1. TITLE PAGE

<table>
<tr><td colspan="3">Title
Gene expression in renal transplant patients with field Actinic Keratosis undergoing Metvix® PDT</td></tr>
<tr><td>Project Name
Metvix® PDT</td><td>Project Number
834</td><td>Clinical Phase
IV Exploratory</td></tr>
<tr><td colspan="2">Investigational Product
Metvix® PDT</td><td>Reference Product
None</td></tr>
<tr><td>Subject Population/Indication
Renal transplant male or female subjects, aged at least 18 years old, with history of immunosuppression from 5 to 15 years, and with a diagnosis of field actinic keratosis on face, scalp, forearms or chest (minimum of 4 discrete mild or moderate AKs), meeting specific inclusion/exclusion criteria.</td><td>Treatment/Study Duration
The study duration for each subject was approximately 16 months.</td><td>Dosage Regimen
Treatment with Metvix® PDT at baseline and week 12.</td></tr>
<tr><td colspan="3">Design
Open, single-center, , exploratory study</td></tr>
<tr><td colspan="2">Study Initiation Date
11 March 2010</td><td>Study Completion/Termination Date
7 October 2011</td></tr>
<tr><td colspan="3">Eudract n°
2008-001603-30</td></tr>
</table>

This study, including the archiving of essential study documents, was performed in compliance with ICH Good Clinical Practice (ICH E6) and local legal requirements. This abbreviated clinical study report addresses the internal reporting needs for Phase IV studies conducted by Galderma R&D.

All data provided to the investigator and his/her staff and all data obtained through this Galderma report will be regarded as confidential and proprietary in nature and will not be disclosed to any third party without Galderma's written consent.

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2. SYNOPSIS

Title of study	Gene expression in renal transplant patients with field Actinic Keratosis undergoing Metvix® PDT
Investigators	1 center participated in this study.

Name & location	Center #	# of recruited subjects	Participation dates FSI - LSO
		9	11Mar2010 – 07Oct2011

Study centers	1 center in the United Kingdom
Period of study	11Mar2010 – 07Oct2011
Publications	Not applicable
Clinical phase	IV exploratory
Study objectives	The aim of this study was to determine possible molecular changes on large scale gene expression profiling after treatment with Metvix® Photodynamic therapy (PDT) of Actinic Keratoses (AK) and cancerised field in renal transplant recipients. It was to be studied if Metvix® reduces the number of molecular aberrations leading to epidermal neoplasia in the treated area. Both the treatment effect [on existing lesions (actinic keratoses)] and the prophylactic effect (prevention of appearance of new lesions) were to be measured and linked to the effect on gene expression.
Methodology	This was an exploratory, mono-center and open study. The total duration of the study was almost 16 months, with a maximum of 6 study visits occurring at Screening, Baseline, Week 12, Week 18, Month 9 and Month 15. Two phone calls for safety assessment are performed at Week 1 and Week 13. Biopsies were performed at Screening and Week 18 for further genomic analyses.
Number of subjects	A total of 10 subjects were planned to be enrolled. A total of 9 subjects were actually enrolled at 1 center.
Inclusion criteria	Renal transplant male or female subjects, aged at least 18 years old, with history of immunosuppression from 5 to 15 years, a diagnosis of field actinic keratosis on face, scalp, forearms or chest (minimum of 4 discrete mild or moderate AKs) and meeting other specific inclusion/ exclusion criteria.
Investigational product Name and form Mode of administration Lot number Duration of treatment	Metvix® Photodynamic Therapy (PDT) Methyl aminolevulinate cream Topical administration on the whole target field (AK field of 5x10cm² localized on face, scalp, forearms or chest) after lesion preparation (if applicable). The border of the target field must be at least at 5mm from the clinically visible edge of each lesion included in it. The target field was then covered with occlusive dressings (Tegaderm® and Cicaplaie® or equivalent). 0176E, and 000527 Two treatment sessions at Baseline and at Week 12. Metvix® cream was applied for 3 hours on the whole target field, and then removed. The target field was then be exposed to red light (using a large-field LED light source: Aktilite® 128 lamp) during 7 to 10 minutes at a dosage of 37 J/cm².
Reference product	None

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Non-Investigational products to be provided for the study:	Urine Pregnancy tests (Elle® test) Occlusive dressing (Tegaderm® dressing 10X12 cm and Cicaplaie® Hypoallergenic dressing 20X10 cm)
Evaluation criteria Efficacy criteria	• Gene expression using micro-arrays Affymetrix® in lesional, peri-lesional skin (at Screening and Week 18) and in healthy skin (at Screening only), • Clinical AK lesions response with a dichotomous scale (complete and non-complete) in the target field assessed at each evaluation visit (including new and recurrent lesion(s)). • Global percent reduction from Baseline in AK lesion count in the target field (including new and recurrent lesions) at Month15,
Safety criteria	• Incidence of Adverse Event, • Subject skin discomfort (including pain) assessed by the subject immediately after each treatment session, by Visual Analogue Scale, at Baseline and Week 12.
Other variables	• Photographs of target field were taken at Screening, Baseline, Week 12, Week 18, Month 9 and Month 15 visits.
Statistical methods	Inter-individual comparison of gene expression in lesional, peri-lesional and healthy skin before and after treatment was analyzed using pairwise comparisons of gene expression profiles between each pair. Other variables were descriptively summarized.

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SUMMARY, RESULTS

	Metvix PDT
Subject Disposition	
N	9
Normal study completion, n (%)	7 (77.8%)
Discontinued, n (%)	2 (22.2%)
Adverse Event	1 (11.1%)
Lost of follow-up	1 (11.1%)
Intent to treat population (ITT)	9 (100%)
Safety population (APT)	9 (100%)
Demographics	
Gender, n (%)	
Female	1 (11.1%)
Male	8 (88.9%)
Age, year (mean ± SD)	59.8 ± 8.89
Race, n (%)	
Caucasian	9 (100%)
Baseline characteristics	
Lesion counts, n	
Mean ± SD	5.6 ± 2.1
Median	4.0
Min, Max	4, 9
Lesion severity, n (%)	
N	50
Mild	26 (52.0%)
Moderate	24 (48.0%)
PDT	
Lesion preparation, n (%)	
Yes	50 (100%)
Total application time (hh:mm)	
Mean ± SD	3:01 ± 0:03
Median	3:00
Min, Max	(3:00, 3:10)
Total illumination time (mm:ss)	
Mean ± SD	7:50 ± 0:00
Median	7:50
Min, Max	(7:50, 7:50)

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SUMMARY, RESULTS

	Metvix PDT
Percent change from baseline in lesion counts (ITT-Observed)	
Week 12	
N	9
Mean ± SD	89.2 ± 13.5
Median	100.0
Min, Max	67, 100
Week 18	
N	8
Mean ± SD	95.5 ± 9.1
Median	100.0
Min, Max	75, 100
Month9	
N	8
Mean ± SD	89.9 ± 12.9
Median	94.4
Min, Max	67, 100
Month15	
N	7
Mean ± SD	91.3 ± 11.0
Median	100.0
Min, Max	78, 100
Subject complete response (ITT-Observed)	
Week 12	
Failure	4 (44.4%)
Success	5 (55.6%)
Week 18	
Failure	2 (25.0%)
Success	6 (75.0%)
Month9	
Failure	4 (50.0%)
Success	4 (50.0%)
Month15	
Failure	3 (42.9%)
Success	4 (57.1%)

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SUMMARY, RESULTS

	Metvix PDT
Skin discomfort after PDT sessions (VAS: 0 to 10)	
Baseline	
N	9
Mean ± SD	4.5 ± 2.3
Median	3.7
Min, Max	2, 9
Week 12	
N	9
Mean ± SD	4.2 ± 1.7
Median	4.1
Min, Max	2, 8
Adverse Events	
Total number of AEs	32
Related AEs	3
Dermatological AEs	11
Serious AEs	1
AEs leading to discontinuation	1
Number (%) of Subjects with AEs	9 (100%)
Related AEs	3 (33.3%)
Dermatological AEs	5 (55.6%)
Serious AEs	1 (11.1%)
AEs leading to discontinuation	1 (11.1%)

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NARRATIVE SUMMARY

This was a single-center, exploratory and open study on the changes of gene expression after treatment with Metvix® PDT of actinic keratoses (AK) and cancerized field in renal transplant recipients. The clinical data of the study is summarized here, and the genomic results are summarized in additional reports.

The main inclusion criteria were renal transplant subjects aged at least 18 years old, with a history of immunosuppression from 5 to 15 years, a diagnosis of field AK on face, scalp, forearms or chest (minimum of 4 discrete mild or moderate AKs). A total of 9 subjects were enrolled in the study and received two treatment sessions with Metvix® PDT at Baseline and Week 12. Subjects were evaluated at Screening visit, Baseline, Week 12, Week 18, Month 9 and Month 15.

A total of 9 subjects were included in the study. At baseline, the subjects had on average 5.6 ± 2.1 lesions and a total of 50 lesions (26 mild and 24 moderate). All lesions were prepared before the treatment, and all subjects received two treatment sessions occuring at Baseline and Week 12. In terms of the procedure, the mean time of application was 3 hours 1 minute and the mean time of illumination was 7 minutes and 50 seconds for each treatment session.

Efficacy analyses were performed in the intent-to-treat population, which consisted of all 9 subjects enrolled into the study. At Week 18, there was a reduction of 95.5% from baseline in lesion count, and the rate was still high at the end of the study at Month 15 (91.3%). Similarly, 6 out of 8 subjects reported having complete response at Week 18, and at Month15, still 57.1% of subjects had complete response.

Skin discomfort after the PDT sessions was judged to be moderate, with an average VAS score of 4.5 ± 2.3 and 4.5 ± 1.7 for the treatment at Baseline and Week 12, respectively. Adverse events were monitored throughout the study period. A total of 32 adverse events were reported in 9 subjects (100%), with 3 AEs related to the study treatment reported in 3 subjects (33.3%): Two subjects reported 2 mild application site pain, and one subject reported mild basal cell carcinoma, who subsequently discontinued the study.

In conclusion, Metvix® PDT was efficacious and safe in the treatment of AK and cancerized field in renal transplant recipients.