Clinical trial results:
Incidence of squamous cell carcinoma and other skin neoplasia in subjects with actinic keratosis treated with ingenol disoxate gel 0.018% or 0.037%, or vehicle.

A phase 3 trial to compare the incidence of SCC and other skin neoplasia on skin areas treated with ingenol disoxate gel or vehicle gel for actinic keratosis on face and chest or scalp.

Summary

EudraCT number	2017-000228-85
Trial protocol	GB DE ES IT
Global end of trial date	12 March 2018

Results information

Result version number	v1 (current)
This version publication date	03 April 2019
First version publication date	03 April 2019

Trial information

Trial identification

Sponsor protocol code	LP0084-1369

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03115476
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 Trial Disclosure, LEO Pharma A/S, +45 44945888, disclosure@leo-pharma.com
Scientific contact	Clinical Trial Disclosure, 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 August 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 March 2018
Global end of trial reached?	Yes
Global end of trial date	12 March 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare the incidence of squamous cell carcinoma after treatment with ingenol disoxate gel and vehicle gel

Protection of trial subjects:

This clinical trial was conducted to conform to the principles of the Declaration of Helsinki as adopted by the 18th World Medical Association General Assembly, 1964, and the amendment from Somerset West, South Africa, October 1996. All subjects received written and verbal information concerning the clinical trial. Subjects were asked to consent that their personal data were recorded, collected, processed and could be transferred to other countries in accordance with any national legislation regulating privacy and data protection.

Background therapy:

none

Evidence for comparator:

This trial was an extension trial. The subjects who qualified for this trial had previously been enrolled in LEO trials LP0084-1193, -1194, -1195, or - 1196 (main trial) in which a treatment area was defined and treatment applied. The trial subjects did not receive investigational medicinal product during the trial

Actual start date of recruitment	28 April 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	United Kingdom: 37
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Germany: 61
Country: Number of subjects enrolled	United States: 272
Country: Number of subjects enrolled	Canada: 158
Worldwide total number of subjects	563
EEA total number of subjects	133

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)	155
From 65 to 84 years	391
85 years and over	17

Subject disposition

Recruitment

Recruitment details:

Eligibility criteria: The subject has been treated in one of the trials LP0084-1193, -1194, -1195, or -1196 (main trials) and has been evaluated at Visit 11 of that trial. The following countries participated: Canada, Germany, Spain, France, UK, and US

Pre-assignment

Screening details:

In the main trials 1234 subjects were randomised and applied study drug. Less than half of the subjects continued into this trial: 82 from LP0084 -1193, 186 from trial -1194, 163 from -1195, and 132 from -1196. 3 subjects discontinued the trial due to death unrelated to trial treatment. The trial was terminated by sponsor decision.

Period 1

Period 1 title	From V2 (Day1) in main trial
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Ingenol disoxate gel 0.018%

Arm description:

Subjects who had been treated with ingenol disoxate gel 0.018% on face or chest in the main trial

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

Dosage and administration details:

This trial was an extension trial. The subjects who qualified for this trial had previously been enrolled in LEO trials LP0084-1193, -1194, -1195, or - 1196 (main trial) in which a treatment area was defined and treatment applied. The trial subjects did not receive investigational medicinal product during this trial

Arm title	Ingenol disoxate gel 0.037%

Arm description:

Subjects who had been treated with ingenol disoxate 0.037% on the scalp in the main trial

Arm type	Experimental
Investigational medicinal product name	Ingenol disoxate gel 0.037%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

This trial was an extension trial. The subjects who qualified for this trial had previously been enrolled in LEO trials LP0084-1193, -1194, -1195, or - 1196 (main trial) in which a treatment area was defined and treatment applied. The trial subjects did not receive investigational medicinal product during this trial

Arm title	Vehicle gel

Arm description:

vehicle gel (to ingenol disoxate gel) that contained no active ingredients

Arm type	Placebo

Investigational medicinal product name	Vehicle gel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

This trial was an extension trial. The subjects who qualified for this trial had previously been enrolled in LEO trials LP0084-1193, -1194, -1195, or - 1196 (main trial) in which a treatment area was defined and treatment applied. The trial subjects did not receive investigational medicinal product during this trial

Number of subjects in period 1	Ingenol disoxate gel 0.018%	Ingenol disoxate gel 0.037%	Vehicle gel
Started	407	418	409
Completed	377	393	316
Not completed	30	25	93
Adverse event, serious fatal	-	-	2
Consent withdrawn by subject	20	11	54
not known	-	3	10
Adverse event, non-fatal	1	-	2
Lost to follow-up	6	10	17
unacceptable local skin reaction	1	-	-
Lack of efficacy	1	1	6
Protocol deviation	1	-	2

Period 2

Period 2 title	LP0084-1369 trial period
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Ingenol disoxate gel 0.018%

Arm description: -

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

Dosage and administration details:

This trial was an extension trial. The subjects who qualified for this trial had previously been enrolled in

LEO trials LP0084-1193, -1194, -1195, or - 1196 (main trial) in which a treatment area was defined and treatment applied. The trial subjects did not receive investigational medicinal product during the trial

Arm title	Ingenol disoxate gel 0.037%
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Ingenol disoxate gel 0.037%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

This trial was an extension trial. The subjects who qualified for this trial had previously been enrolled in LEO trials LP0084-1193, -1194, -1195, or - 1196 (main trial) in which a treatment area was defined and treatment applied. The trial subjects did not receive investigational medicinal product during the trial

Arm title	Vehicle gel
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Vehicle gel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

This trial was an extension trial. The subjects who qualified for this trial had previously been enrolled in LEO trials LP0084-1193, -1194, -1195, or - 1196 (main trial) in which a treatment area was defined and treatment applied. The trial subjects did not receive investigational medicinal product during the trial

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The full analysis set comprise 1234 randomised subjects from the 4 main trials (LP0084-1193, -1194, -1195, or - 1196) who applied investigational medicinal product (This is period 1).

Of these subjects, 563 subjects continued into trial LP0084-1369. This would be period 2 i.e the LP0084-1369 trial period which is the baseline period for the present trial

Number of subjects in period 2[2]	Ingenol disoxate gel 0.018%	Ingenol disoxate gel 0.037%	Vehicle gel
Started	191	210	162
Completed	0	0	0
Not completed	191	210	162
trial terminated by sponsor	190	210	160
death untrelated to AE in the treatment area	1	-	2

Notes:

[2] - 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: The full analysis set comprise 1234 randomised subjects from the 4 main trials (LP0084-1193, -1194, -1195, or - 1196) who applied investigational medicinal product. Of these subjects, 563 subjects continued into trial LP0084-1369

Baseline characteristics

Reporting groups

Reporting group title	LP0084-1369 trial period

Reporting group description: -

Reporting group values	LP0084-1369 trial period	Total	
Number of subjects	563	563	
Age categorical			
1234 subjects in the full analysis set (subjects who applied IMP in the main trials)			
Units: Subjects			
Adults (18-64 years)	155	155	
From 65-84 years	391	391	
85 years and over	17	17	
Gender categorical			
1234 subjects in the full analysis set (subjects who applied IMP in the main trials)			
Units: Subjects			
Female	97	97	
Male	466	466	

Subject analysis sets

Subject analysis set title	Trial period
Subject analysis set type	Safety analysis

Subject analysis set description:

The trial period is from the first visit in trial LP0084-1369 until the end of the trial.
1234 subjects where randomised and applied investigational medicinal product in the 4 main trials and were included in the full analysis set. All subjects in the full analysis set were included in the safety analysis set.

Reporting group values	Trial period		
Number of subjects	563		
Age categorical			
1234 subjects in the full analysis set (subjects who applied IMP in the main trials)			
Units: Subjects			
Adults (18-64 years)	358		
From 65-84 years	828		
85 years and over	48		
Gender categorical			
1234 subjects in the full analysis set (subjects who applied IMP in the main trials)			
Units: Subjects			
Female	212		
Male	1022		

End points

End points reporting groups

Reporting group title	Ingenol disoxate gel 0.018%
Reporting group description:	
Subjects who had been treated with ingenol disoxate gel 0.018% on face or chest in the main trial	
Reporting group title	Ingenol disoxate gel 0.037%
Reporting group description:	
Subjects who had been treated with ingenol disoxate 0.037% on the scalp in the main trial	
Reporting group title	Vehicle gel
Reporting group description:	
vehicle gel (to ingenol disoxate gel) that contained no active ingredients	
Reporting group title	Ingenol disoxate gel 0.018%
Reporting group description: -	
Reporting group title	Ingenol disoxate gel 0.037%
Reporting group description: -	
Reporting group title	Vehicle gel
Reporting group description: -	
Subject analysis set title	Trial period
Subject analysis set type	Safety analysis
Subject analysis set description:	
The trial period is from the first visit in trial LP0084-1369 until the end of the trial. 1234 subjects where randomised and applied investigational medicinal product in the 4 main trials and were included in the full analysis set. All subjects in the full analysis set were included in the safety analysis set.	

Primary: Time to first squamous cell carcinoma (SCC) in the treatment area

End point title	Time to first squamous cell carcinoma (SCC) in the treatment area
End point description:	
Time to first squamous cell carcinoma (SCC) in the treatment area. Relative difference between groups (ingenol disoxate vs vehicle) expressed as hazard ratio. The indicated measured values are the observed incidence rates of the SCC in the treatment area which form the basis of the statistical analysis of the time to event analysis	
End point type	Primary
End point timeframe:	
From Visit 2 to first SCC in the treatment area, up to 24 months	

End point values	Ingenol disoxate gel 0.018%	Ingenol disoxate gel 0.037%	Vehicle gel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	191[1]	210[2]	162[3]	
Units: Incidencerate per 100 patient years				
number (confidence interval 95%)	2.77 (1.55 to 4.57)	0.88 (0.28 to 2.04)	1.26 (0.46 to 2.74)	

Notes:

[1] - actual number of subjects analysed is 407: subjects in the period from Visit 2 in the main trial

[2] - actual number of subjects analysed is 418: subjects in the period from Visit 2 in the main trial

[3] - actual number of subjects analysed is 409: subjects in the period from Visit 2 in the main trial

Statistical analyses

Statistical analysis title	likelihood ratio test

Statistical analysis description:

Relative difference between groups (ingenol disoxate vs vehicle) expressed as hazard ratio

Comparison groups	Ingenol disoxate gel 0.018% v Ingenol disoxate gel 0.037% v Vehicle gel
Number of subjects included in analysis	563
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.43 [4]
Method	likelyhood ratio test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	3.9

Notes:

[4] - ingenol disoxate vs vehicle

Secondary: Time to first SCC or other skin neoplasia in the treatment area

End point title	Time to first SCC or other skin neoplasia in the treatment area

End point description:

To compare the incidence of SCC or other skin neoplasia after treatment with ingenol disoxate gel and vehicle gel.
The indicated measured values are the observed incidence rates of the SCC in the treatment area which form the basis of the statistical analysis of the time to event analysis

End point type	Secondary

End point timeframe:

From Visit 2 to first SCC or other skin neoplasia in the treatment area, up to 24 months

End point values	Ingenol disoxate gel 0.018%	Ingenol disoxate gel 0.037%	Vehicle gel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	162[5]	210[6]	162[7]	
Units: Incidencerate per 100 patient years				
number (confidence interval 95%)	10.24 (7.65 to 13.4)	2.84 (1.62 to 4.61)	3.19 (1.79 to 5.26)	

Notes:

[5] - actual number of subjects analysed is 407: subjects in the period from Visit 2 in the main trial

[6] - actual number of subjects analysed is 418: subjects in the period from Visit 2 in the main trial

[7] - actual number of subjects analysed is 409: subjects in the period from Visit 2 in the main trial

Statistical analyses

Statistical analysis title	likelihood ratio test

Statistical analysis description:

relative difference between treatment groups (ingenol disoxate gel vs vehicle) expressed as hazard ratio, full analysis set

Comparison groups	Ingenol disoxate gel 0.037% v Ingenol disoxate gel 0.018% v Vehicle gel
Number of subjects included in analysis	534
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.01 [8]
Method	likelyhood ratio test
Parameter estimate	Hazard ratio
Point estimate	1.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.17
upper limit	3.62

Notes:

[8] - Ingenol disoxate vs vehicle

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The trial period: from first visit in this trial until the end of the trial

Adverse event reporting additional description:

Safety information is based on actual treatment' i.e. the treatment that was administered to the patient. This differed from 'planned treatment' (wich was used for the Participant Flow). Only events in the treatment area were collected (SAEs outside treatment area only collected if deemed related by the investigator to the study drug)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Ingenol disoxate gel 0.018%

Reporting group description:

Subjects who had been treated with ingenol disoxate gel 0.018% on face or chest in the main trial

Reporting group title	Ingenol disoxate gel 0.037%

Reporting group description:

Subjects who had been treated with ingenol disoxate 0.037% on the scalp in the main trial

Reporting group title	Vehicle gel

Reporting group description:

vehicle gel to ingenol disoxate gel

Serious adverse events	Ingenol disoxate gel 0.018%	Ingenol disoxate gel 0.037%	Vehicle gel
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 191 (0.00%)	1 / 211 (0.47%)	0 / 161 (0.00%)
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 / 191 (0.00%)	1 / 211 (0.47%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Ingenol disoxate gel 0.018%	Ingenol disoxate gel 0.037%	Vehicle gel
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 191 (8.38%)	6 / 211 (2.84%)	10 / 161 (6.21%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	2 / 191 (1.05%)	0 / 211 (0.00%)	3 / 161 (1.86%)
occurrences (all)	2	0	3
Basal cell carcinoma			
subjects affected / exposed	4 / 191 (2.09%)	0 / 211 (0.00%)	0 / 161 (0.00%)
occurrences (all)	4	0	0
Bowen's disease			
subjects affected / exposed	3 / 191 (1.57%)	0 / 211 (0.00%)	1 / 161 (0.62%)
occurrences (all)	3	0	1
Injury, poisoning and procedural complications			
Inflammation of wound			
subjects affected / exposed	1 / 191 (0.52%)	0 / 211 (0.00%)	0 / 161 (0.00%)
occurrences (all)	1	0	0
Skin abrasion			
subjects affected / exposed	0 / 191 (0.00%)	1 / 211 (0.47%)	0 / 161 (0.00%)
occurrences (all)	0	1	0
Scar			
subjects affected / exposed	1 / 191 (0.52%)	0 / 211 (0.00%)	0 / 161 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Application site scar			
subjects affected / exposed	8 / 191 (4.19%)	5 / 211 (2.37%)	7 / 161 (4.35%)
occurrences (all)	8	5	7
Application site papules			
subjects affected / exposed	1 / 191 (0.52%)	0 / 211 (0.00%)	0 / 161 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Rosacea			
subjects affected / exposed	1 / 191 (0.52%)	0 / 211 (0.00%)	0 / 161 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 July 2017	The reason for the amendment is to change the definition of the full analysis set to include all randomised subjects from the main trials

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
12 March 2018	The trial was terminated early by a sponsor decision to close the development program	-

Notes:

Limitations and caveats

None reported