HUMAN REPEATED INSULT PATCH TEST WITH CHALLENGE

Study report – version 1 of (15/04/2019)

STUDY REFERENCE **EUROFINS EVIC romania – ER 19/028-22**

INVESTIGATIONAL PRODUCT	
Denomination	**Nikis Natural Wipes**
Reference	**NN01**
Batch number	**1**

SPONSOR	**Little Nikis Pty Ltd** 2 Jade Circuit Burwood East Vic 3151 Australia
STUDY MONITOR	**Suthan Naganayagam**
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Initiation date of study performance	**18/02/2019**
Completion date of study performance	**29/03/2019**

Date of the study report: 15/04/2019

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HUMAN REPEATED INSULT PATCH TEST WITH CHALLENGE

English synopsis

STUDY OBJECTIVES	Mainly, to confirm, in a panel of healthy human adult subjects, that the application of the investigational product, under maximizing conditions of exposure, did not induce delayed contact sensitisation Secondarily, to assess the skin compatibility of the investigational product during the study
SPONSOR	**Little Nikis Pty Ltd** 2 Jade Circuit Burwood East Vic 3151 Australia
STUDY MONITOR	**Suthan Naganayagam**
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MAIN INVESTIGATOR	**Dr. Rozalia Olsavszky** (dermatologist) Registered N° (Romanian ministry of health): 461524 (specialist in dermato-venerology doctor, doctor in medical science) Tel: +40 21 335 70 90 Fax: +40 21 335 70 91 *e-mail: research@evic.ro*
TYPE OF THE STUDY	Monocentric randomised study performed in simple blind, Study project previously approved by a internal survey committee.
DATES OF STUDY PERFORMANCE	From February 18th to March 29th 2019
INVESTIGATIONAL PRODUCT	**Nikis Natural Wipes – Ref. NN01 – Lot. 1**
	Modalities of application in the study: As supplied, cut at the patch dimension, under semi-occlusive patch – 1 piece

Synopsis (continuation)

STUDY POPULATION	**Number of test subjects: 50** valid cases **Specific inclusion criteria: test subjects** ▪ aged from 18 to 70 ▪ female / male • with sensitive skin on body ▪ with a phototype (Fitzpatrick): II, III or IV **Specific non-inclusion criteria: test subjects** • with personal history of adverse reaction to: ethanol, colophony, rubber, nickel, aluminium, patch materials, adhesive plaster • with family or personal history of atopy
METHODOLOGY	**Application of the investigational product,** in healthy human subjects, by a technician, at the investigating centre, to a skin site on the upper back, under maximizing conditions of exposure (under semi-occlusive patch) for a defined time Repeated applications 9 times to the same site (induction site) over a period of 3 consecutive weeks, period necessary to induce a possible allergy (induction phase) After a minimal 2-week rest period, with no product application, single application of the investigational product, under patch, to the induction site and to a virgin site and for a defined time, enabling to reveal a possible induced allergy (challenge) **Application in parallel of distilled water** under semi-occlusive patch at the same defined times as the investigational product = control site Skin examination of the application site, before the 1st product application of the induction phase and the application of the challenge and after each patch removal by the same investigator / technician, supervised by the investigator Reporting of the sensations of discomfort directly by the test subjects to the investigator / technician, during the study Assessment of the allergic potential - checking of the skin compatibility: • Accurate description of the skin reactions observed • Evaluation of the allergic reaction according to the ICDRG scale: ?+, (+), (++), (+++) • Calculation of the percentage of reactive test subjects during the challenge and the induction phase

Synopsis (continuation)

RESULTS

Characteristics of the included panel

Number of included subjects: 55
Number of exclusions: none
Number of withdrawals: (reason): 1 (ref. 33c) – for personal reasons independent from the study
Number of valid cases: 54

- Age: 31 to 70 (Mean: 52)
- Sex: F/M
- Phototype: II to IV
- Skin types on the application site: with sensitive skin on body

Checking of the skin compatibility

No reaction was noted on the control site.

For the investigational product:

Induction period			
Type of reaction	**Description of the reaction on the induction site**	**Number and percentage of reactive test subjects**	**Total number and percentage of reactive test subjects**
E: Erythema	None	0 / 0%	0 / 0%
M: Complementary mention	None	0 / 0%	
A: ICDRG scale	None	0 / 0%	

Challenge phase			
Type of reaction	**Description of the reactions on the induction site and the virgin site**	**Number and percentage of reactive test subjects**	**Total number and percentage of reactive test subjects**
E: Erythema	None	0 / 0%	0 / 0%
M: Complementary mention	None	0 / 0%	
A: ICDRG scale	None	0 / 0%	

OVERALL CONCLUSION

Under the experimental conditions adopted:

- During the induction period, the repeated applications of the product **Nikis Natural Wipes – Ref. NN01 – Lot. 1,** under semi-occlusive patch, on a panel of 54 test subjects with sensitive of skin on body, induced no reaction of irritation.

- During the challenge phase, the single application of the investigational product to the induction site and virgin site induced no allergic reaction.

Based on these results, the product has a very good skin compatibility and does not show a sensitizing effect.

HUMAN REPEATED INSULT PATCH TEST WITH CHALLENGE

Signatures and dates

Investigator: Dr. Rozalia OLSAVSZKY (dermatologist) / Dr Elena Olsavszky

I the undersigned, Dr. Rozalia Olsavszky, declare that the overall conduct of the study was carried out under my responsibility in accordance with the protocol, the internal procedures and in the spirit of the principles of Good Clinical Practices (International recommendations ICH E6(R1) of 10/06/1996, Directive of the European Parliament and Council 2001/20/EC – OJ/EC of 01/05/2001), Romanian Order No. 904/25.07.2006
I assume the responsibility of the validity of all the raw data obtained during the study which are reported in the present study report.

Date: 17/06/2019

Signature:

Head manager of the investigating centre: Dr. Chem. Eng. Elena Alina NANU / VERONICA DUMITRU

I the undersigned, Dr. Chem. Eng. Elena Alina NANU, declare that the overall conduct of the study was carried out under my responsibility in accordance with the protocol and the internal procedures and in the spirit of the principles of Good Clinical Practices (International recommendations ICH E6(R1) of 10/06/1996, Directive of the European Parliament and Council 2001/20/EC.
I assume the responsibility of the validity of all the raw data obtained during the study which are reported in the present study report.

Date: 17/06/2019

Signature:

Person in charge of the quality control: Cristina Borlescu

I the undersigned, Cristina Borlescu, declare that:

- the draft of the report was audited, on 15/04/2019
- the final report was audited, on 15/04/2019
- the reported results accurately and completely reflected the raw data of the study.

Date: 17/06/2019

Signature:

HUMAN REPEATED INSULT PATCH TEST WITH CHALLENGE

I – INITIAL PROTOCOL DESIGN

I.1. STUDY OBJECTIVES

Mainly, this study intended to confirm, in a panel of healthy human adult subjects, that the application of the investigational product, under maximizing conditions of exposure, did not induce delayed contact sensitization.

Secondarily, the skin compatibility of the investigational product was assessed during the study.

I.2. ETHICS

I.2.1. Ethical conduct of the study

The study was performed in spirit of:

- the general principles of medical ethics in clinical research coming from the Declaration of Helsinki (June 1964) and its successive amendments,
- the international recommendations relating to Good Clinical Practices for conducting clinical trials for drugs ICH E6(R1) of 10/06/1996 (CPMP/ICH/135/95),
- the Directive of the European Parliament and Council 2001/20/EC concerning the harmonization of legislative, statutory and administrative provisions of the member States relating to the application of good clinical practices when conducting clinical trials for drugs for human use – OJ/EC of 01/05/2001,
- the recommendations of Colipa - August 1997: "guidelines for the assessment of human skin compatibility",
- the Romanian Order No. 904/25.07.2006 on approval of rules relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

and was in accordance with the REGULATION (EU) 2016/679 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data.

I.2.2. Relevance of the study

On the one hand, the aims of the study were a better knowledge of the skin safety of the investigational product and the confirmation of the absence of allergic potential and the investigational product was not applied under normal conditions of use. So, the test subject had no direct benefit from this study.

On the other hand, the foreseeable risk incurred by the test subjects was a possible allergic reaction to one or several ingredients of the investigational product or a skin irritation due to the finished product applied under maximized conditions (under patch).

Generally in this type of study, the possible adverse effects (as erythema, vesicles…) are limited on the application sites and decrease in some days.

The applications were performed at the investigating centre and supervised by a dermatologist, so the application had to be quickly stopped if necessary and the clinical follow-up of the reactive test subject(s) had to be done by a competent person.

So, according to the nature and the severity of the possible reaction, the investigator had to define the conduct to be adopted and the suitable steps to ensure the safety of the test subject(s) (for example definitive or temporary exclusion of the test subject(s) concerned from the study, modification of the application conditions of the product…) and had to ensure the clinical follow-up of the test subject(s) concerned, as long as it was necessary.

All the test subjects were included in the study the same day.

So, there was suitability between the aim of the study and its eventual risks and the foreseeable troubles related to the experimental conditions of the protocol.

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

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

The product dose was perfectly controlled, the patch material and the conditions of use of the product were adapted to the product category.

A control site (without investigational product) served as control to take into account the possible effects not directly related to the investigational product but due to the patch material.

The investigational product was tested with other products at the same time, the experimental area chosen (upper back) enabling to test easily several products (maximum 15 product sites at least 1 cm far apart). The sites of application of the different products and the control site(s) were chosen according to a clockwise distribution, altering of one rank from a test subject to another, to take into account the variability of the skin reactivity according to the site.

The observance of the experimental conditions by the subjects, who took part in the study, was assessed by a questionnaire at the end of the induction phase and at the end of the challenge.

I.2.3. Survey committee

The study had to be devoid of any foreseeable serious risk for the safety of the test subjects.

So, according to the procedure of the investigating centre, the protocol, the informed consent form and the information concerning the investigational product (particularly referring to its safety) had to be submitted to the opinion of an Institutional Ethics Committee, formed with members belonging to the staff of the investigating centre, but not directly involved in the study.

The Institutional Ethics Committee gave the approval on February 15th 2019.

The study began after the approval of the Institutional Ethics Committee

I.2.4. Information of the test subject and informed consent form

The information about the study was given to each test subject before the start of the study.

This information was accessible, understandable and suitable for each test subject. It was orally given and then in a written specific document (in Romanian).

This information was completed, if it was necessary, by the investigator (or the competent person designated by him) who answered all the questions asked by the test subject.

The informed consent form was personal and previous to the start of the study.

It was clear, informed and explicit. It was written and given on the same support as the information on the study, in order to avoid any risk of dispute about its content.

The content of this document particularly specified:

- that the test subject had declared 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),
- the reasonable foreseeable risks,
- that skin site photographs could be taken and in this case, that the test subject would not be recognizable,
- that the test subject could be requested, if necessary, to take part in a complementary test to complete the study,
- the opinion of the Institutional Ethics Committee,
- the person to contact and the contact telephone number,
- that the personal data of the test subject were confidentially treated by the study staff, available for the sponsor and possibly consulted (with the authorization of the test subject) by the auditors, the members of the Institutional Ethics Committee and the Health Authorities (subject to non divulgation),
- the ban on taking part simultaneously in other clinical studies that could interfere with the current study,
- the amount of the compensation for the constraints to be undergone,
- the form of compensation in case of possible harm caused by the study (all the costs of health care assumed through the investigating centre),
- the period of exclusion at the end of the study during which the test subject will 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 and will be 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.

This document was previously approved by the Institutional Ethics Committee.

At the beginning of the study, 2 copies of this document were dated and signed by the test subject and by the investigator or the competent person designated. One copy was given to the test subject, the other one was kept at the investigating centre.

I.2.5. Confidentiality and identification of the test subject

The information concerning the test subject, required for his recruitment, his inclusion and particularly that related to his health, obtained during the medical examination prior to his admission in the general panel of the investigating centre, formed part of medical secret and was confidentially treated.

The test subject was coded when included in the current study (according to the corresponding procedure of the investigating centre) in order to preserve his anonymity.

If photographs of the skin had to be taken, the test subject had to be non recognizable.

I.2.6. Insurances

Insurance of the sponsor

The sponsor is covered by an insurance guaranteeing its civil responsibility towards the possible damages resulting from the use of the investigational products in this study.

Insurance of the investigating centre
The investigating centre is covered by an insurance guaranteeing its civil responsibility towards the test subjects: HDI-Gerling Industrie Versicherung AG, Policy no.: 110-01325685-14023 as lead insurer and Axa Corporate Solutions as co-insurer: XFR0074974LI.

I.3. INVESTIGATING CENTRE AND STAFF

I.3.1. Investigating centre

The study was performed at Eurofins Evic Romania, certified ISO 9001, ISO 14001 and OHSAS 18001, equipped with material and technical means suitable for clinical researches on cosmetic products and compatible with the safety requirements for human subjects.

I.3.2. Technical staff

The test was performed by a competent investigator and a trained and qualified technical staff.

Main Investigator: Dr. Rozalia Olsavszky (dermatologist)

Registered N° (Romanian ministry of health): 461524 (specialist in dermato-venerology doctor, doctor in medical science)

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Technician in charge of the study: Nicoleta Dumitru

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I.3.3. Scientific management

Scientific manager: Dr. Chem. Eng. Elena Alina Nanu

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I.3.4. Quality assurance staff

Person responsible for quality control: Cristina Borlescu

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I.4.COORDINATING CENTRE

The study was coordinated by Eurofins Dermatest.

I.5. DATES OF STUDY PERFORMANCE

Initiation date of study performance: 18/02/2019

Completion date of study performance: 29/03/2019

I.6. OVERALL STUDY DESIGN

I.6.1. Type of the study

This monocentric clinical study was randomized and performed in simple blind, in a panel of healthy human subjects.

The test subject was used as own control

I.6.2. General principle of the study

The investigational product had to be applied in **50** test subjects, by a technician, at the investigating centre, under maximized conditions of exposure (under patch) for a defined time. The applications had to be repeated 9 times to the same site (induction site) over a period of 3 consecutive weeks, period necessary to induce a possible allergy (induction phase).

After a minimal 2-weeks rest period, with no product application, a single application of the investigational product, under patch, to the induction site and to a virgin site and for a defined time, enabling to reveal a possible induced allergy (challenge phase), had to be performed.

A skin examination of the application site had to be performed before the 1st product application of the induction phase and the application of the challenge and after each patch removal, by the same investigator / technician, supervised by the investigator.

The sensations of discomfort had to be directly reported by the test subjects to the investigator / technician, during the study.

The results of the skin compatibility were descriptively expressed.

Since sensitisation is not a matter of quantification, the possible reactions had to be classified as allergic or not, according to the observation done during the challenge phase compared with the observation done during the induction phase.

I.6.3. Chronology of the study

Induction phase: 3 consecutive weeks			
Operations at the investigating centre	**Experimental times**		
	D1	**D3 - D5 - D8 - D10 - D12 - D15 – D17 - D19**	**D22**
Pre-inclusion: Delivery of the inform consent form Signature of the informed consent form Checking of the inclusion and non-inclusion criteria	●		
Clinical examination of the application site and questioning of the test subject by the investigator or technician supervised by the investigator, before product application	●		
Final inclusion	●		
Application of the investigational product under patch to the defined induction site	●	●	
Removal of the patch at the investigating centre		●	●
Clinical examination of the application site and questioning of the test subject by the investigator or technician supervised by the investigator		●	●
Control of the observance			●

Rest period: 2 consecutive weeks at least (4 weeks at the most)	**No product application**

Challenge: 1 week			
Operations at the investigating centre	**Experimental times**		
	D36	**D38**	**D40**
Clinical examination of the application site and questioning of the test subject by the investigator or technician supervised by the investigator, before product application	●		
Application of the investigational product under patch to the defined induction site and to a defined virgin site	●		
Removal of the patch at the investigating centre		●	
Clinical examination of the application sites and questioning of the test subject by the investigator or technician supervised by the investigator		●	●
Control of the observance			●

I.7. STUDY POPULATION

I.7.1. Constitution of the panel of test subjects and mode of recruitment

The investigating centre has at its disposal a general panel of subjects constantly renewed. These subjects come from all social categories. They either volunteer spontaneously arise to the investigating centre or reply to a direct call from the latter. Prior to their admission in this general panel, they are subjected to a medical examination and a detailed medical and cosmetological questionnaire, performed by a general practitioner according to the internal procedure of the investigating centre.

All the data concerning the panel are computerized and on paper.

For the study, the test subjects were selected from this general panel on the basis of inclusion criteria and non-inclusion criteria specific to the study and on their ability to respect the constraints required by the protocol. They were definitely included in the study after a specific questioning and a clinical examination.

I.7.2 . Number of test subjects

The number of test subjects with exploitable data (valid cases[(1)]) at the end of the study had to be at least **50.**

[(1)]valid case = test subject that respected the protocol with no significant deviation which could have some influence on the study results.

The number of test subjects necessary to allow a reliable prediction of the sensitising potential of an investigational product depends on the methods used. The statistical considerations involved in extrapolating from a small test population to a large number of users were discussed in the following publication:

- Henderson C.R., Riley E., Certain statistical considerations in patch testing, J. Invest. Dermatology, 1945, 6, pp. 227-232

It is obvious that studies with numbers of test subjects sufficient to obtain statistically valid data applicable to several thousand consumers are not feasible. Therefore, the value of predictive patch testing does not lie in the precision of the prediction but in screening out the rare sensitising products.

So, referring to the experience acquired in the field of contact allergy to cosmetic products, the number of test subjects, empirically defined in the protocol, was sufficient to confirm, before product launching, the absence of allergenic potential of the investigational product and to achieve the study objectives.

At the beginning of the study, complementary test subjects (+5) had to be included to answer the demand and to compensate the possible withdrawals or exclusions from the study independent of the investigational product.

The test subjects excluded from the study for reasons dependent of the investigational product had to be taken into account in the study results and did not have to be replaced.

If during the study, there was a risk not to have the required number of valid cases (great number of withdrawals…), the sponsor had to be informed and an additional quota of subjects had to be possibly included to reach the target.

At the end of the study, in spite of the precautions taken by the investigating centre, if the number of valid cases was less than the number of test subjects requested by the sponsor, the study monitor had to be informed.

I.7.3. Inclusion criteria

I.7.3.1. General inclusion criteria

According to the protocol, had to be included in the study, the subjects:

- suitable to participate in the study (after the clinical examination and questioning) and corresponding to the quality of "healthy subject" as defined in the corresponding procedure of the investigating centre,
- declaring to have a health coverage,
- signing an "informed consent form" for this study,
- certifying not to take part in another clinical study that could interfere with the current study,
- certifying the truth of the personal information declared to the investigator,
- capable of following directions and reliable to respect the constraints of the protocol (living not too far from the investigating centre, no linguistic and intellectual barrier),
- free to ensure the visits to the investigating centre,
- declaring not to have exposed themselves to a risk of pregnancy for at least 3 months before the beginning of the study and committing themselves to use effective contraceptive method throughout the study (for the women of childbearing potential),

I.7.3.2. Specific inclusion criteria

Subjects:

- aged from 18 to 70
- female and/or male,
- with sensitive skin on body,
- with a phototype (Fitzpatrick): II, III or IV

I.7.4. Non inclusion criteria

I.7.4.1 General non inclusion criteria

According to the protocol, did not have to be included in the study, the subjects:

- being in exclusion period,
- deprived of freedom by administrative or legal decision or under guardianship,
- who could not be contacted in case of emergency,
- admitted in a residential care,
- planning an hospitalisation during the study,
- belonging to the staff of the investigating centre,
- being of age but protected by law,

- having received vaccination within the 3 weeks prior to the study or intending to be vaccinated during the course of the study,
- with documented history of contact allergy
- with person al history of adverse reactions to the same type of product as the investigational product
- exhibiting skin marks and/or moles and/or freckles in too great quantity, hyperpilosity on the experimental area able to interfere with the assessment of the possible skin reactions,
- with still visible eczematous reaction, scar or pigmentary after-effects of previous tests on the experimental area,
- under treatment, prior to the study, able to interfere with the interpretation of the study results, particularly:
    - systemic retinoids (isotretinoin per os …) within the 6 months,
    - other systemic anti-acne medication within the 3 months,
    - topical retinoids within the 2 months,
    - other topical anti-acne medication within the month,
    - anti-acne cosmetic products within the 2 weeks (excluding face anti acne products),
    - topical or systemic medication with anti-inflammatory or antihistamine products within the 2 weeks,
    - antibiotics within the 2 weeks,
    - medication for malignancy (of any kind) within the 5 years,
    - desensitization treatment within the 6 months,
- foreseeing, during the study, a treatment able to interfere with the interpretation of the study results (systemic or topical anti-acne medication, anti-acne cosmetic products, topical or systemic medication with anti-inflammatory or antihistamine, antibiotics, desensitization treatment, …),
- having had a fever lasting more than 24 hours, within the 8 days prior to the study,
- breastfeeding or pregnant or planning a pregnancy during the study (for the women of childbearing potential),
- having started or changed oestrogen-progesterone contraception or hormonal treatment, within the 3 months prior to the study or foreseeing it for the duration of the study,
- having had any invasive aesthetic cares on chest and back (peeling, laser…) by a dermatologist within the 2 months prior to the study or foreseeing it for the duration of the study,
- having had any non invasive aesthetic cares on chest and back (scrub, skin cleansing…) by an aesthetician within the month prior to the study or foreseeing it for the duration of the study,
- having received excessive or intensive exposure to sunlight (natural or artificial) within the month prior to the study or foreseeing UV exposures for the duration of the study,
- under treatment with PUVA or UVB within the month prior to the study,
- having participated in a human repeated insult patch test with challenge with or without sun exposure 3 months prior to the study,
- having participated in a cumulative irritability test within the 2 months prior to the study or in a single patch test within the month prior to the study,
- having already participated in 5 clinical studies involving patch test, including 3 human repeated patch tests with or without challenge within the year prior to the study,
- foreseeing bath (in bathtub, sea or swimming-pool), sauna or Turkish bath during the study period,
- regularly practicing intensive sport causing sweating and requiring frequent showers.

I.7.4.2. Specific non inclusion criteria

Subjects:

- with family or personal history of atopy
- with personal history of adverse reaction to: ethanol, colophony, rubber, nickel, aluminium, patch materials, adhesive plaster.

I.7.5. Specific information concerning the test subjects and medication

Skin reactivity, history of atopy, contraception (type) and possible current medication were documented at the inclusion by the technician, supervised by the investigator or the competent person designated, in the collective 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 justified 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.

I.7.6. Exclusion criteria

According to the study protocol and to the procedures of the investigating centre, had to be excluded from the study, the test subjects:

- who did not comply with the protocol and created deviation resulting in un-exploitable results,
- who took part in another clinical study in another investigating centre,
- who had adverse event (for example: inter-current disease requiring a concomitant medication interfering with the study and the interpretation of the results or severe skin intolerance to the investigational product), incompatible with a good protocol observance.

The temporary or definitive discontinuations decided by the investigator and their dates and reasons had to be carefully documented in the collective case report form (CRF).

I.7.7. Withdrawal criteria

According to the study protocol and to the procedures of the investigating centre, had to be considered as withdrawals, the test subjects:

- who discontinued the study for personal reasons independent of the study (for example: moving house, new job),
- who did not come to the investigating centre for the checking in spite of phone calling.

The withdrawals and their dates and reasons had to be carefully documented by the investigator in the collective case report form (CRF).

I.7.8. Study constraints imposed on the test subjects

The constraints defined by the procedures of the investigating centre and partly in the study protocol, imposed on the test subjects during the study, were the following ones:

- if justified and asked by the investigator, participation in a complementary test (additional visits to the investigating centre),
- exclusion period at the end of the study (according to the corresponding procedure of the investigating centre and 3 months minimum before starting a human repeated insult patch test with challenge, 1 month minimum before starting another type of study),
- no participation in another clinical study that could interfere with the current study,
- if justified, description of any concomitant medical treatment not excluded by the inclusion and non inclusion criteria,
- no drug liable to interfere with the study and the interpretation of the results, *e.g.* aspirin (except low dose maintenance therapy), products containing aspirin, antihistamine drugs, anti-inflammatory drugs, antibiotics… (however, if therapeutic requirement: possible exclusion from the study),
- neither initiation of an hormonal treatment nor change of the usual hormonal treatment,
- no change of the mode of contraception,
- no significant change in lifestyle: diet, smoking, sport,…,
- visit to the investigating centre 13/14 times and respect of the dates and hours of visits,
- neither anti-acne nor anti seborrheic local treatment,
- neither invasive body aesthetic cares (peeling, laser…) nor non invasive body aesthetic cares (scrub, skin cleansing…) on chest and back, by a dermatologist or an aesthetician in Beauty Salon,
- no application of cosmetic care products to the back,
- no change in usual body hygiene products,
- no introduction of new cosmetic products,
- no intensive sun or UVA exposure (U.V. lamps) during the study and 2 weeks after the end of the study,
- no wearing of too tight or restraining clothes liable to produce frictions on the experimental area and to cause the un-sticking of the patch(es),
- neither Turkish bath nor sauna nor bath (in bathtub or swimming-pool or sea), liable to cause excessive sweating and/or the un-sticking of the patch(es),
- during shower, protection of the experimental area (no violent projection of water, no application of soap, very gentle wiping if necessary) to avoid the un-sticking of the patch(es) or the appearance of inter-current skin irritation,
- no intensive sport liable to cause excessive sweating and the un-sticking of the patch(es),
- no vaccination.

The test subjects were questioned at the end of the induction phase and at the end of the challenge about the respect of the study constraints. These data were documented in the case report form (CRF). The investigator had to assess the importance of the possible deviations in comparison with the experimental conditions required at the beginning of the study and their incidence on the validity of the results.

I.8. INVESTIGATIONAL PRODUCT

I.8.1. Identification of the investigational product

Denomination	Nikis Natural Wipes
Cosmetic category	Wet wipes
Reference	NN01
Batch number	1
Galenic form and organoleptic characteristics	White wipes
Normal foreseeable conditions of use	As it is

I.8.2. Coding and storage

The sponsor or Eurofins Dermatest supplied to the investigating centre the investigational product in sufficient quantity for the study and the sampling, in neutral packaging, clearly identified.

Upon receipt, the investigating centre noted the date of product receipt checked the supplied quantities, the investigational product aspect and got sure that the labelling is in accordance with the demand of the sponsor.

If requested, the sponsor received an acknowledgement of receipt, mentioning the remarks of the coordinating centre.

The product units were coded and labelled in Romanian according to the corresponding procedure of the investigating centre

Number and type of product units	10 plastic packs
Eurofins Evic Romania code	19-0203

Before starting the study, the storage of the investigational product units were carried out according to the conditions defined by the sponsor, in the product storage area and a product sample was taken and kept in the sample storage area of the investigating centre for 3 years after the end of the study then destroyed, according to the corresponding procedure of the investigating centre.

Apart from the specific demand of the sponsor, the used product units will be kept at least 4 weeks after the sending of the final report then destroyed, according to the corresponding procedure of the investigating centre.

I.8.3. Information concerning the investigational product

The investigational product units had to be supplied with a certificate that particularly referred to:

- the compliance of the ingredients of the investigational product formula with the European Regulation N° 1223/2009 of the European Parliament,
- the safety of the finished investigational product and the absence of foreseeable serious risk for the health of the test subjects.

The qualitative formula of the product had to be supplied to the investigator by the coordinating centre.

I.8.4. Experimental conditions of application of the investigational product

I.8.4.1. Induction phase

The skin site had to be defined by the technician in charge of the study, on the upper back, on a surface free from scars, moles, freckles and any other skin anomaly and avoiding the areas of friction with clothes.

The quantity of investigational product had to be measured by the technician in charge of the study with a tweezer and put into the patch.

Before patching, the skin site had to be wiped with a cotton pad and dried.

The patch containing the investigational product had to be applied, by the technician in charge of the study, on the defined skin site.

According to the protocol, the experimental conditions of patching had to be the following ones:

Patch material	Experimental conditions of use of the investigational product	Quantity to be applied
Semi-occlusive patch absorbent support in Webril® kept in position by a non woven medical adhesive (surface: 400 mm²)	As supplied, cut at the patch dimension	1 piece

A semi-occlusive patch, containing 160 µl of distilled water had to be applied in parallel as control to eliminate, when the results were interpreted, the possible inter-current effects due to the patch material.

The induction consisted of 9 patches applied 3 times a week (for example: Monday, Wednesday and Friday) for a 3 week period.

Patches applied on Mondays and Wednesdays had to be worn for 48 hours ± 4 hours and patches applied on Fridays had to be worn for 72 hours ± 4 hours.

The application was possibly performed on other days of the week, subject to the respect of the three 72-hour contact patches and the six 48-hour contact patches.

Induction phase				
Operations	**Experimental times**			
	D1	**D3 - D5 D10 - D12 D17 - D19**	**D8 - D15**	**D22**
Application of the investigational product under patch to the defined induction site	●	●	●	/
Removal of the patch at the investigating centre	/	● After 48h of contact	● After 72h of contact	● After 72h of contact

The applications had to be repeated on the same site, except in the case of significant irritation/sensitisation reaction.

In case of moderate or severe skin erythema or mild erythema with oedema/infiltration, the sponsor had to be quickly informed and the product application had to be stopped to the induction site defined and continued to a new adjacent site (the change of site being done once only).

In case of suspected allergic reaction the product did not have to be applied again and the case had to be quickly discussed with the coordinating centre and the sponsor. Then, the decision to reapply or not the product had to be jointly taken by the investigator and the sponsor.

During the induction phase, the technician had to precisely locate the test site to be able to retrieve it after the rest period, according to the procedure of the investigating centre.

I.8.4.2. Rest period

No patching had to be performed for a period of 2 weeks minimum (4 weeks maximum) following the end of the induction phase.

The test subjects had to inform the investigator of any reaction occurring during this period.

I.8.4.3. Challenge

The challenge patches had to be applied once after the rest period. The investigational product and the control product had to be applied using the same patching conditions as those used for the induction phase, to 2 sites: a virgin site and the induction site, symmetrically located, if possible. The patches had to be removed 48 hours ± 4 hours after application.

Challenge			
Operations	**Experimental times**		
	D36	**D38**	**D40**
Application of the investigational product under patch to the defined induction site and to a defined virgin site	●	/	/
Removal of the patch at the investigating centre	/	● After 48h of contact	/

I.9. CHECKING OF THE SKIN COMPATIBILITY

I.9.1. Recording of the skin reactions

Skin examinations of the application sites had to be performed visually, by the same investigator / technician, supervised by the investigator, under standard "daylight" source:

- during the induction phase:
  - before patching on D1
  - 15 to 30 minutes after patch removal (or more, if redness appeared after the removal of the adhesive) on D3, D5, D8, D10, D12, D15, D17, D19, D22
- during the challenge phase:
  - before patching on D36
  - 15 to 30 minutes after patch removal on D38 (or more, if redness appeared after the removal of the adhesive)
  - 48h +/- 4 hours after patch removal on D40

In case of delayed skin reaction occurring after the 96h grading, the test subject had to contact the investigating centre and the site had to be re-examined by the investigator as long as necessary until reactions disappear.

All adverse reactions had to be followed until resolution.

Concurrently with the clinical examinations performed, the test subjects had to be questioned about the possible sensations of discomfort they felt.

In case of strong sensations of discomfort felt during the patch wearing at home, the test subjects had to inform by phone the investigator. If necessary, the patch was removed and a skin examination was quickly performed by the investigator (before the next planned visit to the investigating centre).

In case of application to a new adjacent site, the original test site had to be scored in parallel with the new test site until completion of the study and the skin scores of this original test site had to be distinctly documented.

Digital photographs of the skin had to be systematically taken when justified (adverse effects).

All the data were recorded in the collective case report form (CRF).

I.9.2. Expression of the results

All the reactions had to be accurately described at each experimental time using the criteria and the scale hereafter.

E = Erythema d= diffuse p = punctuated peri = peripheral	**0** – no visible erythema **0.5** – very slight erythema – barely perceptible **1** – mild erythema – faint pink **2** – moderate erythema – well defined **3** – severe erythema **4** – caustic effect – erosive aspect and/or necrotic aspect

If erythema E ≥ 1 the investigator had to proceed to palpation to assess infiltration/oedema.

M = Complementary mention : Other reactions	
Sv	Soap effect (shiny skin with possibly wrinkles)
D	Desquamation
Dr	Dryness
Hy	Hypopigmentation
C	Skin coloration – hyperpigmentation
Oe	Homogeneous infiltration / oedema
P	Papules
V	Vesicles
Pe	Petechiae
Fr	Follicular reaction
I	Itching at the test site
S	Spreading beyond the patch area (infiltration or erythema)
F	Fissuring
Cr	Exudation and/or Surface encrustation
B	Bullae
Sc	Scab
He	Heating
Pu	Pustules
/	No reaction

The other visible clinical signs had to be described.

M = Complementary mention : Additional comments	
NA	Product not applied
T	Tape reaction
L	Loss of patch during the first 12 hours
N9G	No 9th grading
X	Succeeding patch not applied and succeeding grade (in brackets) denotes a residual reaction
Abs	Test subject absent

For the induction phase and the challenge phase, the results were expressed in percentage of reactive test subjects: for this calculation only the visible signs of reactivity were taken into account: (erythema, oedema, vesicle, bulla, papule…)

I.9.3. Interpretation of the results

I.9.3.1. Allergy

All the test subjects included in the study were taken into account to appreciate the skin allergic potential of the investigational product as long as they were submitted at least to one post application examination at the defined time or else.

The nature, intensity, appearance period from the application, disappearance period from the application, location (induction site and/or virgin site) of the skin reaction and the phase of the study were taken into account for the interpretation of the results.

A = ICDRG scale	
IR	Irritation reaction
-	No allergic reaction
?+	Doubtful reaction (only slight erythema)
(+)	Weak positive reaction (without vesicle): slight erythema and infiltration with presence of small papular elevations, possibly papules
(++)	Strong positive reaction: erythema, papules, vesicles, infiltration
(+++)	Extreme positive reaction: intense erythema, oedema, coalescent vesicles (bullae)

A site where erythema was graded 2 or more during the challenge (with or without infiltration) had to be evaluated on subsequent days to note whether the reaction diminished or increased, in order to differentiate between an allergic or an irritant reaction. A rapidly diminishing reaction could be indicative of irritation. A reaction with infiltration / oedema that persisted or increased over time usually could indicate an allergic reaction.

If the possible allergic reaction was observed during the induction phase, it could be the revelation of an allergy previously contracted or the revelation of an allergy precociously induced by the investigational product.

If the possible allergic reaction was observed during the challenge phase (similar responses observed on the virgin site and on the induction site), it could be the revelation of an allergy induced during the induction phase by the investigational product.

In case of suspected allergic reaction, the sponsor had to be quickly informed.

In order to confirm the possible allergic reaction, an additional application (rechallenge) had to be proposed to the test subject with the agreement of the sponsor, at least 3 weeks after complete disappearance of the reaction. The experimental conditions of this complementary test had to be jointly defined case by case by the investigator and the study monitor.

I.9.3.2. Irritation

All the test subjects included in the study were taken into account to appreciate the skin irritant potential of the investigational product as long as they were submitted at least to one post application examination at the defined time or any other time.

To appreciate the skin irritant potential, the interpretation of the results was based on the experience of the investigator in this field. The skin compatibility of the investigational product was classified as: very good, good, moderate or bad, in the study conditions.

If justified in case of reactivity in some test subjects, a complementary study had to be possibly carried out in these test subjects, after agreement of the sponsor. The experimental conditions of this study had to be defined by the investigator, case by case.

I.10. SUSPENSION OF THE STUDY

The investigator had to stop the study if it showed a risk for the health or the integrity of the test subjects.

The date of the suspension and the reasons had to be carefully documented by the investigator in the case report form.

The study monitor had to be informed promptly by phone, fax or e-mail by the coordinating centre.

The sponsor was able to stop the study at any time for administrative reasons or other ones.

I.11. ADVERSE EVENTS

I.11.1. Definitions

Any topical product can induce, when used in Human, according to individual sensitivities, a local and 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.

The following definitions will be used:

- **adverse event**: any harmful event with or without relationship with the investigational product, occurring in a test subject during a clinical study.
- **suspicion of adverse effect**: any adverse event with a quite possible relationship with the investigational product.
- **adverse effect**: any harmful and unwanted reaction, due to the investigational product, occurring in a test subject during a clinical study.
- **unexpected adverse effect**: any adverse effect due to the investigational product, the nature, the intensity and/or the evolution of which do not agree with the product information.
- **serious adverse event / effect**: any adverse event or adverse effect that causes death, endangers test subject's life, induces an hospitalisation or the prolongation of the hospitalisation, causes severe and lasting incapacity or handicap or induces congenital anomaly or malformation.

I.11.2. Data collection

The investigator had to accurately describe the adverse event and had to appreciate its seriousness. According to the corresponding procedure of the investigating centre, he had 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 product had to be assessed according to the scale: very likely, likely, possible, questionable, excluded.

I.11.3. Conduct to be adopted in case of adverse event

Faced with an adverse event, the investigator had to freely define, case by case, the conduct to be adopted and the suitable steps to ensure the safety of the test subject concerned and of the other test subjects included in the study.

In case of suspicion of adverse effect (with a quite possible relationship with the investigational product), the investigator had to ensure the clinical follow-up of the test subject concerned, as long as necessary.

I.11.4. Communication with the study monitor

According to the corresponding procedure of the coordinating centre, the serious adverse events and the adverse effects had be notified as soon as possible and within 24 hours at the latest, by the coordinating centre to the study monitor, by phone, fax or e-mail.

The investigator had to send an adverse event form to the study monitor and to the coordinating centre.

If justified, the investigator had to give to the coordinating centre and to the study monitor complementary information when available.

I.12. RAW DATA RECORDING AND STUDY REPORT FILING

All the data gathered during the study were recorded accurately, legibly and indelibly by the investigator or the technician in charge of the study, under his control, in the collective case report form.

Each page of this document was initialled by the technician; the whole was verified and validated by the investigator.

The content of this study report took into account the recommendations of the Colipa related to the assessment of the efficacy of cosmetic products (May 2008) and the explanatory note related to the structure and the content of the reports of clinical studies – ICH E3, of 28/11/1995.

At the end of the study, the information concerning the investigational product, the information concerning the test subjects (collective CRF, informed consent forms) were filed and will be kept for 10 years, in the filing area of the investigating centre and the information related to the conduct of the study (protocol signed by the sponsor, copy of this study report….) were filed and will be kept for 10 years, in the filing area of the investigating centre.

At the end of this period, the sponsor will choose among the 3 options:

- return of the study documentation to the sponsor,
- filing of the study documentation in the filing area of the investigating and/or coordinating centre, based on a specific contract,
- destruction of the study documentation (after sponsor's written and signed authorization).

I.13. REFERENCE

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

II – PRACTICAL CONDITIONS OF STUDY PERFORMANCE

II.1. PROTOCOL ADHERENCE

II.1.1. Study population

II.1.1.1. Number of test subjects

Number of test subjects included in the study	**55**	
Withdrawal	**Test subjects concerned**	**Date and reasons**
	Ref. 33c	20/02/2019 - for personal reasons independent from the study
Exclusion	**Test subjects concerned**	**Date and reasons**
	None	Not applicable
Valid cases	**54**	

The number of recruited test subjects took into account the inclusion criteria, the constraints of the study and the period of the study performance.

At the beginning of the study, complementary test subjects (+5) were included to compensate the possible withdrawals or exclusions from the study independent of the investigational product.

II.1.1.2. Inclusion and non inclusion criteria

All the test subjects corresponded to the inclusion and non inclusion criteria.

The individual typological characteristics of the test subjects are reported in **Appendices 1**, and recapitulated below for the whole panel:

Age (years old)	**Included test subjects**	**Valid cases**
Minimum	31	31
Maximum	70	70
Mean	51	52
Median	53	54

Criteria	Included test subjects		Valid cases	
	Nb	%	Nb	%
Phototype				
II	17	31%	17	31%
III	35	64%	34	63%
IV	3	5%	3	6%
Sex				
Female	51	93%	50	93%
Male	4	7%	4	7%

II.1.1.3. Specific information concerning the test subjects

The answers of the test subjects concerning the skin reactivity, the history of atopy, contraception (type) and the current medication are reported in **Appendices 2.**

II.1.1.4. Study constraints imposed on the test subjects

All the constraints of the study, defined in the protocol, were respected by the test subjects who completed the study.

II.1.2 . Investigational product

Experimental conditions of application of the investigational product

All the experimental conditions of application at the investigating centre were respected, as defined in the protocol.

II.1.3. Checking of the skin compatibility: recording of the skin reactions

All the skin examinations and questioning of the test subjects were performed in accordance with the conditions defined in the protocol.

III – RESULTS

III.1. RESULTS / DISCUSSION

III.1.1. Checking of the skin compatibility

For the investigational product, the individual data of the skin examination and questioning of the test subjects are reported in **Appendices 3**.

Induction phase			
Type of reaction	**Description of the reaction on the induction site**	**Number and percentage of reactive test subjects**	**Total number and percentage of reactive test subjects**
E: Erythema	None	0 / 0%	0 / 0%
M: Complementary mention	None	0 / 0%	
A: ICDRG scale	None	0 / 0%	

Challenge			
Type of reaction	**Description of the reactions on the induction site and the virgin site**	**Number and percentage of reactive test subjects**	**Total number and percentage of reactive test subjects**
E: Erythema	None	0 / 0%	0 / 0%
M: Complementary mention	None	0 / 0%	
A: ICDRG scale	None	0 / 0%	

For the control product, the individual data of the skin examination and questioning of the test subjects are reported in **Appendix 4.**

Induction phase			
Type of reaction	**Description of the reaction on the induction site**	**Number and percentage of reactive test subjects**	**Total number and percentage of reactive test subjects**
E: Erythema	None	0 / 0%	0 / 0%
M: Complementary mention	None	0 / 0%	
A: ICDRG scale	None	0 / 0%	

Challenge			
Type of reaction	**Description of the reactions on the induction site and the virgin site**	**Number and percentage of reactive test subjects**	**Total number and percentage of reactive test subjects**
E: Erythema	None	0 / 0%	0 / 0%
M: Complementary mention	None	0 / 0%	
A: ICDRG scale	None	0 / 0%	

III.2. OVERALL CONCLUSION

Under the experimental conditions adopted:

- During the induction period, the repeated applications of the product **Nikis Natural Wipes – Ref. NN01 – Lot. 1**, under semi-occlusive patch, on a panel of 54 test subjects with sensitive of skin on body, induced no reaction of irritation.

- During the challenge phase, the single application of the investigational product to the induction site and virgin site induced no allergic reaction.

Based on these results, the product has a very good skin compatibility and does not show a sensitizing effect.

III.3. QUALITY CONTROL AND QUALITY ASSURANCE

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.

The personnel of the Quality Assurance department controlled that the study documentation was present, dated and signed.

The personnel of the Quality Assurance department regularly controls that the protocol and working procedures relevant to this type of study are duly applied.

APPENDICES

Appendix 1/1

TYPOLOGICAL CHARACTERISTICS OF THE TEST SUBJECTS

Test subjects		age *(years)*	sex *F=female M=male*	phototype[1]
Ref.	**Code** *initials of the surname and of the first name*			
1c	PD	59	F	II
2c	PD	66	F	II
3c	GS	70	M	III
4c	CM	63	F	III
5c	TA	63	F	III
6c	PC	36	F	II
7c	MA	67	F	IV
8c	DM	57	F	III
9c	NM	46	F	III
10c	MI	63	F	III
11c	DP	63	F	III
12c	CP	67	F	II
13c	DA	61	F	II
14c	GI	63	F	III
15c	UC	35	F	III
16c	IC	49	F	III
17c	PI	62	F	II
18c	MG	69	F	III
19c	CL	31	F	III
20c	PA	59	F	III

Legends:

*[1] **phototype: 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 1/2

TYPOLOGICAL CHARACTERISTICS OF THE TEST SUBJECTS

Test subjects		age *(years)*	sex *F=female M=male*	phototype[1]
Ref.	**Code** *initials of the surname and of the first name*			
21c	NR	48	F	II
22c	NL	39	F	III
23c	IL	44	F	III
24c	MM	50	F	II
25c	TM	33	F	III
26c	GV	57	M	IV
27c	TI	53	F	II
28c	NA	50	F	III
29c	RC	66	F	III
30c	CF	61	F	III
31c	PD	54	F	III
32c	CA	66	F	III
33c	OM	37	F	III
34c	DE	57	F	II
35c	CV	67	F	II
36c	NF	60	F	III
37c	PA	42	F	III
38c	AA	32	F	III
39c	VA	37	F	IV
40c	DP	41	F	III

Legends: *Withdrawal*

*[1] **phototype: 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 1/3

TYPOLOGICAL CHARACTERISTICS OF THE TEST SUBJECTS

Test subjects		age *(years)*	sex *F=female M=male*	phototype[1]
Ref.	**Code** *initials of the surname and of the first name*			
41c	UE	35	F	II
42c	ZP	58	F	III
43c	NA	37	F	II
44c	PD	49	F	III
45c	OA	39	F	III
46c	MN	31	M	III
47c	EE	53	F	III
48c	BM	54	F	III
49c	DV	56	M	II
50c	TE	43	F	II
51c	SM	41	F	II
52c	PM	46	F	III
53c	AM	55	F	III
54c	NA	36	F	II
55c	CF	50	F	III

Legends:

*[1] **phototype: 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 2-1/1

SPECIFIC INFORMATION CONCERNING THE TEST SUBJECTS

Test subjects		Sensitive (declarative) / reactive skin on body	Atopy	Current medication except for contraceptive pills	Contraception
Ref.	**Code** *initials of the surname and of the first name*			**If yes** *(specify commercial denomination, active substance and dosage, pathology treated)*	**If Yes** *(Type to be specified)*
1c	PD	x	/	/	NC (MENOPAUSE)
2c	PD	x	/	/	NC (MENOPAUSE)
3c	GS	x	/	/	NC (MALE)
4c	CM	x	/	/	NC (MENOPAUSE)
5c	TA	x	/	/	NC (MENOPAUSE)
6c	PC	x	/	/	CONDOM
7c	MA	x	/	/	NC (MENOPAUSE)
8c	DM	x	/	/	NC (MENOPAUSE)
9c	NM	x	/	/	CONDOM
10c	MI	x	/	/	NC (MENOPAUSE)
11c	DP	x	/	/	NC (MENOPAUSE)
12c	CP	x	/	/	NC (MENOPAUSE)
13c	DA	x	/	/	NC (MENOPAUSE)
14c	GI	x	/	/	NC (MENOPAUSE)
15c	UC	x	/	/	INTRAUTERINE DEVICE
16c	IC	x	/	/	CONDOM
17c	PI	x	/	/	NC (MENOPAUSE)
18c	MG	x	/	/	NC (MENOPAUSE)
19c	CL	x	/	/	CONDOM
20c	PA	x	/	/	NC (MENOPAUSE)

Legends: / = no *NC: Not Concerned*

Appendix 2-1/2

SPECIFIC INFORMATION CONCERNING THE TEST SUBJECTS

Test subjects		Sensitive (declarative) / reactive skin on body	Atopy	Current medication except for contraceptive pills	Contraception
Ref.	**Code** *initials of the surname and of the first name*			**If yes** *(specify commercial denomination, active substance and dosage, pathology treated)*	**If Yes** *(Type to be specified)*
21c	NR	x	/	/	CONDOM
22c	NL	x	/	/	CONDOM
23c	IL	x	/	/	CONDOM
24c	MM	x	/	/	INTRAUTERINE DEVICE
25c	TM	x	/	/	CONDOM
26c	GV	x	/	/	NC (MALE)
27c	TI	x	/	/	NC (MENOPAUSE)
28c	NA	x	/	/	NC (MENOPAUSE)
29c	RC	x	/	/	NC (MENOPAUSE)
30c	CF	x	/	/	NC (MENOPAUSE)
31c	PD	x	/	/	NC (MENOPAUSE)
32c	CA	x	/	/	NC (MENOPAUSE)
33c	OM	x	/	/	CONDOM
34c	DE	x	/	/	NC (MENOPAUSE)
35c	CV	x	/	/	NC (MENOPAUSE)
36c	NF	x	/	/	NC (MENOPAUSE)
37c	PA	x	/	/	PILL
38c	AA	x	/	/	CONDOM
39c	VA	x	/	/	CONDOM
40c	DP	x	/	/	CONDOM

Legends: / = no *Withdrawal* *NC: Not Concerned*

Appendix 2-1/3

SPECIFIC INFORMATION CONCERNING THE TEST SUBJECTS

Test subjects		Sensitive (declarative) / reactive skin on body	Atopy	Current medication except for contraceptive pills	Contraception
Ref.	**Code** *initials of the surname and of the first name*			**If yes** *(specify commercial denomination, active substance and dosage, pathology treated)*	**If Yes** *(Type to be specified)*
41c	UE	x	/	/	CONDOM
42c	ZP	x	/	/	NC (MENOPAUSE)
43c	NA	x	/	/	CONDOM
44c	PD	x	/	/	CONDOM
45c	OA	x	/	/	CONDOM
46c	MN	x	/	/	NC (MALE)
47c	EE	x	/	/	NC (MENOPAUSE)
48c	BM	x	/	/	NC (MENOPAUSE)
49c	DV	x	/	/	NC (MALE)
50c	TE	x	/	/	CONDOM
51c	SM	x	/	/	CONDOM
52c	PM	x	/	/	CONDOM
53c	AM	x	/	/	NC (MENOPAUSE)
54c	NA	x	/	/	CONDOM
55c	CF	x	/	/	NC (MENOPAUSE)

Legends: / = no *NC: Not Concerned*

Appendix 2-2/1

SPECIFIC INFORMATION CONCERNING THE TEST SUBJECTS: ORTHOERGIC SKIN REACTIVITY

Test subjects		Orthoergic skin reactivity		
Ref.	**Code** *initials of the surname and of the first name*	related to internal factors (1)	related to external factors [2]	related to cosmetic products / detergents [3]
		If yes: *specify to what and describe symptoms (4), intensity & frequency*	**If yes**: *specify to what and describe symptoms (4), intensity & frequency*	**If yes**: *specify to what and describe symptoms (4), intensity & frequency*
1c	PD	/	C, W - slight Dr - when exposed	/
2c	PD	Horm, E - slight R - when occurs	/	/
3c	GS	/	W - slight Dr - when exposed	/
4c	CM	E - slight R - when occurs	/	/
5c	TA	Horm - slight R - when occurs	C - slight R - when exposed	/
6c	PC	E - slight R - when occurs	/	/
7c	MA	E - slight R - when occurs	/	/
8c	DM	Horm - slight R - when occurs	/	/
9c	NM	/	HW - slight Pr - when exposed	/
10c	MI	/	S - slight Pr - when exposed	/
11c	DP	/	CIW - slight Dr - when exposed	/
12c	CP	/	C - slight Pr - when exposed	/
13c	DA	E - slight R - when occurs	/	/
14c	GI	/	W - slight R - when exposed	/
15c	UC	/	W, Hw - slight DR - when exposed	/
16c	IC	/	C - slight Dr - when exposed	/
17c	PI	E - slight R - when occurs	/	/
18c	MG	E - slight R - when occurs	/	/
19c	CL	/	C - slight R - when exposed	/
20c	PA	E - slight R - when occurs	/	/

Legends: / = no

[1] internal triggering factors: stress (Str), emotions (E), fatigue (Fa), hormonal variations (Horm), spicy food (SF), alcoholic beverages (Al), very hot food (VHF), very hot drinks (VHD)
[2] external triggering factors: cold (C), wind (W), heat (Heat), sun (S), sudden changes in temperatures (Temp), dry air (DA), air conditioning (AC), pollution (Po), repeated frictions (Fr), hard water (HW), chlorinated water (ClW), dust (DU)
[3] products: detergents (D), soaps (Sa), cosmetic (Co)
[4] Heating (H), Burning (Bu), Stinging (St), Itching / Pruritus (Pr), Pulling (Pu), Pain (P), Redness/Flush (R), Dryness (Dr)/ Skin roughness/Desquamation/Pityriasis alba, Pimples (Pi)

Appendix 2-2/2

SPECIFIC INFORMATION CONCERNING THE TEST SUBJECTS: ORTHOERGIC SKIN REACTIVITY

Test subjects		Orthoergic skin reactivity		
Ref.	**Code** *initials of the surname and of the first name*	related to internal factors (1)	related to external factors [2]	related to cosmetic products / detergents [3]
		If yes: *specify to what and describe symptoms (4), intensity & frequency*	**If yes**: *specify to what and describe symptoms (4), intensity & frequency*	**If yes**: *specify to what and describe symptoms (4), intensity & frequency*
21c	NR	/	Heat - slight R - when exposed	/
22c	NL	E - slight R - when occurs	/	/
23c	IL	/	CIW - slight Dr - when exposed	/
24c	MM	/	S - slight R - when exposed	/
25c	TM	E - slight R - when occurs	W - slight R - when exposed	/
26c	GV	E - slight R - when occurs	/	/
27c	TI	/	S - slight R - when exposed	/
28c	NA	/	C, S - slight Dr - when exposed	/
29c	RC	/	Temp - slight R - when exposed	/
30c	CF	/	S - slight Bu - when exposed	/
31c	PD	E - slight R - when occurs	C - slight Dr - when exposed	/
32c	CA	E - slight R - when occurs	/	/
33c	OM	E - slight R - when occurs	/	/
34c	DE	E - slight R - when occurs	/	/
35c	CV	E - slight R - when occurs	C - slight R - when exposed	/
36c	NF	E - slight R - when occurs	C, W - slight R - when exposed	/
37c	PA	E - slight R - when occurs	/	/
38c	AA	E - slight R - when occurs	C - slight Dr - when exposed	/
39c	VA	/	C - slight R - when exposed	/
40c	DP	/	C - slight Pr - when exposed	/

Legends: / = no *Withdrawal*

[1] internal triggering factors: stress (Str), emotions (E), fatigue (Fa), hormonal variations (Horm), spicy food (SF), alcoholic beverages (Al), very hot food (VHF), very hot drinks (VHD)
[2] external triggering factors: cold (C), wind (W), heat (Heat), sun (S), sudden changes in temperatures (Temp), dry air (DA), air conditioning (AC), pollution (Po), repeated frictions (Fr), hard water (HW), chlorinated water (ClW), dust (DU)
[3] products: detergents (D), soaps (Sa), cosmetic (Co)
[4] Heating (H), Burning (Bu), Stinging (St), Itching / Pruritus (Pr), Pulling (Pu), Pain (P), Redness/Flush (R), Dryness (Dr)/ Skin roughness/Desquamation/Pityriasis alba, Pimples (Pi)

Appendix 2-2/3

SPECIFIC INFORMATION CONCERNING THE TEST SUBJECTS: ORTHOERGIC SKIN REACTIVITY

Test subjects		Orthoergic skin reactivity		
Ref.	**Code** *initials of the surname and of the first name*	related to internal factors (1)	related to external factors [2]	related to cosmetic products / detergents [3]
		If yes: *specify to what and describe symptoms (4), intensity & frequency*	**If yes**: *specify to what and describe symptoms (4), intensity & frequency*	**If yes**: *specify to what and describe symptoms (4), intensity & frequency*
41c	UE	/	C - slight R - when exposed	/
42c	ZP	E - slight R - when occurs	/	/
43c	NA	E - slight R - when occurs	C - slight Dr - when exposed	/
44c	PD	/	S - slight R - when exposed	/
45c	OA	/	C - slight Dr - when exposed	/
46c	MN	/	DU - slight R - when exposed	/
47c	EE	/	HW - slight Dr - when exposed	/
48c	BM	/	Temp - slight R - when exposed	/
49c	DV	/	DU - slight R - when exposed	/
50c	TE	/	W - slight R - when exposed	/
51c	SM	Str - slight R - when occurs	/	/
52c	PM	/	Po - slight Dr - when exposed	/
53c	AM	E - slight R - when occurs	/	/
54c	NA	E - slight R - when occurs	/	/
55c	CF	Horm - slight R - when occurs	/	/

Legends: / = no

[1] internal triggering factors: stress (Str), emotions (E), fatigue (Fa), hormonal variations (Horm), spicy food (SF), alcoholic beverages (Al), very hot food (VHF), very hot drinks (VHD)
[2] external triggering factors: cold (C), wind (W), heat (Heat), sun (S), sudden changes in temperatures (Temp), dry air (DA), air conditioning (AC), pollution (Po), repeated frictions (Fr), hard water (HW), chlorinated water (ClW), dust (DU)
[3] products: detergents (D), soaps (Sa), cosmetic (Co)
[4] Heating (H), Burning (Bu), Stinging (St), Itching / Pruritus (Pr), Pulling (Pu), Pain (P), Redness/Flush (R), Dryness (Dr)/ Skin roughness/Desquamation/Pityriasis alba, Pimples (Pi)

Appendix 3-1/1

INVESTIGATIONAL PRODUCT: Nikis Natural Wipes – Ref. NN01
SKIN EXAMINATION AND QUESTIONING DURING THE INDUCTION PHASE

***E: Erythema**: **0** = no visible erythema, **0.5** = very slight erythema – barely perceptible, **1** = mild erythema – faint pink, **2** = moderate erythema – well defined, **3** = severe erythema, **4** = caustic effect – erosive aspect and/or necrotic aspect*
d= diffuse / p = punctuated / peri = peripheral

***M: Additional comments/Others reactions: Oe** = Homogeneous infiltration / oedema, **P** = Papules, **V** = Vesicles, **B** = Bullae, **Pe** = Petechiae, **S:** Spreading beyond the patch, **SV** = Soap effect (shiny skin with possibly wrinkles), **F** = Fissuring , **D** = Desquamation, **Dr** = Dryness, **C** = Skin coloration, hyperpigmentation, **HY** = Hypopigmentation, **Fr** = Follicular reaction, **NA** = Product not applied, **T**= Tape reaction, **I** = Itching at the test site, **Cr** = Exsudation and/or Surface encrustation, **Sc** = Scab, **Pr** = Pruritus, **He** = Heating, **Pu** = Pustules, * = Additional free comments, **N9G** = No 9th grade, **X** = Succeeding patch not applied and succeeding grade (in brackets) denotes a residual reaction, **Abs** = Subject absent*
/: no reaction

***A: ICDRG scale**: **IR** = Irritation reaction, **-** = No allergic reaction, **?+ =** Doubtful reaction (only slight erythema), **(+) =** Weak positive reaction (without vesicle): slight erythema and infiltration with presence of small papular elevations, possibly papules, **(++) =** Strong positive reaction: erythema, papules, vesicles, infiltration, **(+++) =** Extreme positive reaction: intense erythema, oedema, coalescent vesicles (bullae)*

Test subjects reference	Type of reaction	Experimental times									
		D1	D3	D5	D8	D10	D12	D15	D17	D19	D22
1c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
2c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
3c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
4c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
5c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
6c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
7c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
8c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
9c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
10c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
11c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
12c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
13c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									

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INVESTIGATIONAL PRODUCT: Nikis Natural Wipes – Ref. NN01
SKIN EXAMINATION AND QUESTIONING DURING THE INDUCTION PHASE

Test subjects reference	Type of reaction	Experimental times									
		D1	D3	D5	D8	D10	D12	D15	D17	D19	D22
14c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
15c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
16c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
17c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
18c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
19c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
20c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
21c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
22c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
23c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
24c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
25c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
26c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
27c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
28c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
29c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
30c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									

Appendix 3-1/3

INVESTIGATIONAL PRODUCT: Nikis Natural Wipes – Ref. NN01
SKIN EXAMINATION AND QUESTIONING DURING THE INDUCTION PHASE

Test subjects reference	Type of reaction	Experimental times									
		D1	D3	D5	D8	D10	D12	D15	D17	D19	D22
31c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
32c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
33c	E	0									
	M	/									
	A	-									
34c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
35c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
36c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
37c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
38c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
39c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
40c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
41c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
42c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
43c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
44c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
45c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
46c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
47c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									

Legends: *Withdrawal*

Appendix 3-1/4

INVESTIGATIONAL PRODUCT: Nikis Natural Wipes – Ref. NN01
SKIN EXAMINATION AND QUESTIONING DURING THE INDUCTION PHASE

Test subjects reference	Type of reaction	Experimental times									
		D1	D3	D5	D8	D10	D12	D15	D17	D19	D22
48c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
49c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
50c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
51c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
52c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
53c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
54c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
55c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									

Appendix 3-2/1

INVESTIGATIONAL PRODUCT: Nikis Natural Wipes – Ref. NN01
SKIN EXAMINATION AND QUESTIONING DURING THE CHALLENGE PHASE

***E: Erythema**: **0** = no visible erythema, **0.5** = very slight erythema – barely perceptible, **1** = mild erythema – faint pink, **2** = moderate erythema – well defined, **3** = severe erythema, **4** = caustic effect – erosive aspect and/or necrotic aspect*
d= diffuse / p = punctuated / peri = peripheral

M: Additional comments/Others reactions: Oe** = Homogeneous infiltration / oedema, **P** = Papules, **V** = Vesicles, **B** = Bullae, **Pe** = Petechiae, **S:** Spreading beyond the patch, **SV** = Soap effect (shiny skin with possibly wrinkles), **F** = Fissuring , **D** = Desquamation, **Dr** = Dryness, **C** = Skin coloration, hyperpigmentation, **HY** = Hypopigmentation, **Fr** = Follicular reaction, **NA** = Product not applied, **T**= Tape reaction, **I** = Itching at the test site, **Cr** = Exsudation and/or Surface encrustation, **Sc** = Scab, **Pr** = Pruritus, **He** = Heating, **Pu** = Pustules, ** = Additional free comments, **N9G** = No 9th grade, **X** = Succeeding patch not applied and succeeding grade (in brackets) denotes a residual reaction, **Abs** = Subject absent*
/: no reaction

***A: ICDRG scale**: **IR** = Irritation reaction, **-** = No allergic reaction, **?+ =** Doubtful reaction (only slight erythema), **(+) =** Weak positive reaction (without vesicle): slight erythema and infiltration with presence of small papular elevations, possibly papules, **(++) =** Strong positive reaction: erythema, papules, vesicles, infiltration, **(+++) =** Extreme positive reaction: intense erythema, oedema, coalescent vesicles (bullae)*

Test subjects reference	Type of reaction	Experimental times					
		Induction site			Virgin site		
		D36	D38	D40	D36	D38	D40
1c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
2c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
3c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
4c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
5c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
6c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
7c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
8c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
9c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
10c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
11c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
12c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
13c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					

Appendix 3-2/2

INVESTIGATIONAL PRODUCT: Nikis Natural Wipes – Ref. NN01
SKIN EXAMINATION AND QUESTIONING DURING THE CHALLENGE PHASE

Test subjects reference	Type of reaction	Experimental times					
		Induction site			Virgin site		
		D36	D38	D40	D36	D38	D40
14c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
15c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
16c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
17c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
18c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
19c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
20c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
21c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
22c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
23c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
24c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
25c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
26c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
27c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
28c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
29c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					

Appendix 3-2/3

INVESTIGATIONAL PRODUCT: Nikis Natural Wipes – Ref. NN01
SKIN EXAMINATION AND QUESTIONING DURING THE CHALLENGE PHASE

Test subjects reference	Type of reaction	Experimental times					
		Induction site			Virgin site		
		D36	D38	D40	D36	D38	D40
30c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
31c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
32c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
33c	E						
	M						
	A						
34c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
35c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
36c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
37c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
38c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
39c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
40c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
41c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
42c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
43c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
44c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
45c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					

Legends: *Withdrawal*

Appendix 3-2/4

INVESTIGATIONAL PRODUCT: Nikis Natural Wipes – Ref. NN01
SKIN EXAMINATION AND QUESTIONING DURING THE CHALLENGE PHASE

Test subjects reference	Type of reaction	Experimental times					
		Induction site			Virgin site		
		D36	D38	D40	D36	D38	D40
46c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
47c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
48c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
49c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
50c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
51c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
52c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
53c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
54c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
55c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					

Appendix 4-1/1

CONTROL PRODUCT: DISTILLED WATER
SKIN EXAMINATION AND QUESTIONING DURING THE INDUCTION PHASE

***E: Erythema**: **0** = no visible erythema, **0.5** = very slight erythema – barely perceptible, **1** = mild erythema – faint pink, **2** = moderate erythema – well defined, **3** = severe erythema, **4** = caustic effect – erosive aspect and/or necrotic aspect*
d= diffuse / p = punctuated / peri = peripheral

***M: Additional comments/Others reactions: Oe** = Homogeneous infiltration / oedema, **P** = Papules, **V** = Vesicles, **B** = Bullae, **Pe** = Petechiae, **S:** Spreading beyond the patch, **SV** = Soap effect (shiny skin with possibly wrinkles), **F** = Fissuring , **D** = Desquamation, **Dr** = Dryness, **C** = Skin coloration, hyperpigmentation, **HY** = Hypopigmentation, **Fr** = Follicular reaction, **NA** = Product not applied, **T**= Tape reaction, **I** = Itching at the test site, **Cr** = Exsudation and/or Surface encrustation, **Sc** = Scab, **Pr** = Pruritus, **He** = Heating, **Pu** = Pustules, * = Additional free comments, **N9G** = No 9th grade, **X** = Succeeding patch not applied and succeeding grade (in brackets) denotes a residual reaction, **Abs** = Subject absent*
/: no reaction

***A: ICDRG scale**: **IR** = Irritation reaction, **-** = No allergic reaction, **?+ =** Doubtful reaction (only slight erythema), **(+) =** Weak positive reaction (without vesicle): slight erythema and infiltration with presence of small papular elevations, possibly papules, **(++) =** Strong positive reaction: erythema, papules, vesicles, infiltration, **(+++) =** Extreme positive reaction: intense erythema, oedema, coalescent vesicles (bullae)*

Test subjects reference	Type of reaction	Experimental times									
		D1	D3	D5	D8	D10	D12	D15	D17	D19	D22
1c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
2c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
3c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
4c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
5c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
6c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
7c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
8c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
9c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
10c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
11c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
12c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
13c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									

Appendix 4-1/2

CONTROL PRODUCT: DISTILLED WATER
SKIN EXAMINATION AND QUESTIONING DURING THE INDUCTION PHASE

Test subjects reference	Type of reaction	Experimental times									
		D1	D3	D5	D8	D10	D12	D15	D17	D19	D22
14c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
15c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
16c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
17c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
18c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
19c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
20c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
21c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
22c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
23c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
24c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
25c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
26c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
27c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
28c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
29c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
30c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									

Appendix 4-1/3

CONTROL PRODUCT: DISTILLED WATER
SKIN EXAMINATION AND QUESTIONING DURING THE INDUCTION PHASE

Test subjects reference	Type of reaction	Experimental times									
		D1	D3	D5	D8	D10	D12	D15	D17	D19	D22
31c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
32c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
33c	E	0									
	M	/									
	A	-									
34c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
35c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
36c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
37c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
38c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
39c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
40c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
41c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
42c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
43c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
44c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
45c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
46c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
47c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									

Legends: *Withdrawal*

Appendix 4-1/4

CONTROL PRODUCT: DISTILLED WATER
SKIN EXAMINATION AND QUESTIONING DURING THE INDUCTION PHASE

Test subjects reference	Type of reaction	Experimental times									
		D1	D3	D5	D8	D10	D12	D15	D17	D19	D22
48c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
49c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
50c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
51c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
52c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
53c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
54c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									
55c	E	0	0	0	0	0	0	0	0	0	0
	M	/	/	/	/	/	/	/	/	/	/
	A	-									

Appendix 4-2/1

CONTROL PRODUCT: DISTILLED WATER
SKIN EXAMINATION AND QUESTIONING DURING THE CHALLENGE PHASE

***E: Erythema**: **0** = no visible erythema, **0.5** = very slight erythema – barely perceptible, **1** = mild erythema – faint pink, **2** = moderate erythema – well defined, **3** = severe erythema, **4** = caustic effect – erosive aspect and/or necrotic aspect*
d= diffuse / p = punctuated / peri = peripheral

M: Additional comments/Others reactions: Oe** = Homogeneous infiltration / oedema, **P** = Papules, **V** = Vesicles, **B** = Bullae, **Pe** = Petechiae, **S:** Spreading beyond the patch, **SV** = Soap effect (shiny skin with possibly wrinkles), **F** = Fissuring , **D** = Desquamation, **Dr** = Dryness, **C** = Skin coloration, hyperpigmentation, **HY** = Hypopigmentation, **Fr** = Follicular reaction, **NA** = Product not applied, **T**= Tape reaction, **I** = Itching at the test site, **Cr** = Exsudation and/or Surface encrustation, **Sc** = Scab, **Pr** = Pruritus, **He** = Heating, **Pu** = Pustules, ** = Additional free comments, **N9G** = No 9th grade, **X** = Succeeding patch not applied and succeeding grade (in brackets) denotes a residual reaction, **Abs** = Subject absent*
/: no reaction

***A: ICDRG scale**: **IR** = Irritation reaction, **-** = No allergic reaction, **?+ =** Doubtful reaction (only slight erythema), **(+) =** Weak positive reaction (without vesicle): slight erythema and infiltration with presence of small papular elevations, possibly papules, **(++) =** Strong positive reaction: erythema, papules, vesicles, infiltration, **(+++) =** Extreme positive reaction: intense erythema, oedema, coalescent vesicles (bullae)*

Test subjects reference	Type of reaction	Experimental times					
		Induction site			Virgin site		
		D36	D38	D40	D36	D38	D40
1c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
2c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
3c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
4c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
5c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
6c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
7c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
8c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
9c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
10c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
11c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
12c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
13c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					

Appendix 4-2/2

CONTROL PRODUCT: DISTILLED WATER
SKIN EXAMINATION AND QUESTIONING DURING THE CHALLENGE PHASE

Test subjects reference	Type of reaction	Experimental times					
		Induction site			Virgin site		
		D36	D38	D40	D36	D38	D40
14c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
15c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
16c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
17c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
18c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
19c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
20c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
21c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
22c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
23c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
24c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
25c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
26c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
27c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
28c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
29c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					

Appendix 4-2/3

CONTROL PRODUCT: DISTILLED WATER
SKIN EXAMINATION AND QUESTIONING DURING THE CHALLENGE PHASE

Test subjects reference	Type of reaction	Experimental times					
		Induction site			Virgin site		
		D36	D38	D40	D36	D38	D40
30c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
31c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
32c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
33c	E						
	M						
	A						
34c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
35c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
36c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
37c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
38c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
39c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
40c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
41c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
42c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
43c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
44c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
45c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					

Legends: *Withdrawal*

Appendix 4-2/4

CONTROL PRODUCT: DISTILLED WATER
SKIN EXAMINATION AND QUESTIONING DURING THE CHALLENGE PHASE

Test subjects reference	Type of reaction	Experimental times					
		Induction site			Virgin site		
		D36	D38	D40	D36	D38	D40
46c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
47c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
48c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
49c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
50c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
51c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
52c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
53c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
54c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					
55c	E	0	0	0	0	0	0
	M	/	/	/	/	/	/
	A	-					