Clinical trial results:
Efficacy and Safety of LEO 43204 in Field Treatment of Actinic Keratosis on Face or Chest 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	2015-002449-71
Trial protocol	GB
Global end of trial date	14 November 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	LP0084-1193

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02547233
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?	No

Global end of trial reached?	Yes
Global end of trial date	14 November 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 (0.018% for face/chest) in AK when applied topically once daily for three consecutive days as field treatment

Protection of trial subjects:

This clinical trial was conducted in accordance with the principles of the revision current at the start of the trial of the World Medical Association (WMA), 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	Spain: 7
Country: Number of subjects enrolled	United Kingdom: 28
Country: Number of subjects enrolled	France: 26
Country: Number of subjects enrolled	United States: 244
Worldwide total number of subjects	305
EEA total number of subjects	61

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)	107
From 65 to 84 years	193
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

A total of 437 subjects were enrolled across 4 countries: United States, United Kingdom, France, and Spain. 130 were screening failures, and 307 subjects were randomised to 1 of the 2 treatment groups

Pre-assignment

Screening details:

437 subjects were enrolled, 130 were screening failures, and 307 subjects were randomised.

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	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	LEO 43204 0.018% Gel

Arm description:

Treatment once daily with LEO 43204 0.018% gel for 3 consecutive days applied on full face or within a contiguous area of approximately 250 cm2 on the chest.

Arm type	Experimental
Investigational medicinal product name	LEO 43204 0.018% Gel
Investigational medicinal product code	
Other name	Ingenol disoxate
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

Applied topically once daily for 3 consecutive days.

Arm title	Vehicle Gel

Arm description:

Treatment once daily with vehicle gel for 3 consecutive days applied on full face or within a contiguous area of approximately 250 cm2 on the chest.

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:

Applied topically once daily for 3 consecutive days

Number of subjects in period 1	LEO 43204 0.018% Gel	Vehicle Gel
Started	205	100
Completed	203	92
Not completed	2	8
Unacceptable Local Skin Response	1	-
Consent withdrawn by subject	-	7
Adverse event, non-fatal	1	-
Lost to follow-up	-	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	Follow-up phase: LEO 43204 0.018% Gel

Arm description:

Treatment once daily for 3 consecutive days applied on full face or within a contiguous area of approximately 250 cm2 on the chest.

Arm type	Experimental
Investigational medicinal product name	LEO 43204 0.018% Gel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

Applied topically once daily for 3 consecutive days.

Arm title	Follow-up phase: Vehicle Gel

Arm description:

Treatment once daily for 3 consecutive days applied on full face or within a contiguous area of approximately 250 cm2 on the chest.

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

Dosage and administration details:

Applied topically once daily for 3 consecutive days

Number of subjects in period 2[1]	Follow-up phase: LEO 43204 0.018% Gel	Follow-up phase: Vehicle Gel
Started	199	84
Completed	185	67
Not completed	14	17
Consent withdrawn by subject	10	10
Other	-	1
Lost to follow-up	3	3
Lack of efficacy	1	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 295 subjects who completed the 3-day treatment and 8-week Follow-up period, 4 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 0.018% Gel
Reporting group description:	
Treatment once daily with LEO 43204 0.018% gel for 3 consecutive days applied on full face or within a contiguous area of approximately 250 cm2 on the chest.	
Reporting group title	Vehicle Gel
Reporting group description:	
Treatment once daily with vehicle gel for 3 consecutive days applied on full face or within a contiguous area of approximately 250 cm2 on the chest.	

Reporting group values	LEO 43204 0.018% Gel	Vehicle Gel	Total
Number of subjects	205	100	305
Age categorical Units: Subjects			
Adults (18-64 years)	73	34	107
From 65-84 years	129	64	193
85 years and over	3	2	5
Age continuous Units: years			
arithmetic mean	68.2	67.4	
standard deviation	± 8.9	± 9.9	-
Gender categorical Units: Subjects			
Female	67	38	105
Male	138	62	200

End points

End points reporting groups

Reporting group title	LEO 43204 0.018% Gel
Reporting group description:	
Treatment once daily with LEO 43204 0.018% gel for 3 consecutive days applied on full face or within a contiguous area of approximately 250 cm2 on the chest.	
Reporting group title	Vehicle Gel
Reporting group description:	
Treatment once daily with vehicle gel for 3 consecutive days applied on full face or within a contiguous area of approximately 250 cm2 on the chest.	
Reporting group title	Follow-up phase: LEO 43204 0.018% Gel
Reporting group description:	
Treatment once daily for 3 consecutive days applied on full face or within a contiguous area of approximately 250 cm2 on the chest.	
Reporting group title	Follow-up phase: Vehicle Gel
Reporting group description:	
Treatment once daily for 3 consecutive days applied on full face or within a contiguous area of approximately 250 cm2 on the chest.	

Primary: Complete Clearance of Actinic Keratosis (AK)

End point title	Complete Clearance of Actinic Keratosis (AK)
End point description:	
Complete clearance was defined as an AK count of zero, i.e. no clinically visible AKs in the treatment area. The table shows the percentage of mean number of subjects across imputations with complete clearance.	
End point type	Primary
End point timeframe:	
At Week 8	

End point values	LEO 43204 0.018% Gel	Vehicle Gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	205	100		
Units: percentage of subjects				
number (confidence interval 95%)	31.3 (24.9 to 37.6)	1.0 (-1.0 to 3.1)		

Statistical analyses

Statistical analysis title	Analysis 1
Statistical analysis description:	
Mean number of subjects across imputations.	
Comparison groups	LEO 43204 0.018% Gel v Vehicle Gel

Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001
Method	Mantel-Haenszel
Parameter estimate	Ratio of clearance rates
Point estimate	30.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.28
upper limit	218

Notes:

[1] - Mantel-Haenszel estimate (0.018% relative to vehicle), adjusted for pooled sites.

Secondary: Partial Clearance (Multiple Imputation)

End point title	Partial Clearance (Multiple Imputation)

End point description:

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 partial clearance.

End point type	Secondary

End point timeframe:

At Week 8

End point values	LEO 43204 0.018% Gel	Vehicle Gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	205	100		
Units: percentage of subjects				
number (confidence interval 95%)	55.8 (49.0 to 62.7)	4.6 (0.3 to 8.9)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Mantel-Haenszel estimate (0.018% relative to vehicle), adjusted for pooled sites. 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	Vehicle Gel v LEO 43204 0.018% Gel

Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mantel-Haenszel
Parameter estimate	Ratio of clearance rates
Point estimate	12.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.73
upper limit	31.78

Secondary: Partial Clearance (Multiple Imputation)

End point title	Partial Clearance (Multiple Imputation)

End point description:

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 partial clearance.

End point type	Secondary

End point timeframe:

At Week 4

End point values	LEO 43204 0.018% Gel	Vehicle Gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	205	100		
Units: percentage of subjects				
number (confidence interval 95%)	56.6 (49.7 to 63.4)	5.5 (0.9 to 10.2)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	LEO 43204 0.018% Gel v Vehicle Gel
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.001
Method	Mantel-Haenszel
Parameter estimate	Ratio of clearance rates
Point estimate	10.31

Confidence interval	
level	95 %
sides	2-sided
lower limit	4.43
upper limit	23.97

Notes:

[2] - Mantel-Haenszel estimate (0.018% relative to vehicle), adjusted for pooled sites. 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.

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 (using multiple imputations to account for missing values). 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 0.018% Gel	Vehicle Gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	205	100		
Units: percentage of reduction				
arithmetic mean (confidence interval 95%)	72.1 (68.3 to 75.5)	7.3 (-7.8 to 20.3)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	LEO 43204 0.018% Gel v Vehicle Gel
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.001 [4]
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	0.37

Notes:

[3] - 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.

[4] - Negative binominal regression with treatment group and pooled site as factors and log baseline count as offset variable.

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 0.018% Gel - Treatment Period Including Follow-up

Reporting group description:

Treatment with LEO 43204 0.018% gel once daily for 3 consecutive days.

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

Reporting group description:

Treatment with vehicle gel once daily for 3 consecutive days.

Reporting group title	LEO 43204 0.018% Gel - Extended Follow-up

Reporting group description:

Treatment with LEO 43204 0.018% gel once daily for 3 consecutive days.

Reporting group title	Vehicle Gel - Extended Follow-up

Reporting group description:

Treatment with vehicle gel once daily for 3 consecutive days.

Serious adverse events	LEO 43204 0.018% Gel - Treatment Period Including Follow-up	Vehicle Gel - Treatment Period Including Follow-up	LEO 43204 0.018% Gel - Extended Follow-up
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 205 (0.98%)	0 / 100 (0.00%)	0 / 199 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Liver function test abnormal			
subjects affected / exposed	1 / 205 (0.49%)	0 / 100 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Rib fracture			

subjects affected / exposed	1 / 205 (0.49%)	0 / 100 (0.00%)	0 / 199 (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
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	1 / 205 (0.49%)	0 / 100 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 205 (0.49%)	0 / 100 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	1 / 205 (0.49%)	0 / 100 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 205 (0.49%)	0 / 100 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 205 (0.49%)	0 / 100 (0.00%)	0 / 199 (0.00%)
occurrences causally related to treatment / all	1 / 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 / 84 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Liver function test abnormal			

subjects affected / exposed	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 84 (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 0.018% Gel - Treatment Period Including Follow-up	Vehicle Gel - Treatment Period Including Follow-up	LEO 43204 0.018% Gel - Extended Follow-up
Total subjects affected by non-serious adverse events			
subjects affected / exposed	134 / 205 (65.37%)	3 / 100 (3.00%)	23 / 199 (11.56%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	4 / 205 (1.95%)	1 / 100 (1.00%)	9 / 199 (4.52%)
occurrences (all)	4	1	9
Squamous cell carcinoma of skin			
subjects affected / exposed	8 / 205 (3.90%)	2 / 100 (2.00%)	10 / 199 (5.03%)
occurrences (all)	8	2	10
Injury, poisoning and procedural complications			
Scar			
subjects affected / exposed	0 / 205 (0.00%)	0 / 100 (0.00%)	9 / 199 (4.52%)
occurrences (all)	0	0	9
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 205 (4.88%)	0 / 100 (0.00%)	0 / 199 (0.00%)
occurrences (all)	10	0	0
General disorders and administration site conditions			
Application site discomfort			
subjects affected / exposed	6 / 205 (2.93%)	0 / 100 (0.00%)	0 / 199 (0.00%)
occurrences (all)	6	0	0
Application site pain			
subjects affected / exposed	120 / 205 (58.54%)	1 / 100 (1.00%)	0 / 199 (0.00%)
occurrences (all)	120	1	0
Application site paraesthesia			
subjects affected / exposed	5 / 205 (2.44%)	0 / 100 (0.00%)	0 / 199 (0.00%)
occurrences (all)	5	0	0
Application site pruritus			
subjects affected / exposed	71 / 205 (34.63%)	0 / 100 (0.00%)	0 / 199 (0.00%)
occurrences (all)	71	0	0
Eye disorders			

Periorbital oedema			
subjects affected / exposed	8 / 205 (3.90%)	0 / 100 (0.00%)	0 / 199 (0.00%)
occurrences (all)	8	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	11 / 205 (5.37%)	0 / 100 (0.00%)	0 / 199 (0.00%)
occurrences (all)	11	0	0
Sleep disorder			
subjects affected / exposed	6 / 205 (2.93%)	0 / 100 (0.00%)	0 / 199 (0.00%)
occurrences (all)	6	0	0

Non-serious adverse events	Vehicle Gel - Extended Follow-up		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 84 (3.57%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences (all)	1		
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Scar			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 84 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Application site discomfort			
subjects affected / exposed	0 / 84 (0.00%)		
occurrences (all)	0		
Application site pain			
subjects affected / exposed	0 / 84 (0.00%)		
occurrences (all)	0		

Application site paraesthesia subjects affected / exposed occurrences (all) Application site pruritus subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0 0 / 84 (0.00%) 0		
Eye disorders Periorbital oedema subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) Sleep disorder subjects affected / exposed occurrences (all)	0 / 84 (0.00%) 0 0 / 84 (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 protocol was updated to specify the method (an interactive web response system) for ensuring that the trial enrolled a minimum of 15% and a maximum of 25% of chest-treated subjects. The amendment also clarified which medications were allowed and prohibited during the extended follow-up period: lesion-directed laser treatment was added to the allowed medications, and Actikerall, even as lesion-directed treatment, and laser treatment as field treatment were prohibited.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported