STUDY/PRODUCT REFERENCES: EF PL 273 / 05-3210 and 05-3211
ER 05 / 040 / 05-0226 and 05-0226 bis

CONFIRMATION IN HUMAN OF THE SKIN COMPATIBILITY AND ABSENCE OF ALLERGENIC POTENTIAL OF ONE COSMETIC PRODUCT AFTER REPEATED APPLICATION UNDER PATCH

Human Repeated Insult Patch Test (HRIPT)

SPONSOR : Laboratoires ANIOS
Pavé du Moulin
59260 LILLE-HELLEMMES
For : Mrs. Monique MANCHE

TEST PRODUCT: ANIOSGEL 85 - Réf. 1613000

Study report

Bucharest, January 19th, 2005

25 pages in this report including 12 in Appendices

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Repeated Insult Patch Test (HRIPT)

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I. AIM AND PRINCIPLE OF THE STUDY

This study intended to confirm the skin compatibility and the absence of allergenic potential of the cosmetic product **ANIOSGEL 85 - Réf. 1613000**, after repeated application to the skin under exaggerated experimental conditions.

The product was applied under patch for a defined time. The applications were repeated 9 times over a period of 3 consecutive weeks, period necessary for the possible induction of an allergy.
After a minimal 2-week rest period, with no treatment, a single application of the product under patch, to the induction site and to a virgin site and for a defined time, enabled to reveal a possible induced allergy.

II. RELEVANCE OF THE STUDY

Ethics

The study aiming at confirming the skin compatibility of the test product and the foreseeable risk incurred by the volunteers who took part in the study being minor, there was a suitability between the aim of the study, its possible risks and the potential troubles related to the modalities planned in the protocol.

All the volunteers were not included in the study the same day, taking into account their number. Consequently, if an important unexpected reactivity occurred in one or several of the first included volunteers, the application of the product could be not performed in the other volunteers.

The applications were performed at the Institute by the dermatologist helped by the technician in charge of the study.

A clinical examination by the dermatologist helped by the technician in charge of the study, was performed after each passage at the Institute.
In case of important reactivity to the product, the applications could be interrupted in the volunteers concerned.

Methodological approach

The skin compatibility of the product was confirmed by the dermatologist who has an appropriate experience.

The experimental conditions adopted created a certain occlusion and favoured the penetration of the ingredients through the skin. If some of them had an allergenic potential, this one could be more easily proved by this kind of approach.

The methodology used was an adaptation from that described by **Marzulli and Maibach** (Human Repeated Insult Patch Test for delayed contact hypersensitivity: HRIPT)

- Marzulli F.N., Maibach H.I., Contact allergy : predictive testing in man, Contact Dermatitis, 1976, 2, pp.1-17

The patch material and the conditions of use of the product were adapted to the type of test product in accordance with the corresponding procedure.

Several products were tested in parallel. The experimental area chosen (back) enabled to test easily the products. The sites of application of the products were chosen at random to get rid of the variability of the skin reactivity according to the site.

Two control sites served as controls to avoid the possible intercurrent effects not directly related to the test product.

The methodology met the requirements of the "Ordinul Comun al ANPC, MSF, MAP" nr. 154/179/9 concerning the methodologies enabling to justify the claim "hypoallergenic products".

Panel

Referring to the experience acquired in the field of contact allergy to cosmetic product and to the accurate knowledge of the ingredients incorporated into the test product, the number of volunteers, defined in the protocol, was acceptable to confirm, in first approach, the absence of allergenic potential of the test product.

Results

The results were mainly expressed as descriptive data and did not require a statistical treatment.

III. TYPE OF THE STUDY

This mono-centric study was performed in open.

The subject was used as own control.

It was performed according to the general conditions of Evic Romania, established for the performance of Human test project.

The test project was submitted to the previous agreement of the internal committee of the coordinator centre, Evic France, before its performance (opinion n° 910/05 of November 25th, 2005) and of the investigator centre, Evic Romania, (opinion n°72/05 of November 28th, 2005).

IV. INVESTIGATOR AND COORDINATOR CENTRES

IV.1. Investigator centre

EVIC Romania
15, Constantin Bosianu Street
040505 Bucharest – Romania
Tel : 0040 21 335 70 90

Investigator : Doctor Rozalia OLSAVSZKY (dermatologist)

Responsible technician : Nicoleta DUMITRU

IV.2 . Coordinator centre

EVIC France
48, Rue Jean Duvert
Z.I.33290 Blanquefort - France
Tel : 05 56 95 59 95

Coordinator: Sylvie PAZZINI

V. DATES OF PERFORMANCE OF THE STUDY

Beginning on: November 28th 2005

End on: January 13th 2006

VI. TEST PRODUCTS

VI.1. Total number of products simultaneously tested in the study

The number of test products was 8.

This number complied with the corresponding procedure which defines the maximal number of test products according to the chosen experimental area and patch material.

This report concerns only the product ANIOSGEL 85 - Réf. 1613000.

Two control patches, corresponding to the type of patch material used, one containing an ad hoc quantity of water for injectable preparation and the other containing an ad hoc quantity of 80% ethanol solution, were applied at the same time.

VI.2. Identification of the test product and the vehicle

	Test product	**Vehicle**
Denomination	ANIOSGEL 85	ETHANOL - Solution à 80 % v/v
Reference	1613000	/
Batch number	G 241 70	G 325 70
Evic France / Evic Romania reference	05-3210 / 05-0226	05-3211 / 05-0226 bis
Galenic form and organoleptic characteristics	Blue transparent fluid gel	Colorless liquid
Number and type of samples	1 white glass flask	1 white glass flask
Content of the samples	125 ml	125 ml

VI.3. Information concerning the test product

The document relating to the test product supplied with the samples was the Sponsor's letter of agreement particularly concerning the conformity of the formula to the regulations in force and its safety and the results of the clinical study previously performed on the product.

VII . VOLUNTEERS

VII.1 . Number

The number of volunteers whose data had to be exploitable at the end of the study was 50, with a lower acceptable limit of 48, in accordance with the corresponding procedure.

In order to compensate for the possible withdrawals during the study and to obtain this quota of volunteers at the end of the study, about 15% of extra people were recruited.

*The volunteers whose data were exploitable at the end of the study:

- to check the skin compatibility of the test product, corresponded to all the volunteers included as long as they were submitted at least to one post application examination at the defined time or else,

- to check the absence of allergenic potential of the test product (in absence of allergic reaction during the induction phase), corresponded to all the volunteers included as long as they were submitted to the challenge.

54 volunteers were included in the study.

2 volunteers (ref. 10 and ref. 51) discontinued for personal reasons independent of the study and no exclusion was decided by the investigator.

The compatibility of the test product was therefore assessed in 52 volunteers.

The confirmation of the absence of allergenic potential of the test product was assessed in 52 volunteers.

VII.2. Specific inclusion criteria

The specific inclusion criteria, defined in the protocol, were the following ones:

- age :18 to 70 years old,

- sex : male and/or female,

- phototype (Fitzpatrick) : I to V,

- all types of skin on body.

All the volunteers corresponded to these specific inclusion criteria. Their typological characteristics are defined in **Appendices 1/1 to 1/3.**

VII.3. Specific non inclusion criteria

The specific non inclusion criteria were the following ones:

- cutaneous marks on the experimental area which could interfere with the assessment of skin reactions (pigmentation troubles, scar elements, over-developed pilosity, ephelides and naevi in too great quantity, sunburn…..),

- eczematoid reaction still visible, scar or pigmentary sequelae of previous tests on the experimental area,

- allergy to colophony, to nickel
- allergy or reactivity to the type of test product,
- skin hyper-reactivity,
- reactivity to adhesive plaster,
- participation in more than 5 tests under exaggerated use conditions (under patch) within 12 months before the study, including 3 hypoallergenicity tests at the most,
- intensive sun exposure within the month before the study,
- forecast of intensive sun or UVA exposure (UV lamps) during the test period,
- forecast of bath (bathtub, sea or swimming-pool), sauna or hammam sessions during the test period,
- intensive or regular practice of one or several sports whose temporary interruption created difficulties,
- treatment with Vitamin A acid or its derivatives within 3 months before the beginning of the study,
- treatment with topical corticoids on the experimental area within 8 days before the study,
- treatment with PUVA or UVB within 1 month before the study,
- forecast of vaccination during the test period or last vaccination within 3 weeks before the study.

All the volunteers corresponded to these specific non inclusion criteria.

VIII. METHODOLOGY

VIII.1. Experimental area and sites of application of the test product

The chosen experimental area was the back.

The site of application of the product was chosen by the dermatologist or the technician in charge of the study. Skin appearance was taken into account and the areas of friction with clothes were avoided.

The product was applied by the dermatologist or the technician in charge of the study, to one of the sites localized by a clockwise distribution, altering of one rank from a subject to another.

VIII.2. Experimental conditions of application of the test product

The experimental conditions defined in the protocol were the following ones:

	Patch material	Experimental conditions of use	Quantity applied
Test product: ANIOSGEL 85 - Réf. 1613000	Finn Chamber standard®	As it is (evaporation for 15 minutes at least before application to the patch)	20 µl
Control: Distilled water	Finn Chamber standard®	As it is	20 µl
Control: Ethanol - Solution 80% v/v	Finn Chamber standard®	As it is (evaporation for 15 minutes at least before application to the patch)	20 µl

Occlusive patch

- Finn Chamber standard® : aluminium cupula in which the product is put down (20 µl or approximately 20 mg), kept in position by an hypoallergenic adhesive: Scanpor® (inner diameter: 8 mm, surface: 50 mm²)

The quantities of product had to be measured with a micropipette with single use tips.

One deviation from the protocol concerning the experimental conditions of application, was noticed by the dermatologist and is the following one : the test product and the two controls were applied under occlusive patch instead of semi-occlusive patch.

VIII.3. Chronology of the study

The applications of the test product, the removal of the patches and the controls were performed by the dermatologist or the technician in charge of the study.

- **induction phase :** 3 consecutive weeks

  * application of the product to a perfectly delimited site, under patch on D1, D3, D5, D8, D10, D12, D15, D17, D19.

  * patch removal
    - after 48 h of contact on D3, D5, D10, D12, D17, D19.
    - after 72 h of contact on D8, D15, D22.

  * controls : skin examination and questioning (paragraph VIII.6) before patching on D1 and about 15 minutes (or more, if redness appeared after removal of the adhesive), after patch removal on D3, D5, D8, D10, D12, D15, D17, D19, D22.

- **Rest period :** 3 consecutive weeks.

  * no application of product.

- **challenge :** 1 week.

  * application of the product to a perfectly delimited virgin site and to the site defined for the induction phase, under patch on D43.

* patch removal after 48 h of contact on D45.

* controls : skin examination and questioning (paragraph VIII.6) before patching on D43 and about 15 minutes (or more, if redness appeared after removal of the adhesive), after patch removal on D45, D46, D47 (48, 72, 96 h after application).

All the experimental conditions of application, defined in the protocol, were respected.

VIII.4. Constraints of the study

The constraints imposed on the volunteers were the following ones:

- no application of other products (than the tested ones) to the experimental area,
- no wearing of too thigh or restraining clothes on the experimental area, liable to produce frictions and to cause unsticking of the patches,
- no bath (bathtub or swimming-pool or sea), no hammam or sauna sessions during the study,
- if shower, protection of the experimental area or no violent projection of water and no application of soap to the experimental area to avoid patch removal or appearance of intercurrent phenomena and very gentle wiping if necessary,
- no excessive sweating and no intensive sport liable to cause unsticking of the patches,
- no intensive sun or UVA exposure (UV lamps) during the study, especially after patch removal,
- neither anti-allergic, anti-inflammatory (systemic or topical corticotherapy…) treatment nor treatment with patent medicines containing vitamin A acid or its derivatives during the study (if therapeutic requirement : exclusion foreseen),
- no vaccination during the study,
- at least 14 passages at the Institute (15 if a pre-inclusion visit was necessary).

VIII.5. Control of the observance of the modalities of the protocol

The investigator checked the respect of the **constraints**.

The volunteers were questioned at the end of the study. The Investigator assessed the importance of the possible deviations in comparison with the experimental conditions required at the beginning of the study.

The synthesis of the answers obtained is enclosed in **Appendices 2/1 and 2/2**.

All the deviations from the protocol were analysed and the investigator assessed their effect on the validity of the results.

All the constraints of the study, defined in the protocol, were respected by the volunteers.

VIII.6. Confirmation of the compatibility (absence of irritant effect) and absence of allergenic potential

VIII.6.1. Frequency of the examinations

The skin examination and joint questioning had to be performed by the dermatologist helped by the technician in charge of the study.

The examination had to be performed, visually under standard "daylight", according to the frequency mentioned on paragraph VIII.3.

All the examinations were performed in accordance with the conditions defined in the protocol.

VIII.6.2. Expression of the results of the skin examination and questioning

The expression of the results of the skin examination and questioning was that defined for this type of study in accordance with the corresponding procedure.

In case of reactivity:

- **the main visible signs were noted, i.e. :**

Erythema, Œdema, Vesicle, Bulla, Papule, Scab, Dryness, Coloration, Soap effect.

The intensity of the **erythema and oedema** was assessed according to an ordinal scale: very slight, slight, moderate, severe.

The appearance of the **erythema** was specified: diffuse, punctuated, peripheral (around the application site).

The importance of the number of **vesicles and papules** was assessed according to an ordinal scale : 1 to 2 vesicles or papules, more than 2 vesicles or papules.

Bulla, scab, dryness, coloration and soap effect were described.

The importance of the **dryness and coloration** was assessed according to an ordinal scale: slight, moderate, severe.

- **the main sensations of discomfort were described, i.e. :**

Heating, Stinging, Pruritus (itching).

The results were expressed:

- **in percentage of reactive volunteers** : for this calculation only the visible signs of reactivity were taken into account : erythema, oedema, vesicle, bulla, papule, scab.

- **in a descriptive manner** for the other visible signs or for the sensations of discomfort : when the frequency of appearance of these signs justified it, the percentage of reactive volunteers was possibly calculated.

VIII.6.3 . Interpretation of the results of the skin examination and questioning

All the volunteers included in the study were taken into account to confirm the skin compatibility of the test product as long as they were submitted at least to one post application examination at the defined time or else.

All the volunteers included in the study were taken into account to confirm the absence of allergenic potential of the test product (in absence of allergic reaction during the induction phase) as long as they were submitted to the challenge.

The interpretation of the results of the skin examination and questioning was that defined for this type of study in accordance with the corresponding procedure.

The possible reactions observed during the induction phase were either **irritation reactions** or **revelation of an allergy previously contracted or revelation of an allergy precociously induced** by the test ingredient.

The possible reactions observed during the challenge on the "virgin" site were compared to those observed on the "induction" site at the same times. They were either **irritation reactions** or **revelation of an allergy induced during the induction phase** by the test ingredient.

The natures, intensity, time of appearance, time of disappearance, location (induction site and/or virgin site) of the skin reaction were taken into account for the interpretation of the results.

To appreciate the skin compatibility and possible irritation reactions, the interpretation of the results, performed by the dermatologist, was absolute (referring to **the experience of the investigator centre** in this field and especially to the **data acquired** on ingredients of same cosmetic category tested under similar conditions). The test product could therefore have a **very good, good, moderate or bad skin compatibility**.

To appreciate the allergenic potential, the interpretation of the results was partly based on the allergenicity evaluation scale established by the **ICDRG** (International Contact Dermatitis Research Group) and took into account the visible reactions (clinical signs) and the possible reactions appeared on the control site :

NT	: non tested
?+	: doubtful reaction, only slight erythema
+	: positive reaction (with no vesicle) : erythema, infiltration, sometimes some papules
++	: strong positive reaction : presence of erythema, papules, vesicles
+++	: violent positive reaction : with presence of bullae
-	: negative reaction
IR	: irritation reaction

IX . RESULTS

The individual data of the skin examination and questioning of the volunteers are enclosed in **Appendices 3/1 to 3/3 and 4/1 to 4/3**.

In brief :

	Induction phase	
	Type of reactivity on the induction site	**Number and percentage of reactive volunteers**
Test product: ANIOSGEL 85 - Réf. 1613000	Very slight to slight punctuated erythema Scab (vol. ref. 12)	1 / 2%
Control: Ethanol - Solution 80% v/v	None	0 / 0%

	Challenge	
	Type of reactivity on the induction site	**Number and percentage of reactive volunteers**
Test product: ANIOSGEL 85 - Réf. 1613000	None	0 / 0%
Control: Ethanol - Solution 80% v/v	None	0 / 0%

X. CONCLUSION

Under the experimental conditions adopted, the repeated applications of the product **ANIOSGEL 85 - Réf. 1613000** under occlusive patch, induced some reactions of irritation and the product **has a good skin compatibility.**

Moreover, the repeated applications **induced no allergic reaction**.

Signatures and dates

Investigator : Doctor Rozalia OLSAVSZKY (dermatologist) 23/01/06

I the undersigned, Rozalia OLSAVSZKY declare that the overall conduct of the study was carried out under my responsibility and in accordance with the principles of Good Clinical Practices for cosmetics (International recommendations ICH E 6, step 4, of 1/5/1996).

Quality Assurance Personnel : Michèle DARRICAU 23/01/06

I the undersigned, Michèle DARRICAU, declare that the final report was examined on January 23rd, 2006

Head manager of the investigator centre : Alina NANU 23/01/06

I the undersigned, Alina NANU, declare to have designated Rozalia OLSAVSZKY as investigator and ensured that she approved the study protocol with full knowledge of the facts and made it available to the Quality Assurance personnel.

APPENDICES

Appendix 1/1

TYPOLOGICAL CHARACTERISTICS OF THE VOLUNTEERS

Volunteers		Age (years)	Sex F=female M=male	Phototype *
Ref.	Name Surname			
1	TROA. F	21	M	III
2	NEAC. C	28	F	III
3	ALEX. T	29	F	II
4	STAN.G	32	F	I
5	GHEN. A	21	M	II
6	DIAC. M	18	F	III
7	RADU. C	21	F	II
8	ARME. A	19	M	II
9	PILE. M	40	F	III
10	VASI. C	20	F	II
11	GAVR. M	21	F	II
12	DOBR. D	23	M	II
13	BACA. I	21	M	III
14	BELU. M	66	F	II
15	STAN. E	21	F	III
16	DIAC. C	22	F	III
17	BOTE. C	41	F	II
18	IVAN. L	20	F	II
19	GRIG. M	65	F	III
20	BANU. M	46	F	II

Appendix 1/2

TYPOLOGICAL CHARACTERISTICS OF THE VOLUNTEERS

Volunteers		Age (years)	Sex F=female M=male	Phototype *
Ref.	Name Surname			
21	DINC. A	56	F	III
22	CIUR. R	21	F	III
23	VISA. E	54	F	III
24	MUSA. D	58	M	II
25	VOIC. D	18	F	II
26	GHIR. C	28	M	II
27	GHIR. F	25	F	II
28	BARB. M	64	F	III
29	UDAT. D	63	F	II
30	ILIE. I	70	M	II
31	ILIE. M	67	F	III
32	ROMA. T	68	F	III
33	TOME. G	32	F	III
34	ZGAV. G	18	F	III
35	SURD. M	25	F	I
36	SIRB. D	56	F	II
37	ANDR. M	21	F	II
38	DOBR. M	40	F	III
39	BELD. N	62	F	II
40	PAUN. M	20	F	III

Appendix 1/3

TYPOLOGICAL CHARACTERISTICS OF THE VOLUNTEERS

Volunteers		Age (years)	Sex F=female M=male	Phototype *
Ref.	Name Surname			
41	CAPO. N	52	M	II
42	CAPO. C	25	F	II
43	VELI. P	46	F	IV
44	TANA. M	41	F	III
45	DINE. R	22	F	II
46	BARD.J	55	F	III
47	SOAR. V	54	F	III
48	SERC. G	21	F	II
49	PASA. R	18	F	II
50	TANA. L	26	F	II
51	CACI. G	36	F	II
52	PATA. E	41	F	III
53	GRAD. E	21	F	III
54	NEDE. V	63	F	II

Legends : / = no x = yes Withdrawal

phototype according to Fitzpatrick, *established on the principle of a first 30 to 40-minute sun exposure after the winter or a period without exposure of an equivalent duration :*

Type I *: Always burns easily, never tans*
Type II *: Always burns easily, tans minimally*
Type III *: Burns moderately, tans gradually*
Type IV *: Burns slightly, always tans easily*
Type V *: Burns rarely, tans intensely*
Type VI *: Never burns, strongly pigmented*

Appendix 2/1

CONTROL OF THE OBSERVANCE
Constraints

Constraints **(52 exploitable results)**	**Number** of volunteers who respected the constraints	**Percentage** of volunteers who respected the constraints
No application of other products than the tested ones to the experimental area Deviation : none	52	100%
No wearing of too tight or restraining clothes on the experimental area, liable to produce frictions and to cause unsticking of the patch Deviation : none	52	100%
No bath (bathtub, swimming pool or sea), no hammam or sauna sessions during the study Deviation : none	52	100%
If shower, protection of the experimental area or no violent projection of water and no application of soap to the experimental area to avoid patch removal or appearance of intercurrent phenomena and very gentle wiping if necessary Deviation : none	52	100%
No excessive sweating and no intensive sport liable to cause unsticking of the patch Deviation : none	52	100%

Appendix 2/2

CONTROL OF THE OBSERVANCE
Constraints

Constraints **(52 exploitable results)**	**Number** of volunteers who respected the constraints	**Percentage** of volunteers who respected the constraints
No intensive sun or UVA exposure (UV lamps) during the study, especially after patch removal Deviation : none	52	100%
Neither anti-allergic, anti-inflammatory (systemic or topical corticotherapy…) treatment nor treatment with patent medicines containing Vitamin A acid or its derivatives during the study (if therapeutic requirement : exclusion foreseen) – no medical treatment which could interfere with the study Deviation : none	52	100%
No vaccination during the study Deviation : none	52	100%
At least 14 passages at the Institute (15 if a pre-inclusion visit was necessary) Deviation : none	52	100%

Appendix 3/1

SKIN EXAMINATION AND QUESTIONING DURING THE INDUCTION PHASE

Volunteers		Reactivity								
Ref.	**Name Surname**	**D3**	**D5**	**D8**	**D10**	**D12**	**D15**	**D17**	**D19**	**D22**
1	TROA. F	/	/	/	/	/	/	/	/	/
2	NEAC. C	/	/	/	/	/	/	/	/	/
3	ALEX. T	/	/	/	/	/	/	/	/	/
4	STAN.G	/	/	/	/	/	/	/	/	/
5	GHEN. A	/	/	/	/	/	/	/	/	/
6	DIAC. M	/	/	/	/	/	/	/	/	/
7	RADU. C	/	/	/	/	/	/	/	/	/
8	ARME. A	/	/	/	/	/	/	/	/	/
9	PILE. M	/	/	/	/	/	/	/	/	/
10	VASI. C	**WITHDRAWAL**								
11	GAVR. M	/	/	/	/	/	/	/	/	/
12	DOBR. D	/	/	/	/	/	/	/	pE1	pE0.5 Sc
13	BACA. I	/	/	/	/	/	/	/	/	/
14	BELU. M	/	/	/	/	/	/	/	/	/
15	STAN. E	/	/	/	/	/	/	/	/	/
16	DIAC. C	/	/	/	/	/	/	/	/	/
17	BOTE. C	/	/	/	/	/	/	/	/	/
18	IVAN. L	/	/	/	/	/	/	/	/	/
19	GRIG. M	/	/	/	/	/	/	/	/	/
20	BANU. M	/	/	/	/	/	/	/	/	/

Appendix 3/2

SKIN EXAMINATION AND QUESTIONING DURING THE INDUCTION PHASE

Volunteers		Reactivity								
Ref.	**Name Surname**	**D3**	**D5**	**D8**	**D10**	**D12**	**D15**	**D17**	**D19**	**D22**
21	DINC. A	/	/	/	/	/	/	/	/	/
22	CIUR. R	/	/	/	/	/	/	/	/	/
23	VISA. E	/	/	/	/	/	/	/	/	/
24	MUSA. D	/	/	/	/	/	/	/	/	/
25	VOIC. D	/	/	/	/	/	/	/	/	/
26	GHIR. C	/	/	/	/	/	/	/	/	/
27	GHIR. F	/	/	/	/	/	/	/	/	/
28	BARB. M	/	/	/	/	/	/	/	/	/
29	UDAT. D	/	/	/	/	/	/	/	/	/
30	ILIE. I	/	/	/	/	/	/	/	/	/
31	ILIE. M	/	/	/	/	/	/	/	/	/
32	ROMA. T	/	/	/	/	/	/	/	/	/
33	TOME. G	/	/	/	/	/	/	/	/	/
34	ZGAV. G	/	/	/	/	/	/	/	/	/
35	SURD. M	/	/	/	/	/	/	/	/	/
36	SIRB. D	/	/	/	/	/	/	/	/	/
37	ANDR. M	/	/	/	/	/	/	/	/	/
38	DOBR. M	/	/	/	/	/	/	/	/	/
39	BELD. N	/	/	/	/	/	/	/	/	/
40	PAUN. M	/	/	/	/	/	/	/	/	/

Appendix 3/3

SKIN EXAMINATION AND QUESTIONING DURING THE INDUCTION PHASE

Volunteers		Reactivity								
Ref.	**Name Surname**	**D3**	**D5**	**D8**	**D10**	**D12**	**D15**	**D17**	**D19**	**D22**
41	CAPO. N	/	/	/	/	/	/	/	/	/
42	CAPO. C	/	/	/	/	/	/	/	/	/
43	VELI. P	/	/	/	/	/	/	/	/	/
44	TANA. M	/	/	/	/	/	/	/	/	/
45	DINE. R	/	/	/	/	/	/	/	/	/
46	BARD.J	/	/	/	/	/	/	/	/	/
47	SOAR. V	/	/	/	/	/	/	/	/	/
48	SERC. G	/	/	/	/	/	/	/	/	/
49	PASA. R	/	/	/	/	/	/	/	/	/
50	TANA. L	/	/	/	/	/	/	/	/	/
51	CACI. G	**WITHDRAWAL**								
52	PATA. E	/	/	/	/	/	/	/	/	/
53	GRAD. E	/	/	/	/	/	/	/	/	/
54	NEDE. V	/	/	/	/	/	/	/	/	/

Legends :

/ : nothing to report
E : Erythema
Oe : Œdema
V : Vesicle
D : Dryness
S : Soap effect

Bu : Bulla
Pa : Papule
Sc : Scab
C : Coloration
Pr : Pruritus
Hea : Heating
St : Stinging

0.5 : Very slight intensity
1 : Slight intensity
2 : Moderate intensity
3 : Severe intensity
d : diffuse
p : punctuated
peri : peripheral
Vesicles or papules

1 : nb = 1 or 2
2 : nb > 2

Appendix 4/1

SKIN EXAMINATION AND QUESTIONING DURING THE CHALLENGE

Volunteers		Reactivity								According to the ICDRG criteria
		Induction site				Virgin site				
Ref.	Name Surname	D43	D45	D46	D47	D43	D45	D46	D47	
1	TROA. F	/	/	/	/	/	/	/	/	-
2	NEAC. C	/	/	/	/	/	/	/	/	-
3	ALEX. T	/	/	/	/	/	/	/	/	-
4	STAN.G	/	/	/	/	/	/	/	/	-
5	GHEN. A	/	/	/	/	/	/	/	/	-
6	DIAC. M	/	/	/	/	/	/	/	/	-
7	RADU. C	/	/	/	/	/	/	/	/	-
8	ARME. A	/	/	/	/	/	/	/	/	-
9	PILE. M	/	/	/	/	/	/	/	/	-
10	VASI. C	**WITHDRAWAL**								NT
11	GAVR. M	/	/	/	/	/	/	/	/	-
12	DOBR. D	/	/	/	/	/	/	/	/	-
13	BACA. I	/	/	/	/	/	/	/	/	-
14	BELU. M	/	/	/	/	/	/	/	/	-
15	STAN. E	/	/	/	/	/	/	/	/	-
16	DIAC. C	/	/	/	/	/	/	/	/	-
17	BOTE. C	/	/	/	/	/	/	/	/	-
18	IVAN. L	/	/	/	/	/	/	/	/	-
19	GRIG. M	/	/	/	/	/	/	/	/	-
20	BANU. M	/	/	/	/	/	/	/	/	-

Appendix 4/2

SKIN EXAMINATION AND QUESTIONING DURING THE CHALLENGE

Volunteers		Reactivity								According to the ICDRG criteria
		Induction site				Virgin site				
Ref.	Name Surname	D43	D45	D46	D47	D43	D45	D46	D47	
21	DINC. A	/	/	/	/	/	/	/	/	-
22	CIUR. R	/	/	/	/	/	/	/	/	-
23	VISA. E	/	/	/	/	/	/	/	/	-
24	MUSA. D	/	/	/	/	/	/	/	/	-
25	VOIC. D	/	/	/	/	/	/	/	/	-
26	GHIR. C	/	/	/	/	/	/	/	/	-
27	GHIR. F	/	/	/	/	/	/	/	/	-
28	BARB. M	/	/	/	/	/	/	/	/	-
29	UDAT. D	/	/	/	/	/	/	/	/	-
30	ILIE. I	/	/	/	/	/	/	/	/	-
31	ILIE. M	/	/	/	/	/	/	/	/	-
32	ROMA. T	/	/	/	/	/	/	/	/	-
33	TOME. G	/	/	/	/	/	/	/	/	-
34	ZGAV. G	/	/	/	/	/	/	/	/	-
35	SURD. M	/	/	/	/	/	/	/	/	-
36	SIRB. D	/	/	/	/	/	/	/	/	-
37	ANDR. M	/	/	/	/	/	/	/	/	-
38	DOBR. M	/	/	/	/	/	/	/	/	-
39	BELD. N	/	/	/	/	/	/	/	/	-
40	PAUN. M	/	/	/	/	/	/	/	/	-

Appendix 4/3

SKIN EXAMINATION AND QUESTIONING DURING THE CHALLENGE

Volunteers		Reactivity								According to the ICDRG criteria
		Induction site				Virgin site				
Ref.	Name Surname	D43	D45	D46	D47	D43	D45	D46	D47	
41	CAPO. N	/	/	/	/	/	/	/	/	-
42	CAPO. C	/	/	/	/	/	/	/	/	-
43	VELI. P	/	/	/	/	/	/	/	/	-
44	TANA. M	/	/	/	/	/	/	/	/	-
45	DINE. R	/	/	/	/	/	/	/	/	-
46	BARD.J	/	/	/	/	/	/	/	/	-
47	SOAR. V	/	/	/	/	/	/	/	/	-
48	SERC. G	/	/	/	/	/	/	/	/	-
49	PASA. R	/	/	/	/	/	/	/	/	-
50	TANA. L	/	/	/	/	/	/	/	/	-
51	CACI. G	**WITHDRAWAL**								NT
52	PATA. E	/	/	/	/	/	/	/	/	-
53	GRAD. E	/	/	/	/	/	/	/	/	-
54	NEDE. V	/	/	/	/	/	/	/	/	-

Legends :

/ : nothing to report
E : Erythema
Oe : Œdema
V : Vesicle
D : Dryness
S : Soap effect

Bu : Bulla
Pa : Papule
Sc : Scab
C : Coloration
Pr : Pruritus
Hea : Heating
St : Stinging

1 : Slight intensity
2 : Moderate intensity
3 : Severe intensity
d : diffuse
p : punctuated
peri : peripheral
Vesicles or papules *1 : nb = 1 or 2*
2 : nb > 2

ICDRG

NT	*:*	*non tested*
?+	*:*	*uncertain reaction, only slight erythema*
+	*:*	*positive reaction (with no vesicle) : erythema, infiltration, sometimes some papules*
++	*:*	*strong positive reaction : presence of erythema, papules, vesicles*
+++	*:*	*violent positive reaction : with presence of bullae*
-	*:*	*negative reaction*
IR	*:*	*irritation reaction*