3 month application of the test product. Corresponding standard deviation of 20 change rates was 31 %, indicating a meaningful decrease.

After 6 month applying the test product a reduction of out fallen hair by 54 % was detected in mean, by 67 % in median over the 20 subjects. However, the corresponding standard deviation was 61 %.

The efficacy of the test product **CARON BIO C3 SHAMPOO** to increase the percentages of anagen hair and terminal hair, while decreasing percentages of telogen hair and vellus hair was investigated by TrichoScan. In the context of this method also the efficacy of the test product to increase thickness of hair and density of terminal hair was analysed next to density of vellus hair. After 3 month applying the test product a positive change of anagen hair percentage and corresponding negative change of telogen hair percentage were detected in mean (+2 %, -3 %) and median (+4 %, -4 %) over the 20 subjects. However, corresponding standard deviations of change rates were 2fold bigger and more (9 – 8 %). After 6 month application of test product an enhanced increase of anagen hair percentage (+9 % in mean and median) as well as corresponding decrease of telogen hair percentage (10 % in mean and median) were determined, next to standard deviations of 11 % (anagen) and 10 % (telogen).

This indication of positive efficacy on hair was accompanied by detection of augmented terminal hair per cm² scalp (+22 in mean, +20 in median) after 6 month of test product application. Still the standard deviation of corresponding 20 changes rates was 25. In parallel density of vellus hair was not determined changed. Sorting changes rates of terminal hair density reflects, that 16 subjects exhibited an increase of terminal hair density between 67 and 2 terminal hair per cm², while 4 subjects displayed a reduction (-8 - -24), explaining magnitude of standard deviation.

Percentage of vellus hair was not detected changed. Percentage of terminal hair was determined enhanced by 4 % in mean and median of 20 analysed subjects after 6 month applying test product, next to a standard deviation of 8 %.

Regarding median thickness of analysed hair after 6 month application of test product, a change of +5 µm was determined in mean and median over all 20 subjects, next to a standard deviation of 7 µm. As mean thickness of analysed hair after 6 month test product, a change of +4 µm was detected in mean and median with a standard deviation of 6 µm.

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Biochemist

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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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Muenster, April 8th 2021

Certificate

about the cosmetic product

CARON BIO C3 SHAMPOO

Clinical application study under dermatological control

The test product was applied over a period of 6 month by 20 subjects once daily onto the hair and scalp. From the clinical-dermatological point of view no relevant skin reactions occurred in the test area; the product was tolerated

excellently.

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 for the tested product when used as intended.

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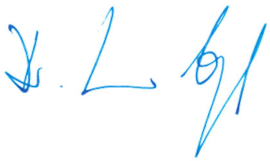

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about the cosmetic product

CARON BIO C3 SHAMPOO

Clinical application study under dermatological control and determination of hair loss by quantifying out fallen hair

The test product was applied over a period of 6 month by 20 subjects once daily onto the hair and scalp. After 3 month application of test product a

Reduction of out fallen hair by 50 % in mean and 45 % in median

was quantified on the 20 subjects. The corresponding 20 results about change of out fallen hair quantity exhibited a standard deviation of 31 %.

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The test product was applied over a period of 6 month by 20 subjects once daily onto the hair and scalp. After 6 month application of test product a

Reduction of out fallen hair by 54 % in mean and 67 % in median

was quantified on the 20 subjects. The corresponding 20 results about change of out fallen hair quantity exhibited a standard deviation of 61 %.

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about the cosmetic product

CARON BIO C3 SHAMPOO

Clinical application study under dermatological control and determination of anagen and telogen hair percentage by TrichoScan

The test product was applied over a period of 6 month by 20 subjects once daily onto the hair and scalp. After 6 month application of test product an

Increase of anagen hair percentage by 9 %

was quantified in mean and median of the 20 subjects. The corresponding 20 results about change of anagen hair percentage exhibited a standard deviation of 11 %.

In parallel a

Decrease of telogen hair percentage by 10 %

was quantified in mean and median of the 20 subjects. The corresponding 20 results about change of telogen hair percentage exhibited a standard deviation of 10 %.

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about the cosmetic product

CARON BIO C3 SHAMPOO

Clinical application study under dermatological control and determination of terminal hair density by TrichoScan

The test product was applied over a period of 6 month by 20 subjects once daily onto the hair and scalp. After 6 month application of test product an

Augmentation of terminal hair per cm² scalp by 22 hair in mean / 20 in median

was quantified on the 20 subjects. The corresponding 20 results about change of terminal hair density exhibited a standard deviation of 25 hair per cm².

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CARON BIO C3 SHAMPOO

Clinical application study under dermatological control and determination of median hair thickness by TrichoScan

The test product was applied over a period of 6 month by 20 subjects once daily onto the hair and scalp. After 6 month application of test product a

Change of hair thickness by +5 µm

was quantified in mean and median of the 20 subjects. The corresponding 20 results about change of median hair thickness exhibited a standard deviation of 7 µm.

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