STUDY/TEST ELEMENT REFERENCES: 02/SB-HRIPT-S_247_18-001

Study Report - Version nº 2

ASSESSMENT IN HUMANS OF THE CUTANEOUS COMPATIBILITY AND THE ABSENCE OF ALLERGENIC POTENTIAL OF A COSMETIC PRODUCT AFTER REPEATED UNDER PATCH APPLICATIONS WITH DERMATOLOGICAL CONTROL

HUMAN REPEATED INSULT PATCH TEST (HRIPT)

SPONSOR: C.V. MEDICA, S.L.
TESTED ELEMENT: ESPONJA JABONOSA
REFERENCE: -

Madrid, 24th January 2019

REPORT INDEX

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1. IDENTIFICATION OF THE STUDY

Name of the study: Assessment in human of the cutaneous compatibility and the absence of allergenic potential of a cosmetic product after repeated under patch applications (HRIPT) with dermatological control.

Director of the laboratory: Irene Zaldívar Notario

Director of the study: María Barbero Calderón

Sponsor: C.V. MEDICA, S.L.

Sponsor address: Pol. Ind. La plana C/ Ponent, 1 43424 Sarral (Tarragona)

Tested element: ESPONJA JABONOSA, reference: -, batch: 180319

2. OBJECTIVE AND PRINCIPLE OF THE STUDY

This study had as an objective verifying the cutaneous compatibility and the absence of allergenic potential of a cosmetic product (Reference: -), after repeated skin applications, under exaggerated experimental conditions.

The product was applied to the skin under patch 9 times during 3 consecutive weeks.

The compatibility of the product with the skin was verified, after removing the patch, and through visual examination of the experimental area, by the responsible technical expert and the dermatologist in charge of the study.

The method used is an adaptation of the one described by Marzulli and Maibach (Marzulli F.N., Maibach H.I., Contact allergy: predictive testing in man, Contact dermatitis, 1976, 2, pp.1-17).

3. TYPE OF STUDY

This study has been carried out in the Experimental Center under dermatological control.

Each volunteer that participated was his/her own controller. The negative control excluded false positives.

The study was carried out following general conditions in Zurko Research, established for the execution of study project on humans (Structure and Content of Clinical Study Reports from ICH Harmonised Tripartite Guideline; Guideline for good clinical practice E6 (R2) of June 14th 2017, EMA/CHMP/ICH/135/1995 of May 1st 1996, European Parliament and Council Guideline 2001/20/CE – May 1st 2001).

Previously, Zurko Research assessed the suitability of the product for the type of study and methodology to be employed.

4. RESEARCH CENTER AND TECHNICAL TEAM

4.1 Research Center

ZURKO RESEARCH S.L.

Almansa St 110, local 18

28040 Madrid (Spain)

Tel: (+34) 91.521.15.88

4.2 Technical Team

Director of the study: María Barbero Calderón, Pharmacist.

Researcher: Ana García Blanco, Biologist.

Dermatologist: Eliana San Juan Lasser. Medical license number: 283805700.

5. STUDY EXECUTION SCHEDULE

Beginning of the experimental phase: April 16th, 2018

Finalizing of the experimental phase: May 25th, 2018

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6. TESTED PRODUCT

6.1 Identification of the tested product

PRODUCT	ESPONJA JABONOSA
Reference of product	-
Batch of product	180319
Zurko Research Reference	02/SB-HRIPT-S_247_18-001
Cosmetic Form and organoleptic characteristcs	Sponge impregnated with soap
Number, type and volume of container	24 units

The tested element was stored at room temperature, following the indications of the sponsor.

The identity and stability of the tested element are in the product data sheet provided by C.V. MEDICA, S.L.

6.2 Information regarding the tested product

The documents related to the tested product that were supposed to accompany the samples were the qualitative formula and the letter of commitment from the Sponsor, particularly the one referring to the consistency of the formula with the current regulations and its safety.

7. VOLUNTEERS

7.1 Number

62 volunteers were included in the study. The number of volunteers who were supposed for the development of the study was 50. Considering that the number of volunteers used in this type of study is sufficient to verify compatibility and allergenic potential of a cosmetic dermal product.

6 volunteers (ref. V17, V39, V52, V53, V59 and V62) discontinued the study for reasons unrelated to it. One volunteer (ref. V5) was excluded by the researcher due to a non-compliance of the protocol.

The compatibility of the tested product was therefore verified on 55 volunteers.

All volunteers continued the following recommendations of the study's principal investigator:

- No intense sun exposure prediction (direct sun or UV rays), during the study.
- No vaccination prediction during the study period, having had the last vaccine within the 3 weeks previous to the study.
- No intention to bath in the bath, swimming pool or the sea, or having sauna or Turkish baths during the study.
- No intention to practice intense sport while the patch is on the back, that could produce intense sweating and affect the patch.
- No apply other cosmetic product in the experimental area

7.2 Specific inclusion criteria

The specific inclusion criteria, defined in the protocol, were as follow:

- Age: 18-70 years old
- Sex: both
- Photo-type (Fitzpatrick): I to VI
- All types of skin.

All volunteers responded to the specific inclusion criteria. Their typology is defined in **Annex I.**

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7.3 Specific exclusion criteria

The specific exclusion criteria, defined in the protocol, were as follow:

- Cutaneous marks on the experimental area that could interfere with the evaluation of the skin reactions (pigmentation disruptions, scars, excessive hair areas, excessive freckles and moles, solar skin burns ...).
- Tattoos in the experimental area.
- Injuries or infection in the experimental area.
- Pathologies in the experimental area.
- Eczematous reaction which has not fully disappeared, scar or pigmentation complications from previous studies in the experimental area.
- Allergies to metals.
- Reactivity to medical tape.
- Intense sun exposure or UVA treatment during the month previous to the study.
- Carrying out a treatment containing acid vitamin A or its by-products, during the 3 months previous to the study.
- Carrying out a treatment containing topical corticoids, on the experimental area during the 8 days previous to the beginning of the study.
- Treatment with any medicine for psoriasis, vitiligo, within one month before the study.
- After the vaccination within 3 weeks prior to the study;
- Being pregnant or breastfeeding.
- Preview using any cosmetic product in the test area ,
- Participation during the previous 30 days in any study under exaggerated conditions (under a patch).

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8. EQUIPMENT

- Finn Chamber Std® occlusive patch
- Curatest® semiocclusive patch
- Finn Chamber Aqua® occlusive patch
- Finn chambers filter paper discs
- Pasteur pipettes 1ml
- Sterile containers
- Finn chamber tray
- Distilled water
- Micropipette Siner lab (Ref. HG20566) 20-200µl
- Tweezers
- Sanitary alcohol 96º
- Cotton
- Precision Balance Model: PS 750. R2. Radwag

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9. METHODOLOGY

9.1 Criteria for application the product

Type of product: Rinse off soapy sponge

Experimental area: Upper Back

Product preparation: The sample is diluted to 5% on aqueous solution.

Applied quantity: 20 µl of product preparation over occlusive patch (Finn Chamber Aqua/Std® occlusive patch).

9.2 Chronology of the study

- Test duration: 6-8 consecutive weeks (40 days) without considering the re-challenge phase.

The first phase: Induction Phase lasts three weeks:

- Application of the product under patch on days 1, 3, 5, 8, 10, 12, 15, 17, 19.
- Patch removal by the volunteer at home on days 2, 4, 6, 9, 11, 13, 16, 18, 20 (after 24 hours of the application of the patch).
- Skin examination at 24 hours after patch removal on days 3, 5, 10, 12, 17 and 19.
- Skin examination at 48 hours after patch removal on days 8, 15 and 22.

The second phase: Rest phase. The duration was minimum 2 consecutive weeks and maximum 4. In this phase the product under study was not applied.

The third phase: **Challenge** or **Memory phase**: 1 week.

- Skin examination and application of the product under patch on day 36.
- Patch removal by the volunteer him/herself at home on day 37.
- Skin examination on days 38 (24 hours after the patch removal) and on day 39 (48 hours after the patch removal). On day 40 (72 hours) the skin is examined in those volunteers who were reactive during the memory phase. For those volunteers in which no reaction was observed, a negative result is assumed also on day 40.

In this phase the patch is applied in two areas, the induction area and the virgin area.

Alternatively, the fourth phase: **Re-challenge phase.** It can be performed between 4 and 12 weeks after the initial challenge phase. Volunteers who exhibit in challenge phase an inconclusive response and/or more information about challenge response is

needed, a re-challenge can be performed between 4 and 12 weeks after the initial challenge phase. The experimental procedure is the same that challenge phase.

9.3 Experimental procedure

The first day of the test, instructions of the study were given to the volunteers. Before starting the study they filled the informed consent and the exclusion criteria. The principal investigator examined the study area each participant and verify the inclusion criteria and none of the exclusion criteria.

- **Day 1, 3, 5, 8, 10, 12, 15, 17, 19, 36 – Sample preparation and application**. After cleaning the experimental area, the product under study was applied under an occlusive patch to the same site on the top of the back for 24 hours except in challenge phase, which the product was applied in two sites (induction area and virgin area). If excessive irritation is developed at any site, the sample which has caused the irritation is not applied again. One patch without product was applied in the same experimental conditions (negative control).
- **Day 3, 5, 8, 10, 12, 15, 17, 19, 22, 36, 38, 39, 40 – Clinical Examination and Scoring.** A score on the Erythema and Oedema scale was assigned each clinical examination day (Table 1).

Score	Assessment of reaction	PARAMETERS EVALUATED	
		Erythema (E)	Oedema (OE)
-: 0	Absence	No erythema	No oedema
+: 1	Slight	Slight erythema (quiet pinked coloration of the complete tested area or rather visible on one part of the tested area)	Slight oedema (palpable and visible)
++: 2	Moderate	Obvious erythema (clear erythema covering all of the tested area)	Obvious oedema with or without vesicle/s
+++: 3	Severe	Intense erythema (severe erythema covering all the tested area or erythema diffusing outside the tested area)	Intense oedema (extended area outside the tested area) with or without vesicle/s or blister/s

- **Table 1. Clinical Examination of Erythema and Oedema Scoring**

Other elevated responses could be observed, if present, are graded as independent responses:

- **P** Papules – many small, red, solid elevations; surface of reaction has granular feeling
- **PU** Pustules – small, circumscribed, elevated and inflamed skin lesions, with pus at its centre.
- **V** Vesicles – small, circumscribed elevations having translucent surfaces so that fluid is visible (blister – like). Vesicles are no larger than 0.5 cm in diameter.
- **B** Bullae – vesicles with a diameter> 0.5 cm; vesicles may coalesce to form one or a few large blisters that fill the patch site.

Other responses could be observed:

- **S** Spreading – evidence of the reaction beyond the patch area
- **W** Weeping – evidence of release of fluid from a vesicular or bullous reaction
- **A** Marked reaction to adhesive (patch relocated).
- **X** Succeeding patch not applied and succeeding grade is for residual reaction
- **L** Patch lost (came off) during first 12th hours.

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9.4 Interpretation of Results

The interpretation of the results of an HRIPT was carried out on a case-by-case basis using immunological principles, general interpretation guidelines and experience. The standard scoring scale used to interpret skin responses was provided in Table 1 and Table 2.

The following guidelines have been developed for the interpretation of reactions that may occur during an HRIPT.

· Skin sensitization reactions are most frequently erythematous, papular and edematous. Conversely, primary irritation reactions (unless severe), are generally erythematous only. An irritation reaction is usually uniform with a well-defined border, whereas an allergic response (especially if weak) is typically non-uniform and has an irregular border, and a strong response may spread beyond the patch site.

· Responses which are more severe at challenge than in early induction are suggestive of induction of skin sensitization.

· Responses confined to induction site during challenge phase are suggestive of irritation. True allergic reactions in challenge phase will occur at both site (induction site and virgin site) and persist through 2 delayed scorings at least 24 hours apart. However, unilateral allergic reactions can sometimes be observed. For this reason all reactions considered suggestive of induction of skin sensitization should be followed up, for example, by re-challenge.

· Responses that increase or maintain severity with time from the 48 to 96 hours challenge gradings are presumptive of skin sensitization. Those that subside from the 48 to 96 hours grading period are generally considered to be irritant in nature.

· Edematous reactions that occur and persist during the latter part of the induction phase and the challenge phase are indicative of induced skin sensitization and should be confirmed by re-challenge.

. Persistent skin responses with papules and/or edema occurring in week 1 of induction suggest pre-existing skin sensitization. Similar reactions that occur later in induction suggest induction of skin sensitization by the test material.

· Reactions and reaction patterns that are suggestive of allergic reactions or questionable/equivocal reactions should be verified through appropriate re-challenge procedures.

· The reactions of any volunteers(s) in question should always be compared with those of all other exposed volunteers. Except in rare instances, allergic reactivity occurs in

only a very small number of subjects, while irritation occurs more widely throughout the exposed population.

The HRIPT objective was to verify the absence of allergenic potential and the skin sensitization of a cosmetic product according to results from Induction phase and Challenge Phase. In parallel, a conclusion of the induction phase related to the cutaneous compatibility, could be drawn according to the calculation of the Mean Irritation Index (M.I.I.) global which was obtained according to average of the calculation of the daily Mean Irritation Index:

$$\text{Daily M.I.I.} = \frac{\Sigma\,(\bar{x} \text{ of the grade erythema and oedema})}{\text{Number of volunteers}}$$

The obtained index is used to classify the studied cosmetic product according to the following scale:

M.I.I.	Product Classification
M.I.I.=0.000	Non Irritating (NI)/Very Good Cutaneous Compatibility
M.I.I<0.022	Non Irritating (NI) / Good Cutaneous Compatibility
0.022≤M.I.I<0.055	Slightly Irritating (SI) / Intermediate Cutaneous Compatibility
0.055≤M.I.I<0.111	Moderately Irritating (NI) / Bad Cutaneous Compatibility
M.I.I≥0.111	Irritating (I) / Very Bad Cutaneous Compatibility

Table 2. Cutaneous compatibility cosmetic product classification index

10. RESULTS

The individual reading results was presented in Annex II.

Next table showed the Global M.I.I. after induction phase.

M.I.I.	Results	Number of reactive volunteers	Reactive volunteers %
0,002	Non Irritating/ Good Cutaneous Compatibility	1	2%

Next table showed the results of Challenge or Memory phase:

Challenge (Memory phase)	Number of reactive volunteers		Percentage of reactive volunteers	
	Induction area	Virgin area	Induction area	Virgin area
	0	0	0%	0%

The individual reading results was presented in Annex III.

Allergenicity result:

The allergenicity result was set up from the results obtained in the induction phase and in the memory phase (induction area and virgin area).

Results	Number of volunteers showing some kind of allergic reaction	Percentage of reactive volunteers
	0	0%

6 volunteers (ref. V17, V39, V52, V53, V59 and V62) discontinued the study for reasons unrelated to it. One volunteer (ref. V5) was excluded by the researcher due to a non-compliance of the protocol. 55 volunteers finished the study.

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11. CONCLUSION

Under the experimental conditions adopted the product **ESPONJA JABONOSA,** reference: -, has a **Good Cutaneous Compatibility**, as 2% of the volunteers showed some kind of erythema or oedema reaction to the product during the induction phase.

Under the experimental conditions adopted, **No allergenicity** has been observed in any of the tested volunteers.

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12. SAMPLES AND DOCUMENTS TO BE STORED

The following documents will be stored in the Zurko Research archive:

- Signed informed consents.
- Signed non-inclusion criteria.
- Laboratory notebook containing the evaluation data collected by the technician.
- Final report.
- Documents provided by the sponsor.

The documents will be stored during 5 years. After 5 years the sponsor will be asked about the possibility of extension because of the commercialization of the tested element.

The sample of the tested product will be stored in the Zurko Research archive for samples, during 1 year.

13. BIBLIOGRAPHY REFERENCES

1. The SCCS´S Notes of Guidance for the Testing of Cosmetic Substances and their Safety Evaluation 9th Revision

2. Patel, S.M., E. Patrick, and H.I. Maibach, 1976 "Animal, Human, and In Vitro Test Methods for Predicting Skin Irritation". Dermatotoxicology, Chpt. 33; 5th Ed., F.N. Marzulli; H.I. Maibach; Taylor and Frances.

3. Pauline M. McNamee, Anne Marie Api, David A. Basketter, G. Frank Gerberick, Deborah A. Gilpin, Barbar M. Hall, Ian Jowsey, Michael K. Robinson. A review of critical factors in the conduct and interpretation of the human repeat insult patch test. Regulatory Toxicology and Pharmacology 52 (2008) 24-34.

4. Valerie T. Politano, Anne Marie Api. The Research Institute for Fragance Materials´human repeated insult patch test protocol. Regulatory Toxicology and Pharmacology 52 (2008) 35-38.

5. Nueva Clasificación de tipos piel y sus implicaciones en Dermatología Cosmética. Revisión Dermatología Venezolana. Vol. 43, Nº 4, 2005. Leslie Baumann, Sadegh Amini, Eduardo Weiss

SIGNATURES

Researcher: Ana García Blanco, Biologist. I, the undersigned, Ana Garcia Blanco, declare that this study has been carried out under my responsibility and in the essence of the Clinical Good Practices (Guideline for good clinical practice E6 (R2) of June 14th 2017, EMA/CHMP/ICH/135/1995 of May 1st 1996, European Parliament and Council Guideline 2001/20/CE – May 1st 2001).

-The results here presented reflect accurately and completely the raw data of the study.

Signature:

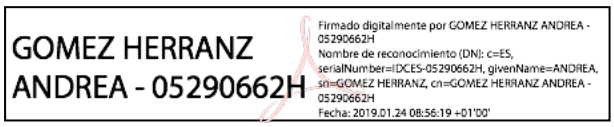
Dermatologist: Eliana San Juan Lasser. Medical license number: 283805700

Signature:

Responsible of the Area of Quality Management: Andrea Gómez Herranz, Quality Guarantee Technician. I, the undersigned, Andrea Gómez Herranz, declare that this study has been carried out under my responsibility and under the principles of ICH Good Clinical Practice (Guideline for good clinical practice E6 (R2) of June 14th 2017, EMA/CHMP/ICH/135/1995 of May 1st 1996, European Parliament and Council Guideline 2001/20/CE – May 1st 2001)

The inspections that have been made, allow to confirm that the final report reflects accurately the primary data of the study.

Signature:



ANNEXES

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Annex I: Information relating to volunteers

Volunteers		Age (Years)	Sex F= Female M=male	Phototype	Skin Type (R/S)
Ref.	Acronym				
1	V1	49	M	II	S
2	V2	48	F	II	S
3	V3	31	F	III	R
4	V4	42	F	III	S
5	V6	65	M	III	R
6	V7	56	F	II	S
7	V8	33	M	II	R
8	V9	37	F	II	S
9	V10	23	F	III	R
10	V11	53	M	IV	R
11	V12	46	F	II	S
12	V13	62	M	III	R
13	V14	54	F	II	R
14	V15	37	F	III	R
15	V16	26	M	III	R
16	V18	54	F	III	S
17	V19	63	F	III	S
18	V20	70	M	III	S
19	V21	50	F	II	R
20	V22	61	F	II	S
21	V23	26	M	IV	R
22	V24	65	F	II	S
23	V25	70	F	II	S

24	V26	52	F	II	S
25	V27	32	F	II	S
26	V28	67	M	II	S
27	V29	34	M	II	S
28	V30	56	F	II	S
29	V31	50	F	II	S
30	V32	36	F	IV	S
31	V33	34	M	IV	R
32	V34	57	F	II	S
33	V35	67	F	II	S
34	V36	30	F	II	R
35	V37	27	F	III	S
36	V38	33	F	III	S
37	V40	55	F	III	R
38	V41	63	F	III	R
39	V42	57	M	III	R
40	V43	40	F	IV	S
41	V44	47	M	II	S
42	V45	34	M	IV	R
43	V46	18	F	IV	S
44	V47	24	F	IV	R
45	V48	50	F	III	S
46	V49	28	M	III	R
47	V50	48	F	II	S
48	V51	28	M	III	R
49	V54	65	F	II	R

50	V55	59	M	II	S
51	V56	67	M	II	R
52	V57	53	F	II	S
53	V58	57	F	II	R
54	V60	40	M	III	S
55	V61	42	M	III	S

R = Resistant

S= Sensitive

Annex II: Individual results from Induction phase

Volunteer		Reaction in Induction Phase (according to Table 1)																								
		DAY 3			DAY 5			DAY 8			DAY 10			DAY 12			DAY 15			DAY 17			DAY 19			DAY 22		
Ref	Acr.	E	OE	Ot	E	OE	Ot	E	OE	Ot	E	OE	Ot	E	OE	Ot	E	OE	Ot	E	OE	Ot	E	OE	Ot	E	OE	Ot
1	V1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	V2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	V3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	V4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	V6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	V7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7	V8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
8	V9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	V10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10	V11	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11	V12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12	V13	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

13	V14	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
14	V15	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
15	V16	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
16	V18	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
17	V19	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18	V20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
19	V21	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
20	V22	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
21	V23	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
22	V24	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
23	V25	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
24	V26	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
25	V27	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
26	V28	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
27	V29	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
28	V30	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

29	V31	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
30	V32	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
31	V33	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
32	V34	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
33	V35	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
34	V36	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
35	V37	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
36	V38	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
37	V40	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
38	V41	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
39	V42	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
40	V43	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
41	V44	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42	V45	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
43	V46	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
44	V47	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

45	V48	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
46	V49	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
47	V50	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
48	V51	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
49	V54	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
50	V55	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
51	V56	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0
52	V57	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
53	V58	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
54	V60	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
55	V61	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Daily M.I.I.		**0,000**			**0,000**			**0,000**			**0,000**			**0,009**			**0,000**			**0,000**			**0,009**			**0,000**	
Global M.I.I.		**0,002**																									

Summary of induction phase:

- D3: there has been no reaction
- D5: there has been no reaction
- D8: there has been no reaction
- D10: there has been no reaction
- D12: one volunteer (ref. V56) presented a slight reaction of erythema
- D15: there has been no reaction
- D17: there has been no reaction
- D19: one volunteer (ref. V56) presented a slight reaction of erythema
- D22: there has been no reaction

Annex III: Individual Results from Challenge phase

Volunteers		Reaction in Challenge Memory phase (according to Table 1 and Table 2)								
		Induction Area				Virgin Area				Allergeniciy Result (-/+)
Ref.	Acron.	D36	D38	D39	D40	D36	D38	D39	D40	
1	V1	-	-	-	-	-	-	-	-	-
2	V2	-	-	-	-	-	-	-	-	-
3	V3	-	-	-	-	-	-	-	-	-
4	V4	-	-	-	-	-	-	-	-	-
5	V6	-	-	-	-	-	-	-	-	-
6	V7	-	-	-	-	-	-	-	-	-
7	V8	-	-	-	-	-	-	-	-	-
8	V9	-	-	-	-	-	-	-	-	-
9	V10	-	-	-	-	-	-	-	-	-
10	V11	-	-	-	-	-	-	-	-	-
11	V12	-	-	-	-	-	-	-	-	-
12	V13	-	-	-	-	-	-	-	-	-
13	V14	-	-	-	-	-	-	-	-	-
14	V15	-	-	-	-	-	-	-	-	-
15	V16	-	-	-	-	-	-	-	-	-
16	V18	-	-	-	-	-	-	-	-	-
17	V19	-	-	-	-	-	-	-	-	-
18	V20	-	-	-	-	-	-	-	-	-
19	V21	-	-	-	-	-	-	-	-	-
20	V22	-	-	-	-	-	-	-	-	-
21	V23	-	-	-	-	-	-	-	-	-

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22	V24	-	-	-	-	-	-	-	-	-
23	V25	-	-	-	-	-	-	-	-	-
24	V26	-	-	-	-	-	-	-	-	-
25	V27	-	-	-	-	-	-	-	-	-
26	V28	-	-	-	-	-	-	-	-	-
27	V29	-	-	-	-	-	-	-	-	-
28	V30	-	-	-	-	-	-	-	-	-
29	V31	-	-	-	-	-	-	-	-	-
30	V32	-	-	-	-	-	-	-	-	-
31	V33	-	-	-	-	-	-	-	-	-
32	V34	-	-	-	-	-	-	-	-	-
33	V35	-	-	-	-	-	-	-	-	-
34	V36	-	-	-	-	-	-	-	-	-
35	V37	-	-	-	-	-	-	-	-	-
36	V38	-	-	-	-	-	-	-	-	-
37	V40	-	-	-	-	-	-	-	-	-
38	V41	-	-	-	-	-	-	-	-	-
39	V42	-	-	-	-	-	-	-	-	-
40	V43	-	-	-	-	-	-	-	-	-
41	V44	-	-	-	-	-	-	-	-	-
42	V45	-	-	-	-	-	-	-	-	-
43	V46	-	-	-	-	-	-	-	-	-
44	V47	-	-	-	-	-	-	-	-	-
45	V48	-	-	-	-	-	-	-	-	-
46	V49	-	-	-	-	-	-	-	-	-
47	V50	-	-	-	-	-	-	-	-	-

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48	V51	-	-	-	-	-	-	-	-	-
49	V54	-	-	-	-	-	-	-	-	-
50	V55	-	-	-	-	-	-	-	-	-
51	V56	-	-	-	-	-	-	-	-	-
52	V57	-	-	-	-	-	-	-	-	-
53	V58	-	-	-	-	-	-	-	-	-
54	V60	-	-	-	-	-	-	-	-	-
55	V61	-	-	-	-	-	-	-	-	-

Erythema scale and other types of reactions:

- Negative erythema and oedema reaction

- Induction area:
  - D36: there has been no reaction
  - D38: there has been no reaction
  - D39: there has been no reaction
  - D40: there has been no reaction

- Virgin area:
  - D36: there has been no reaction
  - D38: there has been no reaction
  - D39: there has been no reaction
  - D40: there has been no reaction

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