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Study Number 2005294736

Muenster, September 24th 2020

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

on 20 subjects with application daily on hair and scalp over a period of four weeks

Test for dermal tolerability

CARON BIO C3 SHAMPOO

and

CARON BIO C3 HAIR TONIC

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Amtsgericht Münster HRB 1348
USt-ID: DE126040147

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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 products	**CARON BIO C3 SHAMPOO,** **CARON BIO C3 HAIR TONIC**
Product types	Shampoo, Tonic
Study design	Single-centre
Testing body	Dermatest GmbH Engelstr. 37 D-48143 Münster
Expert report version and date	V1 24.09.2020
Test period	July – September 2020
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.
Quantity of subjects	20
Application period	4 weeks
Test area	Hair and scalp
Frequency of application	once daily both products (Tonic was also applied on scalp, if shampoo was not applied on a day)
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 28
Information of the subjects	✔	
Informed Consent Form Sheet	✔	
Medical history	✔	
Dermatological examination	✔	✔
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 of the products **CARON BIO C3 SHAMPOO** and **CARON BIO C3 HAIR TONIC** 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 Study parameters

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

4 Selection of subjects

The study was carried out with 5 female and 15 male subjects aged 25 years up to 65 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]
1	BrTh	m	43
2	BüTa	f	43
3	BuMa	m	40
4	DiMa	f	65
5	FlJö	m	39
6	HeMa	m	50
7	KlSu	f	53
8	LaDa	m	37
9	MaSu	f	61
10	NiGe	m	30
11	NiMa	m	38
12	ReDa	m	36
13	ScTi	m	33
14	ScNi	m	25
15	SpJö	m	41
16	SpJa	m	39
17	StKa	m	44
18	TöLe	m	27
19	VaAl	m	45
20	WaNi	f	48

5 Test products

5.1 Application of the investigational products

The shampoo was applied on hair and scalp, the tonic was applied on scalp, both 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 Results

7.1 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 products **CARON BIO C3 SHAMPOO** and **CARON BIO C3 HAIR TONIC** were 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 Assessment of the study results

8.1 Skin tolerability

The test products **CARON BIO C3 SHAMPOO** and **CARON BIO C3 HAIR TONIC** were applied over a period of four weeks 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 products were tolerated very well. Neither intolerance reactions in terms of irritation nor allergic reactions (contact dermatitis) were detected.

Accordingly, from dermatological view, the tested products **CARON BIO C3 SHAMPOO** and **CARON BIO C3 HAIR TONIC** exhibit no high potential for irritation and sensitisation, when used as intended.

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Signature

Dr. med. Gerrit Schlippe
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Signature

PhD Dominik Schmaltz
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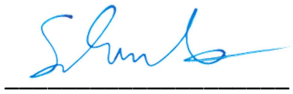

Signature

9 Addendum

9.1 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.

9.2 Certificates

- Skin tolerability

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SEOUL
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Muenster, September 24th 2020

Certificate

about the cosmetic products

CARON BIO C3 SHAMPOO and CARON BIO C3 HAIR TONIC

Clinical application study under dermatological control

The test products were applied over a period of four weeks 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 products were 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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