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	2015-002452-27
Trial protocol	DE
Global end of trial date	27 October 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	LP0084-1196

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02549352
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	27 October 2017
Global end of trial reached?	Yes
Global end of trial date	27 October 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	Italy: 35
Country: Number of subjects enrolled	United States: 205
Country: Number of subjects enrolled	Germany: 70
Worldwide total number of subjects	310
EEA total number of subjects	105

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)	77
From 65 to 84 years	214
85 years and over	19

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:

391 subjects were enrolled, 80 were screening failures, and 311 subjects were randomised. Only 310 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.
1 subject randomised to the vehicle group received a mix of ingenol disoxate gel and vehicle in error and was therefore included in the ingenol disoxate gel group in the safety set.

Arm type	Placebo
Investigational medicinal product name	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	101
Completed	207	96
Not completed	2	5
Consent withdrawn by subject	2	2
Adverse event, non-fatal	-	1
Other	-	2

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	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	207	93
Completed	199	81
Not completed	8	12
Consent withdrawn by subject	4	5
Other	1	3
Death	-	1
Lost to follow-up	3	2
Protocol deviation	-	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 303 subjects who completed the 3-day treatment and 8-week Follow-up period, 3 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.
1 subject randomised to the vehicle group received a mix of ingenol disoxate gel and vehicle in error and was therefore included in the ingenol disoxate gel group in the safety set.

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	101	310
Age categorical Units: Subjects			
Adults (18-64 years)	60	17	77
From 65-84 years	139	75	214
85 years and over	10	9	19
Age continuous Units: years			
arithmetic mean	69.7	71.0	
standard deviation	± 9.0	± 9.3	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	209	101	310

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.
1 subject randomised to the vehicle group received a mix of ingenol disoxate gel and vehicle in error and was therefore included in the ingenol disoxate gel group in the safety set.

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 actinic keratosis lesions (AKs) identified in the treatment area was recorded at Day 1 (baseline), Weeks 4, and 8.
Complete clearance was defined as no clinically visible AKs in the treatment area.
The table shows the percentage of mean number of participants across imputations with complete clearance at Week 8.

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	101		
Units: percentage of subjects				
number (confidence interval 95%)	22.0 (16.4 to 27.7)	3.0 (-0.3 to 6.3)		

Statistical analyses

Statistical analysis title	Analysis 1
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	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	Mantel-Haenszel
Parameter estimate	Ratio of clearance rates
Point estimate	7.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.58
upper limit	23.71

Notes:

[1] - Mantel-Haenszel estimate (0.037% relative to vehicle), adjusted for pooled sites.

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 the percentage of mean number of subjects across imputations with complete clearance at Week 8.

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	101		
Units: percentage of subjects				
number (confidence interval 95%)	63.1 (56.5 to 69.7)	11.0 (4.9 to 17.2)		

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.
Mantel-Haenszel estimate (0.037% relative to vehicle), adjusted for pooled sites.

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	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mantel-Haenszel
Parameter estimate	Ratio of clearance rates
Point estimate	5.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.32
upper limit	10.51

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, Week 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 the percentage of mean number of subjects across imputations with complete clearance at Week 4.

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	101		
Units: percentage of subjects				
number (confidence interval 95%)	53.4 (46.5 to 60.3)	7.1 (2.0 to 12.1)		

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.
Mantel-Haenszel estimate (0.037% relative to vehicle), adjusted for pooled sites.

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	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mantel-Haenszel
Parameter estimate	Ratio of clearance rates
Point estimate	7.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.7
upper limit	15.61

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 number of clinically visible Actinic keratosis lesions (AKs) identified in the treatment area was recorded at Day 1, Weeks 4, and Week 8.

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	101		
Units: percentage of subjects				
number (confidence interval 95%)	74.0 (70.6 to 77.1)	13.7 (0.2 to 25.3)		

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	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mantel-Haenszel
Parameter estimate	Week 8 AK count ratio
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	0.36

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

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

Reporting group description:

Treatment with vehicle gel once daily for 3 days

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 for 3 days Vehicle gel

Serious adverse events	LEO 43204 0.037% Gel	Vehicle Gel	LEO 43204 0.037% Gel - Extended Follow-up
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 210 (1.43%)	3 / 100 (3.00%)	0 / 208 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 210 (0.48%)	0 / 100 (0.00%)	0 / 208 (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
Atrial fibrillation			
subjects affected / exposed	0 / 210 (0.00%)	1 / 100 (1.00%)	0 / 208 (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

Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 210 (0.48%)	0 / 100 (0.00%)	0 / 208 (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
Syncope			
subjects affected / exposed	0 / 210 (0.00%)	1 / 100 (1.00%)	0 / 208 (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
Gastrointestinal disorders			
Rectal haemorrhage			
subjects affected / exposed	1 / 210 (0.48%)	0 / 100 (0.00%)	0 / 208 (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
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 210 (0.00%)	1 / 100 (1.00%)	0 / 208 (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

Serious adverse events	Vehicle Gel - Extended Follow-up		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 92 (0.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 1		
Atrial fibrillation			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			

Cerebrovascular accident			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 1		
Syncope			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorders			
Rectal haemorrhage			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 1		
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	LEO 43204 0.037% Gel	Vehicle Gel	LEO 43204 0.037% Gel - Extended Follow-up
Total subjects affected by non-serious adverse events			
subjects affected / exposed	146 / 210 (69.52%)	12 / 100 (12.00%)	5 / 208 (2.40%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 210 (0.00%)	0 / 100 (0.00%)	5 / 208 (2.40%)
occurrences (all)	0	0	5
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 210 (5.24%)	1 / 100 (1.00%)	0 / 208 (0.00%)
occurrences (all)	11	1	0
General disorders and administration site conditions			

Application site pain			
subjects affected / exposed	118 / 210 (56.19%)	3 / 100 (3.00%)	1 / 208 (0.48%)
occurrences (all)	118	3	1
Application site pruritus			
subjects affected / exposed	68 / 210 (32.38%)	8 / 100 (8.00%)	1 / 208 (0.48%)
occurrences (all)	68	8	1
Eye disorders			
Eyelid oedema			
subjects affected / exposed	9 / 210 (4.29%)	0 / 100 (0.00%)	0 / 208 (0.00%)
occurrences (all)	9	0	0
Periorbital oedema			
subjects affected / exposed	9 / 210 (4.29%)	0 / 100 (0.00%)	0 / 208 (0.00%)
occurrences (all)	9	0	0
Eye irritation			
subjects affected / exposed	5 / 210 (2.38%)	0 / 100 (0.00%)	0 / 208 (0.00%)
occurrences (all)	5	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	15 / 210 (7.14%)	0 / 100 (0.00%)	0 / 208 (0.00%)
occurrences (all)	15	0	0

Non-serious adverse events	Vehicle Gel - Extended Follow-up		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 92 (1.09%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 92 (1.09%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Application site pain			
subjects affected / exposed	0 / 92 (0.00%)		
occurrences (all)	0		
Application site pruritus			

subjects affected / exposed occurrences (all)	0 / 92 (0.00%) 0		
Eye disorders Eyelid oedema subjects affected / exposed occurrences (all) Periorbital oedema subjects affected / exposed occurrences (all) Eye irritation subjects affected / exposed occurrences (all)	 0 / 92 (0.00%) 0 0 / 92 (0.00%) 0 0 / 92 (0.00%) 0		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 0 / 92 (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