OPEN LABEL, UNCONTROLLED CLINICAL INVESTIGATION ON THE SAFETY AND CLINICAL PERFORMANCE OF PAPIX ACNE SCAR IN THE PREVENTION AND IMPROVEMENT OF SCARS AND LESIONS ASSOCIATED WITH ACNE

Clinical Investigation Plan (CIP) code: ReGl/19/PAS-Acn/001

Version 2.0, 02/07/2020

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Investigator's Approval Page

I understand that all information concerning the product Papix Acne Scar supplied by Relife Srl and/or the CRO in connection with this study protocol are confidential information. This information include: CIP, Case Report Form, product documents.

I understand that any change in this study protocol must be approved in writing by Relife Srl the Co-ordinating Investigator and the Ethics Committee before implementation, except where necessary to eliminate apparent immediate hazard to patients.

I confirm that I will conduct the study according to this protocol (except when mutually agreed to in writing with Relife Srl or its delegate Latis Srl, the Good Clinical Practice (GCP), the UNI EN ISO 14155, the Declaration of Helsinki current edition and laws and regulations in the Country where the study is to be conducted.

I confirm that I will record and report all adverse events occurring during the study, according to this protocol.

I confirm that I am informed about the need of data records retention, according to current regulations and that no data can be destroyed without the written consent of Relife Srl.

I confirm that I will transfer adequate ownership of my responsibilities for the clinical investigation and will inform the Sponsor, in case I retire from my PI role.

I confirm that in case the Trial Center File is stolen or anyhow damaged, I will promptly inform the Sponsor and declare it to the Competent Authorities.

Principal Investigator: …….

Signature & Date: _____

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Principal Investigator: …….

Signature & Date: _____

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1. SYNOPSIS OF THE CLINICAL INVESTIGATION PLAN

CIP Title	OPEN LABEL, UNCONTROLLED CLINICAL INVESTIGATION ON THE SAFETY AND CLINICAL PERFORMANCE OF PAPIX ACNE SCAR IN THE PREVENTION AND IMPROVEMENT OF SCARS AND LESIONS ASSOCIATED WITH ACNE
CIP Code	ReGl/19/PAS-Acn/001
Sponsor	Relife Srl
Countries and Sites	Two recruiting clinical sites will be involved in Italy: 1. Clinica Dermatologica, IRCCS AOU San Martino – IST, Genova 2. UOC Dermatologia e Centro Angiomi, Istituto G. Gaslini, Genova
Indication	Prevention and improvement of lesions and scars associated with acne.
Study Design	Multicenter, open label, uncontrolled, single arm, post-market clinical follow-up study.
Objectives	*Primary objective* To evaluate and confirm the performance of PAPIX ACNE SCAR in the prevention and improvement of scars in subject suffering for mild to moderate acne, after 4 weeks of treatment. *Secondary objectives* - To evaluate the performance of PAPIX ACNE SCAR in the prevention and improvement of scars after 2 and 8 weeks of treatment. - To evaluate the performance of PAPIX ACNE SCAR in the prevention of lesions after 2, 4 and 8 weeks of treatment. - To evaluate acne severity after 2, 4 and 8 weeks of treatment, through the Investigator Global Assessment. - To evaluate the improvement of the skin roughness after 2, 4 and 8 weeks of treatment. - To evaluate the change in skin texture after 2, 4 and 8 weeks of treatment. - To evaluate the subject's adherence to treatment by the product accountability. - To evaluate the subject's and Investigator's global evaluation of satisfaction with regards to the performance of PAPIX ACNE SCAR. - To evaluate the subject's overall acceptability of the treatment. *Safety objectives* To evaluate the local and general tolerability of PAPIX ACNE SCAR.
Study Treatment	PAPIX ACNE SCAR is a CE marked, Class IIa medical device. It contains silicones, humectant, emollient and film-forming protective ingredients. PAPIX ACNE SCAR is indicated in the symptomatic treatment of acneic

	skin while reducing the appearance of acne scars. It is a multi-action treatment, which treats acneic skin, improves acne scar appearance and lighten dark spots, prevents the development of new acne lesions and scars. Within this clinical investigation PAPIX ACNE SCAR will be applied for 8weeks, twice daily, on the affected area. PAPIX ACNE SCAR will be used according to its Instructions For Use.
Study Duration	For each subject the investigation will be of 8 weeks (56 days ±3). The recruitment phase will be of 2 months The overall project duration (from First Subject-In to Last Subject-Out) will be of 4 months
Number of Patients	40 planned.
Target Study Population	Outpatients, ≥12 years, of both sexes, affected by mild to moderate acne.
Selection Criteria	*Inclusion Criteria:* 1. Subject's or parents or guardian (depending on the age of the subject) written informed consent obtained prior to any study-related procedures; 2. Male or female subjects aged ≥ 12 years of any race; 3. Subjects with any Fitzpatrick skin phototype; 4. Subjects with clinical diagnosis of mild to moderate acne vulgaris (IGA score 2 or 3) on the face; 5. Presence of acne scars (all types included), of grade mild or moderate according to SGA; 6. Subjects with cooperative attitude, able to comprehend the full nature and the purpose of the investigation, including possible risks and side effects, and able to comply with the requirements of the entire investigation (including ability to attend the planned visits according to the time limits), based on Investigator's judgement. *Exclusion Criteria:* 1. Pregnant women 2. Severe acne at inclusion or any acne requiring systemic treatment; 3. Presence of facial warts or fungal infections; 4. Active dermatitis on the face, rosacea, active herpes simplex; 5. Keloids presence in the area to be treated or keloids development during the treatment period; 6. History of radiation or skin tumors in the/close to the area to be treated in the past 5 years; 7. Laser ablative procedures within the last month;

	8. Chemical peels within the last 6 months; 9. Use of topical treatments like antibiotics, corticosteroids, benzoyl peroxide, azelaic acid, hydroxy acids and other antinflammatory drugs within 2 weeks; 10. Use of topical retinoids within 4 weeks; 11. Use of systemic corticosteroids or antibiotics in the previous 30 days; 12. Use of systemic spironolactone/drospirenone or immunomodulators in the previous 3 months; 13. Use of oral retinoids or cyproterone acetate/chlormadinone acetate in the previous 6 months; 14. Use of scrub, alpha hydroxy acid (AHA), skin irritant products in the 2 days before study treatment start; 15. Subjects with any other clinically significant or unstable concurrent disease or skin condition or general condition that, in the Investigator's opinion, might interfere with the study evaluations; 16. Allergy, sensitivity or intolerance to the components of the investigational device formulations ingredients; 17. Concomitant or previous participation in other interventional clinical study in the past 3 months; 18. Subjects planning sun exposure or tanning booths or UV sources throughout the course of the study. In case of sun exposure this shall be limited and a protection cream (SPF 50+) shall be applied.
Concomitant Treatments	*Non-permitted treatments*: - topical treatments like antibiotics, corticosteroids, benzoyl peroxide, azelaic acid, hydroxy acids, retinoids and other antinflammatory drugs; - chemical peels; - systemic antibiotics, corticosteroids, spironolactone/drospirenone or immunomodulators, oral retinoids or cyproterone acetate/chlormadinone acetate; - scrub, alpha hydroxy acid (AHA), skin irritant products; - laser ablative procedures; - radiotherapies; - sun exposure (unless limited and with protection cream SPF 50+) or tanning booths or UV sources. The subject will be recommended not to use any other cleanser for the face than Papix cleanser, that will be provided by the Investigator.
Primary study endpoint	Proportion of subjects with improved acne scars and marks at week 4 of treatment (Visit 3) and, at the same time, without any new facial acne

	scars with respect to baseline (Visit 1).
Secondary study endpoints	*Performance endpoints* - Proportion of subjects with improved acne scars and marks at week 2 and 8 of treatment (Visits 2 and 4) and, at the same time, without any new facial acne scars with respect to baseline (Visit 1). - Proportion of subjects at week 2, 4 and 8 of treatment, without any new facial acne lesions with respect to baseline (Visit 1). - Change from baseline (Visit 1) to each following time point in the acne severity, according to the Investigator Global Assessment. - Change from baseline (Visit 1) to each following time point in the skin roughness, on a 4-point scale from 0 (none; very smooth) to 3 (severe; very rough). - Change from baseline (Visit 1) to each following time point in the skin texture on a 6-point scale from 0 (worse) to 5 (complete improvement). - The subject's adherence to treatment by the product accountability; - The subject's and Investigator's global evaluation of satisfaction with regards to the performance of PAPIX ACNE SCAR, through a specific questionnaire. - To evaluate the subject's overall acceptability of the treatment, through a specific questionnaire. *Safety endpoints* 1. Number and type of adverse events (AEs) occurring during the study (seriousness, severity, and relation to study treatment) 2. Local tolerability at the site of application.
Sample size determination	An exact binomial test with a nominal 5% two-sided significance level will have 80% power to detect the difference between the Null hypothesis proportion, π_0 of 0.5 (i.e., 50% of patients with treatment success) and the Alternative proportion, π_1, of 0.75 (i.e., 75% of patients with treatment success) when the sample size is 30 subjects. Assuming a possible 25% dropout rate, 40 subjects will be enrolled.
Statistical Analysis – Primary performance endpoint	The primary objective of this clinical investigation is to evaluate and confirm the performance of PAPIX ACNE SCAR in terms of improvement of visible acne scars and marks from baseline, assessed using the qualitative Scar Global Assessment (SGA) by Goodman and Baron (2006) and the prevention of new acne scars, by count, in subject suffering for mild to moderate acne, after 4 weeks of treatment. The primary endpoint will be proportion of subjects with improved acne scars and marks with respect to baseline and, at the same time, without any new facial acne scars after 4 weeks of treatment (treatment

	success). The primary endpoint will be described using number (N) and the proportion of patients (%). The proportion of treatment successes will be compared to a referent proportion (50%, Null hypothesis proportion) using the exact binomial test.
Statistical Analysis – Secondary performance endpoints	The proportion of subjects with improved acne scars and marks with respect to baseline, assessed using the qualitative Scar Global Assessment (SGA) by Goodman and Baron (2006) and, at the same time, without any new facial acne scars after 2 and 8 weeks of treatment (treatment success) will be described using number (N) and the proportion of patients (%). The proportion of subjects without any new facial acne lesions after 2, 4 and 8 weeks of treatment (treatment success) will be described using number (N) and the proportion of patients (%). Acne severity after 2, 4 and 8 weeks of treatment will be assessed through the IGA. Changes from baseline will be compared using Wilcoxon signed rank-sum test. The improvement of skin roughness will be assessed on a 4-point scale from 0 (none; very smooth) to 3 (severe; very rough). Changes from baseline will be compared using Wilcoxon signed rank-sum test. Skin texture change will be assessed on a 6-point scale from 0 (worse) to 5 (complete improvement), after 4 and 8 weeks of treatment and it will be summarized through the number (N) and the proportion of patients (%) for each item. The number of applications will be self-reported by the subject and the product accountability will be summarized to assess adherence to treatment. Subject's and Investigator's global evaluation on performance of the study product obtained at the end of the study (Visit 4) by means of a 7-items scale will be summarized through number (N) and proportion of patients (%) for each item. Subject's evaluation of overall acceptability with treatment, obtained by means of a 5-item scale will be summarized through number (N) and the proportion of patients (%) for each item.
Statistical Analysis – Safety endpoints	AEs and ADEs will be tabulated by System Organ Class (SOC) and Preferred Term (PT) after medical coding using the Medical Dictionary for Regulatory Activities (MedDRA). An overview of AEs and ADEs will be prepared showing the number of AEs and ADEs and the number of patients with any AEs or ADEs, serious AEs or ADEs, severity of AEs or ADEs and AEs or ADEs leading to withdrawal. Summary tables showing the number of patients with at least one AE or ADE and event counts by SOC and PT (Preferred Term) will be prepared. Local tolerability at the site of administration will be summarized.

Population	The following populations are defined for this investigation: •Safety analysis set (SAF): all patients enrolled who sign informed consent and receive at least one administration of the investigational device. •Full analysis set (FAS): all patients of the SAF who have performed the baseline assessments and have at least one post-baseline assessment of any performance endpoint. •Per-Protocol analysis set (PPAS): all patients of the FAS who meet all inclusion/exclusion criteria and who do not have any major protocol deviation. The analysis of safety endpoints will be performed in the Safety population (SAF). Analysis of performance endpoints will be performed on the FAS population. The analysis of primary endpoint will be repeated in the PPAS.

Table 1: *Study Flow-Chart*

	Visit 1	Visit 2	Visit 3	Visit 4*
	Week 0	Week 2	Week 4	Week 8
	Day 1	Day 14 ± 3	Day 28 ± 3	Day 56 ± 3
	Screening Baseline Treatment start	Follow-up visit	Follow-up visit	End of treatment End of study
Written informed consent	✓			
Demographic data	✓			
Medical and surgical history	✓			
Physical examination (only dermatologic)	✓			✓
Inclusion and exclusion criteria	✓			
Acne scars and lesions count	✓	✓	✓	✓
Scars Global Assessment (SGA)	✓	✓	✓	✓
Acne Investigator Global Assessment (IGA)	✓	✓	✓	✓
Face photos	✓	✓	✓	✓
Skin evaluation (roughness, texture)	✓	✓	✓	✓
Study product dispensed	✓		✓	
Study product administration	→ (twice daily)			
Study product returned			✓	✓
Global evaluation of performance[1]				✓
Global evaluation of product acceptability[2]				✓
Treatment compliance		✓	✓	✓
Concomitant medications/treatments	✓	✓	✓	✓
Local and general adverse events		✓	✓	✓

*Or Early termination Visit
[1]To be evaluated by both the subject and the Investigator
[2]To be evaluated by the subject

2. Identification and Description of the Investigational Device

PAPIX ACNE SCAR is a silicone gel for acne lesions and scars. It is indicated to treat oily, blemished or acneic skin.

With regular use, PAPIX ACNE SCAR helps to improve acne skin and visibly improves the appearance of acne scars, while moisturising the skin. Thanks to its formulation, the medical device helps:

• improving acneic skin within 30 days;

• improving visible acne scars & marks;

• preventing the development of new acne lesions and scars.

PAPIX ACNE SCAR is a CE marked medical device class IIa, manufactured by Relife Srl, that is the Sponsor of this post-market clinical follow-up investigation.

The mechanism of action of the product is based on the creation of a sheer physical barrier which separates the skin from surrounding environment and creates favorable conditions for the maintenance and/or recovery of the physiological skin barrier in case of acne lesion. It improves skin by keeping it hydrated and works to prevent and reduce acne scars, also thanks to the presence of humectant/moisturizing ingredients.

Also, PAPIX ACNE SCAR plays an important role in the control of the optimal skin pH (4.6-5.6), which alteration is proposed to be one of the important factors for acne development.

In this clinical investigation PAPIX ACNE SCAR will be used for the symptomatic treatment of acneic skin, in the full respect of its Instructions for Use (IFU).

3. Justification for the Design of the Clinical Investigation

Acne vulgaris is a common and widespread dermatological disorder that predominantly affects teenagers but can also affect preadolescents and post-teen individuals. The Global Burden of Disease Project estimated that acne affects 9.4% of the global population, making it the eighth most prevalent disease worldwide [1].

Facial scarring is frequent skin disorder in patients with acne, especially if acne is not treated early and effectively [2]. Acne scars impose a considerable burden for patients, with a negative impact on their social life, by generating psychological pain, low self-esteem, and reduced quality of life [3].

In general, the prevalence of scars increases with acne severity, in the presence of large lesions and severe inflammation, but also patients with mild acne are at risk of scarring [2].

Patients who have already developed scarring and still have active disease are at high risk for additional scarring. Moreover, the incidence of scarring may be increased above the background injury with manipulation or “picking” by the patient; these scars may be aesthetically unappealing, and if hypertrophic, they may be painful as well.

Scarring can occur as a result of damage to the skin during the healing of active acne, as scar formation is the normal and natural response of tissue to wound healing following an injury. The majority of people affected by acne scars have “atrophic scars” that are associated with a loss of collagen; a minority show “hypertrophic scars” and “keloids” [4], that are indeed characterized by more abundant collagen stretched and aligned in the same plane as the epidermis [5].

Early treatment of active acne remains the best way to prevent or limit acne-related scarring. It is also imperative to ensure active acne has been treated before approaching scar treatment so as not to create a cycle where active lesions continue to scar in areas already addressed [6]. The choice of agents used to treat acne involves the integration of multiple factors such as the severity of lesions present, duration of disease, past and present response to therapy, and tendency for scarring and post-inflammatory pigmentation. Therapy is therefore tailored to the individual patient depending on the nature and severity of their acne.

Oral antibiotics (e.g. tetracycline, minocycline, doxycycline, lymecycline) are highly effective for inflammatory acne and are widely used in clinical practice. Oral retinoids (retinol) are usually given in cases of severe acne, or for patients in whom inflammatory or pustular acne does not respond to other approaches [7].

Topical therapy is the standard of care for mild to moderate acne [8]. Many types of drugs are used, like antibiotics and retinoids, with other agents including benzoyl peroxide, salicylic acid, azelaic acid, and alpha-hydroxy acids [7]. Retinoids and antimicrobials such as benzoyl peroxide and antibiotics are the mainstay of topical acne therapy: such treatments are active at application sites, and they can prevent new lesions [9]. The main side effect is local irritation.

Gels, pledgets (medication-soaked pads), washes and solutions tend to be drying and are helpful for oily skin. Lotions, creams and ointments are beneficial for dry, easily irritated skin.

There are no general guidelines available to optimize acne scar treatment. However, there is a variety of therapies that may reduce the prominence of acne scars. The selection of an approach to treatment is based upon multiple factors such as the type and degree of acne scarring, patient preference, side effects, cost, and treatment availability [10].

Surgical methods include subcutaneous incision (subcision), dermabrasion, and laser skin resurfacing. Among these procedures, subcision and microneedling are the most popular with good efficacy in

atrophic acne scars. Laser treatments are relatively expensive and have their own risks, such as post-inflammatory hyperpigmentation – particularly in ethnic skin – and scarring [11].

Nonsurgical methods include subcutaneous or dermal fillers such as autologous fat, bovine collagen, human collagen, hyaluronic acid derivatives and polymethylmethacrylate microspheres with collagen [12,13].

Topical approaches also include chemical peels, with glycolic acid, pyruvic acid, salicylic acid and trichloroacetic acid [14]. Deep peels with trichloroacetic acid alone or in combination with other peels or microneedling can improve atrophic scars, however, repeated treatments may be necessary depending on the depth of the scars [15]. The side effects of peeling are generally mild and transient and include erythema and dryness [16]. Retinoids, specifically, have supporting sparse reports of treatment to keloids, hypertrophic scars and very superficial scars. The benefit is attributed to an increase in elasticity with dermal collagen deposition and alignment [17,18].

Intralesional steroids can be used for hypertrophic scars and keloids; however, steroid injections are painful and cutaneous use does include side effects that might include telangiectases, bruising, atrophy, pain, or pigmentary change [19,20].

Another treatment modality used for acne scarring is silicone. There is variable support to the silicone itself, with results more likely attributable to occlusion or hydration; silicon is inert and does not inhibit microbial growth, but it can act as a bacterial barrier.

PAPIX ACNE SCAR, the medical device tested in the present post market clinical follow-up investigation, is a silicone gel indicated for acne lesions and scars; this acts by creating a sheer physical barrier that separates the skin from surrounding environment, useful for generating favorable conditions for the maintenance and/or recovery of the physiological cutaneous layer in case of acne lesion. Thus, PAPIX ACNE SCAR improves skin by keeping it hydrated and works to prevent and reduce acne scars, also thanks to the presence of humectant/moisturizing ingredients.

In the acneic patient, skin care is integral in reducing and preventing lesions and maintaining healthy skin, especially in those patients – such as Asian – that tend to scar the most. A review done by Chularojanamontri et al. analyzed key components of 52 moisturizers that claim to be suitable for acne skin [21]. Dimethicone and glycerin were found to be the most commonly utilized agents as they can reduce transepidermal water loss. Hyaluronic acid and sodium pyrrolidone carboxylic acid were used to counterbalance the stickiness of glycerin in the same formulations. Moisturizers specifically made for acneic skin were found to improve the tolerability by decreasing the dryness and stinging sensation associated with barrier disruption, thus improving compliance to treatment [22-25]. PAPIX ACNE SCAR composition includes these ingredients, known to be well tolerated and useful to treat acneic skins.

The present study will be conducted in Italy with the purpose of confirming and supporting the CE mark of PAPIX ACNE SCAR in the post-market phase. In this post-market clinical follow-up investigation PAPIX ACNE SCAR will be used according to its Instructions for Use (IFU), in males and females ≥ 12 years of age, affected by mild to moderate acne.

4. Risk and Benefits of the Investigational Device and Clinical Investigation

To date a large variety of products for the treatment of acne scars are available, many of them are not without side effects.

PAPIX ACNE SCAR is a medical device that is CE marked for the symptomatic treatment of acneic skin while reducing the appearance of acne scars. In this clinical investigation PAPIX ACNE SCAR will be used in adult subjects with mild to moderate acne and with oily, blemished, acneic skin, according its IFU.

PAPIX ACNE SCAR will be recommended twice daily for 8 weeks maximum.

The product's components are known to be safe and well tolerated. PAPIX ACNE SCAR is dermatologically tested, non-phototoxic, paraben, fragrance and alcohol free, nickel and heavy metals tested. Moreover, biocompatibility assessments conducted by the manufacturer on PAPIX ACNE SCAR have shown no contraindications or undesirable effects, therefore no side effects are expected deriving from its application, when in the respect of its IFU.

The only precaution for users is to avoid contact of the product with eyes and mucous membranes (if contact does occur rinse immediately with plenty of water).

Within the clinical investigation the subject will be also provided with a specific product, Papix cleanser, and instructions for face cleansing, in order to further improve skin care and safety.

No tests or invasive examinations are foreseen in this study that can increase the risk for participants.

In the light of the above, no additional risk arising from the participation to this clinical investigation can be envisioned.

5. Objectives and Hypotheses of the Clinical Investigation

5.1 Primary Objective and Endpoint

The primary objective of this clinical investigation is to evaluate and confirm the performance of PAPIX ACNE SCAR in the prevention and improvement of acne scars in subject suffering for mild to moderate acne, after 4 weeks of treatment.

The primary endpoint will be the proportion of subjects with improved acne scars and marks with respect to baseline and, at the same time, without any new facial acne scars after 4 weeks of treatment. The improvement of acne scars and marks will be assessed as the change in the qualitative Scar Global Assessment (SGA) by Goodman and Baron (2006) [26] between baseline and Week 4. The number of acne scars, to identify any new scars, will be assessed through the scars count and comparison with baseline.

5.2 Secondary Objectives and Endpoints

The secondary objectives of this clinical investigation are:

- To evaluate the performance of PAPIX ACNE SCAR in the prevention and improvement of acne scars after 2 and 8 weeks of treatment. This endpoint will be assessed as the proportion of subjects with improved acne scars and marks with respect to baseline and, at the same time, without any new facial acne scars after 2 and 8 weeks of treatment. The improvement of acne scars and marks will be assessed as the change in the qualitative Scar Global Assessment (SGA) by Goodman and Baron (2006) [26] between baseline and Week 2 and 8. The number of acne scars, to identify any new scars, will be assessed through the scars count and comparison with baseline.
- To evaluate the performance of PAPIX ACNE SCAR in the prevention of acne lesions after 2, 4 and 8 weeks of treatment. The number of acne lesions, to identify any new lesions, will be assessed through the lesions count and comparison with baseline.
- To evaluate the improvement in acne severity after 2, 4 and 8 weeks of treatment, through the Investigator Global Assessment, ranging from 0 (clear; clear skin with no lesions) to 4 (severe; many inflammatory and non- inflammatory lesions).
- To evaluate the improvement of the skin roughness on a 4-point scale from 0 (none; very smooth) to 3 (severe; very rough) after 2, 4 and 8 weeks of treatment.
- To evaluate the improvement of the skin texture on a 6-point scale from 0 (worse) to 5 (complete improvement), after 2, 4 and 8 weeks of treatment.
- To evaluate the subject's adherence to treatment by the product accountability and information asked to the subject.
- To evaluate the subject's and Investigator's global evaluation of satisfaction with regards to the performance of PAPIX ACNE SCAR, through a specific questionnaire.
- To evaluate the subject's overall acceptability of the treatment, through a specific questionnaire.

5.3 Tolerability and Safety Objectives

To evaluate the local and general tolerability of PAPIX ACNE SCAR.

Adverse events and adverse reactions will be recorded and evaluated.

6. Design of the Clinical Investigation

6.1 General

This is a multicenter, open label, uncontrolled, post-market clinical follow-up investigation.

All the subjects will be allocated to the following treatment group:

- PAPIX ACNE SCAR, topically applied twice a day for 8 weeks.

The subject will start treatment on the first day of study and will go on until 8 weeks after the first administration.

Each subject for whom written consent is obtained will be assigned a five-digit screening code, consisting of the site code (01 or 02) and a progressive number within the site: for example the first subject screened at site 01 will be assigned the code 01-001, the second one 01-002 etc.

All screened subjects will receive the code irrespective of whether or not they will receive the treatment. If a subject discontinues from the study at any time, the code will not be re-used.

All subjects who will sign the informed consent and receive the screening code will be entered into a Subject's Register, containing the name and surname of the patients and their Screening numbers. The Subject's Register will be accessible for source data verification but will be preserved only at clinical site.

Once eligibility of a patient is established (see Inclusion/Exclusion Criteria) the study treatment will be assigned.

The Investigator will keep record of all enrolled patients in the Subject's Screening/Enrolment Log: the subject screening number, the date of consent, the treatment assigned to the patient, if applicable, or the reason for not actively entering the study will be recorded.

6.2 Investigational device

6.2.1 PAPIX ACNE SCAR

The product under investigation is PAPIX ACNE SCAR.

Manufacturer: Relife Srl, Via dei Sette Santi 3 - 50131 Firenze (FI) - Italy

Formattato: Italiano (Italia)

Device Name:	PAPIX ACNE SCAR
Formulation:	silicone gel
Route of administration:	topical application on breached/compromised skin (body surface)
Composition:	Aqua, cyclopentasiloxane, dimethicone, glycerin, butylene glycol, polyacrylate-13, polysilicone-11, polyisobutene, Octyldodecyl lactate, Niacinamide, ethylexylglycerin, hydroxypropylmethylcellulose, citric acid, disodium phosphate, lactic acid, sodium hydroxide, polysorbate 20, malic acid, glycoproteins, tocopheryl aceate, xanthan gum, taurine, zinc gluconate, hexamidine diisethionate, decyl glucoside, hydrolyzed glycosamminoglycans, sodium hyaluronate, caprylyl glycol, Hexylene glycol, phenoxyethanol, copper gluconate, sodium PCA. It does not contain fragrance, parabens and alcohol. It is heavy metals tested.

PAPIX ACNE SCAR is a CE marked, Class IIa medical device. It contains silicones, humectant, emollient and film-forming protective ingredients. PAPIX ACNE SCAR is indicated in the symptomatic treatment of acneic skin while reducing the appearance of acne scars. It is a multi-action treatment, which it treats acneic skin, improves acne scar appearance and lighten dark spots, prevents the development of new acne lesions and scars.

PAPIX ACNE SCAR creates a sheer physical barrier that separates the skin from surrounding environment, useful for generating favorable conditions for the maintenance and/or recovery of the physiological cutaneous layer in case of acne lesion. It improves skin by keeping it hydrated. It works to prevent and reduce acne scars.

6.2.1.1 Packaging and labelling

PAPIX ACNE SCAR will be provided for the study by the Sponsor of this clinical investigation.

The study product shipment to the study site will be done only after the completion of all Ethics and Administrative procedures.

The product will be labeled as experimental treatment in accordance with applicable Good Manufacturing Practice (GMP, Annex 13).

The primary package is a tube containing 7 ml of gel. Subjects will receive a total of no. 6 tubes.

6.2.1.2 Study device instructions for use

Patients will be instructed to use PAPIX ACNE SCAR applied twice a day, in the morning and in the evening before bedtime, and massaged gently into the skin until absorbed. PAPIX ACNE SCAR shall be applied only on the lesions, where possible. The treatment duration will be of 8 weeks.

6.2.1.3 Handling and storage

It is the Investigator/Institution's responsibility to set up a system for handling the clinical investigation treatment, so as to ensure that:

- deliveries of product supply from the Sponsor are correctly received
- products are handled and stored safely and properly in a secured area
- treatments are only dispensed to study subjects in accordance with the clinical investigation plan
- any unused, used, partially used product is returned to the Investigator (including empty tubes).

The study product shall be carefully stored at the study site, in a safe area and separately from other devices/drugs/products. It shall be stored in a dry and cool place, away from direct sunlight or heat.

The pharmacist and/or the Investigator shall maintain records of the study products receipt by the study site and an updated inventory of the study product.

Treatments will be dispensed to the subjects enrolled in this clinical investigation only by authorized personnel.

After study conclusion, all unused study product shall be returned to the Sponsor or destroyed at site after written Sponsor approval.

6.2.1.4 Study product accountability and compliance

The Investigator is responsible for ensuring the accountability of the study product.

Accountability records will include:

- confirmation of product delivery and receipt to/at the clinical site
- records concerning the product delivery to each subject and the return from each subject
- the return to the Sponsor or alternative disposition of unused products.

The Investigator should maintain records that adequately document:

- that the subjects were provided with the quantities specified by the clinical investigation plan/amendment(s)
- that all study products provided by the Sponsor were fully reconciled.

Unused products must not be discarded or used for any purpose other than the present clinical investigation.

Products that have been allocated to one subject must not be re-dispensed to a different subject.

Subjects will be reminded of the importance of strictly complying with the instructions received from the Investigator and to return all unused treatment or empty tubes to the Investigator.
Compliance to the treatment will be visually checked by the Investigators when the subjects are bringing back to the site the used/unused products.

6.2.2 Concomitant Medications/Treatments

Any medications (other than those excluded by the clinical investigation plan) that were considered necessary for the patients' well-being and do not interfere with the study product can be given at the Investigator's discretion.
According to exclusion criteria, the following prior and concomitant medications are prohibited:

- topical treatments like antibiotics, corticosteroids, benzoyl peroxide, azelaic acid, hydroxy acids, retinoids and other antinflammatory drugs
- chemical peels
- systemic antibiotics, corticosteroids, spironolactone/drospirenone or immunomodulators, oral retinoids or cyproterone acetate/chlormadinone acetate;
- scrub, alpha hydroxy acid (AHA), skin irritant products;
- laser ablative procedures
- radiotherapies
- sun exposure (unless limited and with the use of protection cream SPF 50+) or tanning booths or UV sources.

The subject will be recommended not to use any other cleanser for the face than Papix cleanser, provided by the Investigator.
Any concomitant medication/treatment shall be recorded in the appropriate section of the CRF.

6.3 Subjects

In this clinical investigation 40 subjects will be enrolled fulfilling the following eligibility criteria.

6.3.1 Inclusion criteria

1. Subject's or parents or guardian (depending on the age of the subject) written informed consent obtained prior to any study-related procedures;
2. Male or female subjects aged ≥ 12 years of any race;
3. Subjects with any Fitzpatrick skin phototype;
4. Subjects with clinical diagnosis of mild to moderate acne vulgaris (IGA score 2 or 3) on the face
5. Presence of acne scars (all types included), of grade mild or moderate according to SGA;

6. Subjects with cooperative attitude, able to comprehend the full nature and the purpose of the investigation, including possible risks and side effects, and able to comply with the requirements of the entire investigation (including ability to attend the planned visits according to the time limits), based on Investigator's judgement.

6.3.2 Exclusion criteria

1. Pregnant women
2. Severe acne at inclusion or any acne requiring systemic treatment;
3. Presence of facial warts or fungal infections;
4. Active dermatitis on the face, rosacea, active herpes simplex;
5. Keloids presence in the area to be treated or keloids development during the treatment period;
6. History of radiation or skin tumors in the/close to the area to be treated in the past 5 years;
7. Laser ablative procedures within the last month;
8. Chemical peels within the last 6 months;
9. Use of topical treatments like antibiotics, corticosteroids, benzoyl peroxide, azelaic acid, hydroxy acids and other anti-inflammatory drugs within 2 weeks;
10. Use of topical retinoids within 4 weeks;
11. Use of systemic corticosteroids or antibiotics in the previous 30 days;
12. Use of systemic spironolactone/drospirenone or immunomodulators in the previous 3 months;
13. Use of oral retinoids or cyproterone acetate/chlormadinone acetate in the previous 6 months;
14. Use of scrub, alpha hydroxy acid (AHA), skin irritant products in the 2 days before study treatment start;
15. Subjects with any other clinically significant or unstable concurrent disease or skin condition or general condition that, in the Investigator's opinion, might interfere with the study evaluations;
16. Allergy, sensitivity or intolerance to the components of the investigational device formulations ingredients;
17. Concomitant or previous participation in other interventional clinical study in the past 3 months;
18. Subjects planning sun exposure or tanning booths or UV sources throughout the course of the study. In case of sun exposure this shall be limited and a protection cream (SPF 50+) shall be applied.

6.4 Procedures

6.4.1 Study Visits and Assessments

Visit 1 screening – baseline- treatment start (day 1):

Subjects will be evaluated with regard to the inclusion and exclusion criteria that will allow their participation into the study.

Before any study specific evaluation is carried out, subjects will receive all the information about the study by the Investigators and will sign an informed consent form. In the case of minors, the informed consent form shall be signed by the parents or the guardian.

The following activities will be performed:

- Collection of information about demography
- Medical and surgical history
- Acne medical history (duration, previous treatments)
- Physical examination (only dermatologic)
- Face cutaneous examination:
  - type of skin (dry/normal/oily)
  - site of acne lesions (on the face) and count
  - acne scars count
  - acne scars global assessment by the SGA
  - acne global assessment by IGA
  - roughness and skin texture evaluations
- Photographs of the face
- Previous (in the 6 months before) and concomitant medications/treatments recording
- Inclusion/exclusion criteria assessment
- Study product delivery to subject and instructions on how to use it
- Recommendations for face cleaning to follow.

***Recommendations for face cleaning to follow*:** throughout the study subjects will be required to avoid soap and use only the product Papix cleanser for their face. The product will be provided by the Sponsor of the study. No other cleanser other than the product provided by the Investigator will be permitted.

PAPIX ACNE SCAR application: apply twice a day for 8 weeks, 2 FTU (finger tip units) in the morning and in 2 FTU the evening before bedtime, on the face, and massaged gently into the skin until absorbed.

Visits 2 and 3 – follow-up (Day 14 ± 3 and 28 ± 3, respectively):

The following activities will be done at visit 2 and 3:

- Face cutaneous examination:
  - acne scars and lesions count
  - acne scars global assessment by the SGA
  - acne global assessment by IGA
  - roughness and skin texture evaluations
- Photographs of the face
- Changes in concomitant medications/treatments recording
- Study product collection and new delivery to subject (only at visit 3)
- Treatment adherence check with the subject
- Recommendations for face cleaning to follow
- Adverse events (occurred since previous visit) recording.

Visit 4 – End of treatment and end of study (Day 56 ±3):

The following activities will be done at visit 4:

- Brief physical examination (dermatologic physical examination)
- Face cutaneous examination:
  - acne scars and lesions count
  - acne scars global assessment by the SGA
  - acne global assessment by IGA
  - roughness and skin texture evaluations
- Photographs of the face
- Changes in concomitant medications/treatments recording
- Study product collection
- Treatment adherence check with the subject
- Adverse events (occurred since previous visit) recording
- Subject global evaluation of performance
- Investigator global evaluation of performance

- Subject global acceptability evaluation on the study product.

6.4.2 Scar Global Assessment (SGA)

The qualitative scarring grading system proposed by Goodman and Baron [26] is simple and universally applicable. According to this classification, four different grades can be used to identify an acne scar, as shown in the table below.

Qualitative scarring grading system SGA.

Grades of Post Acne Scarring	Level of disease	Clinical features
1	Macular	These scars can be erythematous, hyper- or hypopigmented flat marks. They do not represent a problem of contour like other scar grades but of color.
2	Mild	Mild atrophy or hypertrophy scars that may not be obvious at social distances of 50 cm or greater and may be covered adequately by makeup or the normal shadow of shaved beard hair in men or normal body hair if extrafacial.
3	Moderate	Moderate atrophic or hypertrophic scarring that is obvious at social distances of 50 cm or greater and is not covered easily by makeup or the normal shadow of shaved beard hair in men or body hair if extrafacial, but is still able to be flattened by manual stretching of the skin (if atrophic).
4	Severe	Severe atrophic or hypertrophic scarring that is evident at social distances greater than 50 cm and is not covered easily by makeup or the normal shadow of shaved beard hair in men or body hair if extrafacial and is not able to be flattened by manual stretching of the skin.

6.4.3 Acne Investigator's Global Assessment (IGA)

IGA is a tool used in the clinical routine to define acne vulgaris severity. The Investigator's Global Assessment is based on a 5-point scale:

Investigator's Global Assessment (IGA) for acne vulgaris

Grade	Description
0	Clear skin with no inflammatory or non-inflammatory lesions
1	Almost clear; rare non-inflammatory with no more than one small inflammatory lesion
2	Mild severity; greater than Grade 1; some non-inflammatory lesions with no more than a few inflammatory lesions (papules/pustules only; no active nodulo-cystic lesions)
3	Moderate severity; greater than Grade 2; up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than one active small nodular lesion
4	Severe; greater than Grade 3; up to many non-inflammatory and inflammatory lesions, but no more than a few active nodular lesions

6.4.4 Skin Roughness and Texture Assessment

Skin roughness will be scored through a 4-point scale:

0 = none; very smooth

1 = mild, slightly rough

2 = moderate, rough

3 = severe; very rough

Skin texture change from baseline will be scored through a 6-point scale:

0 = worse

1 = slightly worse

2= no change

3= slightly improved

4 = improved

5 = complete improvement.

6.4.5 Subject and Investigator Global Evaluation of Performance – Appendices 2 and 3

Subjects' and Investigator's global evaluation of the performance of PAPIX ACNE SCAR will be performed by means of the 7-item scale, where 1 = very much improved, 2 = improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = worse, 7 = very much worse at the end of the study (Visit 4).

6.4.6 Subject Overall Acceptability – Appendix 4

Subjects' evaluation of overall acceptability with the study treatment, which takes into account the pleasant or unpleasant feeling with the product and the ease of use, will be performed by means of a 5-item scale, where 1 = very much satisfied, 2 = satisfied, 3 = neither satisfied nor dissatisfied, 4 = dissatisfied, 5= very much dissatisfied.

Global acceptability evaluation by the subject will be assessed at the end of the treatment (Visit 4).

6.5 Monitoring Plan

The study will be monitored on a regular basis by the CRO's adequately qualified and trained clinical Monitors throughout the study period to ensure the proper conduct of the clinical Investigation.

The purposes of study monitoring are to verify that the rights and well-being of study subjects are protected, that the reported study data are accurate, complete and verifiable against the source documents, and that the study is conducted in accordance with the current clinical investigation plan, Good Clinical Practice guideline (UNI EN ISO 14155) and applicable regulatory requirements.

During the monitoring visits, Monitors will verify the following, including but not limited to: subject informed consent, subject's eligibility, safety data and reporting, quality of source documents and CRF data against subject's medical records. If inconsistencies are found, the corresponding corrections to the CRF data will have to be made by the Investigator or designated person. Monitors will also check subject compliance, accrual, study product handling, including dispensing procedures and accountability logs, delegation of responsibilities within the Investigator's team, relevant communications with family doctors, if any, ancillary equipment and facilities, etc. The Investigator and other site staff involved in the study must allocate enough time to the Monitor at these visits.

Upon request by the Sponsor, on-site study audits may be conducted in order to ensure the study is in compliance with GCP, applicable regulatory requirements, and the clinical investigation plan. The auditing activities may also be conducted after study completion.

The Investigator agrees to allow Sponsor/auditors/CRO monitors to have direct access to his/her study records for review, being understood that they are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

Regulatory Authorities may wish to conduct on-site inspections (during the study or after its completion). If a Regulatory Authority notifies the Investigator of an inspection or visits the site unannounced for purposes of conducting an inspection, the Investigator must inform the Sponsor and CRO immediately. The Investigator will make all efforts to facilitate the conduct of the audits and inspections giving access to all necessary facilities, data and documents.

Any result or information arising from the inspection will be immediately communicated by the Investigator to the Sponsor. The Investigator will take all appropriate measures required by the Sponsor to implement corrective actions for all problems found during audits or inspections.

7. Statistical Considerations

This section summarizes the statistical principles and methods planned to analyze the data for this clinical investigation.

7.1 Sample Size Determination

An exact binomial test with a nominal 5% two-sided significance level will have 80% power to detect the difference between the Null hypothesis proportion, π_o of 0.5 (i.e., 50% of patients with treatment success) and the Alternative proportion, π_1, of 0.75 (i.e., 75% of patients with treatment success) when the sample size is 30 subjects. Assuming a possible 25% dropout rate, 40 subjects will be enrolled.

7.2 Definition of Study Populations for Analysis

The following populations are defined for this investigation:

- Safety analysis set (SAF): all patients enrolled who sign informed consent and receive at least one administration of the investigational device.
- Full analysis set (FAS): all patients of the SAF who have performed the baseline assessments and have at least one post-baseline assessment of any performance endpoint (primary or secondary).
- Per-Protocol analysis set (PPAS): all patients of the FAS who also meet all inclusion/exclusion criteria and who do not have any major protocol deviation (i.e. wrong inclusion, use of forbidden concomitant medications, etc.).

The analysis of safety endpoints will be performed in the Safety population (SAF). Analysis of performance endpoints will be performed on the FAS population. The analysis of primary endpoint will be repeated in the PPAS.

7.3 Statistical Analysis

Descriptive statistical analysis of all relevant variables will be performed. Continuous variables will be summarized by the number of patients (N), mean, standard deviation, median, minimum, maximum. Categorical variables will be summarized by the number (N) and the proportion of patients (%). Where appropriate, 95% confidence intervals for the target variables will be estimated.

The significance level of statistical tests will be set at 0.05. Parametric tests (e.g., paired t-test) will be used to analyze continuous variables; when continuous variables are not normally distributed, the corresponding non-parametric tests (e.g. Wilcoxon signed-sum rank test) will also be performed. Details of statistical analysis are provided in the following paragraphs.

The statistical analysis will be performed using SAS 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

7.3.1 Missing Data

Missing data will not be replaced in any statistical analysis.

7.3.2 Multiplicity

This is a single-arm clinical investigation and no adjustment for multiplicity will be used.

7.3.3 Covariates, Interactions and Subgroups

This is a single-arm clinical investigation. No covariates or interaction analysis will be performed. Subgroup analyses could be performed to better describe the performance and safety of the study device.

7.3.4 Analysis of Demographics and Baseline Variables

Demographic (gender, age) and baseline characteristics will be summarized using mean, median, standard deviation, minimum and maximum for continuous variables and frequencies and percentages for categorical variables.

7.3.5 Efficacy analysis

7.3.5.1 Primary endpoint

The primary objective of this clinical investigation is to evaluate and confirm the performance of PAPIX ACNE SCAR in the prevention and improvement of acne scars, in terms of improvement of visible acne scars and marks from baseline and prevention of new acne scars, in subject suffering for mild to moderate acne, after 4 weeks of treatment.

The primary endpoint will be the proportion of subjects with acne scars and marks improved with respect to baseline and, at the same time, without any new facial acne scars after 4 weeks of treatment (treatment success). The improvement of acne scars and marks will be assessed as the change of at least one grade in the qualitative Scar Global Assessment (SGA) by Goodman and Baron [26] between baseline and Week 4. The number of new lesions will be assessed by count and comparison with baseline.

The primary endpoint will be described using number (N) and the proportion of patients (%). The proportion of treatment successes will be compared to a referent proportion (50%, Null hypothesis proportion) using the exact binomial test.

7.3.5.2 Secondary endpoints

The prevention and improvement of acne scars after 2 and 8 weeks of treatment will be assessed as the difference from baseline and analysed using paired t-test. The number of new scars will be assessed by count and comparison with baseline. The improvement of acne scars and marks will be assessed as the change of at least one grade in the qualitative Scar Global Assessment (SGA) by Goodman and Baron [26] between baseline and Week 2 and 8.

The number of new lesions will be assessed by count after 2 and 8 weeks and comparison with baseline.

Acne severity after 2, 4 and 8 weeks of treatment will be assessed through the IGA. Changes from baseline will be compared using Wilcoxon signed rank-sum test.

The improvement of skin roughness will be assessed on a 4-point scale from 0 (none; very smooth) to 3 (severe; very rough). Changes from baseline will be compared using Wilcoxon signed rank-sum test.

Skin texture change will be assessed on a 6-point scale from 0 (worse) to 5 (complete improvement), after 2, 4 and 8 weeks of treatment and it will be summarized through the number (N) and the proportion of patients (%) for each item.

The number of applications will be self-reported by the subject and the product accountability will be summarized to assess adherence to treatment.

Subject's and Investigator's global evaluation on performance of the study product obtained at the end of the study (Visit 4) by means of a 7-items scale will be summarized through number (N) and proportion of patients (%) for each item.

Subject's evaluation of overall acceptability with treatment, obtained by means of a 5-item scale will be summarized through number (N) and the proportion of patients (%) for each item.

7.3.6 Safety Analysis

All enrolled subjects receiving at least one treatment application will be included in the safety analysis.

Adverse events (AEs) and Adverse Device Events (ADEs) will be coded using the last updated version of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary to give a preferred term (PT) and a system/organ class term (SOC) for each event. The number of subjects who experienced at least one

AE or ADE, study product-related AE or ADE, serious AE or ADE, severe AE or ADE and the number of subjects withdrawn due to AE will be summarized.

For each SOC and preferred term, summaries will be made with respect to the proportion of subjects having at least one occurrence of that event during the study and the total number of events. The incidence of AEs and ADEs will be presented overall, by SOC and preferred term, and additional grouping by severity and relationship to the study treatment.

Local tolerability at the site of administration (e.g. skin increased itching or redness or irritation) will be reported and summarized.

7.4 Planned Interim Analysis

No interim analysis is planned.

8. Data Management

During each study visit, the study Investigator (or designee) will collect and report study data in the relevant patient's chart, documenting all significant observations.

Any contact with the patient via telephone or other means that provides significant clinical information shall be documented in the source data.

Paper Case Report Forms (CRFs) will be used for recording patient's study data. It is the responsibility of the Investigator to ensure that the Case Report Forms are properly and completely filled in. The CRFs must be completed for all subjects who have been included in the clinical investigation. The Investigator will review all CRFs and sign and date them for each subject, verifying that the information is complete, true and correct.

Subjects will be provided with paper questionnaires. Such documents will be filled by the subjects during the study visits, to record data concerning their QoL with respect to acne scars condition.

It is responsibility of the Investigators to instruct the study participants on how to fill in questionnaires in a clear way and preferably in black ball-point pen. The questionnaires will be anonymous, each subject is identified through the subject code. Questionnaires will be considered source data.

All CRF entries are to be done in black ballpoint ink. Changes and/or additions to data entered on original CRFs must be made in the following manner: the original entry will be lined out with a single line through the error (neither erasures nor correction fluid may be used) so as to leave it legible. The correction will be entered, initialed, and dated by the person making the correction. The Investigator or personnel authorized by the Investigator may enter corrections on the original CRFs.

All fields on the CRF must be completed as applicable.

After the CRFs are approved and signed by the Investigator, the monitor will collect and forward them to the CRO in charge of data management where they will be processed. Data Clarification Forms generated by Data Management after data entry will be sent to the clinical site for resolution. The Investigator is responsible for the review and approval of all query resolutions.
The data collected by CRFs will be entered in a dedicated database. The access to the database will be controlled by user-specific account and password combinations and audit trailed.

9. Amendments to the CIP

Changes to the clinical investigation plan may only be made by means of a written amendment, which has to be approved and signed by the authorized representatives of the Sponsor, and by the Investigator.
Exhaustive justifications that motivate the amendment to the clinical investigation plan should clearly be addressed in the document.
All substantial Clinical Investigation Plan amendments must be submitted for approval to IEC and notified to the Regulatory Authority. In case of non-substantial amendment the IEC and the Regulatory Authority (when applicable) will be only notified of the amendment without the request to review and approve it.
The Investigator, the Sponsor and IEC, separately or together, should decide whether the subject's informed consent form needs to be changed.

10. Deviations from Clinical Investigation Plan

The Investigator is to conduct the study in accordance with the relevant, current clinical investigation plan and will only deviate when necessary to protect the safety, rights and welfare of the subjects. In the event that an isolated, unforeseen instance occurs resulting in a clinical investigation plan deviation, the Investigator is to document this deviation and notify the CRO or the Sponsor as soon as possible. In no instance should this increase the subject's risk or affect the validity of the study.

11. Device Accountability

The Investigator is responsible of ensuring accountability of the study product, including reconciliation of study product and maintenance of records.

Upon receipt of the study product, the Investigator (or designee) will check the contents and acknowledge receipt by signing (or initialing) and dating the documentation provided by the Sponsor and returning it to the Sponsor. A copy will be retained in the Investigator File.

The dispensing of the study product will be carefully recorded on the appropriate accountability forms provided by the Sponsor and an accurate accounting will be available for verification by the Study Monitor at each monitoring visit.

Study product accountability records will include:

- Confirmation of study product receipt at the clinical site.
- The inventory at the site of study product provided by the Sponsor.
- The tubes delivery to each subject.
- The tubes return from each subject.
- The return to the Sponsor or alternative disposition of unused study product.

The Investigator should maintain records that adequately document:

- That the subjects were provided with the quantities specified by the Clinical Investigation Plan/amendment(s), and
- That all study products provided by the Sponsor were fully reconciled.

Unused study product must not be discarded or used for any purpose other than the present study. Study product that has been dispensed to a subject must not be re-dispensed to a different subject.

The Study Monitor will periodically collect the study product accountability forms and will check all returns (both unused and used containers) before arranging for their return to the Sponsor or authorizing their destruction by the clinical site.

12. Statement of Compliance

The study will be conducted in compliance with the current version of the Declaration of Helsinki (Appendix 5), with the clinical investigation plan, the ISO 14155:2012, the Italian laws in force and the principles of the Good Clinical Practice.

The clinical investigation will start at clinical site only after obtaining the approval of the relevant Ethics Committee.

13. Informed Consent Process

The Investigator is responsible for and will obtain informed consent from each subject or from parents or guardian, according to the subject's age, in accordance with the UNI EN ISO 14155, and the current version of the Declaration of Helsinki.

All subjects invited to participate in the study are entitled to make their voluntary decision based on all current available information provided to them by the Investigator/designee. In addition, they will be given a document in native language written in clear concise lay language for review and consideration. Minors will receive an information sheet specifically adapted for their young age. The document will previously have been approved by the relevant independent Ethics Committee (IEC) and may further be updated as new important information becomes available that may affect subject's willingness to participate or continue in the study.

The subject must be made aware that he/she may refuse to join the study or may withdraw his/her consent at any time without prejudicing further medical care and that he/she is covered by the Sponsor's indemnity insurance in the event of a study related injury. Subjects must also know that their personal medical records may be reviewed in confidence by the Sponsor's staff or representatives and by Regulatory Authority and IEC and that personal information will be collected and retained in a confidential database. Consent will always be given in writing after the subject has had adequate time to review the information and ask questions, if need be. Consent for minors will be requested to both parents or the guardian, where applicable.

14. Adverse Events, Adverse Device Effects and Devices Deficiencies

14.1 Definitions

Adverse Event (AE)

Any undesirable experience occurring to a subject, whether or not it is considered causally related to the investigational medical device. An AE may be a clinical finding, a clinical laboratory abnormality or a symptomatic complaint which is considered by the Investigator to be outside the normal variation for that parameter.

Adverse Device Effect (ADE)

Any untoward and unintended response to a medical device. This includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device and any event that is a result of a user error.

Device Deficiency

Inadequacy of a medical device with respect to its identity, quality, durability, safety or performance (included malfunctions, use errors and inadequate labelling).

Serious Adverse Event (SAE)

A serious adverse event (SAE) could be any event that suggests a significant hazard, contraindication, side effect, or precaution. The seriousness of an AE relates to its clinical significance and its potential impact on health.

An AE will be considered as serious when:

Lead to death

Lead to serious deterioration in the health of the subject, that either results in:

a. a life-threatening illness or injury, or
b. a permanent impairment of a body structure or a body function, or
c. in-patient or prolonged hospitalization, or
d. medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function

Lead to foetal distress, foetal death or a congenital abnormality or birth defect.

Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the risk analysis report.

Incident

Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any lack of labelling or instructions for use which, directly or indirectly, may cause or have caused death or serious deterioration in the health of the patient or of a user or of other persons.

14.2 Adverse Event Intensity/Causality

The Investigator, based on his direct observation or on subjects' report, will record the event according to the current version of CTCAE:

Description	Definition
Grade 1 (Mild):	asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 (Moderate):	minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental daily life activities.
Grade 3 (**Severe):**	medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self -care daily life activities.
Grade 4 (Life-threatening consequences):	urgent intervention indicated.
Grade 5:	death related to AE

The relationship of any AE to the product will be classified by the Investigator as follows:

Description	Definition
Certain	The AE is clearly related to the study product
Probable	The AE is likely related to the study product
Possible	The AE may be related to the study product
Doubtful	The AE is unlikely related to the study product
None	The AE is clearly not related to the study product
Unknown	Causality is not assessable, for one reason or another, e.g. because of insufficient evidence, conflicting data or poor documentation

14.3 Adverse Event, Device Deficiency, Adverse Device Effect, reporting

The Investigator will record any AEs, Device Deficiency and ADEs occurring during the study. He/She will also co-operate with the Sponsor in connection with the reporting of any SAE/SADE, Serious Incident to the Competent Authority and to the Independent EC, if applicable.

All AEs regardless of severity occurring between recruitment and completion of the study by a subject must be recorded on the AE form provided with the CRF.

If there is a significant worsening of a medical condition that was present before starting the study, this should be considered as a new AE and a complete evaluation recorded.
Signs and symptoms considered as lack of efficacy and occurring during the study will not be recorded on the AEs Section of the CRF except on the condition that, in the Investigator's opinion, these signs and symptoms are caused by any reason different from lack of efficacy of the study product or meet the definition of serious AE.

In the event of a SADE/SAE, Serious Incident the Investigator has to:

- Complete the relevant CRF pages and a reporting form with the all available initial information,
- Immediately inform the Sponsor or the CRO by telephone,
- Fax the completed report form to the contact person at the Sponsor or the CRO as soon as possible.

SAE/SADE, Serious Incidents reporting contacts are on page 4 of this Clinical Investigation Plan.
The Investigator is responsible for ensuring the follow-up of any subject who experiences an SAE/SADE/ Serious Incident during the study. The investigator must re-examine the subject at regular intervals until the symptoms have completely disappeared or stabilized.
The Sponsor or its delegate will be responsible for reporting the SAE/SADE/Serious Incident to the appropriate Authorities and EC, according to the local regulations.

15. Vulnerable Population

Minors will be recruited for participating in this study. They will receive specifically considered protection in accordance with international and national regulations, GCP guidelines and the provisions of the Declaration of Helsinki.

16. Suspension or Premature Termination of the Clinical Investigation

Unless premature interruption occurs, the end of the study will be the last closure visit at the clinical sites.

16.1 Study Discontinuation

Subjects may be discontinued at any time from the study for any of the following reasons:

- An AE occurs that, in the opinion of the Investigator, makes it unsafe for the subject to continue in the study

- Lack of compliance of the subject to the study treatment or assessments
- The subject needs to use a medication/treatment not allowed
- The subject is lost to follow-up
- The subject dies
- The subject withdraws consent
- The Investigator, for any reason, terminates the entire study, or terminates the study for that subject or the attending physician requests that the subject be withdrawn for any medical reason
- The Sponsor or the Regulatory Authority or the Ethics Committee, for any reason, terminates the entire study or terminates the study for this site or this particular subject.

If a subject is discontinued from the study, the Investigator will, as far as possible, complete the end of study visit (Visit 4) CRF pages. The Investigator should try to ascertain the reason(s) for withdrawal, while fully respecting the subject's rights.

16.2 Study Interruption

The Sponsor may consider study closure at the clinical site if the following occurs:

- serious and/or persistent non-compliance with the Clinical Investigation Plan
- inadequate collaboration of site personnel with CRO/Sponsor
- administrative reasons
- non-compliance with GCP, SOPs or regulatory requirements
- lack of confidentiality and/or non-compliance with the contract spread with the Sponsor.

17. Publication Policy

All information obtained as a result of the study will be regarded as confidential.

The results of the clinical study will be documented in an integrated clinical study report according to ISO 14155.

The Sponsor and the Investigators agree that no publications presenting or discussing data and/or results from this clinical study sponsored by Relife Srl will take place until the participating centers have completed the study, the data have been interpreted, and the final report has been issued.

As a rule, the Sponsor is free to use the data collected in the sponsored study for world-wide scientific product documentation, and for publication.

In general, the Sponsor has no objections if the Investigator publishes the results of the study. However, the Investigator is requested to provide the Sponsor with a copy of the manuscript for review before submitting it to the publisher with a cover letter informing the Sponsor about the intention to publish the study results. When permission for presentation or for publication is granted, Investigators, prior to submission of a manuscript or abstract to the publisher, shall forward a copy of said manuscript or abstract to the Sponsor who shall have 45 days to request any reasonable amendment thereto, which shall be taken into due account and consideration by the Investigator.

The Sponsor is entitled to include as authors of the publication all Sponsor's personnel who contributed substantially to the theoretical or experimental work and also to take part in the decision that establishes the order in which the authors' names will be given. Costs for publication must be regulated by written agreement between the parties.

If publication of the results of the study, either in part or in full, is prepared by the Sponsor, the Investigators will be provided with a copy of the manuscript before the submission to the publisher and asked to give approval of the document. The Investigators will be asked in writing if they accept to be included as authors of the publication. Answers should be sent in writing to the Sponsor within a reasonable time limit (30 days). If no answer is received, it is assumed that the Investigators agrees to the Sponsor's proposal.

18. Data protection requirements

All clinical trial information shall be recorded, processed, handled, and stored in such a way that it can be accurately reported, interpreted and verified; at the same time, the confidentiality of records and of the personal data of the patients shall remain protected in accordance with the applicable law on personal data protection (such as the EU General Data Protection Regulation 679/2016).

Acknowledgment

The Site, the Principal Investigator, the CRO as well as their appointed staff and service providers acknowledge that:

(a) the performance of the study will imply processing of sensitive personal data;

(b) personal data processing is regulated by the applicable EU General Data Protection Regulation 679/2016 the ISO 14155and local laws as well as by the Sponsor's national legislation. In particular, it is hereby acknowledged that being the Sponsor a company incorporated under Italian law, it has to mandatorily comply with Italian legal provisions on data protection: therefore The Site, the Principal Investigator, the CRO shall cooperate with the Sponsor to allow the fulfillment of such obligations;

(c) strict compliance with the applicable data protection laws and this section of the protocol is deemed by the Sponsor as an essential condition of collaboration with the The Site, the Principal Investigator, the CRO.

Data Controllers and Data Processors

The Sponsor, the Site, the Principal Investigator and the CRO acknowledge that according to the applicable privacy laws, Sponsor and Site will act as independent data controllers while CRO and the Principal investigator will act as data processors respectively of the Sponsor and of Site. Before the beginning of the study, the Site will instruct in writing Principal Investigator as its data processor. However, if specific local laws or regulations mandate a different definition of the privacy roles, the Sponsor, the Site, the Principal investigator and the CRO will implement the relevant legal instruments (e.g. if pursuant to the local laws the Site is a data processor of the Sponsor, a Data Processing Agreement will be finalised; if pursuant to the local laws Sponsor and Site are join controllers, a Joint Controllership Agreement will be finalised).

Duties of the Parties involved in the performance of the study

Collection and use of patients' personal data (i.e. subjects' data), will be carried out in full respect of the provisions of the information notices submitted to patients, as well as the privacy rights, the fundamental freedoms and the dignity of data subjects. All the parties involved in this study undertake to adopt adequate measures to warrant that data will always be processed securely and in compliance with privacy laws.

The Site, the Principal Investigator, the Sponsor and the CRO as well as their appointed staff and service providers, each in its respective remit and within the limits of their specific role in the study, shall implement the following safety measures (physical, logical, organizational, technical, electronic, I.T. etc) to ensure adequate protection of the personal data of the patients involved in the study. In particular:

(i) DATA SAFETY. The Site and/or the Principal Investigator shall adopt all the necessary measures to prevent or minimise the risks of theft, fire, flooding, partial or total loss, accidental disclosure or illegal/unauthorised access to patient's data or Sponsor's proprietary confidential information; to this extent, before the beginning of the study, the Site and/or the Principal Investigator shall ensure that the actual measures they have implemented are fit-for-purpose and law-compliant, and in particular:

- in order to minimise the risk of unauthorized access and theft, the hardware on which patients' personal data are stored shall be placed in a restricted-access area, accessible only to those individuals who need to retrieve the patients' personal data included in the database for professional purposes; the same safeguards shall be put in place for non-electronic databases;

- any electronic database containing the patients' personal data shall be password-protected by means of a strong password. Systems shall be set so that passwords must be updated at least every three months and feature at least 8 characters, with upper-case and lower-case recognition, containing at least three "special" characters, such as upper case letters [A-Z], lower case letters [a-z], numbers [0-9], symbols [!, #, $, etc.] or other special characters [Á, ë, ö etc.]. Passwords shall not include elements which may easily be associated with the assignee or information regarding him/her , such as name and year of birth (e.g. "johnbrown80") or easily predictable strings of characters (e.g. "qwerty", "12345", "admin", "user", etc.);

- adequate cryptographic protection measures shall be put in place for data “at rest” and “in transit” (these include, for example, file system or database cryptography, or any other equivalent IT measure which renders data unintelligible to those who are not authorised to access them);

- high level security measures shall be implemented also on the files or databases which contain the “key” to match the patients’ personal data (i.e. name, surname, etc.) with their respective “Patient IDs” (as defined at point (iv) below);

- Backup processes and other measures that ensure rapid restoration of business critical systems shall be implemented;

- Updated Antivirus and firewall programs shall be installed on the IT devices.

The Site shall, regularly test and update the measures listed above.

The Site shall, upon request from the Sponsor and/or the CRO, provide detailed written information about the measures listed above.

The CRO shall ensure that the selected sites for the study have implemented the above listed measures.

(ii) TRANSMISSION OF DATA. All the parties that transfer data through internet and/or to the centralised database(s) used to process study’s data or to generate statistical analyses shall implement secure protocols based on cryptographic standards which make data unintelligible to unauthorized individuals.

(iii) SECURITY OF THE CENTRALISED DATA BASE. The centralised database held by the Sponsor shall have the following safeguards in place:

- appropriate authentication methods, which differentiate between different users according to their respective roles so as to ensure that access to a specific set of subjects' data is permitted exclusively to those for whom access to such data is essential in the context of their work for the study;

- appropriate measures to ensure that the authentication credentials are periodically updated (i.e. password change);

(iv) PSEUDONYMIZATION. All personal data that may allow identification of the patients involved in the study shall be adequately dissociated from the other data pertaining to the study ("pseudo-anonymisation" process). The Principal investigator shall adequately dissociate the identification data of patients from the data pertaining to the study by linking results to a an alphanumerical code "Patient ID", whose format shall not make it possible to identify the patient directly or indirectly, so as to ensure that only anonymous data are transmitted to the Sponsor and the CRO. Site/Principal Investigator shall securely store a separate list (e.g: identification log) with the identification code, together with all signed informed consents, in accordance with the security measures as defined above. (v) TRAINING. The parties shall ensure that any personnel involved in the study have received proper training on data protection issues.

All actions related to the implementation of the afore mentioned measures shall be provided by the Sponsor, the CRO to the competent authorities (including data protection authorities) and Ethics Committees if and when requested. If such authorities or the Sponsor consider the implementation of the afore mentioned measures insufficient to guarantee an adequate level of protection of the patients' personal data, The Site, the Principal investigator and the CRO undertake to adopt all the necessary activities to overcome such remarks to assure the full compliance with the data protection laws.

Archiving of the clinical trial master file and patients' personal data

Unless other EU laws require archiving for a longer period, the Sponsor the Centre and the Principal Investigator shall archive the content of the clinical trial master file, including the relevant patients' personal data, for at least 10 years after the end of the clinical trial. However, medical records shall be archived in accordance with the national laws of the country where the study is performed. The patient code pairing list (i.e. the list that where the Patient ID is linked to the patients' identification data such as name and surname), shall be archived care of the Principal Investigator.

The content of the clinical trial master file shall be archived in a way that ensures that it is readily available and accessible, upon request, to the competent authorities.

Any transfer of ownership of the content of the clinical trial master file shall be documented. The new owner shall undertake the responsibilities set out in this protocol.

The sponsor appoints the clinical trial coordinator and Study medical expert for archives within the Sponsors' organisation as responsible persons for archives. Access to archives shall be restricted to those individuals.

The media used to archive the content of the clinical trial master file shall be such that the content remains complete and legible throughout the period referred to in the first paragraph. Any modification to the content of the clinical trial master file shall be traceable.

Data Breach

Data Breach is an incident regarding personal data security and leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, personal data transmitted, stored or otherwise processed. In particular: destruction of personal data is where the data no longer exists, or no longer exists in a form that is of any use to the Site, Sponsor, CRO, Principal Investigator.; data loss is when the data may still exist, but the Site, sponsor, CRO, Principal Investigator etc has lost control or access to it, or no longer has it in its possession; damage is where personal data has been altered, corrupted, or is no longer complete; data unavailability is where, following a data incident (such as a network outage, a natural or man-made disaster, etc.), personal data become temporarily inaccessible to the Site, sponsor, CRO, Principal Investigator etc.

Anomalous Event is an event that is not part of the standard operational scope of an infrastructure, network or service and which affects, or is likely to affect, personal data; this may include theft or loss of IT devices and other physical events (e.g. an unauthorised access to a locked storage room containing paper files with personal data), and/or electronic/IT anomalies (e.g. cyber-attacks, default or hacking of cloud services), which may in any way entail loss, unavailability, alteration, theft, copy or dissemination of personal data.

Whoever becomes aware in any way of an Anomalous Event and/or of a Data Breach (see definitions above) affecting the patients' personal data and/or personal data collected in the context of the study, shall, as appropriate, immediately (and in any case no later than 24 hours from the knowledge of an Anomalous Event and/or of a Data Breach) inform the SME, the Sponsor's Data Protection Officer, who may be contacted at dpo@menarini.com, the Sites at dpo@hsanmartino.it and dpo@gaslini.org and the CRO at dpo@latis.it and shall provide the following information:

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(i) Anomalous Event / Data Breach Type (e.g. data loss, unauthorized access, loss of company device, etc.);

(ii) Person or source that first reported the Anomalous Event/ Data Breach;

(iii) Date and Time when the person who first reported the Anomalous Event / Data Breach became aware of it;

(iv) Anomalous Event / Data Breach Date and Time (actual or presumed);

(v) Place (specify if actual or alleged) where the Anomalous Event / Data Breach occurred;

(vi) Anomalous Event / Data Breach Description;

(vii) Indicate the source of the Anomalous Event / Data Breach (e.g. I.P. source) - (if relevant);

(viii) Indicate the affected infrastructure / system / application / cloud/ software / hardware / database and their location;

(ix) List or describe the processing/storage systems affected by the Anomalous Event/Data Breach (if relevant);

(x) Number of data subjects involved (if known);

(xi) Amount of allegedly breached data

(xii) Other relevant information

Once all the above information have been provided, the Sponsor and the Site should have a reasonable degree of certainty that a security incident has occurred that has led to personal data being compromised.

Then, as appropriate, Sponsor and Site, each one in its respective remit, shall manage the Data Breach in accordance with the applicable data protection regulations.

For Data Breach affecting personal data of patients enrolled within the European Union, Sponsor and Site autonomously or jointly depending on the circumstances and their privacy responsibilities as defined by the Regulation 679/2016- shall:

1. Collect the necessary evidence and information;

2. Categorise the breach;

3. Determine the risk probability and level to the rights and freedom of the concerned patients;

4. Identify and put in place appropriate remedies to minimise the impact of the Data Breach

5. Determine the notification and communication duties vis à vis the competent supervisory authority and/or the concerned patients.

Information notice on personal data protection and pseudo-anonymisation

Prior to patients' enrolment in the study, the Principal Investigator and the Site (including their personnel) shall provide each patient with adequate, law-compliant "information notices and consent forms to process personal data" as included in the ICF (or, as the case may be, through a separate, specific form) provided by the Sponsor or delegated CRO and shall collect his/her written consent to the processing of personal data according to the actual performance conditions in which the study is carried out. The Principal Investigator is responsible to archive the signed ICF in accordance with the security measures described above.

Among other things, the ICF (or the separate form) shall inform patients about:

(i) the applicable data protection legislation

(ii) what kind of data shall be collected during the study by listing them in detail or by category;

(iii) the purpose of data processing

(iv) whether granting the consent(s) to process personal data is a necessary or an optional condition to take part in the study;

(v) the pseudonymisation procedure and scope;

(vi) who can access patients' data and under what circumstances

(vii) the period of data retention/storage as defined in 10 years;

(viii) patients' data protection rights as defined by the EU General Data Protection Regulation 679/2016.

(ix) Data Controllers / Data Processors and the relevant contact details

(x) Sponsor's Data Protection Officer contacts (DPO)

Transfer of patients' data outside the European union

The study performance does not entail transferring patients' personal data (coded data) outside the EU.

Exercise of patients' data privacy rights

Each study patient has the right to contact the Sponsor, the Site, the Principal investigator, the CRO to exercise the rights afforded to the patient by the law, including the afforded ones under articles 15 to 22 of Regulation (EU) 2016/679, namely: knowing whether or not any data referring to his/her is being processed in the context of the study; access his/her data; verify the data's content, origin, exactness, location (including, where applicable, the non EU countries where the data might be); obtain a copy of the data including their transmission to another entity indicated by the patient; ask that the data are supplemented, updated, amended; in the circumstances set forth by the law, ask that the processing of data is restricted, that data are anonymised or frozen; oppose to the processing of his/her data for legitimate reasons. Each patient has the right to lodge a complaint with his/her local supervisory authority and/or to notify to the Data Protection Officer any use of his/her personal data the patient regards as inappropriate.

Each study patient is free to withdraw at any time from the study. In such case, each study patient may ask the Sponsor, the Site, the Principal investigator, the CRO to destroy/delete his/her personal data, thus preventing any further processing or analysis of his/her data. However, data and results of tests that may have been used to determine the results of the study shall not be deleted, to avoid altering or impairing altogether the results of the study.

The request shall be fulfilled within the term set forth by the applicable privacy laws (normally 30 days). The Sponsor, the Site, the Principal investigator, the CRO shall implement adequate organisational measures to reply to patients within the above mentioned deadline.

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APPENDIX 1

List of Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
CIP	Clinical Investigation Plan
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index questionnaire
FAS	Full Analysis Set
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonization
IFU	Instructions For Use
IGA	Investigator Global Assessment
IEC	Indipendent Ethics Committee
MedDRA	Medical Dictionary for Regulatory Activities
PPAS	Per-Protocol Analysis Set
PT	Preferred Term
ml	Milliliters
SADE	Serious Adverse Device Effect
SAF	Safety Analysis Set
SAE	Serious Adverse Event
SGA	Scar Global Assessment

SOC	System Organ Class
SOP	Standard Operating Procedure
USADE	Unanticipated Serious Adverse Device Effect

Appendix 2

Questionnaire for the patient's evaluation of the performance

Subject n°: |___|___|-|___|___|___|

Date of completion of the questionnaire: |___|___| |___|___| |___|___|___|___|

day month year

How do you rate the appearance of your facial skin overall, in relation to scars and signs caused by acne, compared to before treatment with the PAPIX ACNE SCAR product?

☐ Very improved

☐ Improved

☐ Only slightly improved

☐ No changes compared to before

☐ Sightly worse worsened

☐ Worsened

☐ Much worse

Appendix 3

Questionnaire for the evaluation by the Investigator of the performance

Subject n°: |___|___|-|___|___|___|

Date of completion of the questionnaire: |___|___| |___|___| |___|___|___|___|

day month year

How do you rate the overall skin of your patient's face, in relation to scars and marks caused by acne, compared to before treatment with the product PAPIX ACNE SCAR?

☐ Very improved

☐ Improved

☐ Only slightly improved

☐ No changes compared to before

☐ Sightly worse worsened

☐ Worsened

☐ Much worse

Appendix 4

Questionnaire for assessing acceptability by the patient

Subject n°: |___|___|-|___|___|___|

Date of completion of the questionnaire: |___|___| |___|___| |___|___|___|___|
day month year

Regarding the pleasant sensation of the PAPIX ACNE SCAR product on the skin, we ask you to express your level of satisfaction:

☐ Very satisfied

☐ Satisfied

☐ Neither satisfied nor dissatisfied

☐ Not satisfies

☐ Definitely not satisfied

Appendix 5

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest,

incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the

study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for

ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.