HAMILTON

REPORT No. 101448/21/CGDA/S

Sponsor:		Investigational product *(according to declaration of the Sponsor)*
Sheleg consulting , 3877701 Industrial Park Emek Hefer, 5 Nahal Alexander		**MANUKA SERUM**
Report date:	10.03.2021	

Sensitive Skin Test (50 subjects, min. 10 with sensitive skin)

REPORT No. 101448/21/CGDA/S

CONTENT OF THE RAPORT

Authorised by: Karolina – Osiecka, Dermatologist - Venereologist, 2487308 (qualified electronic signature),
Marta Rosińska, Cosmetic Laboratory Manager (qualified electronic signature).

Laboratory: ul. Bajana 3D, 80-463 Gdańsk, Poland
The results relate to the analysed samples only.

J.S. HAMILTON POLAND Sp. z o.o
ul. Chwaszczyńska 180, 81-571 Gdynia, Poland, tel. +48 58 766 99 00

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MANUKA SERUM

STUDY REFERENCE

SPONSOR	**Sheleg consulting , 3877701 Industrial Park Emek Hefer, 5 Nahal Alexander**
STUDY MONITOR	Vardit Hadad
INVESTIGATING CENTRE	**J.S. HAMILTON POLAND Sp. z o.o.** Ul. Bajana 3D 80-463 Gdańsk, POLAND
PROJECT MANAGER	Marta Rosińska
MAIN INVESTIGATOR	**Dr Karolina Osiecka** (dermatologist-venerologist) Registered N° **2487308**
ETHICAL COMMITTEE APPROVAL	26.02.2021

Authorised by: Karolina – Osiecka, Dermatologist - Venereologist, 2487308 (qualified electronic signature),
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1. INITIAL STUDY DESIGN

1.1. STUDY OBJECTIVES

This study intended to assess the irritating properties (skin tolerance) of the product **MANUKA SERUM** in a panel of healthy human subjects with normal and sensitive skin, with applied patch test, during 48 consecutive hours.

1.2. ETHICAL CONDUCT OF THE STUDY

The described study was conducted in the spirit of the Good Clinical Practice defined by the ICH Topic E6 "Note for Guidance and good clinical practice" (CPMP/ICH/135/95), the Helsinki Declaration (1964, WMA) and its successive updates. The study was conducted according to Standard Operating Procedures and to the study protocol defined by the sponsor. All study events recorded during the study was reported. Controls on data veracity and conformity with the protocol was performed and confirmed by persons participating in the study.

SCOPE OF TESTS COMPLIANT WITH:

- Regulation of the European Parliament and of the Council (EC) No. 1223/2009 of 30 November 2009 on cosmetic products.
- Cosmetics Europe – The Personal Care Association (previously COLIPA) Guidelines "Product Test Guidelines for the Assessment of Human Skin Compatibility 1997."
- Cosmetics Europe – The Personal Care Association (previously COLIPA) Guidelines for the Evaluation of the Efficacy of Cosmetic Products 2008.

1.3. QUALITY CONTROL

The study was performed in compliance with the procedures of the investigating centre, established according to the regulations in force.
The investigator, in charge of the performance of the study, made sure of the quality of the work of the technical staff, particularly concerning the respect of the protocol and its appendices, the collection of raw data, the management of the investigational product.

1.4. RELEVANCE OF THE STUDY

Based on the existing data, the main aim of the study being a better knowledge of the skin safety of the investigational product **MANUKA SERUM**. The purpose of the test is to examine whether a certain substance may cause an initial irritation in subjects with normal and sensitive, healthy skin.

The skin examination was performed by the investigator or by the technician, controlled by the investigator having the appropriate experience.

1.5. ETHICAL COMMITTEE

According to the procedure of investigating center, the protocol, the informed consent form and the preclinical information concerning the investigational product **MANUKA SERUM** was submitted to the internal committee of the investigating center.

The committee got sure that the project meets the conditions of optimal scientific rigor, assessed its general relevance, the suitability between the aim followed and the means implemented and was gave an opinion on the protection of the test subjects.

The study do not begin without the approval of the Survey committee.

1.6. INFORMATION OF THE TEST SUBJECT AND INFORMED CONSENT FORM

The information about the study was given orally and as a written document to each test subject before the start of the study. This information is accessible, understandable and suitable for each test subject. This information was completed, if necessary, by the investigator (or the competent person designated) who answered all the questions asked by the test subject.

The content of this document particularly specified:

· that the test subject declares to have a health coverage,
· the aim of the study,
· the study design and the experimental conditions of the study,
· the investigational product conditions of use,
· the approximate number of test subjects involved in the study,

· the expected duration of the study (for the test subject),
· the number of visits to the investigating centre, their dates and their duration,
· the study constraints (obligations, restrictions and troubles),
· that skin site photographs can be taken and in this case, that the test subject would not be recognizable,
· the opinion of the internal committee,
· the person to contact and the contact telephone number,
· that the personal data of the test subject would be confidentially treated by the study staff, available for the study monitor and possibly consulted (with the authorization of the test subject) by the auditors and the members of the internal committee,
· the ban on taking part simultaneously in other clinical studies,
· the amount of the compensation for the constraints to be undergone,
· the period of exclusion at the end of the study during which the test subject would not be allowed to take part in another clinical study,
· the confidential treatment of the study data,
· that the anonymity of the test subject was preserved,
· the freedom for the test subject to refuse to participate or to stop his participation at any time without any justification and any legal consequences.

At the beginning of the study, two copies of this document was dated and signed simultaneously by the test subject and by the investigator or the competent person designated. One copy was given to the test subject, the other was kept at the investigating centre.

1.7. CONFIDENTIALITY OF THE SUBJECT

The information concerning the subject, required for his recruitment, inclusion and particularly that related to his health, obtained during the medical examination, formed part of medical secret and was confidentially treated.

The test subject was coded when included in the study to preserve his anonymity.

1.8. THE BASIS TO CONDUCT THE STUDY

- Samples delivered by the Sponsor.
- The qualitative composition of the product delivered by the Sponsor.
- The results of microbiological purity of the product provided by the Sponsor (or declaration from the Sponsor about microbiological purity).

The Sponsor is responsible for conformity with the declared quality composition of the product as well as microbiological purity test of the delivered samples.

2. SUBJECT OF THE TEST

2.1 DESCRIPTION OF THE PRODUCT

Parameter	**Description**
Intended use	Serum
Appearance	Dense liquid
Color	Beige
Fragrance	Characteristic for used raw materials
Packaging	Repackaging containing the name and the number of sample

2.2 QUALITATIVE COMPOSITION OF THE PRODUCT (INCI)

Aqua
Water & Sodium Hyaluronate & Phenoxyethanol
Honey
Propanediol
Xanthan Gum
Phenoxyethanol 0.534% & Ethylhexylglycerin 0.056%
Squalane
Ascorbyl Tetraisopalmitate
Alovera Barbadensis Leaf Juice powder
Simmondsia Chinesis Seed Oil
Rosa Moschata Oil
Butyrospermum parkii (Shea) Oil
Helianthus Annuus Seed Oil & Calendula Officinalis Flower Extract
Tocopherol (mixed), Beta-Sitosterol, Squalene

Olea Europaea Fruit Oil
Bisabolol
Fragrance(Green)
Linoleic Acid & Oleic Acid & Linoleic Acid & Tocopherol
Retinyl palmitate
Pichia/Resveratrol Ferment Extract
Bee Venom
Linalool
Limonene
Citronellol
Hexyl Cinnamal
Geraniol
Hydroxycitronellal

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3. STUDY DESIGN

3.1 AIM OF THE STUDY

The aim of the study is to determine whether an ingredient or a cosmetic product can cause initial irritation on a healthy, adult, normal and sensitive skin, with applied patch test. Pre and post skin examinations was performed by a trained technician.

3.2 GENERAL PRINCIPLE OF THE STUDY

The test starts with a group of around 50 subjects, out of which at least 10 subjects are selected who were found to have sensitive skin in the lactic acid stinging test. The investigational product **MANUKA SERUM** has to be applied on the intrascapular region of the back or upper area of the arm, by the trained technician. The sealing patch was kept on for 48 hours, after which it was removed and the area was marked for a response' assessment.

3.3 SCHEDULE OF THE STUDY

DELIVERY OF PRODUCT	23.02.2021
START OF STUDY	02.03.2021
END OF STUDY	06.03.2021
REPORT DATE	10.03.2021

3.4 TESTING METHODOLOGY

3.4.1 SENSITIVE SKIN TEST (50 SUBJECTS, MIN. 10 WITH SENSITIVE SKIN)

The objectives of this study are:

I. To select panels of sensitive skin subjects.

Ten percent racemic D-L Lactic acid is prepared in distilled water from 85% syrup (Sigma Chemical). 50µl is then pipetted onto the absorbent pad Finn Chamber/Hill Top

Chamber/Leukotest or any other similar chamber. This volume saturates the pad without leakage. The adhesive around the chamber is trimmed to leave two short 2 mm tabs on opposite sides near the skin folds by the nose base (nostrils), sufficient to seal the chamber to the skin. The exposure time is ten minutes, after which the chamber is removed and the nose is briefly hand-washed with a mild liquid soap. During the exposure, the subject records stinging each minute on a 0 to 3 scale:

0 = none, 1 = slight, 2 = moderate, 3 = severe.

At least 10 out of the 50 subjects who were examined and who reacted in a moderate or severe manner (degree 2, 3) were considered as having sensitive skin and thus were suitable candidates for further testing. The subjects are comfortably seated during the exposure. Two values are recorded: (1) the time in minutes when stinging is first unequivocally perceived (short times usually presage intense stinging); (2) the peak intensity reached during the ten-minute exposure, on a 0 to 3 scale. Occasionally, stinging declines before the end of ten minutes. An alternative system is to sum up the ten scores and calculate the mean.

II. To determine whether any of a series of test materials produces primary irritation with a single patch test (on the selected subjects).

The test was conducted on 50 volunteers, on a mixture of the wipe fabric and the material with which the wipe is impregnated. The test article was tested 15µl of the test material was applied in a patch test (filter paper discs manufactured by SmartPractice® + surgical patch/ Finn Chamber or any other similar chamber). In the single patch test design, after 48 hours of a single exposure, test patches was removed and the test area was marked to facilitate locating treatment sites for evaluation. Evaluation of the response was made 1 hr, 24hr and 48hrs after patch removal. If the response of the skin is positive after 48h, the skin is also observed after 72 and 96 hours.

Reactions was graded:

0 = negative, no observed reaction

± = questionable erythema not covering entrie area

1 = definite erythema

2 = vesiculation

3 = bullous reaction

The test is acceptable only when there are no reactions (0 on the scale).

3.5 SUSPENSION OF THE STUDY

The investigator has to stop the study if it shows a risk for the health or the integrity of the test subjects. The date of the suspension and the reasons has to be carefully documented by the investigator in the case report form (CRF).
The investigating centre has to inform promptly the study monitor, by phone, fax or e-mail. The sponsor was able to stop the study at any time for administrative reasons or other ones.

3.6 ADVERSE EVENTS

According to individual sensitivities, any product can induce a minor reactivity, defined as follows: any slight local reaction of intolerance or sensation of discomfort, occurring in a test subject during a clinical study, completely reversible, expected, due to the investigational product and which does not question the observance of the study protocol or the good implementation of the study.
- **adverse event**: any harmful event with or without relationship with the investigational product, occurring in a test subject during a clinical study.
- **serious adverse event**: any adverse event that causes death, endangers test subject's life, induces an hospitalization or the prolongation of the hospitalization, causes severe and lasting incapacity or handicap or induces congenital anomaly or malformation.

The investigator has to accurately describe the adverse event and has to appreciate its seriousness. According to the corresponding procedure of the investigating centre, he has to define the link of causality between this event and the investigational product, on the basis of the symptoms, the chronology, the results of the possible specific complementary tests undertaken and any available information.
The imputability of the investigational product has to be assessed according to the scale: very likely, likely, possible, questionable, excluded. In case of adverse effect (with a quite possible relationship with the investigational product), the investigator has to ensure the clinical follow-up of the test subject concerned, as long as necessary.

The serious adverse events had to be notified as soon as possible and within 24 hours at the latest, by the investigating centre to the study monitor, by phone, fax or e-mail.
The investigator had to send an adverse event form to the study monitor.

3.7 RAW DATA RECORDING

All the data gathered during the study was recorded accurately, legibly and indelibly by the investigator and the technician in charge of the study, under his control, in the case report form. This document was initialed by the technician or investigator.
At the end of the study, the information concerning the investigational product, the information concerning the test subjects (CRF(s), daily logs, informed consent forms) and the information related to the conduct of the study (protocol signed by the sponsor, copy of this study report….) were filed and was kept for 10 years, in the filing area of the investigating centre.
At the end of this period the study documentation was destructed (after sponsor's authorization), unless he decides otherwise.

4. DESCRIPTION OF SUBJECTS

GENERAL INCLUSION CRITERIA	Healthy subject.	
	Sign an informed consent to participate in the study, were informed about the purpose of the study, the manner of its conduct and the possible side effects.	
	Skin without irritation and changes requiring pharmacological treatment.	
	Cooperative subject, aware of the necessity and duration of controls.	
SPECIFIC INCLUSION CRITERIA	Amount of subjects:	50 subjects
	Gender:	Woman (recommended gender), men
	Age:	18+ years old
	Skin type:	Normal, at least 10 subjects with sensitive skin (degree 2, 3)
	Other:	Phototype: I – IV on Fitzpatrick scale; caucasians

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NON INCLUSION CRITERIA	Subjects who use any treatment on the studied zone.
	Subject exhibiting or having a known history of acute or chronic dermatological, medical and/or physical conditions that could influence the outcome of the test.
	Pregnant or breastfeeding woman or woman planning a pregnancy during the study.
	Subject having a known history of allergic reactions to cosmetics, soaps or toiletries.
	Subject abusing alcohol and/or drugs.
	Subject undergoing treatment with sympathomimetics, antihistamines, non-steroidal anti-inflammatory agents, corticosteroids and/or any other medications that could have interfered with the results of this study, within one week prior to initiation of this test.
	Subject enrolled in another study during the study period (concerning the studied zone).
	Subject considered by the investigator to be likely not compliant to the protocol.
INFORMED CONSENT	After an explanation of the protocol, reasons for the study, possible associated risks and potential benefits of the treatment each subject signed an informed consent form before starting the study.

The qualified subjects must not use any products on the back of one day before the study and was instructed to continue their usual cosmetic regiment, except no new cosmetic can be introduced during the study period.

Skin reactivity, history of atopy and contraception was documented by the investigator, in the case report form (CRF). No medication likely to interfere with the study was allowed during the study; however, if the health state of the subjects justifies some medication (particularly anti-inflammatory drugs), any information relating to this concomitant medication had to be carefully documented in the case report form. The investigator had to exclude the test subjects taking concomitant medication likely to interfere with the study and the interpretation of the results.

5. TRIAL SCHEDULE

D0:

- The subjects come to the laboratory.
- Subjects sign and consent informed forms in duplicate.
- Verification of inclusion and non-inclusion criteria.
- The trained technician examine the study zone.
- At least 10 subjects with sensitive skin are selected in the lactic acid stinging test.
- The sealing patch is sticked.

D1 (after 48h):

- The subjects come to the laboratory.
- The sealing patch is removed and the test area is marked to facilitate locating treatment sites for evaluation. Evaluation of the response is made 1hr after patch removal.

D2 (after 24h from patch removal):

- The subjects come to the laboratory again.
- The marked test area is evaluate of the response again.

D3 (after 48h from patch removal):

- The subjects come to the laboratory again.

The marked test area is evaluate of the response again.

If the response of the skin is positive after 48h, the skin is also observed after 72 and 96 hours. If the response of the skin is positive (grade min. 2), a visit to a dermatologist is arranged.

6. RESULTS

6.1 CHARACTERISTICS OF SUBJECTS

No. of subject	Identification of subject	Begining of the study	Age	Sex	Phototype	Degree of stinging
1	SZY.MA	02.03.2021	49	F	II	3
2	LIS.MI	02.03.2021	26	F	II	0
3	STE.MA	02.03.2021	58	F	II	0
4	ALE.DA	02.03.2021	69	F	II	0
5	CZO.SY	02.03.2021	48	F	II	0
6	SOS.AG	02.03.2021	32	F	II	3
7	PAS.AU	02.03.2021	68	F	II	0
8	DIE.BE	02.03.2021	46	F	II	0
9	KIZ.MA	02.03.2021	39	F	II	0
10	PIS.KA	02.03.2021	57	F	II	0
11	BER.AN	02.03.2021	50	F	II	2
12	PIO.EL	02.03.2021	50	F	II	2
13	KUR.AN	02.03.2021	47	F	II	0
14	LUC.BA	02.03.2021	26	M	II	0
15	MAT.RE	02.03.2021	67	F	II	0
16	BRZ.SY	02.03.2021	22	F	II	3
17	BER.MA	02.03.2021	61	F	II	0
18	KAR.DA	02.03.2021	43	M	II	0
19	KAL.GR	02.03.2021	62	F	II	0
20	KOZ.JO	02.03.2021	49	F	II	0
21	GRA.AL	02.03.2021	45	F	II	2
22	GRA.MA	02.03.2021	69	F	II	0
23	URB.BA	02.03.2021	62	F	II	0
24	OGI.AL	02.03.2021	55	F	II	0
25	MAC.PA	02.03.2021	27	F	II	0
26	WIE.MA	02.03.2021	23	F	II	0
27	ROM.KI	02.03.2021	26	F	II	0
28	SEK.EL	02.03.2021	68	F	II	2
29	ONI.AN	02.03.2021	38	F	II	0
30	HIR.DA	02.03.2021	33	M	II	0
31	MLY.MI	02.03.2021	62	F	II	0
32	OKU.AG	02.03.2021	48	F	II	3
33	POR.MO	02.03.2021	24	F	II	0
34	MIS.IW	02.03.2021	54	F	II	0
35	TAR.AG	02.03.2021	56	F	II	3
36	DAS.EW	02.03.2021	68	F	II	0
37	WAN.MA	02.03.2021	61	F	II	0
38	CIE.AL	02.03.2021	25	F	II	0
39	ROZ.AG	02.03.2021	38	F	II	0

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40	DUD.IR	02.03.2021	64	F	II	3
41	JAC.RA	02.03.2021	37	M	II	0
42	LIS.DA	02.03.2021	34	F	II	0
43	RYD.WI	02.03.2021	61	F	II	0
44	KUR.MA	02.03.2021	49	F	II	0
45	NIE.AG	02.03.2021	41	F	II	0
46	TRE.MI	02.03.2021	54	F	II	0
47	RAD.MA	02.03.2021	48	F	II	0
48	ZAL.IZ	02.03.2021	42	F	II	0
49	WIE.SL	02.03.2021	53	M	II	0
50	KRZ.GR	02.03.2021	36	M	II	0

Min	20	**No. F**	**phototype I**	**degree 0**
Max	69	44	0	0
Average	48	**No. M**	**phototype II**	**degree 1**
		6	50	0
			phototype III	**degree 2**
			0	4
			phototype IV	**degree 3**
			0	6

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6.2. TABLE OF SKIN RESPONSE

No. of subject	Evaluation 1 hour after removal of application	Evaluation 24 hour after removal of application	Evaluation 48 hour after removal of application
	04.03.2021	05.03.2021	06.03.2021
1	0	0	0
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
6	0	0	0
7	0	0	0
8	0	0	0
9	0	0	0
10	0	0	0
11	0	0	0
12	0	0	0
13	0	0	0
14	0	0	0
15	0	0	0
16	0	0	0
17	0	0	0
18	0	0	0
19	0	0	0
20	0	0	0
21	0	0	0
22	0	0	0
23	0	0	0
24	0	0	0
25	0	0	0
26	0	0	0
27	0	0	0
28	0	0	0
29	0	0	0
30	0	0	0
31	0	0	0
32	0	0	0
33	0	0	0

34	0	0	0
35	0	0	0
36	0	0	0
37	0	0	0
38	0	0	0
39	0	0	0
40	0	0	0
41	0	0	0
42	0	0	0
43	0	0	0
44	0	0	0
45	0	0	0
46	0	0	0
47	0	0	0
48	0	0	0
49	0	0	0
50	0	0	0

Legend:
na – not applicable

7. SUMMARY OF RESULTS:

Single insult patch test was performed on a group of 50 volunteers, including 10 volunteers with sensitive skin. No subjects discontinued or missed any of evaluation. No reaction (irritation) was observed in any of the 50 volunteers.

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SIGNATURES

PROJECT MANAGER	Sign and date:  10.03.2021
QUALITY ASSURANCE AUDITOR	Sign and date:  10.03.2021
DERMATOLOGIST	Sign and date:  10.03.2021 Registered N° **2487308**

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