Clinical trial results:
Efficacy and Safety of LEO 43204 in Field Treatment of Actinic Keratosis on Balding Scalp including 12-month follow-up
Part 1: 3-day treatment period including an 8-week follow-up period
Part 2: extended 12-month follow-up period
A phase 3, multi-centre, randomised, parallel group, double-blind, vehicle controlled trial

Summary

EudraCT number	2015-002451-10
Trial protocol	GB
Global end of trial date	06 September 2017

Results information

Result version number	v1 (current)
This version publication date	20 December 2018
First version publication date	20 December 2018

Trial information

Trial identification

Sponsor protocol code	LP0084-1195

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02547363
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	LEO Pharma A/S
Sponsor organisation address	Industriparken 55, Ballerup, Denmark, 2750
Public contact	Clinical Disclosure Specialist, LEO Pharma A/S, +45 44945888, disclosure@leo-pharma.com
Scientific contact	Clinical Disclosure Specialist, LEO Pharma A/S, +45 44945888, disclosure@leo-pharma.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:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 February 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 September 2017
Global end of trial reached?	Yes
Global end of trial date	06 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm the efficacy of LEO 43204 gel (0.037% for scalp) in actinic keratosis (AK) when applied topically once daily for 3 consecutive days as field treatment

Protection of trial subjects:

This clinical trial was conducted in accordance with the revision current at the start of the trial of the World Medical Association's Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects.

All subjects received written and verbal information concerning the clinical trial. This information emphasised that participation in the clinical trial was voluntary and that the subject could withdraw from the clinical trial at any time and for any reason. All subjects were given an opportunity to ask questions and were given sufficient time to consider before consenting

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 November 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Canada: 106
Country: Number of subjects enrolled	United States: 160
Worldwide total number of subjects	313
EEA total number of subjects	47

Notes:

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)	73
From 65 to 84 years	225
85 years and over	15

Subject disposition

Recruitment

Recruitment details:

Subjects were followed for 8 weeks following the first application of investigational medicinal product (IMP) at Day 1 (3-day treatment period including an 8-week follow-up period) and for an additional 12 months following Week 8 (extended 12-month follow-up period).

Pre-assignment

Screening details:

373 subjects were enrolled, 57 were screening failures, and 316 subjects were randomised. Only 313 of the randomised subjects were treated with investigational medicinal product (IMP), the number of subjects treated is reflected as the number of subjects started in the first period.

Period 1

Period 1 title	3-day Treatment and 8-week Follow-up
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	LEO 43204 0.037% Gel - Treatment Period Including Follow-up

Arm description:

Treatment once daily with LEO 43204 0.037% gel for 3 consecutive days applied on the scalp.

Arm type	Experimental
Investigational medicinal product name	LEO 43204 gel
Investigational medicinal product code	
Other name	Ingenol disoxate
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

Ingenol disoxate 0.037% gel applied on the scalp once-daily for 3 consecutive days.

Arm title	Vehicle Gel - Treatment Period Including Follow-up

Arm description:

Treatment once daily with vehicle gel for 3 consecutive days applied on the scalp.

Arm type	Placebo
Investigational medicinal product name	LEO 43204 Vehicle Gel
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

Vehicle gel applied on the scalp once-daily for 3 consecutive days.

Number of subjects in period 1	LEO 43204 0.037% Gel - Treatment Period Including Follow-up	Vehicle Gel - Treatment Period Including Follow-up
Started	209	104
Completed	207	94
Not completed	2	10
Consent withdrawn by subject	-	7
Adverse event, non-fatal	-	1
Other	1	1
Lost to follow-up	1	1

Period 2

Period 2 title	12-month Follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	LEO 43204 0.037% Gel - Extended Follow-up

Arm description:

Treatment once daily with LEO 43204 0.037% gel for 3 consecutive days applied on the scalp.

Arm type	Experimental
Investigational medicinal product name	LEO 43204 gel
Investigational medicinal product code	
Other name	Ingenol disoxate
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

Ingenol disoxate 0.037% gel applied on the scalp once-daily for 3 consecutive days.

Arm title	Vehicle Gel - Extended Follow-up

Arm description:

Treatment once daily with vehicle gel for 3 consecutive days applied on the scalp.

Arm type	Placebo
Investigational medicinal product name	LEO 43204 Vehicle Gel
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

Vehicle gel applied on the scalp once-daily for 3 consecutive days.

Number of subjects in period 2[1]	LEO 43204 0.037% Gel - Extended Follow-up	Vehicle Gel - Extended Follow-up
Started	204	86
Completed	194	81
Not completed	10	5
Consent withdrawn by subject	4	3
Other	1	-
Lost to follow-up	4	1
Lack of efficacy	1	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Of the 301 subjects who completed the 3-day treatment and 8-week Follow-up period, 3 subjects in the ingenol disoxate gel group and 8 subjects in the vehicle group were not included in the 12-month Follow-up because they withdrew after Week 8.

Baseline characteristics

Reporting groups	
Reporting group title	LEO 43204 0.037% Gel - Treatment Period Including Follow-up
Reporting group description:	
Treatment once daily with LEO 43204 0.037% gel for 3 consecutive days applied on the scalp.	
Reporting group title	Vehicle Gel - Treatment Period Including Follow-up
Reporting group description:	
Treatment once daily with vehicle gel for 3 consecutive days applied on the scalp.	

Reporting group values	LEO 43204 0.037% Gel - Treatment Period Including Follow-up	Vehicle Gel - Treatment Period Including Follow-up	Total
Number of subjects	209	104	313
Age categorical Units: Subjects			
Adults (18-64 years)	45	28	73
From 65-84 years	155	70	225
85 years and over	9	6	15
Age continuous Units: years			
arithmetic mean	70.9	69.9	
standard deviation	± 9.1	± 9.3	-
Gender categorical Units: Subjects			
Female	1	0	1
Male	208	104	312

End points

End points reporting groups

Reporting group title	LEO 43204 0.037% Gel - Treatment Period Including Follow-up
Reporting group description:	
Treatment once daily with LEO 43204 0.037% gel for 3 consecutive days applied on the scalp.	
Reporting group title	Vehicle Gel - Treatment Period Including Follow-up
Reporting group description:	
Treatment once daily with vehicle gel for 3 consecutive days applied on the scalp.	
Reporting group title	LEO 43204 0.037% Gel - Extended Follow-up
Reporting group description:	
Treatment once daily with LEO 43204 0.037% gel for 3 consecutive days applied on the scalp.	
Reporting group title	Vehicle Gel - Extended Follow-up
Reporting group description:	
Treatment once daily with vehicle gel for 3 consecutive days applied on the scalp.	

Primary: Complete Clearance of Actinic Keratosis (AK)

End point title	Complete Clearance of Actinic Keratosis (AK)
End point description:	
The number of clinically visible AKs identified in the treatment area was recorded at Day 1 (Baseline), Week 4, and Week 8. Complete clearance was defined as no clinically visible AKs in the treatment area. The table shows percentage of subjects with complete clearance.	
End point type	Primary
End point timeframe:	
At Week 8	

End point values	LEO 43204 0.037% Gel - Treatment Period Including Follow-up	Vehicle Gel - Treatment Period Including Follow-up		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	104		
Units: percentage of subjects				
number (confidence interval 95%)				
Yes	25.8 (20.4 to 32.2)	0.0 (0.0 to 3.6)		

Statistical analyses

Statistical analysis title	Complete clearance of AK at Week 8
Comparison groups	LEO 43204 0.037% Gel - Treatment Period Including Follow-up v Vehicle Gel - Treatment Period Including Follow-up

Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact test

Secondary: Partial Clearance

End point title	Partial Clearance

End point description:

The number of clinically visible Actinic keratosis lesions (AKs) identified in the treatment area was recorded at Day 1, Weeks 4 and Week 8. Partial clearance was defined as at least 75% reduction from baseline in the number of clinically visible AKs in the treatment area.
The table shows percentage of subjects with complete clearance.

End point type	Secondary

End point timeframe:

At Week 8

End point values	LEO 43204 0.037% Gel - Treatment Period Including Follow-up	Vehicle Gel - Treatment Period Including Follow-up		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	104		
Units: percentage of subjects				
number (confidence interval 95%)				
Yes	58.9 (52.1 to 65.3)	1.0 (0.2 to 5.2)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The p-values for secondary endpoints have been corrected by the Holm-Bonferroni method to account for multiplicity. The prespecified multiplicity adjustment by the Holm-Bonferroni method requires the ordering of the p-values for the secondary endpoints by size.

Comparison groups	LEO 43204 0.037% Gel - Treatment Period Including Follow-up v Vehicle Gel - Treatment Period Including Follow-up
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mantel-Haenszel
Parameter estimate	Ratio of clearance rates
Point estimate	62.59

Confidence interval	
level	95 %
sides	2-sided
lower limit	8.68
upper limit	451.08

Secondary: Partial Clearance

End point title	Partial Clearance

End point description:

The number of clinically visible Actinic keratosis lesions (AKs) identified in the treatment area was recorded at Day 1, Weeks 4 and Week 8. Partial clearance was defined as at least 75% reduction from baseline in the number of clinically visible AKs in the treatment area.
The table shows percentage of subjects with complete clearance.

End point type	Secondary

End point timeframe:

At Week 4

End point values	LEO 43204 0.037% Gel - Treatment Period Including Follow-up	Vehicle Gel - Treatment Period Including Follow-up		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	104		
Units: percentage of subjects				
number (confidence interval 95%)				
Yes	57.4 (50.6 to 63.9)	1.0 (0.2 to 5.2)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The p-values for secondary endpoints have been corrected by the Holm-Bonferroni method to account for multiplicity. The prespecified multiplicity adjustment by the Holm-Bonferroni method requires the ordering of the p-values for the secondary endpoints by size.

Comparison groups	LEO 43204 0.037% Gel - Treatment Period Including Follow-up v Vehicle Gel - Treatment Period Including Follow-up
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	Mantel-Haenszel
Parameter estimate	Ratio of clearance rates
Point estimate	59.21

Confidence interval	
level	95 %
sides	2-sided
lower limit	8.44
upper limit	415.35

Notes:

[1] - Nominal p-value

Secondary: Percent Reduction in AK Count in the Treatment Area Compared to Baseline

End point title	Percent Reduction in AK Count in the Treatment Area Compared to Baseline

End point description:

The percent reduction at Week 8 from baseline was analysed using a negative binomial regression for the AK count at Week 8 with treatment group and pooled sites as factors and baseline count as offset variable. The table presents adjusted mean percent reduction at Week 8 from baseline.

End point type	Secondary

End point timeframe:

At Week 8

End point values	LEO 43204 0.037% Gel - Treatment Period Including Follow-up	Vehicle Gel - Treatment Period Including Follow-up		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209	104		
Units: percentage of reduction				
arithmetic mean (confidence interval 95%)	72.3 (69.1 to 75.2)	-2.0 (-16.0 to 10.3)		

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

The p-values for secondary endpoints have been corrected by the Holm-Bonferroni method to account for multiplicity. The prespecified multiplicity adjustment by the Holm-Bonferroni method requires the ordering of the p-values for the secondary endpoints by size.

Comparison groups	LEO 43204 0.037% Gel - Treatment Period Including Follow-up v Vehicle Gel - Treatment Period Including Follow-up
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mantel-Haenszel
Parameter estimate	Week 8 AK count ratio
Point estimate	0.27

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	0.32

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment period including follow-up (from Day 1 to Week 8) and extended follow-up (from Week 8 up to Month 14)

Adverse event reporting additional description:

Adverse events presented in the table are investigator-reported terms.
Adverse events of special interest within system organ class (SOC) Neoplasm benign, malignant and unspecified (incl cysts and polyps), were adjudicated by an Independent Adjudication Committee based on central biopsy review.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	LEO 43204 0.037% Gel - Treatment Period including Follow-up

Reporting group description:

Treatment once daily for 3 consecutive days with LEO 43204 0.037% gel

Reporting group title	Vehicle Gel - Treatment Period Including Follow-up

Reporting group description:

Treatment once daily for 3 days with vehicle gel

Reporting group title	LEO 43204 0.037% Gel - Extended Follow-up

Reporting group description:

Treatment once daily for 3 consecutive days LEO 43204 0.037% gel

Reporting group title	Vehicle Gel - Extended Follow-up

Reporting group description:

Treatment once daily for 3 days Vehicle gel

Serious adverse events	LEO 43204 0.037% Gel - Treatment Period including Follow-up	Vehicle Gel - Treatment Period Including Follow-up	LEO 43204 0.037% Gel - Extended Follow-up
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 209 (1.91%)	2 / 104 (1.92%)	1 / 204 (0.49%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	0 / 209 (0.00%)	0 / 104 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm of appendix			

subjects affected / exposed	1 / 209 (0.48%)	0 / 104 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma			
subjects affected / exposed	0 / 209 (0.00%)	1 / 104 (0.96%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 209 (0.48%)	0 / 104 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	1 / 209 (0.48%)	0 / 104 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	0 / 209 (0.00%)	1 / 104 (0.96%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 209 (0.48%)	0 / 104 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis perforated			
subjects affected / exposed	1 / 209 (0.48%)	0 / 104 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Vehicle Gel - Extended Follow-up		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 86 (0.00%)		
number of deaths (all causes)	0		

number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neoplasm of appendix			
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatic carcinoma			
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pericarditis			
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sinus node dysfunction			
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis perforated			

subjects affected / exposed	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	LEO 43204 0.037% Gel - Treatment Period including Follow-up	Vehicle Gel - Treatment Period Including Follow-up	LEO 43204 0.037% Gel - Extended Follow-up
Total subjects affected by non-serious adverse events			
subjects affected / exposed	134 / 209 (64.11%)	3 / 104 (2.88%)	18 / 204 (8.82%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 209 (0.00%)	0 / 104 (0.00%)	5 / 204 (2.45%)
occurrences (all)	0	0	5
Nervous system disorders			
Headache			
subjects affected / exposed	21 / 209 (10.05%)	2 / 104 (1.92%)	0 / 204 (0.00%)
occurrences (all)	21	2	0
General disorders and administration site conditions			
Application site pain			
subjects affected / exposed	127 / 209 (60.77%)	3 / 104 (2.88%)	0 / 204 (0.00%)
occurrences (all)	127	3	0
Application site pruritus			
subjects affected / exposed	64 / 209 (30.62%)	2 / 104 (1.92%)	0 / 204 (0.00%)
occurrences (all)	64	2	0
Application site discomfort			
subjects affected / exposed	6 / 209 (2.87%)	2 / 104 (1.92%)	0 / 204 (0.00%)
occurrences (all)	6	2	0
Application site injury			
subjects affected / exposed	8 / 209 (3.83%)	0 / 104 (0.00%)	0 / 204 (0.00%)
occurrences (all)	8	0	0
Face oedema			
subjects affected / exposed	5 / 209 (2.39%)	0 / 104 (0.00%)	0 / 204 (0.00%)
occurrences (all)	5	0	0
Application site scar			

subjects affected / exposed	1 / 209 (0.48%)	1 / 104 (0.96%)	10 / 204 (4.90%)
occurrences (all)	1	1	10
Eye disorders			
Periorbital oedema			
subjects affected / exposed	14 / 209 (6.70%)	0 / 104 (0.00%)	0 / 204 (0.00%)
occurrences (all)	14	0	0
Skin and subcutaneous tissue disorders			
Post inflammatory pigmentation change			
subjects affected / exposed	0 / 209 (0.00%)	0 / 104 (0.00%)	5 / 204 (2.45%)
occurrences (all)	0	0	5
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 209 (2.39%)	0 / 104 (0.00%)	0 / 204 (0.00%)
occurrences (all)	5	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 209 (2.87%)	1 / 104 (0.96%)	0 / 204 (0.00%)
occurrences (all)	6	1	0

Non-serious adverse events	Vehicle Gel - Extended Follow-up		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 86 (13.95%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 86 (1.16%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 86 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Application site pain			
subjects affected / exposed	0 / 86 (0.00%)		
occurrences (all)	0		
Application site pruritus			

subjects affected / exposed occurrences (all) Application site discomfort subjects affected / exposed occurrences (all) Application site injury subjects affected / exposed occurrences (all) Face oedema subjects affected / exposed occurrences (all) Application site scar subjects affected / exposed occurrences (all)	0 / 86 (0.00%) 0 0 / 86 (0.00%) 0 0 / 86 (0.00%) 0 0 / 86 (0.00%) 0 7 / 86 (8.14%) 7		
Eye disorders Periorbital oedema subjects affected / exposed occurrences (all)	0 / 86 (0.00%) 0		
Skin and subcutaneous tissue disorders Post inflammatory pigmentation change subjects affected / exposed occurrences (all)	5 / 86 (5.81%) 5		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 86 (0.00%) 0		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 86 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 March 2016	The amendment clarified which medications were allowed and prohibited during the extended follow-up period: lesiondirected laser treatment was added to the allowed medications, and Actikerall, even as lesiondirected treatment, and laser treatment as field treatment were prohibited. The remaining changes in the amendment were either administrative changes or matters that needed further clarification.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported