SYNOPSIS

Protocol no.:	SMR-3839
Title:	A double-blind, randomised and placebo controlled clinical trial of the safety and efficacy of 3SKIN Sunscreen (SPF50+ with 5-ALA and Vit D3) to reduce severity and prevent progression of actinic keratosis in patients with sun-damaged skin, and in healthy subjects.
Indication:	Those with epidermal skin damage from excessive sun exposure or those at risk for developing epidermal skin damage from exposure to the sun.
Investigational medical device:	3SKIN Sunscreen, a class IIa medical device containing a sunscreen cream (SPF100+; containing 0.0005% (5µg/g) cholecalciferol (Vit D3)) and a gel containing 0.5% (5 mg/g) 5-aminolevulinic acid (5-ALA).
Development phase:	Pre-market (non-CE marked device)
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Sponsor:	3SKIN AS, Forskningsparken, Gaustadallèen 21, N-0349 Oslo, Norway.
Contract Research Organisation:	Smerud Medical Research International AS Thunes vei 2, N-0274 Oslo, Norway

Study role	**Company/organisation/personal name, title, address, telephone and e-mail.**
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CIP title	A double-blind, randomised and placebo controlled clinical trial of the safety and efficacy of 3SKIN Sunscreen (SPF50+ with 5-ALA and Vit D3) to reduce severity and prevent progression of actinic keratosis in patients with sun-damaged skin, and in healthy subjects.
Objectives	The primary study objective is to assess the efficacy of 3SKIN Sunscreen to reduce progression of AK when exposed over 3 months (± 2 weeks) to patients with sun-damaged skin with AK. Secondary objectives are to measure efficacy and safety and tolerability by comparing 3SKIN Sunscreen against placebo (sunscreen alone) in patients with AK and in a control group of healthy subjects. Both Investigator and subject-reported outcomes will be used.
Study design	This study is prospective, single-centre, randomised, double-blind and placebo-controlled.

Safety variables	• Adverse events (incl. adverse events of special interest, such as pain, burning, stinging, prickling sensations, erythema, itching)
	• Local skin reaction score (assessed by investigator)
	  ○ Components: erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, erosions(ulcerations)
	  ○ Grades: 0=absent, 1=mild, 2=moderate, 3=severe
	• Tolerability (reported by subject)
	  ○ Verbal rating scale (VRS), categories 0-10 for pain, burning, stinging, prickling sensations, erythema and itching
	• Discontinuation rate

Efficacy variables	• Physician's global assessment
	  ○ 0 = much worsened, 1=somewhat worsened, 2=no change, 3= somewhat improved, 4=much improved
	• Actinic keratosis (AK) severity (clinically assessed, as per Olsen grading system: 0-3)
	• Modified actinic keratosis and severity index (mAKASI) score (0-10.8)
	• Total (AK) lesion count, TLC
	• Dermatoscopic grade, as per Zalaudek (2014)
	• Skin (collagen) density
	• Skin elasticity
	• Cosmetic outcome (assessed by Investigator using the Fitzpatrick wrinkle scale, FWS)
	• Dermatology life quality index (DLQI)
	• Cosmetic outcome (reported by subject)
	  ○ 0=much worsened, 1=somewhat worsened, 2=no change, 3= somewhat improved, 4=much improved)
	• Overall treatment satisfaction (reported by subject)

Selection criteria (abbreviated)	Inclusion	• Patient cohort:
		  ○ Clinical (visual inspection and palpation) diagnosis of sun-damaged skin of the face with clinically typical, visible, and distinct facial AK lesion(s); Olsen global lesion scale grade 1-2
		  ○ Subjects who in the judgement of the Investigator, are in good general health, based on medical history
		  ○ Both genders; males and females
		  ○ Aged 18-75 years
		  ○ Signed informed consent form
		• Healthy subject cohort
		  ○ Subjects who in the judgement of the Investigator, are in good general health, based on patient-reported medical history and have an absence of dermatological disorders affecting the face
		  ○ Both genders; males and females
		  ○ Aged 18-75 years
		  ○ Signed informed consent form

	Exclusion	• *Current, active* skin cancer on the face; melanoma or non-melanoma (e.g. basal cell carcinoma (BCC), squamous cell carcinoma (SCC), Bowen's disease) • History of photosensitivity • Known hypersensitivity or allergy to any of the substances under study • Porphyria • Use of any photosensitising drugs • Immunocompromised or immunosuppressed subjects for any idiopathic, disease-specific or therapeutic reasons • Use of any systemic or topical immunosuppressive treatment (e.g. corticosteroids, systemic retinoids, chemotherapy) • Any topical treatment of sun-damaged skin or AK on the face (incl. medication, cryotherapy, curettage, photodynamic therapy, UV therapy, excision surgery, chemical peeling (e.g. retinol or other acids) in the 28 days prior to randomisation • Open wounds on the face • Concurrent use of any vitamin D3 supplement at the time of consent • Participation in any trial with an investigational device or drug in the last 28 days (or 5x half-life of an investigational medicinal product; whichever is the longest) prior to randomisation • Known pregnancy or nursing mothers • Any clinically unstable medical conditions (e.g. recent diagnosis of a concomitant disease), at the discretion of the Investigator • Expected poor protocol compliance or any mental or psychiatric co-morbidities that may interfere with the study procedures or assessments in the opinion of the Investigator • Prior participation in this study
Methods & procedures		Eligible subjects, with a history of sun-damaged skin and a clinical diagnosis of actinic keratosis (AK) and healthy subjects will be recruited from the Investigator's existing pool of subjects and/or from collaborating referral dermatology clinics or other physicians, such as general practitioners. After providing information about the study, written informed consent will be obtained from each subject before any study-related procedure is undertaken. Following an on-site screening assessment including medical history and concomitant medication, a detailed characterisation of the face will be performed in the patient cohort, including AK lesions and dermoscopy of targeted lesions to exclude any BCC or SCC. Up to five target lesions will be identified in subjects in the patient cohort. Temporal skin elasticity and collagen density will be measured by cutometer and ultrasound, respectively, in all subjects. Upon successful compliance with the selection criteria, subjects will be randomised to blinded active or placebo IMD administration. Subjects will be instructed in how

		to apply the IMD and how to complete the daily electronic diary. Patients will also complete the DLQI. All subjects will be discharged with enough IMD bottles to allow for 3 months(± 2 weeks) of use. Subjects will be asked to come back to the clinic for the end-of-study visit at 3 months (± 2 weeks). The investigator will conduct a new assessment of the face, including AK lesions in the patient cohort, and assess any local skin reactions. The subjects will accordingly report outcome, both in terms of overall treatment satisfaction and cosmetic outcome. Patients will complete the dermatology life quality index (DLQI) general dermatology questionnaire. All subjects will be asked about any adverse events, tolerability issues and/or any device complaints. In addition, all IMD bottles (empty or not) will be returned for control weighing at the clinic to determine volume of IMD having been used and thus indirectly the compliance. During the entire study, the investigator will inspect the e-diary on a routine basis (weekly) to assess overall compliance with the IMD application, with sufficient outdoor sun exposure as well as reviewing any adverse events.
Investigational Medical Device, IMD (dose, route, duration)	Test	3SKIN Sunscreen, a class IIa medical device containing a sunscreen cream (Sun Protection Factor Sun protection filter (SPF) 100+) containing 0.0005% (5 µg/g) cholecalciferol (Vit D3) and an active gel containing 0.5% (5 mg/g) 5-aminolevulinic acid (5-ALA). The product is delivered as a two-chamber device, with two different formulations that are meant to be mixed after actuating the pump system of the container. This is done by one single press, releasing 0.5g of each substance. The subject then mixes the two substances in the palm of their hand and applies to the face (not including the scalp). It is recommended to wait 15 minutes before sun exposure to ensure that the filters, 5-ALA and vitamin D3 are all absorbed into the epidermis. The product should be reapplied every two hours when the patient is outdoors in daylight since chemical SPFs will degrade after being exposed to UV-radiation.
	Comparator(s)	A sunscreen cream (Sun Protection Factor 100) without cholecalciferol (Vit D3) and a placebo gel without 5-ALA. To be supplied in the same container and applied in a similar manner as the test device, as described above.
Statistics	Sample size	A total of 80 subjects (70 subjects with sun-damaged skin and AK(s) in the face, and 10 healthy subjects) will be randomised (1:1) into active (35+5) or placebo (35+5). The primary objective of the study is to assess the efficacy of 3SKIN Sunscreen in reducing progression of AK in patients with sun damaged skin. The sample size has been calculated based on data from previous studies of 3SKIN Sunscreen: 35 subjects in each group of the patient cohort would be able to show a statistically significant difference ($p<0.05$) and power of 80% between responder rates of e.g. 75% vs 30% or 55% vs 20%, when using responder vs non-responder based on the physician's global assessment as variable.

	Statistical analysis methods	A statistical analysis plan detailing all analyses to be performed will be developed and completed (signed off) prior to database lock. Results will be presented by study group (active or placebo), for each of the patient and healthy subject cohorts; and total unless otherwise indicated in the statistical analysis plan (SAP). Categorical data will be presented as absolute and relative frequencies. Chi-square and Fisher's exact tests will be used to determine any differences in the distribution of categorical variables. Continuous data will be summarised using descriptive statistics, where the following parameters will be reported: number of evaluable and missing observations, mean and standard deviation, median, quartiles, and extreme values (minimum and maximum). For each variable, also mean change (absolute and relative) from baseline to each assessment time-point will be presented. *Primary test (on efficacy endpoint)* The primary statistical analysis will be made on the proportions of subjects (3SKIN Sunscreen vs placebo) being a responder at the end of treatment visit based on the physician's global assessment (PGA) as variable (see 6.5.11). A responder is defined as having a score of 3 (somewhat improved) or 4 (much improved). The comparison will be made using Pearson's chi-square test.