Clinical trial results:
Risk of Squamous Cell Carcinoma on Skin Areas Treated with Ingenol Mebutate Gel, 0.015% and Imiquimod Cream, 5%

Summary

EudraCT number	2012-003112-31
Trial protocol	GB DE FR
Global end of trial date	11 July 2019

Results information

Result version number	v1 (current)
This version publication date	06 August 2020
First version publication date	06 August 2020

Trial information

Trial identification

Sponsor protocol code	LP0041-63

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01926496
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, LEO Pharma A/S, +45 44945888, disclosure@leo-pharma.com
Scientific contact	Clinical 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	22 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 July 2019
Global end of trial reached?	Yes
Global end of trial date	11 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the cumulative incidence of squamous cell carcinoma (SCC) after treatment with ingenol mebutate gel and imiquimod cream.

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 subsequent amendments. All subjects or their legally acceptable representative received written and verbal information concerning the clinical trial. Subjects or their legally acceptable representative were asked to consent that their personal data were recorded, collected, processed and could be transferred to EU and non-EU countries in accordance with any national legislation regulating privacy and data protection

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 June 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 162
Country: Number of subjects enrolled	France: 123
Country: Number of subjects enrolled	Germany: 200
Worldwide total number of subjects	485
EEA total number of subjects	485

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)	76

From 65 to 84 years	390
85 years and over	19

Subject disposition

Recruitment

Recruitment details:

The clinical trial was performed at 44 sites in 3 countries: France, 11 sites; Germany, 15 sites; and United Kingdom, 18 sites

Pre-assignment

Screening details:

A total number of 578 male or female subjects aged 18–94 years with actinic keratosis in face or scalp were screened. Of these were 68 screening failures and 25 were not assigned to treatment. In total, 485 subjects were randomized 1:1 to treatment.

Period 1

Period 1 title	Open-label (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Ingenol mebutate gel, 0.015%

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Ingenol mebutate gel, 0.015%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous solution
Routes of administration	Cutaneous use

Dosage and administration details:

Topical application; 0.015% gel was applied to the selected treatment area (actinic keratosis lesions within a contiguous 25 cm² treatment area on the face or the scalp) once-daily for 3 consecutive days followed by 8 weeks of rest. Retreatment was done if the treatment fields were not completely cleared of AK.

Arm title	Imiquimod cream, 5%

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Imiquimod cream, 5%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use

Dosage and administration details:

Topical application; 5% cream was applied to the selected treatment area (actinic keratosis lesions within a contiguous 25 cm² treatment area on the face or the scalp) once-daily for 3 days per week (e.g. Monday, Wednesday, and Friday) for 4 weeks followed by 4 weeks of rest. Retreatment was done if the treatment fields were not completely cleared of AK.

Number of subjects in period 1[1]	Ingenol mebutate gel, 0.015%	Imiquimod cream, 5%
Started	240	244
Completed	203	197
Not completed	37	47
Adverse event, serious fatal	8	5
Consent withdrawn by subject	14	15
Exclusion criteria emerging	-	2
Adverse event, non-fatal	3	4
Not known	2	7
Unacceptable LSR	-	3
Lost to follow-up	10	11

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: In total, 485 subjects were randomised (full analysis set), but 1 subject (randomised in United Kingdom) was not treated. To support the primary safety endpoints, all baseline and safety results are based on the 484 subjects. Efficacy analysis are based on all 485 randomized subjects due to the intention-to-treat principle.

Baseline characteristics

Reporting groups	
Reporting group title	Ingenol mebutate gel, 0.015%
Reporting group description: -	
Reporting group title	Imiquimod cream, 5%
Reporting group description: -	

Reporting group values	Ingenol mebutate gel, 0.015%	Imiquimod cream, 5%	Total
Number of subjects	240	244	484
Age categorical Units: Subjects			
Adults (18-64 years)	34	42	76
>=65	206	202	408
<=18	0	0	0
Gender categorical Units: Subjects			
Female	10	15	25
Male	230	229	459
Ethnicity Units: Subjects			
Unknown or Not Reported	0	0	0
Hispanic or Latino	226	232	458
Not Hispanic or Latino	14	12	26
Region of Enrollment Units: Subjects			
United Kingdom	80	81	161
Germany	100	100	200
France	60	63	123

Subject analysis sets	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

In total, 485 subjects were randomised (full analysis set), but 1 subject (randomised in United Kingdom) was not treated. To support the primary safety endpoints, all baseline and safety results are based on the 484 subjects. Efficacy analysis are based on all 485 randomized subjects due to the intention-to-treat principle. 240 subjects were randomized to ingenol mebutate, and 245 were randomized to imiquimod.

Reporting group values	Full analysis set		
Number of subjects	485		
Age categorical Units: Subjects			
Adults (18-64 years)	76		
>=65	408		
<=18	0		

Gender categorical Units: Subjects			
Female	25		
Male	459		
Ethnicity Units: Subjects			
Unknown or Not Reported	0		
Hispanic or Latino	26		
Not Hispanic or Latino	458		
Region of Enrollment Units: Subjects			
United Kingdom	161		
Germany	200		
France	123		

End points

End points reporting groups

Reporting group title	Ingenol mebutate gel, 0.015%
Reporting group description: -	
Reporting group title	Imiquimod cream, 5%
Reporting group description: -	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

In total, 485 subjects were randomised (full analysis set), but 1 subject (randomised in United Kingdom) was not treated. To support the primary safety endpoints, all baseline and safety results are based on the 484 subjects. Efficacy analysis are based on all 485 randomized subjects due to the intention-to-treat principle. 240 subjects were randomized to ingenol mebutate, and 245 were randomized to imiquimod.

Primary: Incidence of SCC

End point title	Incidence of SCC[1]

End point description:

Cumulative incidence of SCC after treatment with ingenol mebutate gel and imiquimod cream.
The primary response criterion is diagnosis of SCC (defined as invasive SCC i.e. excludes SCC in situ) in the treatment field across the 3-year trial period. Kaplan-Meier estimate based on time to SCC or censoring.

End point type	Primary

End point timeframe:

3 years

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary response criterion is diagnosis of SCC (defined as invasive SCC i.e. excludes SCC in situ) in the treatment field across the 3-year trial period. Kaplan-Meier estimate based on time to SCC or censoring.
No comparison between treatment groups was made.

End point values	Ingenol mebutate gel, 0.015%	Imiquimod cream, 5%		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	244		
Units: Percentage of Subjects				
number (confidence interval 95%)	3.1 (1.4 to 6.0)	0.4 (0.0 to 2.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of SCC and Other Neoplasia

End point title	Incidence of SCC and Other Neoplasia

End point description:

Cumulative incidence of SCC and other neoplasia after treatment with ingenol mebutate gel and imiquimod cream.
The secondary response criterion is diagnosis of SCC and other

neoplasia in the treatment field across the 3-year trial period.
Kaplan-Meier estimate based on time to SCC and other neoplasia, or censoring.

End point type	Secondary

End point timeframe:

3 years

End point values	Ingenol mebutate gel, 0.015%	Imiquimod cream, 5%		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	244		
Units: Percentage of Subjects				
number (confidence interval 95%)	6.2 (3.5 to 9.8)	2.3 (0.9 to 4.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Clearance of AK Lesions After Last Treatment

End point title	Complete Clearance of AK Lesions After Last Treatment

End point description:

To compare the complete clearance of AK lesions in the selected treatment area after the last treatment cycle (at Week 8 or 16)

End point type	Secondary

End point timeframe:

8-16 weeks

End point values	Ingenol mebutate gel, 0.015%	Imiquimod cream, 5%		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	244[2]		
Units: Count of Participants	168	192		

Notes:

[2] - One additional subject was analyzed (N=245). See description under the 'Full analysis set'

Statistical analyses

Statistical analysis title	Comparison of relative risk

Statistical analysis description:

Cochran-Mantel-Haenszel relative risk (ingenol mebutate / imiquimod), stratified by country, anatomical location and history of squamous cell

carcinoma.

Comparison groups	Imiquimod cream, 5% v Ingenol mebutate gel, 0.015%
Number of subjects included in analysis	484
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	0.99

Secondary: Partial Clearance of AK Lesions

End point title	Partial Clearance of AK Lesions

End point description:

To compare the partial (at least 75%) clearance of AK lesions in the selected treatment area after the last treatment cycle (at Week 8 or 16)

End point type	Secondary

End point timeframe:

8-16 weeks

End point values	Ingenol mebutate gel, 0.015%	Imiquimod cream, 5%		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	244[3]		
Units: Count of Participants	195	210		

Notes:

[3] - One additional subject was analyzed (N=245). See description under the 'Full analysis set'

Statistical analyses

Statistical analysis title	Comparison of relative risk

Statistical analysis description:

Cochran-Mantel-Haenszel relative risk (ingenol mebutate / imiquimod), stratified by country,anatomical location and history of squamous cell carcinoma.

Comparison groups	Ingenol mebutate gel, 0.015% v Imiquimod cream, 5%
Number of subjects included in analysis	484
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	0.95

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.03

Secondary: Complete Clearance of AK Lesions at 12 Months

End point title	Complete Clearance of AK Lesions at 12 Months

End point description:

To compare the complete clearance of AK lesions at 12 months, defined as no AK lesions in the selected treatment area at any time from the last treatment cycle at Week 8 or 16 through to Month 12.

End point type	Secondary

End point timeframe:

1 year

End point values	Ingenol mebutate gel, 0.015%	Imiquimod cream, 5%		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	244[4]		
Units: Count of Participants	70	108		

Notes:

[4] - One additional subject was analyzed (N=245). See description under the 'Full analysis set'

Statistical analyses

Statistical analysis title	Comparison of relative risk

Statistical analysis description:

Cochran-Mantel-Haenszel relative risk (ingenol mebutate / imiquimod), stratified by country, anatomical location and history of squamous cell carcinoma.

Comparison groups	Ingenol mebutate gel, 0.015% v Imiquimod cream, 5%
Number of subjects included in analysis	484
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.84

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were reported differently before and after Week 20. Before Week 20, all AEs and serious AEs were recorded; after Week 20, all AEs inside the treatment area but only BCC/SCC and related SAEs outside the treatment area, were recorded.

Adverse event reporting additional description:

Adverse events (AEs) were reported differently before and after Week 20. Before Week 20, all AEs and serious AEs were recorded; after Week 20, all AEs inside the treatment area but only BCC/SCC and related SAEs outside the treatment area, were recorded.
Week 20 is the first week of the follow-up period.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Imiquimod until week 20
Reporting group description: -	
Reporting group title	Imiquimod after week 20
Reporting group description: -	
Reporting group title	Ingenol mebutate after week 20
Reporting group description: -	
Reporting group title	Ingenol mebutate until week 20

Reporting group description: -

Serious adverse events	Imiquimod until week 20	Imiquimod after week 20	Ingenol mebutate after week 20
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 244 (5.74%)	2 / 244 (0.82%)	11 / 240 (4.58%)
number of deaths (all causes)	1	5	8
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 244 (0.00%)	0 / 244 (0.00%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign neoplasm of skin			
subjects affected / exposed	1 / 244 (0.41%)	0 / 244 (0.00%)	0 / 240 (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
Bowen's disease			

subjects affected / exposed	1 / 244 (0.41%)	2 / 244 (0.82%)	3 / 240 (1.25%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic squamous cell carcinoma			
subjects affected / exposed	0 / 244 (0.00%)	0 / 244 (0.00%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Hodgkin's lymphoma stage I			
subjects affected / exposed	0 / 244 (0.00%)	0 / 244 (0.00%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal carcinoma			
subjects affected / exposed	1 / 244 (0.41%)	0 / 244 (0.00%)	0 / 240 (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
Squamous cell carcinoma of skin			
subjects affected / exposed	2 / 244 (0.82%)	0 / 244 (0.00%)	5 / 240 (2.08%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 244 (0.41%)	0 / 244 (0.00%)	0 / 240 (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
Patella fracture			
subjects affected / exposed	0 / 244 (0.00%)	0 / 244 (0.00%)	0 / 240 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound complication			
subjects affected / exposed	0 / 244 (0.00%)	0 / 244 (0.00%)	0 / 240 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Arrhythmia			
subjects affected / exposed	0 / 244 (0.00%)	0 / 244 (0.00%)	0 / 240 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 244 (0.41%)	0 / 244 (0.00%)	0 / 240 (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
Surgical and medical procedures			
Skin neoplasm excision			
subjects affected / exposed	1 / 244 (0.41%)	0 / 244 (0.00%)	0 / 240 (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
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 244 (0.00%)	0 / 244 (0.00%)	0 / 240 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 244 (0.00%)	0 / 244 (0.00%)	0 / 240 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reversible ischaemic neurological deficit			
subjects affected / exposed	0 / 244 (0.00%)	0 / 244 (0.00%)	0 / 240 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 244 (0.00%)	0 / 244 (0.00%)	0 / 240 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 244 (0.00%)	0 / 244 (0.00%)	0 / 240 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Transient ischaemic attack			
subjects affected / exposed	1 / 244 (0.41%)	0 / 244 (0.00%)	0 / 240 (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			
Anaemia			
subjects affected / exposed	1 / 244 (0.41%)	0 / 244 (0.00%)	0 / 240 (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
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 244 (0.41%)	0 / 244 (0.00%)	0 / 240 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 244 (0.41%)	0 / 244 (0.00%)	0 / 240 (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
Gastrointestinal disorders			
Abdominal wall haematoma			
subjects affected / exposed	0 / 244 (0.00%)	0 / 244 (0.00%)	0 / 240 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 244 (0.41%)	0 / 244 (0.00%)	0 / 240 (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
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 244 (0.00%)	0 / 244 (0.00%)	0 / 240 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular perforation			

subjects affected / exposed	0 / 244 (0.00%)	0 / 244 (0.00%)	0 / 240 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum			
subjects affected / exposed	0 / 244 (0.00%)	0 / 244 (0.00%)	0 / 240 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 244 (0.00%)	0 / 244 (0.00%)	0 / 240 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal achalasia			
subjects affected / exposed	1 / 244 (0.41%)	0 / 244 (0.00%)	0 / 240 (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
Respiratory, thoracic and mediastinal disorders			
Alveolitis			
subjects affected / exposed	0 / 244 (0.00%)	0 / 244 (0.00%)	0 / 240 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 244 (0.00%)	0 / 244 (0.00%)	0 / 240 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 244 (0.41%)	0 / 244 (0.00%)	0 / 240 (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
Urinary tract infection			
subjects affected / exposed	0 / 244 (0.00%)	0 / 244 (0.00%)	0 / 240 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Ingenol mebutate until week 20		
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 240 (8.75%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 240 (0.42%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Benign neoplasm of skin			
subjects affected / exposed	0 / 240 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bowen's disease			
subjects affected / exposed	0 / 240 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastatic squamous cell carcinoma			
subjects affected / exposed	0 / 240 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Non-Hodgkin's lymphoma stage I			
subjects affected / exposed	0 / 240 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oesophageal carcinoma			
subjects affected / exposed	0 / 240 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma of skin			

subjects affected / exposed	4 / 240 (1.67%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 240 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Patella fracture			
subjects affected / exposed	1 / 240 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Postoperative wound complication			
subjects affected / exposed	1 / 240 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 240 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	0 / 240 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Skin neoplasm excision			
subjects affected / exposed	1 / 240 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral infarction			

subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reversible ischaemic neurological deficit				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sciatica				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	1 / 240 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
General physical health deterioration				
subjects affected / exposed	0 / 240 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 240 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal wall haematoma			
subjects affected / exposed	1 / 240 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	0 / 240 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea haemorrhagic			
subjects affected / exposed	1 / 240 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticular perforation			
subjects affected / exposed	1 / 240 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulum			
subjects affected / exposed	1 / 240 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	1 / 240 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal achalasia			
subjects affected / exposed	0 / 240 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
Alveolitis			
subjects affected / exposed	1 / 240 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 240 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 240 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 240 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Imiquimod until week 20	Imiquimod after week 20	Ingenol mebutate after week 20
Total subjects affected by non-serious adverse events			
subjects affected / exposed	70 / 244 (28.69%)	50 / 244 (20.49%)	51 / 240 (21.25%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	12 / 244 (4.92%)	36 / 244 (14.75%)	33 / 240 (13.75%)
occurrences (all)	15	62	56
Squamous cell carcinoma of skin			
subjects affected / exposed	3 / 244 (1.23%)	24 / 244 (9.84%)	24 / 240 (10.00%)
occurrences (all)	3	38	42
Nervous system disorders			
Headache			

subjects affected / exposed	13 / 244 (5.33%)	0 / 244 (0.00%)	0 / 240 (0.00%)
occurrences (all)	14	0	0
General disorders and administration site conditions			
Application site pain			
subjects affected / exposed	15 / 244 (6.15%)	0 / 244 (0.00%)	1 / 240 (0.42%)
occurrences (all)	17	0	2
Application site pruritus			
subjects affected / exposed	13 / 244 (5.33%)	0 / 244 (0.00%)	0 / 240 (0.00%)
occurrences (all)	15	0	0
Fatigue			
subjects affected / exposed	8 / 244 (3.28%)	0 / 244 (0.00%)	0 / 240 (0.00%)
occurrences (all)	9	0	0
Influenza like illness			
subjects affected / exposed	16 / 244 (6.56%)	0 / 244 (0.00%)	0 / 240 (0.00%)
occurrences (all)	19	0	0
Eye disorders			
Eye swelling			
subjects affected / exposed	0 / 244 (0.00%)	0 / 244 (0.00%)	0 / 240 (0.00%)
occurrences (all)	0	0	0
Eyelid oedema			
subjects affected / exposed	0 / 244 (0.00%)	0 / 244 (0.00%)	0 / 240 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	5 / 244 (2.05%)	0 / 244 (0.00%)	0 / 240 (0.00%)
occurrences (all)	5	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 244 (1.23%)	0 / 244 (0.00%)	0 / 240 (0.00%)
occurrences (all)	3	0	0
Back pain			
subjects affected / exposed	3 / 244 (1.23%)	0 / 244 (0.00%)	0 / 240 (0.00%)
occurrences (all)	3	0	0
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	11 / 244 (4.51%)	0 / 244 (0.00%)	0 / 240 (0.00%)
occurrences (all)	11	0	0

Non-serious adverse events	Ingenol mebutate until week 20		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	67 / 240 (27.92%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	6 / 240 (2.50%)		
occurrences (all)	8		
Squamous cell carcinoma of skin			
subjects affected / exposed	4 / 240 (1.67%)		
occurrences (all)	4		
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 240 (4.17%)		
occurrences (all)	12		
General disorders and administration site conditions			
Application site pain			
subjects affected / exposed	22 / 240 (9.17%)		
occurrences (all)	28		
Application site pruritus			
subjects affected / exposed	14 / 240 (5.83%)		
occurrences (all)	15		
Fatigue			
subjects affected / exposed	0 / 240 (0.00%)		
occurrences (all)	0		
Influenza like illness			
subjects affected / exposed	1 / 240 (0.42%)		
occurrences (all)	1		
Eye disorders			
Eye swelling			
subjects affected / exposed	6 / 240 (2.50%)		
occurrences (all)	6		
Eyelid oedema			

subjects affected / exposed occurrences (all)	8 / 240 (3.33%) 9		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	 3 / 240 (1.25%) 3		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	 5 / 240 (2.08%) 5 6 / 240 (2.50%) 6		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 11 / 240 (4.58%) 12		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported