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	2015-002450-12
Trial protocol	DE IT
Global end of trial date	10 August 2017

Results information

Result version number	v1 (current)
This version publication date	16 September 2018
First version publication date	16 September 2018

Trial information

Trial identification

Sponsor protocol code	LP0084-1194

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02549339
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	10 August 2017
Global end of trial reached?	Yes
Global end of trial date	10 August 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 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	Spain: 21
Country: Number of subjects enrolled	Germany: 36
Country: Number of subjects enrolled	Italy: 18
Country: Number of subjects enrolled	United States: 158
Country: Number of subjects enrolled	Canada: 73
Worldwide total number of subjects	306
EEA total number of subjects	75

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	101
From 65 to 84 years	196
85 years and over	9

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:

383 subjects were enrolled, 74 were screening failures, and 309 subjects were randomised. Only 306 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	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	LEO 43204 0.018% Gel - Treatment Period Including Follow-up

Arm description:

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

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

Dosage and administration details:

Ingenol disoxate 0.018% gel applied topically on full face or within a contiguous area of approximately 250 cm2 on the chest once daily for 3 consecutive days.

Arm title	Vehicle Gel - Treatment Period Including Follow-up

Arm description:

Treatment with vehicle gel 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	Placebo
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

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

Number of subjects in period 1	LEO 43204 0.018% Gel - Treatment Period Including Follow-up	Vehicle Gel - Treatment Period Including Follow-up
Started	202	104
Completed	201	99
Not completed	1	5
Consent withdrawn by subject	-	3
Lost to follow-up	-	2
Protocol deviation	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 0.018% Gel - Extended Follow-up

Arm description:

Treatment with LEO 43204 0.018% gel 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
Investigational medicinal product code	
Other name	Ingenol disoxate
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

Ingenol disoxate 0.018% gel applied topically on full face or within a contiguous area of approximately 250 cm2 on the chest once daily for 3 consecutive days.

Arm title	Vehicle Gel - Extended Follow-up

Arm description:

Treatment with vehicle gel 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	Placebo
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

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

Number of subjects in period 2[1]	LEO 43204 0.018% Gel - Extended Follow-up	Vehicle Gel - Extended Follow-up
Started	201	98
Completed	192	87
Not completed	9	11
Consent withdrawn by subject	8	3
Other	-	3
Lost to follow-up	1	3
Lack of efficacy	-	2

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 300 subjects who completed the 3-day treatment and 8-week follow-up period, 1 subject in the vehicle group was not included in the 12-month Follow-up period because they withdrew after Week 8.

Baseline characteristics

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 applied on full face or within a contiguous area of approximately 250 cm2 on the chest.	
Reporting group title	Vehicle Gel - Treatment Period Including Follow-up
Reporting group description:	
Treatment with vehicle gel once daily 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 - Treatment Period Including Follow-up	Vehicle Gel - Treatment Period Including Follow-up	Total
Number of subjects	202	104	306
Age categorical Units: Subjects			
Adults (18-64 years)	63	38	101
From 65-84 years	131	65	196
85 years and over	8	1	9
Age continuous Units: years			
arithmetic mean	69.1	66.3	
standard deviation	± 9.2	± 9.1	-
Gender categorical Units: Subjects			
Female	65	41	106
Male	137	63	200

End points

End points 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 applied on full face or within a contiguous area of approximately 250 cm2 on the chest.	
Reporting group title	Vehicle Gel - Treatment Period Including Follow-up
Reporting group description:	
Treatment with vehicle gel 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	LEO 43204 0.018% Gel - Extended Follow-up
Reporting group description:	
Treatment with LEO 43204 0.018% gel 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	Vehicle Gel - Extended Follow-up
Reporting group description:	
Treatment with vehicle gel 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:	
The number of clinically visible actinic keratosis lesions (AKs) identified in the treatment area was recorded at Day 1, Week 4, and Week 8. Complete clearance was defined as 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 - Treatment Period Including Follow-up	Vehicle Gel - Treatment Period Including Follow-up		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	104		
Units: percentage of subjects				
number (confidence interval 95%)	20.4 (14.9 to 26.0)	2.9 (-0.3 to 6.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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

Comparison groups	LEO 43204 0.018% Gel - Treatment Period Including Follow-up v Vehicle Gel - Treatment Period Including Follow-up
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Mantel-Haenszel
Parameter estimate	Ratio of clearance rates
Point estimate	7.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.26
upper limit	25.31

Secondary: Partial Clearance (Multiple Imputation)

End point title	Partial Clearance (Multiple Imputation)

End point description:

The number of clinically visible 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.

End point type	Secondary

End point timeframe:

At Week 8

End point values	LEO 43204 0.018% Gel - Treatment Period Including Follow-up	Vehicle Gel - Treatment Period Including Follow-up		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	104		
Units: percentage of subjects				
number (confidence interval 95%)	60.3 (53.5 to 67.1)	10.7 (4.7 to 16.7)		

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 (0.018% relative to vehicle), adjusted for pooled sites.

Comparison groups	Vehicle Gel - Treatment Period Including Follow-up v LEO 43204 0.018% Gel - Treatment Period Including Follow-up
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mantel-Haenszel
Parameter estimate	Ratio of clearance rates
Point estimate	5.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.3
upper limit	10.54

Secondary: Partial Clearance (Multiple Imputation)

End point title	Partial Clearance (Multiple Imputation)

End point description:

The number of clinically visible 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.

End point type	Secondary

End point timeframe:

At Week 4

End point values	LEO 43204 0.018% Gel - Treatment Period Including Follow-up	Vehicle Gel - Treatment Period Including Follow-up		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	104		
Units: percentage of subjects				
number (confidence interval 95%)	61.1 (54.4 to 67.8)	10.8 (4.8 to 16.9)		

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 (0.018% relative to vehicle), adjusted for pooled sites.

Comparison groups	LEO 43204 0.018% Gel - Treatment Period Including Follow-up v Vehicle Gel - Treatment Period Including Follow-up
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mantel-Haenszel
Parameter estimate	Ratio of clearance rates
Point estimate	5.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.24
upper limit	10.2

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:

End point type	Secondary

End point timeframe:

At Week 8

End point values	LEO 43204 0.018% Gel - Treatment Period Including Follow-up	Vehicle Gel - Treatment Period Including Follow-up		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	104		
Units: percentage of reduction				
number (confidence interval 95%)	74.8 (71.8 to 77.4)	15.0 (3.4 to 25.2)		

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 0.018% Gel - Treatment Period Including Follow-up v Vehicle Gel - Treatment Period Including Follow-up
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
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	0.35

Notes:

[1] - 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:

Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.

Adverse events presented in the table are investigator-reported terms.

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 once daily for 3 days with LEO 43204 0.018% 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 0.018% Gel - Extended Follow-up

Reporting group description: -

Reporting group title	Vehicle Gel - Extended Follow-up

Reporting group description:

Treatment once daily for 3 days Vehicle gel

Serious adverse events	LEO 43204 0.018% 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	0 / 202 (0.00%)	0 / 104 (0.00%)	1 / 201 (0.50%)
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)			
Squamous cell carcinoma of skin	Additional description: The event was classified as serious because the participant was hospitalized.		
subjects affected / exposed	0 / 202 (0.00%)	0 / 104 (0.00%)	1 / 201 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
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 / 98 (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)			
Squamous cell carcinoma of skin	Additional description: The event was classified as serious because the participant was hospitalized.		
subjects affected / exposed	0 / 98 (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: 0 %

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	136 / 202 (67.33%)	32 / 104 (30.77%)	35 / 201 (17.41%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	5 / 202 (2.48%)	3 / 104 (2.88%)	9 / 201 (4.48%)
occurrences (all)	5	3	9
Squamous cell carcinoma of skin			
subjects affected / exposed	5 / 202 (2.48%)	0 / 104 (0.00%)	6 / 201 (2.99%)
occurrences (all)	5	0	6
Bowen's disease			
subjects affected / exposed	1 / 202 (0.50%)	2 / 104 (1.92%)	10 / 201 (4.98%)
occurrences (all)	1	2	10
Seborrhoeic keratosis			
subjects affected / exposed	0 / 202 (0.00%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	0	0	0
Malignant melanoma			
subjects affected / exposed	0 / 202 (0.00%)	0 / 104 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			

subjects affected / exposed	0 / 202 (0.00%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Application site pain			
subjects affected / exposed	113 / 202 (55.94%)	5 / 104 (4.81%)	0 / 201 (0.00%)
occurrences (all)	113	5	0
Application site pruritus			
subjects affected / exposed	63 / 202 (31.19%)	5 / 104 (4.81%)	0 / 201 (0.00%)
occurrences (all)	63	5	0
Application site discomfort			
subjects affected / exposed	9 / 202 (4.46%)	3 / 104 (2.88%)	0 / 201 (0.00%)
occurrences (all)	9	3	0
Application site warmth			
subjects affected / exposed	3 / 202 (1.49%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	3	1	0
Application site paraesthesia			
subjects affected / exposed	2 / 202 (0.99%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	2	1	0
Chills			
subjects affected / exposed	3 / 202 (1.49%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	3	0	0
Pain			
subjects affected / exposed	1 / 202 (0.50%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	1	1	0
Application site dryness			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Application site haematoma			
subjects affected / exposed	0 / 202 (0.00%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	0	1	0
Application site laceration			
subjects affected / exposed	0 / 202 (0.00%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	0	1	0
Application site nodule			

subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Chest discomfort			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Facial pain			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Hangover			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	0 / 202 (0.00%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	0	1	0
Application site scar			
subjects affected / exposed	0 / 202 (0.00%)	0 / 104 (0.00%)	3 / 201 (1.49%)
occurrences (all)	0	0	3
Application site discolouration			
subjects affected / exposed	0 / 202 (0.00%)	0 / 104 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	0	1
Application site dermatitis			
subjects affected / exposed	0 / 202 (0.00%)	0 / 104 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	0	1
Application site macule			
subjects affected / exposed	0 / 202 (0.00%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	2 / 202 (0.99%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	2	0	0
Prostatomegaly			
subjects affected / exposed	0 / 202 (0.00%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			

Sinus congestion			
subjects affected / exposed	0 / 202 (0.00%)	2 / 104 (1.92%)	0 / 201 (0.00%)
occurrences (all)	0	2	0
Asthma			
subjects affected / exposed	0 / 202 (0.00%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	202	1	0
Cough			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Dysphonia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 202 (1.49%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	3	0	0
Anxiety			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Depression			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Sleep disorder			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Liver function test abnormal			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			

Laceration			
subjects affected / exposed	4 / 202 (1.98%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	4	0	0
Fall			
subjects affected / exposed	1 / 202 (0.50%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	1	1	0
Ligament sprain			
subjects affected / exposed	1 / 202 (0.50%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	1	1	0
Skin abrasion			
subjects affected / exposed	1 / 202 (0.50%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	1	1	0
Accidental exposure to product			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Arthropod bite			
subjects affected / exposed	0 / 202 (0.00%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	0	1	0
Concussion			
subjects affected / exposed	0 / 202 (0.00%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	0	1	0
Face injury			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Muscle strain			
subjects affected / exposed	0 / 202 (0.00%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	0	1	0
Periorbital haematoma			
subjects affected / exposed	0 / 202 (0.00%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	0	1	0
Sunburn			
subjects affected / exposed	0 / 202 (0.00%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	0	1	0
Scar			
subjects affected / exposed	0 / 202 (0.00%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	0	0	0

Nervous system disorders			
Headache			
subjects affected / exposed	12 / 202 (5.94%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	12	0	0
Anosmia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Sciatica			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Tension headache			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Periorbital oedema			
subjects affected / exposed	8 / 202 (3.96%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	8	0	0
Eye irritation			
subjects affected / exposed	4 / 202 (1.98%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	4	1	0
Lacrimation increased			
subjects affected / exposed	2 / 202 (0.99%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	2	1	0
Eye pain			
subjects affected / exposed	2 / 202 (0.99%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	2	0	0
Conjunctival haemorrhage			
subjects affected / exposed	0 / 202 (0.00%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	0	1	0
Dry eye			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Eczema eyelids			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Eyelid oedema			

subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Eyelid pain			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Photophobia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Vision blurred			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 202 (0.99%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	2	0	0
Vomiting			
subjects affected / exposed	2 / 202 (0.99%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	2	0	0
Rectal polyp			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Ingrowing nail			
subjects affected / exposed	0 / 202 (0.00%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	0	1	0
Intertrigo			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Post inflammatory pigmentation change			
subjects affected / exposed	0 / 202 (0.00%)	1 / 104 (0.96%)	4 / 201 (1.99%)
occurrences (all)	0	1	4
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 202 (0.00%)	0 / 104 (0.00%)	3 / 201 (1.49%)
occurrences (all)	0	0	3
Hypertrophic scar			

subjects affected / exposed	0 / 202 (0.00%)	0 / 104 (0.00%)	2 / 201 (1.00%)
occurrences (all)	0	0	2
Papule			
subjects affected / exposed	0 / 202 (0.00%)	0 / 104 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	0	1
Rosacea			
subjects affected / exposed	0 / 202 (0.00%)	0 / 104 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 202 (0.50%)	2 / 104 (1.92%)	0 / 201 (0.00%)
occurrences (all)	1	2	0
Rotator cuff syndrome			
subjects affected / exposed	1 / 202 (0.50%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	1	1	0
Exostosis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	0	1	0
Muscular weakness			
subjects affected / exposed	0 / 202 (0.00%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Osteoarthritis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	6 / 202 (2.97%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	6	1	0
Nasopharyngitis			

subjects affected / exposed	3 / 202 (1.49%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	3	1	0
Rhinitis			
subjects affected / exposed	3 / 202 (1.49%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	3	0	0
Herpes simplex			
subjects affected / exposed	2 / 202 (0.99%)	0 / 104 (0.00%)	1 / 201 (0.50%)
occurrences (all)	2	0	1
Application site infection			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Cellulitis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Folliculitis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	0	1	0
Furuncle			
subjects affected / exposed	0 / 202 (0.00%)	1 / 104 (0.96%)	0 / 201 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0
Postoperative wound infection			
subjects affected / exposed	0 / 202 (0.00%)	0 / 104 (0.00%)	1 / 201 (0.50%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0

Hyperkalaemia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 104 (0.00%)	0 / 201 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Vehicle Gel - Extended Follow-up		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 98 (14.29%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Squamous cell carcinoma of skin			
subjects affected / exposed	3 / 98 (3.06%)		
occurrences (all)	3		
Bowen's disease			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	2		
Seborrhoeic keratosis			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	2		
Malignant melanoma			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Application site pain			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Application site pruritus			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Application site discomfort			

subjects affected / exposed	0 / 98 (0.00%)			
occurrences (all)	0			
Application site warmth				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences (all)	0			
Application site paraesthesia				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences (all)	0			
Chills				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences (all)	0			
Pain				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences (all)	0			
Application site dryness				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences (all)	0			
Application site haematoma				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences (all)	0			
Application site laceration				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences (all)	0			
Application site nodule				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences (all)	0			
Chest discomfort				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences (all)	0			
Facial pain				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences (all)	0			
Hangover				
subjects affected / exposed	0 / 98 (0.00%)			
occurrences (all)	0			
Pyrexia				

subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Application site scar			
subjects affected / exposed	3 / 98 (3.06%)		
occurrences (all)	3		
Application site discolouration			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Application site dermatitis			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Application site macule			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Prostatomegaly			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Sinus congestion			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Asthma			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Dysphonia			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Epistaxis			

subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Anxiety			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Sleep disorder			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Liver function test abnormal			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Laceration			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Ligament sprain			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Skin abrasion			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Accidental exposure to product			

subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Arthropod bite			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Concussion			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Face injury			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Muscle strain			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Periorbital haematoma			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Sunburn			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Scar			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Anosmia			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Sciatica			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Tension headache			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		

Eye disorders			
Periorbital oedema			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Eye irritation			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Lacrimation increased			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Eye pain			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Conjunctival haemorrhage			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Dry eye			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Eczema eyelids			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Eyelid oedema			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Eyelid pain			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Photophobia			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Vision blurred			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Rectal polyp			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Ingrowing nail			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Intertrigo			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Post inflammatory pigmentation change			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Hypertrophic scar			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Papule			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Rosacea			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Rotator cuff syndrome			

subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Exostosis			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Muscular weakness			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Osteoarthritis			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Rhinitis			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Herpes simplex			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences (all)	1		
Application site infection			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		
Cellulitis			
subjects affected / exposed	0 / 98 (0.00%)		
occurrences (all)	0		

Conjunctivitis subjects affected / exposed occurrences (all)	0 / 98 (0.00%) 0		
Folliculitis subjects affected / exposed occurrences (all)	0 / 98 (0.00%) 0		
Furuncle subjects affected / exposed occurrences (all)	0 / 98 (0.00%) 0		
Influenza subjects affected / exposed occurrences (all)	0 / 98 (0.00%) 0		
Sinusitis subjects affected / exposed occurrences (all)	0 / 98 (0.00%) 0		
Postoperative wound infection subjects affected / exposed occurrences (all)	0 / 98 (0.00%) 0		
Metabolism and nutrition disorders			
Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 98 (0.00%) 0		
Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 98 (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. 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