



## Clinical trial results:

### Multicentre, Randomised, Investigator-blind, Intra-individual, Active and Vehicle Controlled study, Comparing Metvix Natural Daylight Photodynamic Therapy versus Metvix Conventional Photodynamic Therapy in Subjects with Actinic Keratosis

#### Summary

EudraCT number	2013-000973-54
Trial protocol	SE DE NL ES
Global end of trial date	06 January 2014

#### Results information

Result version number	v1 (current)
This version publication date	11 March 2021
First version publication date	11 March 2021

#### Trial information

##### Trial identification

Sponsor protocol code	RD.03.SRE.29112
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01821391
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Galderma R&D
Sponsor organisation address	2400 route des colles, Biot, France, 06410
Public contact	CTA Coordinator, Galderma R&D, 33 493-95-70-85, cta.coordinator@galderma.com
Scientific contact	CTA Coordinator, Galderma R&D, 33 493-95-70-85, cta.coordinator@galderma.com

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

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**Results analysis stage**

Analysis stage	Final
Date of interim/final analysis	06 January 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 January 2014
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

Main objective of the trial:

The main objective of the study was to show the non-inferior efficacy of Metvix natural daylight photodynamic therapy (NDL-PDT) versus Metvix conventional photodynamic therapy (c-PDT) in subjects with mild and/or moderate actinic keratosis (AK) at Week 12.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 July 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects****Subjects enrolled per country**

Country: Number of subjects enrolled	France: 40
Country: Number of subjects enrolled	Germany: 43
Country: Number of subjects enrolled	Netherlands: 12
Country: Number of subjects enrolled	Spain: 24
Country: Number of subjects enrolled	Sweden: 12
Worldwide total number of subjects	131
EEA total number of subjects	131

Notes:

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**Subjects enrolled per age group**

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	21
From 65 to 84 years	110
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted at 18 sites in 5 countries between 25 July 2013 to 06 January 2014.

### Pre-assignment

Screening details:

A total of 131 subjects were randomized and 130 completed the study.

### Period 1

Period 1 title	Baseline Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator <sup>[1]</sup>

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Group 1

Arm description:

Subjects applied single dose of Metvix cream topically followed by NDL-PDT (test treatment) on one half-face/scalp and on the contra-lateral side of face/scalp applied Metvix cream topically followed by c-PDT (active comparator) on Day 0 (Baseline).

Arm type	Experimental
Investigational medicinal product name	Metvix natural daylight photodynamic therapy (Metvix NDL-PDT)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

Subjects applied topically a single dose of Metvix cream followed by NDL-PDT on Day 0 (Baseline).

Investigational medicinal product name	Metvix conventional photodynamic therapy (Metvix c-PDT)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

Subjects applied topically a single dose of Metvix cream followed by C-PDT on Day 0 (Baseline).

<b>Arm title</b>	Group 2
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Arm description:

Subjects applied a single dose of Metvix cream topically followed by NDL-PDT (test treatment) on one half-face/scalp and on the contra-lateral side of face/scalp applied Metvix vehicle cream (placebo) followed by c-PDT on Day 0 (Baseline).

Arm type	Experimental
Investigational medicinal product name	Metvix natural daylight photodynamic therapy (Metvix NDL-PDT)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

Subjects applied topically a single dose of Metvix cream followed by NDL-PDT on Day 0 (Baseline).

Investigational medicinal product name	Metvix vehicle cream (placebo) conventional photodynamic therapy (c-PDT)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

Subjects applied topically a single dose of Metvix vehicle cream followed by C-PDT on Day 0 (Baseline).

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: This is an investigator blinded study.

<b>Number of subjects in period 1</b>	Group 1	Group 2
Started	108	23
Completed	107	23
Not completed	1	0
Adverse Events	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	Group 1
Reporting group description:	
Subjects applied single dose of Metvix cream topically followed by NDL-PDT (test treatment) on one half-face/scalp and on the contra-lateral side of face/scalp applied Metvix cream topically followed by c-PDT (active comparator) on Day 0 (Baseline).	
Reporting group title	Group 2
Reporting group description:	
Subjects applied a single dose of Metvix cream topically followed by NDL-PDT (test treatment) on one half-face/scalp and on the contra-lateral side of face/scalp applied Metvix vehicle cream (placebo) followed by c-PDT on Day 0 (Baseline).	

Reporting group values	Group 1	Group 2	Total
Number of subjects	108	23	131
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	19	2	21
From 65-84 years	89	21	110
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	72.8	73.9	
standard deviation	± 9.9	± 7.9	-
Gender categorical			
Units: Subjects			
Female	9	1	10
Male	99	22	121
Race			
Units: Subjects			
Caucasian	108	22	130
Other	0	1	1
Phototype			
Units: Subjects			
Phototype I	10	1	11
Phototype II	69	17	86
Phototype III	24	3	27
Phototype IV	5	2	7

## End points

### End points reporting groups

Reporting group title	Group 1
Reporting group description: Subjects applied single dose of Metvix cream topically followed by NDL-PDT (test treatment) on one half-face/scalp and on the contra-lateral side of face/scalp applied Metvix cream topically followed by c-PDT (active comparator) on Day 0 (Baseline).	
Reporting group title	Group 2
Reporting group description: Subjects applied a single dose of Metvix cream topically followed by NDL-PDT (test treatment) on one half-face/scalp and on the contra-lateral side of face/scalp applied Metvix vehicle cream (placebo) followed by c-PDT on Day 0 (Baseline).	
Subject analysis set title	Group I: Metvix NDL-PDT
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subjects applied topically a single dose of Metvix cream followed by NDL-PDT on Day 0 (Baseline).	
Subject analysis set title	Group I: Metvix c-PDT
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subjects applied topically a single dose of Metvix cream followed by C-PDT on Day 0 (Baseline).	
Subject analysis set title	Group II: Metvix NDL-PDT
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subjects applied topically a single dose of Metvix cream followed by NDL-PDT on Day 0 (Baseline).	
Subject analysis set title	Group II: Metvix c-PDT Vehicle
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subjects applied topically a single dose of Metvix cream followed by vehicle C-PDT on Day 0 (Baseline).	

### Primary: Percentage (%) Change from Baseline in Total Lesion Complete Response at Week 12 in Group 1

End point title	Percentage (%) Change from Baseline in Total Lesion Complete Response at Week 12 in Group 1
End point description: The lesion complete response rate was defined as the percentage of pre-existing and treated lesions at Baseline that were assessed as clear (complete disappearance of the lesion, visually and by palpation) at Week 12. New lesions or the lesions in non-complete response were not not considered in the lesion response assessment. Intent-to-treat (ITT) population included entire population enrolled and randomized. ITT analysis imputed missing data using a worst case approach and considered the lesions with missed lesion response assessment as not responded (ITT/Worst-case) lesions. Here, the "N" number of subjects analyzed signifies subjects who were evaluable for this endpoint.	
End point type	Primary
End point timeframe: Week 12	

End point values	Group I: Metvix NDL- PDT	Group I: Metvix c-PDT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	108	108		
Units: % change from baseline				
arithmetic mean (standard deviation)	68.4 (± 27.7)	71.5 (± 27.6)		

### Statistical analyses

<b>Statistical analysis title</b>	Total lesion response at week 12 in GROUP 1
Comparison groups	Group I: Metvix c-PDT v Group I: Metvix NDL-PDT
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2665
Method	Paired Student's t test

### Primary: Percentage Change from Baseline in Total Lesion Complete Response at Week 12 in Group 2

End point title	Percentage Change from Baseline in Total Lesion Complete Response at Week 12 in Group 2
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#### End point description:

The lesion complete response rate was defined as the percentage of pre-existing and treated lesions at Baseline that were assessed as clear (complete disappearance of the lesion, visually and by palpation) at Week 12. New lesions or the lesions in non-complete response were not considered in the lesion response assessment. Intent-to-treat (ITT) population included entire population enrolled and randomized. ITT analysis imputed missing data using a worst case approach and considered the lesions with missed lesion response assessment as not responded (ITT/Worst-case) lesions. Here, the "N" number of subjects analyzed signifies subjects who were evaluable for this endpoint.

End point type	Primary
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#### End point timeframe:

Week 12

End point values	Group II: Metvix NDL- PDT	Group II: Metvix c-PDT Vehicle		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	23		
Units: % change from baseline				
arithmetic mean (standard deviation)	78.3 (± 18.0)	61.2 (± 25.7)		

### Statistical analyses



<b>Statistical analysis title</b>	Total lesion response at week 12 in GROUP 2
Comparison groups	Group II: Metvix c-PDT Vehicle v Group II: Metvix NDL-PDT
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Paired Student's t test

### Primary: Change from Baseline in Self-Assessed Maximal Pain at Week 12

End point title	Change from Baseline in Self-Assessed Maximal Pain at Week 12 <sup>[1]</sup>
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End point description:

Change from baseline in maximal pain of both Group 1 and Group 2 at week 12 were reported. After the treatment procedure on each side had been completed, the subject assessed the maximal pain felt during the duration of the light exposure (assessment after NDL-PDT illumination first, and then assessment after c-PDT lamp illumination). The pain sensation was assessed on an 11-point numeric rating scale, where 0 was no pain at all, and 10 was extreme pain. Analysis was performed on safety population (all subjects treated [APT] population) was defined as comprising the ITT population subjects who were administered the study treatment.

End point type	Primary
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End point timeframe:

Baseline, Week 12

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was only performed within the group and not comparatively.

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	23		
Units: Score on scale				
arithmetic mean (standard deviation)	-3.8 (± 2.7)	0.3 (± 2.3)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage Change from Baseline in Mild Lesion Response at Week 12 in Group 1

End point title	Percentage Change from Baseline in Mild Lesion Response at Week 12 in Group 1
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End point description:

ITT population included entire population enrolled and randomized. ITT analysis imputed missing data using a worst case approach and considered the lesions with missed lesion response assessment as not responded (ITT/Worst-case) lesions. Here, the number of subjects analyzed signifies subjects who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Week 12

End point values	Group I: Metvix NDL- PDT	Group I: Metvix c-PDT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	92	91		
Units: % change from baseline				
arithmetic mean (standard deviation)	71.0 (± 31.9)	71.7 (± 32.3)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage Change from Baseline in Mild Lesion Response at Week 12 in Group 2

End point title	Percentage Change from Baseline in Mild Lesion Response at Week 12 in Group 2
End point description: ITT population included entire population enrolled and randomized. ITT analysis imputed missing data using a worst case approach and considered the lesions with missed lesion response assessment as not responded (ITT/Worst-case) lesions. Here, the number of subjects analyzed signifies subjects who were evaluable for this endpoint.	
End point type	Secondary
End point timeframe: Baseline, Week 12	

End point values	Group II: Metvix NDL- PDT	Group II: Metvix c-PDT Vehicle		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	20		
Units: % change from baseline				
arithmetic mean (standard deviation)	79.6 (± 21.1)	66.4 (± 26.4)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Subject-side Complete Response (CR) Rate at Week 12

End point title	Subject-side Complete Response (CR) Rate at Week 12
End point description: Subject-side CR rate was defined as the percentage of subjects with all treated lesions at Baseline clear in the corresponding TA at Week 12. ITT population included entire population enrolled and randomized. ITT analysis imputed missing data using a worst case approach and considered the lesions with missed	

lesion response assessment as not responded (ITT/Worst-case) lesions.

End point type	Secondary
End point timeframe:	
Week 12	

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	23		
Units: percentage of subjects				
number (not applicable)	-8.3	8.7		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From start of study drug application up to Week 12

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.0
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### Reporting groups

Reporting group title	Metvix NDL-PDT
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Reporting group description:

Subjects applied topically a single dose of Metvix cream followed by NDL-PDT on Day 0 (Baseline).

Reporting group title	Metvix c-PDT
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Reporting group description:

Subjects applied topically a single dose of Metvix cream followed by C-PDT on Day 0 (Baseline).

Reporting group title	c-PDT Vehicle
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Reporting group description:

Subjects applied topically a single dose of Metvix cream followed by vehicle C-PDT on Day 0 (Baseline).

Serious adverse events	Metvix NDL-PDT	Metvix c-PDT	c-PDT Vehicle
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 131 (0.00%)	0 / 108 (0.00%)	0 / 23 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Metvix NDL-PDT	Metvix c-PDT	c-PDT Vehicle
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 131 (49.62%)	66 / 108 (61.11%)	7 / 23 (30.43%)
Injury, poisoning and procedural complications			
Post procedural hemorrhage			
subjects affected / exposed	5 / 131 (3.82%)	4 / 108 (3.70%)	1 / 23 (4.35%)
occurrences (all)	5	4	1
Vascular disorders			
Haemorrhage			
subjects affected / exposed	0 / 131 (0.00%)	1 / 108 (0.93%)	0 / 23 (0.00%)
occurrences (all)	0	1	0

Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	2 / 131 (1.53%)	1 / 108 (0.93%)	0 / 23 (0.00%)
occurrences (all)	2	1	0
Dermatitis			
subjects affected / exposed	1 / 131 (0.76%)	1 / 108 (0.93%)	1 / 23 (4.35%)
occurrences (all)	1	1	1
Erythema			
subjects affected / exposed	31 / 131 (23.66%)	39 / 108 (36.11%)	4 / 23 (17.39%)
occurrences (all)	31	39	4
Pain of skin			
subjects affected / exposed	8 / 131 (6.11%)	11 / 108 (10.19%)	0 / 23 (0.00%)
occurrences (all)	8	11	0
Photosensitivity reaction			
subjects affected / exposed	10 / 131 (7.63%)	8 / 108 (7.41%)	1 / 23 (4.35%)
occurrences (all)	10	8	1
Pruritus			
subjects affected / exposed	13 / 131 (9.92%)	16 / 108 (14.81%)	1 / 23 (4.35%)
occurrences (all)	13	16	1
Purpura			
subjects affected / exposed	1 / 131 (0.76%)	1 / 108 (0.93%)	0 / 23 (0.00%)
occurrences (all)	1	1	0
Scab			
subjects affected / exposed	12 / 131 (9.16%)	16 / 108 (14.81%)	0 / 23 (0.00%)
occurrences (all)	12	17	0
Skin burning sensation			
subjects affected / exposed	12 / 131 (9.16%)	16 / 108 (14.81%)	0 / 23 (0.00%)
occurrences (all)	12	17	0
Skin discomfort			
subjects affected / exposed	1 / 131 (0.76%)	0 / 108 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Skin erosion			
subjects affected / exposed	0 / 131 (0.00%)	5 / 108 (4.63%)	0 / 23 (0.00%)
occurrences (all)	0	5	0
Skin exfoliation			

subjects affected / exposed occurrences (all)	2 / 131 (1.53%) 2	4 / 108 (3.70%) 4	1 / 23 (4.35%) 1
Skin oedema subjects affected / exposed occurrences (all)	2 / 131 (1.53%) 2	1 / 108 (0.93%) 1	0 / 23 (0.00%) 0
Skin swelling subjects affected / exposed occurrences (all)	1 / 131 (0.76%) 1	1 / 108 (0.93%) 1	0 / 23 (0.00%) 0
Skin tightness subjects affected / exposed occurrences (all)	0 / 131 (0.00%) 0	1 / 108 (0.93%) 1	0 / 23 (0.00%) 0
Infections and infestations Rash pustular subjects affected / exposed occurrences (all)	1 / 131 (0.76%) 1	2 / 108 (1.85%) 2	0 / 23 (0.00%) 0

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported