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Title

A phase II study evaluating the non-inferiority of a photodynamic therapy protocol involving the Flexitheralight device compared to the conventional protocol. (FLEXITHERALIGHT study)

Name and contact information for the trial sponsor:

Centre Hospitalier Universitaire de Lille (CHRU of Lille), Direction de la Recherche et de l'Innovation (DRI), 6 rue Pr Laguesse, 59037 Lille Cedex, tel : +33 (0)3 20 44 59 69, Fax : +33 (0)3.20.44.57.11
ABSTRACT

Background: Actinic Keratosis (AK) are common pre-invasive cancerous lesions in sun-exposed skin, which negatively affect the quality of life in patients and may progress to invasive squamous cell carcinoma (SCC). Studies have shown that if untreated, AK may regress, or alternatively, may progress to SCC, with significant morbidity and possible lethal outcome. The most commonly used treatments for AK are cryotherapy, topical chemotherapy and, more recently, photodynamic therapy (PDT). This clinical study is part of a project, which aims at the creation of specific light emitting fabrics (LEF) in order to strongly improve the efficiency and reliability of PDT.

Objectives: This study aims to compare the effectiveness and tolerability of a new PDT protocol involving the device Flexitheralight (N-PDT) versus the classical protocol involving the device Aktilite®128 (Galderma) (C-PDT) for the treatment of AK. All participants receive both protocols. The primary objective is to compare the lesion response rate at 3 months of N-PDT versus C-PDT. Secondary objectives are the evaluation of the pain and local tolerance during treatment, the clinical evolution of the subject's skin aspect, the quality of life and satisfaction of patients.

Methods: The study is a split-face intra-individual comparison of two PDT protocols. The number of patients to be recruited is 42. Patients are exposed to a continuous red light spectrum with Aktilite®128 on one face, and, to a fractionated illumination with the new device Flexitheralight on the other face.

Males or females over the age of 18 years with a clinical diagnosis of at least 10 previously untreated, non-pigmented, non-hyperkeratotic AK of Grade I and II of the forehead and/or scalp (according to Olsen et Al. JAAD 1991) are included in the department of dermatology of the Lille University Hospital. The patients come to the investigational center for one treatment session (Day 1) and they are followed at Day 7, Month 3 and Month 6. A second session of treatment can be performed at Day 111 in case of incomplete response at Month 3. Data are analysed using SAS software version 9.4 (SAS Institute Inc., Cary, North Carolina, USA). Continuous variables are expressed as the mean and standard deviation and categorical variables are expressed as the frequency and percentage. The Shapiro-Wilk test will be used to assess the normality of the distribution.

Results: Investigations are achieved but data analysis is ongoing. The statistical results will be analyzed by the end of 2018.

Conclusion: In case of non-inferior efficiency and better tolerability than C-PDT, N-PDT could become the treatment of choice for AK. Moreover, N-PDT is easy to implement in hospitals.

Ethical Approval

This study was performed in accordance with the ethical principles of the Declaration of Helsinki (2008) and the International Conference on Harmonisation - Good Clinical Practices (ICH-GCP) and in compliance with article L. 1121-4 of the French Public Health Code. The study design was reviewed and approved by the French National Agency for the Safety of Medicines and Health Products (ANSM) (authorization number: 2013-A01096-39) and the French Ethics Committee (CPP) (authorization number: CPP-03/051/2013).

Registered Report Identifier: N° ID-RCB 2013-A01096-39
Keywords
Photodynamic therapy, actinic keratosis, light emitting fabrics, Aktilite.

Word Count: 3446
INTRODUCTION

Background and rationale

Actinic Keratosis (AK) are common pre-invasive cancerous lesions in sun-exposed skin [1], which negatively affect the quality of life in patients and may progress to invasive squamous cell carcinoma (SCC) [2].

AK usually develop on areas that are frequently exposed to the sun (e.g., face, ears, scalp, neck, forearms, and back of the hands). Patients with AK often express embarrassment, worry, and irritation related to the change in appearance of their skin and unsightly nature of the lesions [3]

In addition to the emotional strain, AK can be painful and easily traumatised causing bleeding [4] [5] [6] [7].

Studies have shown that if untreated, AK may regress, or alternatively, may progress to SCC, with significant morbidity and possible lethal outcome [8].

The malignant potential and the fact that it is impossible to predict which AK will evolve into SCC have led to the common consensus that AK have to be treated [9].

The most commonly used treatments for AK are cryotherapy, topical chemotherapy and, more recently, photodynamic therapy (PDT).

PDT is based on activation of light-sensitive molecules (photosensitizers) localized in the diseased tissues resulting in the formation of reactive oxygen species, which cause tissue injury and cell death. 5-Aminolevulinic acid (ALA) and its ester methyl aminolevulinate (MAL) are most often used in topical PDT. Metvixia® is a 16% MAL cream. PDT with MAL (MAL PDT) has been shown to be an attractive treatment modality for AK because it allows treatment of large areas, it has a high response rate and results in an excellent cosmesis [10].

Conventional PDT (C-PDT) usually includes the incubation of ALA or MAL for several hours. Applied on the skin this photosensitizer is endogenously converted by the heme biosynthetic pathway to protoporphyrin IX (PpIX) and other intermediate photosensitizing porphyrins [11] leading to a high and selective accumulation of PpIX in the target lesion [12].

Indeed abnormal cells accumulate more photosensitizer than normal cells, resulting in selective destruction of abnormal cells.

C-PDT is already well developed, but the existing light sources are rigid plan devices, which do not allow a homogeneous illumination on convex surfaces such as a scalp. Accordingly, we do not know the light dose really delivered during C-PDT. Some lesions may be under-treated. This could explain some treatment failures.

Moreover, C-PDT is only available in specialized environments (hospitals, clinics) and not sufficiently developed and spread.

This clinical study is part of a project, which aims at creation of specific light emitting fabrics (LEF) in order to strongly improve the efficiency and reliability of PDT.
Flexitheralight is a new device, which seems to be perfectly adapted to treat skin zones because of its homogeneity, low weight, flexibility and its cheaper cost. Therefore, it should be possible to use it at home after the diagnosis and treatment definition by specialists.

METHODS AND ANALYSES

Trial design

The trial is a proof of concept study, comparative (split-face intra-individual comparison), randomized, open-label, single center evaluation of the non-inferiority of N-PDT versus C-PDT.

Setting

The study has been conducted at the Lille University Hospital in the department of dermatology over a period of 24 months until the end of 2017. 42 patients had to be included and followed during 6 months.

Device

Flexitheralight is a new illumination device consisting of light emitting fabrics (LEF) connected to a laser source.

Figure 1: Flexitheralight device
In order to perform fractionated illumination, 3 LEF, having a size of 20 cm x 5 cm are positioned on the patient’s head.

Figure 2: Illumination protocol.
Each LEF is connected to a 635 nm laser source, which is tuned in order to deliver an irradiance of 12.3 mW/cm². This irradiance is controlled by a power meter (OPHIR, PD 300).

The 3 LEF are activated sequentially as follow:

- ON: 60 s - OFF : 120 s
- This sequence is repeated 50 times.

When using these parameters, the total fluence is 37 J/cm² for an illumination time of 2h30.

Participants

Table 1: in/exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Males or females over the age of 18 years</th>
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<tbody>
<tr>
<td>Clinical diagnosis of at least 10 previously untreated, not-pigmented, non-</td>
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<tr>
<td>hyperkeratotic AK of Grade I and II of the forehead and/or scalp (according to</td>
<td></td>
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<tr>
<td>Olsen et Al. JAAD 1991, [13]).</td>
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<tr>
<td>Other therapies not unacceptable or considered medically less appropriate</td>
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<tr>
<td>Symmetrical repartition of AK in terms of number and severity of lesions on both</td>
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<tr>
<td>areas of the forehead and/or scalp. The axis of symmetry between the two areas</td>
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<tr>
<td>is defined by the investigator according to the distribution of lesions.</td>
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<tr>
<td>Diagnosis of AK is determined upon clinical evaluation (i.e. visual inspection and</td>
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<tr>
<td>palpation) by the investigator</td>
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<tr>
<td>No treatment of AK in the previous 30 days</td>
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<tr>
<td>The two areas to be treated should not be coalescing. A minimum distance of 10</td>
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<tr>
<td>mm is required between the lesions located on the 2 symmetrical areas. A minimum</td>
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<tr>
<td>distance of 2 mm is required between the lesions on the same side.</td>
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<tr>
<td>Minimum 5 lesions and maximum 7 lesions with similar dimensions at both symmetrical</td>
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<tr>
<td>areas are treated. If the number of lesions is &gt;7, only 7 lesions on each area are</td>
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<td>considered.</td>
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<tr>
<td>Exclusion criteria</td>
<td>Patients with porphyria</td>
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<tr>
<td>Exclusion Criteria</td>
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<tr>
<td>Immunosuppressed patients for idiopathic, disease specific or therapeutic reasons</td>
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<tr>
<td>Use of topical corticosteroids to lesional areas within 2 weeks before PDT</td>
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<tr>
<td>Patients receiving local treatment (including cryotherapy and curettage-electrocoagulation any PDT treatment) in face / scalp area within the last 30 days.</td>
<td></td>
</tr>
<tr>
<td>Patients receiving topical treatment (including imiquimod, 5-FU and diclofenac, ingenol mebutate) in face / scalp area within the last 3 month.</td>
<td></td>
</tr>
<tr>
<td>Use of topical retinoids or alpha-hydroxy acids, urea or systemic retinoids, chemotherapy or immunotherapy within 4 weeks of PDT</td>
<td></td>
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<tr>
<td>Pigmented AK lesions. Known allergy to Metvixia®, a similar PDT compound or excipients of the cream including arachis oil, or peanut or soya.</td>
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</tr>
</tbody>
</table>

| Additional exclusion criteria | Participation in other clinical studies either currently or within the last 30 days  
<table>
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<tbody>
<tr>
<td>Female subjects must be of either:</td>
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</table>
| ▪ Non-childbearing potential, i.e. post-menopausal or have a confirmed clinical history of sterility (e.g. the subject is without a uterus) or  
| ▪ Childbearing potential, provided there is a confirmed negative urine pregnancy test or blood analysis prior to study treatment, to rule out pregnancy. |
| Any condition which may be associated with a risk of poor protocol compliance. |
| Patients currently receiving regular ultraviolet radiation therapy |

**Study Objectives / Outcomes**

**Primary Objective**

- Comparison of the lesion response rate at month 3 of N-PDT versus C-PDT.

**Key Secondary Objectives**

- Treatment tolerability
- Complete response rate at month 6
- Cosmetic results.
- Patient quality of life and satisfaction
Outcomes for objectives are described in Table 2.

Table 2. Outcomes

<table>
<thead>
<tr>
<th>Complete Response Rate</th>
<th>Total disappearance of each lesion</th>
<th>Visit 3, month 3</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Number of patients having a 75% lesion reduction rate</td>
<td>Visit 3, month 3</td>
</tr>
<tr>
<td></td>
<td>Total disappearance of each lesion</td>
<td>Visit 4, month 6</td>
</tr>
<tr>
<td></td>
<td>Number of patients having a 75% lesion reduction rate</td>
<td>Visit 4, month 6</td>
</tr>
<tr>
<td>Tolerability</td>
<td>Evaluation of pain (Visual Analogical Scale)</td>
<td>Visit 1, Day 1</td>
</tr>
<tr>
<td></td>
<td>Evaluation of pain (Visual Analogical Scale)</td>
<td>Visit V3bis, Day 111</td>
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<tr>
<td></td>
<td>Local tolerance (Adverse event, Serious adverse event, Concomitant treatments)</td>
<td>Visit 2, Day 7</td>
</tr>
<tr>
<td></td>
<td>Local tolerance (Adverse event, Serious adverse event, Concomitant treatments)</td>
<td>Visit 1, Day 1</td>
</tr>
<tr>
<td></td>
<td>Local tolerance (Adverse event, Serious adverse event, Concomitant treatments)</td>
<td>Visit V3bis, Day 111</td>
</tr>
<tr>
<td>Cosmetic results</td>
<td>4 points scale for clinical assessment of the subject's skin aspect (Excellent, good, fair, poor)</td>
<td>Visit 1, Day 1</td>
</tr>
<tr>
<td></td>
<td>4 points scale for clinical assessment of the subject's skin aspect (Excellent, good, fair, poor)</td>
<td>Visit 3, Month 3</td>
</tr>
<tr>
<td></td>
<td>4 points scale for clinical assessment of the subject's skin aspect (Excellent, good, fair, poor)</td>
<td>Visit 4, Month 6</td>
</tr>
<tr>
<td>Quality of Life &amp; Satisfaction</td>
<td>DLQI +Questionnaire of satisfaction</td>
<td>Visit 1, Day 1</td>
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</table>
Sample size

The study is designed to have a statistical power of 80% with a one-sided alpha level of 0.025 to demonstrate non-inferiority in terms of lesion complete response rate versus incomplete response at Month 3 of N-PDT compared to C-PDT. Assuming a lesion complete response rate of 75% in both areas, an intra-patient correlation in both lesions and areas, and a non-inferiority margin of 10%, the number of required lesions per area is 245. This corresponds, based on 12 lesions per patient (6 lesions per patient per area), to 42 patients.

Allocation/randomization

Patient, who met all of the eligibility criteria, were included in the study for a central randomization.

The randomization schedule was generated by the statistician using the PROC PLAN procedure of SAS (SAS Institute Inc., Cary, North Carolina, USA) with a 1:1 allocation ratio and a block size of six. Allocation was concealed by using sequentially numbered, opaque, sealed envelopes that were opened sequentially by the investigator at the beginning of the treatment.

Implementation/ Blinding

The study was not blinded, patients and investigator knew the procedure allocation. The evaluation of efficacy and tolerability was made knowing the type of treatment assigned to each area. Data analysis will also be made without blinding.

Interventions

Before the implementation of any trial procedure, the patient, who has been informed of the study, has signed his / her consent at the screening visit

Figure 3: Schema of the study
As shown in Figure 3, after screening, patients who met all the criteria for inclusion and non-inclusion, were randomized and invited to come to the investigation site for 4 visits at Day 1, Day 7; Month 3 and Month 6. In case of incomplete clinical response at Month 3, patients were re-treated with PDT during a visit 3bis at Day 111.

Visit 1:

Subject skin aspect was evaluated and the treatment of the two areas was administered according to study protocol and randomization. In order to avoid mistakes in the selection, the randomization was performed after the definition of the axis of symmetry.

Figure 4: Schema of the randomization process for area A and area B

The global area of the scalp and front was divided, randomly, into two symmetrical areas (Zone A and Zone B) with the same number and the same grade of AK. The areas to be treated were localized between the eyebrows and the neck. Included AK were located, counted, graded and photographed.
For each patient, “n” lesions on the A area were treated by a technique 1 (N-PDT or C-PDT) and “n” lesions on the B area were treated by the second technique 2 (N-PDT or C-PDT) (5≤n≤7).

**Preparation and treatment of the lesions**

Before applying Metvixia® cream, the area were prepared by removing the crusts with a small curette and by scraping gently the surface of the lesion in order to roughen the surface.

**Area A: C-PDT:**
Metvixia® cream was applied with a spatula (about 1 mm thick) on the selected lesions and over a range of 5 to 10 mm of normal skin around the lesions. The treated area was covered with an occlusive and lightproof dressing for 3 hours.

The dressing was removed and the area cleaned with a saline solution, then immediately exposed to a continuous red light spectrum (between 7 and 10 minutes) from 570 to 670 nm for a total light dose of 37 J/cm² to the surface of the lesion area.

**Figure 5: Metvixia application and dressing**

**Area B: N-PDT:**
Metvixia® cream was applied as for the area A and the area is covered with an occlusive and transparent
dressing (Tegaderm) for 30 minutes. After 30 minutes, the dressing was not removed and irradiation was applied during 2h30. A total light dose of 37 J/cm² was administered within a spectrum of 635 nm.

Figure 7: Illustration of the treatment procedure with N-PDT

The total duration of the treatment procedure (treatment of areas A and B) was approximately 3 hours and 20 minutes.

The pain was scored by the patient in the two treated areas after treatment: first for the N-PDT area and then for the C-PDT area.

Patients completed the quality of life questionnaire (DLQI) and the satisfaction questionnaire at the end of the procedure.

Visit 2 was made 7 days after treatment to evaluate the tolerability and adverse effects. Patients filled the dermatology life quality index (DLQI) and satisfaction questionnaires. Photographs of the treated areas were taken under standardized conditions.

Visit 3 was made at Month 3. The investigator evaluated the response of treatment by comparing the lesions between the current visit and the first one (referring to the tracing paper and photographs taken during the first visit). If some of the treated AK remained, a new visit was scheduled within three weeks to treat these remaining lesions.

The remaining lesions of each area were located, counted and graded. Only the presence of lesions was taken into account but not any change in their size. If a new lesion appeared, it was treated (by the same procedure), but it was not be considered for the comparison of lesions between Month 3 and 6.

A photograph of the two treated areas was taken. Patients completed the DLQI and the satisfaction questionnaires and all adverse events and concomitant medications were notified.

Concerning the patients whose AK have completely disappeared, they were invited to the assessment visit of the response at Month 6.
Visit 3bis was optional and carried out only in case of at least one remaining AK after 1st treatment and if the investigator considered that it was necessary to treat again by PDT.

The same treatment as at visit 1 was applied.

Visit 4 was made at Month 6. The investigator evaluated the response of treatment by comparing the lesions between the current visit and the first one. A photograph of the two treated areas was taken. Patients completed the DLQI and the satisfaction questionnaires and all adverse events and concomitant medications were notified.

The tolerability of the device was verified on the first five included patients. The study was completely interrupted if:

- There was at least one patient (in the first 5 patients included) whose pain measured by the pain assessment scale was greater than or equal to 5/10 on the N-PDT area.
- There was at least one Serious Adverse Event related to N-PDT.

DATA COLLECTION, MANAGEMENT AND ANALYSIS

Variables/data collection

The collected data consisted of: demographic data, medical history review, previous radiotherapy, surgery and treatment of AK, definition of AK (localisation, number, grade and photography), and assessment of the subjects' skin aspect.

Biological analysis (urine pregnancy test) was realized for women with childbearing potential. Several scales (pain, aesthetic aspect, treatment tolerance) and questionnaires (DLQI, satisfaction) were used.

Data management

All medical observations were kept in the patient's file; the data regarding the study were reported on an electronic case report form (e-CRF) according to good clinical practice and the sponsor Standard Operating Procedures. The data collection was exhaustive and checked regularly by a clinical research associate, according to the protocol procedures. Any deviation from the protocol must be noted, and the reason for the deviation must be documented. Discrepancies in the data were brought to the attention of the clinical team, and investigational site personnel, if necessary, in the form of a query. Resolutions to these issues were reflected in the database.

Statistical methods
Continuous variables will be expressed as the mean and standard deviation, and categorical variables will be expressed as the frequency and percentage. The Shapiro-Wilk test will be used to assess the normality of the distribution. This normality will also be evaluated graphically.

Analysis of the main objective
In this study, each patient could have several lesions. We have to take into account the “patient” effect. Indeed, it could exist a correlation between the outcome measures in a same patient (cluster effect). The complete response rate of lesions will be analysed according to the group using the generalized linear mixed model to consider the cluster effect with adjustment on the period (by the area). The confidence interval of 95% of the difference in response rates between the two groups will be calculated ($D = N-PDT-C-PDT$). We will conclude to the non-inferiority if the lower limit of the confidence interval is greater than - 10%. In case of non-inferiority, a superiority test will be performed.

Analysis of the secondary objectives
The rate of patients with at least 75% of reduction of the lesion ($\geq 4$ destroyed if five lesions $\geq 5$ if 6 lesions and $\geq 6$ if 7 lesions) will be calculated in each group and compared using a generalized linear mixed model.
For other comparisons, the previous method will be used to compare qualitative variables from two groups. For continuous variables, we will use the linear mixed model. The pain levels reported at the end of each treatment will be compared using a linear mixed model with patients as random effects (the significance level was set at 0.05).

All of the statistical analyses will be performed using SAS software version 9.4 (SAS Institute Inc., Cary, North Carolina, USA) by the platform of methodological assistance of CHRU of Lille (Head Prof. Duhamel A).

RESULTS AND DISCUSSION

Given the premature termination of the Flexitheralight study, only 27 patients were recruited instead of the planned 42. 23 patients completed all visits of the study and their data will be analysable.

The figure below shows the evolution of the number of subjects included, followed and analysable

Figure 8: Study flow chart
As part of the primary objective, we hope to demonstrate that N-PDT is not inferior as C-PDT in terms of lesion response rate at Month 3.

As part of the secondary objectives, we will demonstrate that N-PDT is less painful and better tolerated than C-PDT to treat AK.

The adverse effects associated with C-PDT are usually, a local reaction at the treatment site attributable to the toxic effects of PDT (phototoxicity) or the preparation of the lesion. The most common symptoms are: pain and discomfort described as burning and stinging, erythema, encrusting sensations of skin pain. Usually, the symptoms begin at the moment of illumination or just after and for a few hours, and usually disappear on the day of treatment.

The possible risks relating to the N-PDT are minimal. The fabrics used are made of microfibres and polymers of polymethyl methacrylate. These two materials do not cause any problem when in contact with the skin for short periods. In addition, the use of an occlusive dressing between skin and tissue significantly reduces exposure.

With regard to the light delivered, the objective is to deliver 12.3 mW/cm², which is low compared to, for example, the power of the sunlight at midday in summer in Munich (22 mW/cm²).

The expected benefit for the patients participating in the study are to reduce the pain experienced during the treatment and thus make it comfortable. Indeed, illumination during C-PDT is intensively administered for a short period of time, which can make it more painful.

In addition to the impact on pain, the illumination achieved by N-PDT may be more homogeneous, which should lead to better efficiency. The size and texture of the fibers may be better suited to areas without hair. N-PDT could be performed in all weather conditions, in any geographic location, year-round and could therefore become the treatment of choice for AK.

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The author wish to thank all research and medical personnel involved in the design and conduct of this study

Author contributions

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Dr C. Vicentini (Hôpital Claude Huriez, Rue Michel Polonowski, 59000 Lille, Tel: +33 (0)3 20 44 48 68, Fax: +33 (0)3 20 44 59 16, claire.vicentini @chru-lille.fr) drafted the manuscript, selected and followed patients.

AS. Vignion Dewalle, E. Thecua, P. Deleporte, Inserm U1189 ONCO THAI, 1 avenue Oscar Lambret, 59037 LILLE, Tel: +33 (0)3 20 44 67 09 helped revising the protocol, participated in the conception, technical maintenance of the device.

Pr S. Mordon, critically reviewed and approved the final manuscript for publication.

A. Duhamel, wrote the statistical analysis plan and his unit will analyse results of the study.

**Funding**

This study is supported by the French National Research Agency (ANR) [Projet-ANR-12-EMMA-0018, http://www.flexitheralight.com/] and sponsored by the University Hospital of Lille (CHU).

Galderma International provided graciously Metvixia.

**Conflicts of Interest:** Claire Vicentini received travel grants and accommodation expenses to attend the 16th Annual Congress of the European Society for Photodynamic Therapy in Munich, Germany, February 10-11, 2017.

All other authors declare to have no conflicts of interest.

The full study protocol can be accessed by contacting the corresponding author FL.

**BIBLIOGRAPHIE**


**ABBREVIATIONS**

AK Actinic Keratosis

ALA Aminolevulinic Acid

C-PDT Classical Photodynamic Therapy

DLQI Dermatology Life Quality Index

E-CRF Electronic Case Report Form

LEF Light Emitting Fabrics
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>MAL</td>
<td>Ester Methyl Aminolevulinate</td>
</tr>
<tr>
<td>N-PDT</td>
<td>New Photodynamic Therapy</td>
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<tr>
<td>PDT</td>
<td>Photodynamic Therapy</td>
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<tr>
<td>PpIX</td>
<td>Protoporphyrin IX</td>
</tr>
<tr>
<td>SCC</td>
<td>Squamous Cell Carcinoma</td>
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