An open, multicentre, randomised, inter-individual comparative, prospective clinical trial with MD-3511356 versus standard sun protection measures in immunosuppressed outpatients after solid organ transplantations for the prevention of UV-induced infections and carcinogenic skin alterations

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3. TRIAL OBJECTIVES AND PURPOSE3.1 Primary ObjectiveThe primary objective is the prevention of actinic keratoses and squamous cell carcinomas by local application of MD-3511356 in comparison to standard sun protection measures in immuno-suppressed...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Skin neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON34543

Source
ToetsingOnline

Brief title
Sunscreen to prevent skin cancer

Condition

- Skin neoplasms malignant and unspecified

Synonym
skin cancer, squamous cell carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Spirig Pharma AG
Source(s) of monetary or material Support: Spirig Pharma AG

Intervention

Keyword: organ transplantation, prevention, skin cancer, sunscreen

Outcome measures

Primary outcome

7. ASSESSMENT OF EFFICACY

7.1 Specification of the Efficacy Parameters

7.1.1 Primary efficacy parameter

• Number of new clinically diagnosed actinic keratoses or squamous cell carcinomas within two years.

7.1.2 Secondary efficacy parameter

• Number of patients with new actinic keratoses, squamous cell carcinomas or basal cell carcinomas within two years

Secondary outcome

7.1.3 Other exploratory efficacy parameters

These parameters are assessed on the whole body surface

• Median time to occurrence of new squamous cell carcinomas within two years

• Median time to occurrence of new squamous cell or basal cell carcinomas within two years

• Median time to occurrence of new basal cell carcinomas within two years

• Number of actinic keratoses after the two years period

• Median time to occurrence of other new skin tumours (Keratoacanthoma, Bowen*s disease, Merkel cell carcinoma, malignant melanoma, sebaceous carcinoma) within two years

• Number of patients with new warts within two years

• Number of new warts within two years

• Occurrence of skin infections (Herpes simplex and HPV-infection) within two years

7.2 Methods and Timing for Assessing, Recording and Analysing Efficacy Parameters

7.2.1 Dermatological examinations

Within the scope of dermatological examination the following parameters will be investigated prior trial inclusion (at Screening), at time of enrolment (Day 1) and in three-monthly intervals (Months 3, 6, 9, 12, 15, 18, 21 and 24):

• Skin tumours (squamous cell carcinoma, basal cell carcinoma, keratoacanthoma, Bowen*s disease, actinic keratoses, Merkel cell carcinoma, malignant melanoma, sebaceous carcinoma)

• Skin infections (viral warts, Herpes simplex and HPV-infection)

• General dermatological skin condition (hypertrichosis/alopecia, pruritus, seborrhoea, sebaceous gland hyperplasia, xerosis)

All skin changes will be documented in trial charts and lesions associated with the primary or secondary outcome (i.e. AK, HPV-induced warts) will be

additionally documented onto a documentation grid for numerical follow up.

8. ASSESSMENT OF SAFETY

Study description

Background summary

2. BACKGROUND INFORMATION

2.1 Name and Description of the Investigational Medical Device
MD-3511356 is a sun protection product for prophylaxis of some UV-caused skin damages. It has the status of a Medical Device. MD-3511356 is a further development of the medical device Daylong actinica® that is available as a CE-marked product on several markets. The UV-filters have been changed in order to get a better UVA-protection and to meet the international norms. The product is a lotion, previously filled in tubes and now in dispensers.
Whereas most commercially available sunscreen products consist of UV-reflecting metal-oxides (zinc, titanium), Spirig sunscreen products consequently use liposomal drug delivery mechanisms. The latter promotes adequate delivery of barely visible UV-absorbing filters into the upper part of the epidermis (stratum corneum) and ensures lasting, waterproof UV-protection (> 12 hrs) with a minimum of unwanted side effects (greasiness, whitening effect, sticky feeling on the skin etc). Especially the sustainable protective effect of UV-filters in combination with the low rate of unwanted side effects ensures a high acceptance and compliance of patients in need of permanent UV-protection.
Further to the above mentioned UV-protective measures, the newly formulated sunscreen has superior cosmetic features as a moisturizer and, because of comparably low oiliness, should be favourable for patients with CNI (i.e. cyclosporine) dominated immunosuppression regiments, suffering from associated seborrhoeic facial skin. The vehicle is free from fragrances.

2.2 Rationale for the Present Trial
Sunscreens were described to delay, if not prevent, two major types of skin malignancies:
1. UV-radiation-induced skin malignancies
2. UV-radiation-induced photo-immunosuppression (i.e. depletion of certain T-cell subtypes and Langerhans cells, increase of IL-10).
Whereas the first characteristic is of specific interest for the prevention of skin cancer in younger transplant-patients, prevention against the immunosuppressive aspect of UV-radiation may help to decrease rapid proliferation of early forms of skin cancer, especially actinic keratoses (AK),

invasive squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), but also skin infections (viral warts and others).
Due to above described cosmetic side effects, the compliance regarding the medically advised daily use of sunscreens even in high-risk patients is low, well accepted liposomal sunscreens specifically designed for the requirements of targeted high risk patients could offer a promising alternative for the prevention of subsequent skin cancers.
A first, single-centre, case-control pilot study with Daylong actinica® showed a decrease of AK and a prophylaxis against development of subsequent SCC (and partially BCC) in patients applying liposomal sunscreens on a regular basis for at least 24 months. However, larger, multicentre trials are needed to prove sufficient prophylactic effects for different skin types in differently UV-exposed countries across Europe for this high-risk population of chronically immuno-compromised patients.
2.2.1 Summary of findings from non-clinical and clinical trials
2.2.1.1 Findings from non-clinical trials
No particular toxicological studies have been conducted with the product. Data obtained in animals regarding acute and chronic toxicity as well as from reproductive and mutagenic/carcinogenic studies demonstrate that the excipients/individual constituents should be almost free of toxicity if administered in the recommended manner.
The photoallergic potential of the product was tested according to a standard protocol in volunteers. It could be demonstrated that the product exhibits neither allergic nor photoallergic potential.
In a further trial the irritancy and sensitisation potential of the product have been evaluated in healthy volunteers. After multiple applications the product has not induced sensitisation reactions and it was classified as very well tolerated. The phototoxic potential of a single application of the product was tested in volunteers also according to a standard protocol. Neither an irritating nor a phototoxic potential could be detected.
2.2.1.2 Findings from clinical trials
A preliminary study was performed with 5 different eligible sunscreen products (SPF > 50, High-UVA absorption) to elicit a sunscreen product preference. 9 out of 12 randomly recruited organ transplant recipients (OTRs) (4 kidney (KTR), 4 heart (HTR), 4 liver (LTR) transplant patients) expressed a preference for a liposomal sunscreen product (Daylong actinica®). Thereafter, two groups of 60 OTRs (verum and control) of a specialised transplant outpatient dermatology unit were recruited. Patients in the control group received aside from the initial sun protection education no further support and no free sunscreen products. All patients underwent full body examination prior and throughout the study. Skin cancers from the past medical history since receiving the graft as well as during the study were documented. Within the 24 month study interval 42 of the 120 patients developed 82 new AK (-102 verum vs. 82 control; $p < 0.01$, mean difference 3.07, 95% Confidence Interval of the difference [2.47-3.65]), eight (8) new invasive SCC (0 vs. 8; $p < 0.01$, mean difference 0.133 [0.03-0.23]) and 15 BCC (6 vs. 9; n.s., mean difference 0.05 [-0.08- 0.17]). With an average of 5.6 applications per week, year round for a total of 24

months the compliance and acceptance of the previously chosen liposomal sunscreen was excellent. In spite of equal numbers of AK at baseline a marked difference in favour of the intent-to-treat sunscreen group was recorded after 24 months (89 vs. 273; $p < 0.01$, mean difference 3.07 [1.76-4.36]). The lesion count was significantly lower as compared to the initial visit (89 vs. 191; $p < 0.01$, mean difference 1.7 [0.68-2.72]), indicating even remission of AK under sunscreen protection. There were no statistically significant differences in the incidence of BCC, but the proportion of patients who developed a SCC was markedly reduced in the intent-to-treat group.
In a monocentric placebo controlled study with 10 patients Daylong actinica® has been shown to exhibit excellent skin-protective effects after induction of a polymorphous photodermatosis by UV-Radiation. It could be convincingly demonstrated that adverse dermatological reactions such as infiltrated erythema, pruritus and development of papules were completely prevented in all persons.
2.2.1.3 Risk-Benefit Assessment
Organ transplant recipients (OTR) are highly susceptible to develop non-melanoma skin cancer, such as actinic keratoses, invasive squamous cell carcinomas and basal cell carcinomas. Between 35-50% of OTR develop one or more skin cancers by the tenth year following organ transplantation. The skin cancers are mainly localised on sun-exposed areas (face, head, neck, trunk, hands and arms) in both immuno-competent and immuno-compromised populations. OTR have the opportunity to modify their skin cancer risk by reducing exposure to UV-radiation through the use of sunscreen products, sun-protecting clothing or by avoiding direct sun exposure.
Both the non-clinical trials with volunteers and the clinical trials with patients support the low sensitisation and skin irritation potential of the product. The toxicity profile of Daylong actinica® does not give rise to safety concerns. Clinically insignificant irritation potential may be suggested after administration to the skin. No deaths, serious adverse or other significant adverse events were seen in any of the studies. Postmarketing surveillance data confirmed the safety and tolerability profile of Daylong actinica® (59 reports; one allergic reaction, 45 irritation reactions and 13 further adverse reactions).
Daylong actinica® is an essential treatment for people who are at risk for non-melanoma skin cancers. Taking into consideration the chemical structure and the toxicological profile of the ingredients as well as the results of finished product Daylong actinica® may be considered safe also during long term application when used as recommended. It can be therefore concluded that the therapeutic benefit of the Daylong actinica® formulation outweighs by far possible risks. MD-3511356 is a further development of Daylong actinica® in order to meet the patients* needs in a better way.

2.3 Description of the Route of Administration, Dosage Form, Dosage Regimen and Treatment Period
For Daylong actinica®, the original medical device and precursor product of MD-3511356, the official instruction for use detains under *instruction on

application and dosage* that the lotion should be applied every morning before exposing to the sun to those areas of skin that are or could be exposed to direct sunlight. So the normal dosage recommendation for the product is once daily in the morning. After applying, one should wait a few minutes to allow the lotion to be absorbed into the skin. In this case the product protects for several hours in a maximal way. Reapplying the lotion is only considered following longer periods in the water or having been sweating heavily. The same dosage recommendation is valid for MD-3511356, too.
During the clinical investigations of Daylong actinica® a dose of 2 mg lotion for each cm2 skin surface showed therapeutic efficacy. Therefore for an area of 100 cm2 0.2 g lotion should be used. Based on this assumption, a single dose of 0.5 g lotion (1 pump out of the dispenser) is adequate to treat an area of 250 cm2 (i.e. one hand).
MD-3511356 is provided as a lotion in dispensers of 80 g. The duration of treatment is 2 years. MD-3511356 has to be applied every day without exception.

2.4 Compliance Statement
This clinical trial will be conducted in compliance with this Clinical Investigation Plan, the international guidelines for Good Clinical Practice (GCP) and the applicable local and international regulatory requirements.
The clinical trial follows the European Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of Good Clinical Practice in the conduct of clinical trials on medical products for human use and the harmonised European standards EN ISO 14155-1 and 14155-2. The device used within the clinical trial is developed according to the European Medical Devices Directive 93/42/EEC.

2.5 Description of Trial Population
At total of 300 female and male solid organ-transplant recipients (>= 40 years) with a history of kidney- (including pancreas-), liver-, lung- or heart-transplantation are planned to be enrolled into this clinical trial.

2.6 Literature Background for the Trial
Organ transplant recipients have a particularly high rate of squamous cell carcinoma with a relative risk approximately 100-fold higher than the immuno-competent population.
Studies with renal transplant recipients show that about 93.5% of all squamous cell carcinomas occurring on the traditional *sunny-terraces* of the body mainly head, neck, dorsum of the hands, and forearms. Basal cell carcinoma is increased *only* by a factor of 10 in organ transplant recipients. Whereas, in immuno-competent patients, only approximately 10% of individual lesions of actinic keratosis advance to invasive squamous cell carcinoma during a 5-10 year time frame, in organ transplant recipients the rate of progression of actinic keratosis is apparently accelerated (months) and the incidence of progression higher. Apart from the direct effect of UV radiation causing DNA damage in keratinocytes, increasing evidence supports the hypothesis that UV

radiation has also a negative effect on the local immuno-surveillance of exposed skin and even on systemic immunity. UV radiation inhibits the function of antigen-presenting cells (Langerhans cells) and T-cells with suppressor activities. This inhibition enables previous UV radiation-induced mutant clones to escape from local immuno-surveillance and to proliferate. Systemic immuno-suppression is mainly supported by the induction and release of IL-10 by keratinocytes caused by UV radiation.
UV radiation is not only the major risk factor for non-melanoma skin cancer in organ transplant recipients, but it is presumably the only factor which is *avoidable* in the immuno-compromised organ transplant recipients. Two studies from Australia have shown good evidence that sunscreen products use reduces the prevalence of actinic keratosis and of recurrent squamous cell carcinoma in immuno-competent populations. Sun avoidance and sun protection measures, including sunscreen products application techniques, are usually cornerstones of dermatological education programmes designed for organ transplant recipients worldwide. It has been speculated, that the reason for the early post-transplant development of skin cancer in organ transplant recipients, particularly in elderly patients, is the fact that *dormant* precursor cells of squamous cell carcinoma and lesions (including subclinical actinic keratosis) are frequent, even in the middle-aged population. As long as these earliest steps towards invasive squamous cell carcinoma are well controlled by the local cutaneous immune system, they remain clinically invisible. In contrast, in individuals who are chronically or repetitively exposed to UV radiation, and in systemically immuno-compromised patients such as organ transplant recipients and haemodialysis patients etc as well as the elderly with impaired immuno-surveillance, progression to an invasive squamous cell carcinoma occurs in a relatively short time frame. This fact highlights the need to protect the remaining cutaneous immunity against the UV hazard. This provides the rationale that such primary and even secondary prevention should be part and parcel of the management of organ transplant recipients.
The fact that sun protection can influence previtamin D3 synthesis in skin and the question about the importance of optimal vitamin D levels for general health are a current hot topic both in popular press and in scientific literature, although this still remains currently controversial. In all patients with regular sun protection, it is believed that vitamin D levels should be monitored regularly and should be substituted per os to prevent vitamin D deficiency. On the other hand, excessive sun exposure may also have unwanted side effects on vitamin D metabolism: vitamin D synthesis is maximal at suberythemal UV doses and further UV exposure only increases the conversion of previtamin D3 to lumisterol and tachysterol, both biologically inert compounds. Furthermore, continued sun exposure degrades the active form of the photolabile Vitamin D3.
Taken together, there is good evidence that regular sunscreen products use could prevent immuno-competent patients from developing UV-induced skin cancers. However, there is only one pilot single centre study published so far indicating that daily sun protection is also able to prevent SCC, and to a lesser extend BCC in organ transplant recipients and could even lead towards a

decrease of AK in this high-risk patient group.

Study objective

3. TRIAL OBJECTIVES AND PURPOSE

3.1 Primary Objective
The primary objective is the prevention of actinic keratoses and squamous cell carcinomas by local application of MD-3511356 in comparison to standard sun protection measures in immuno-suppressed solid organ transplant recipients.

3.2 Secondary Objective
The secondary objective is the prevention of actinic keratoses and carcinogenic skin alterations by local application of MD-3511356.

3.3 Safety Objectives
Safety will be assessed by means of treatment related adverse events, local tolerability and Vitamin D serum levels (25-OH-Vitamin D3).

Study design

4. TRIAL DESIGN
4.1 Endpoints
All efficacy endpoints will primarily be assessed on treated target areas (face, scalp, head, neck, forearms and hands) only (with exception of SCC), within the period of two years.
4.1.1 Primary efficacy endpoint
• New actinic keratoses or squamous cell carcinomas
4.1.2 Secondary efficacy endpoints
Secondary efficacy endpoints will be:
• New actinic keratoses, squamous cell carcinomas or basal cell carcinomas
• New squamous cell carcinomas
• New squamous cell or basal cell carcinomas

4.1.3 Exploratory efficacy endpoints
Exploratory efficacy endpoints will be:
• New basal cell carcinomas
• Actinic keratoses (numbers within two years and at the end of the two years period)
• Other new skin tumours
• New warts
• Skin infections
4.1.4 Safety endpoints
• Related adverse events
• Local tolerability

• Vitamin D serum levels

4.2 Design of Trial

4.2.1 Trial design and schedule of assessments

The clinical trial is designed as an open-label, randomised, comparative, multicentre trial comparing UV-protection treatment with MD-3511356 versus standard sun protection measures (inc. commercially available UV-protection sunscreen products) in immunosuppressed solid organ transplant recipients for 24 months. All patients considered for screening must have a confirmed history of kidney- (with or without pancreas), liver-, lung- or heart-transplantation.

After all the inclusion and the exclusion criteria have been checked and all screening procedures have been performed, the patient will be elected for trial participation by the Investigator. Recruitment phase is expected to last 3 months. Treatment per patient will be 24 months.

A minimum number of 20 patients need to be enrolled in each centre. A total of 300 patients is planned to be randomly assigned in a ratio of 2:1 to one of two treatment arms:

Group A: Patients will receive detailed information on standardised sun protection measures. Additionally, they will be provided free of charge with MD-3511356 for application to sun exposed skin areas once daily in the morning for 24 months. MD 3511356 lotion will be applied topically on the sun-exposed skin areas (face, neck, head, forearms and hands) in doses corresponding to the surface extent (see chapter 6.1). The dispensers will be provided with a dosage pump to allow application of reproducible amounts (each pump 0,5 g).

Group B: Detailed information on standardised sun protection measures and application of self-provided sunscreen products. The Investigator may decide on an individual reimbursement of patient's expenditure (out of the centre's budget).

Trial procedures will include dermatological examinations every 3 months, (assessment of skin infections and general dermatological skin condition) and keeping of a dosing- and UV-exposition diary by the patient.

4.3.1 Randomisation procedure

Patients who meet all of the inclusion criteria and none of the exclusion criteria will be eligible for randomisation. Eligible patients will be centrally randomised in a 2:1 ratio to one of the two treatment arms, either MD-3511356 or standard sun protection measures. By the use of a randomisation FAX within each centre each patient will receive a unique random. The trial medication behind this random number is pre-determined by a computer-generated randomisation procedure. Randomisation will be conducted on a competitive basis across all trial centres.

4.3.2 Blinding procedure

Not applicable, as this will be an open-label trial.

4.4 Treatment, Trial Medication, Dosage, Application Form and Labelling

4.4.1 Application, period of application

In Group A the lotion MD-3511356 will be applied topically each morning on the sun-exposed areas (face, neck, head, forearms and hands) in doses corresponding to the surface extent. After application, patients need to wait for 2-3 minutes to allow the lotion to dry. The dispensers will be provided with a dosage pump

to allow application of reproducible amounts (each pump 0.5 g). MD-3511356 will be used once daily for 24 months.
Group B will use self-provided sunscreen products.
4.4.2 Investigational product
The investigational product supplied by the Sponsor will have been manufactured, tested and released according to current GMP guidelines. MD-3511356 is provided by Spirig Pharma AG. The comparator sun protection products will be bought from a pharmacy or from drug stores by the patient himself.
4.4.3 Packaging and labelling
The investigational medical device is signed for use in clinical trials only. Each dispenser is labelled with the following information: patient random number, Group A, protocol number, batch number, expiry date, name of the sponsor, to store at room temperature, for clinical trial use only.
4.4.4 Storage
The medical device should be stored at room temperature.
4.5 Trial Period/Duration of Patient Participation
Before enrolment and treatment, patients at each trial centre will be pre-screened for eligibility in the 1st quarter 2010. The following recruitment period is expected to last 3 months. The duration of the trial for each patient will last 24 months.
Patients* recruitment is planned to start in the 2nd quarter 2010 (First-patient-in) and is planned to end 3 months after recruitment start (Last-patient-in). Recruitment is completed when the planned patient number is achieved. Last-patient-out is scheduled for 3rd / 4th quarter 2012.
4.6 Accountability Procedures for the Investigational Medical Device
The number of dispensers used will be documented. The dispensers will be weighted to determine the remaining amount of sun protection lotion in the container.

Intervention

6. TREATMENT OF PATIENTS

6.1 Administration and Treatment Period
Patients will be randomly assigned in a ratio of 2:1 to one of two treatment arms:
Group A: Patients will receive detailed information on sun protection measures. Additionally, they will be provided free of charge with MD-3511356 for application to sun exposed skin areas once daily in the morning for 24 months. Every morning MD-3511356 should be applied liberally to those skin areas exposed to direct sunlight before exposing to the sun. It should be applied before using the normal cosmetics (allow a few minutes for MD-3511356 to be absorbed by the skin). Following longer periods in the water or after sweating heavily reapplication is indicated.
Group B: Detailed information on standardised sun protection measures and

application of commercially available self-provided sunscreen products.

Study burden and risks

Not applicable

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients must meet all of the following criteria in order to be eligible for entry into the trial:
1. Out-Patients of either sex aged >= 40 years
2. Life-expectancy of 2 years at minimum
3. Solid organ-transplant recipients who received a kidney (including pancreas), liver, lung, or

heart transplant
4. Patients treated for 5 years with an immunosuppressant medication
5. Severe sun damage of the skin
6. Multiple actinic keratoses (2-5 lesions) and/or multiple dysplastic naevi
7. No present squamous cell carcinoma, basal cell carcinoma or malignant melano-ma; but history of cutaneous/cutaneous invasive malignancy with restitutio ad integrum is allowed
8. Patients who are able to understand and provide written informed consent to participate in the clinical trial (signed informed consent) according to ICH-GCP

Exclusion criteria

Patients must not be enrolled in the trial if any of the following criteria is met:
1. Non-Caucasian
2. Absence of sun damage i.e. no signs of AK
3. Multi-organ transplantation (exception: simultaneous transplantation of kidney and pancreas)
4. Evidence of systemic infection, except viral hepatitis, at the time of recruitment
5. Known or supposed systemic malignant tumour or systemic chemotherapy within the last 5 years prior to randomisation
6. Patients participating in a clinical trial within the last four weeks before trial
7. Patients treated with the antitumour/antiangiogenetic immunosuppressant sirolimus, respectively everolimus, or acitretin or any other systemic treatment for AK at the time of randomisation
8. Patients treated with a topical drug for the AK at the time of randomisation (exception: excision or kryotherapy for hyperkeratotic lesions are allowed)
9. Change of the immunosuppression-treatment less than 3 months ago or planned
10. Present or planned interferon therapy (in liver transplant patients with hepatitis B/C)
11. Female patients with childbearing potential with a positive pregnancy test, breast feeding, or female patients with childbearing potential without adequate contraception

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-03-2011
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO

Date:	15-09-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL32571.058.10