



Clinical trial results: Clinical Study Protocol

Safety and efficacy of escalating doses of LEO 43204 applied once daily for two consecutive days on full balding scalp in subjects with actinic keratosis

Part 1: A phase 1, multicentre, open-label, dose escalation, 2-week trial

Part 2: A phase 2, multicentre, randomised, double-blind, parallel group, vehicle-controlled, 8-week trial

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2014-000037-23
Trial protocol	DE
Global end of trial date	02 March 2015

Results information

Result version number	v1 (current)
This version publication date	28 July 2016
First version publication date	28 July 2016

Trial information

Trial identification

Sponsor protocol code	LP0084-1014
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02100813
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 Manager, LEO pharma A/S, +45 4494 5888, ctr.disclosure@leo-pharma.com
Scientific contact	Clinical Trial Disclosure Manager, LEO pharma A/S, +45 4494 5888, ctr.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
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Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 March 2015
Global end of trial reached?	Yes
Global end of trial date	02 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part 1: To identify the Maximum Tolerated Dose (MTD) of LEO 43204 after once daily treatment for two consecutive days.

Part 2: To evaluate efficacy of two doses of LEO 43204 given as once daily treatment for two consecutive days.

Protection of trial subjects:

NA

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 May 2014
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	Germany: 39
Country: Number of subjects enrolled	United States: 181
Worldwide total number of subjects	220
EEA total number of subjects	39

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)	47
From 65 to 84 years	163
85 years and over	10

Subject disposition

Recruitment

Recruitment details:

65 subjects from 7 centres in the US were enrolled into Part 1 of the trial. First subject was enrolled on 14-May-2014 and the last subject's last visit (LSLV) was on 12-Aug-2014.

197 subjects from 11 centres in the US and 5 centres in Germany were enrolled into Part 2 of trial. First subject was enrolled on 03-Sep-2014 and LSLV was on 02-Mar-2014

Pre-assignment

Screening details:

Part 1: 7 subjects were screening failures, 1 was excluded as recruitment goals were met. 57 subjects were included and received trial medication.

Part 2: 25 subjects did not meet inclusion/exclusion criteria, 7 voluntary withdrawals, 1 randomisation closed, and 1 lost to follow-up. Thus, 163 subjects were randomised.

Period 1

Period 1 title	Part 1 and Part 2 (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Treatment in Part 1 was open label.

Treatment in Part 2, was double-blinded i.e. the sponsor, the investigator, trial site personnel, and the subject were blinded to the trial medication (treatment with LEO 43204 or vehicle) assigned to each individual subject.

The packaging and labelling of the investigational products contained no evidence of their identity.

It was not considered possible to differentiate between the investigational products solely by sensory evaluation.

Arms

Are arms mutually exclusive?	Yes
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Arm title	Part 1 - 0.018% cohort
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Arm description:

Part 1 - Dose escalation

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

Dosage and administration details:

Dosage and administration details are applicable for all arms in Part 1 and 2.

Once daily for two consecutive days on balding scalp. The applications were done by trained research staff.

Treatment area was marked on study transparencies with permanent marker using 3-point landmark technique (e.g. ear, eyebrow, scars, moles, birthmarks, bony landmarks, etc.). This was used to locate the treatment area for subsequent trial visits.

Arm title	Part 1 - 0.025% cohort
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Arm description:

Part 1 - Dose escalation

Arm type	Experimental
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Investigational medicinal product name	ingenol disoxate gel 0.025%
Investigational medicinal product code	LEO 43204 gel 0.025%
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use
Dosage and administration details: For description see 0.018% cohort.	
Arm title	Part 1 - 0.037% cohort
Arm description: Part 1 - Dose escalation	
Arm type	Experimental
Investigational medicinal product name	ingenol disoxate gel 0.037%
Investigational medicinal product code	LEO 43204 gel 0.037%
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use
Dosage and administration details: For description see 0.018% cohort.	
Arm title	Part 1 - 0.05% cohort
Arm description: Part 1 - Dose escalation	
Arm type	Experimental
Investigational medicinal product name	ingenol disoxate gel 0.5%
Investigational medicinal product code	LEO 43204 gel 0.5%
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use
Dosage and administration details: For description see 0.018% cohort.	
Arm title	Part 1 - 0.075% cohort
Arm description: Part 1 - Dose escalation	
Arm type	Experimental
Investigational medicinal product name	ingenol disoxate gel 0.075%
Investigational medicinal product code	LEO 43204 gel 0.075%
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use
Dosage and administration details: For description see 0.018% cohort.	
Arm title	Part 2 - Vehicle
Arm description: Based on the general tolerability profile observed in Part 1 - Dose escalation, it was decided to move forward with the two doses 0.05% and 0.037% in Part 2. See more information under Part 1 - Primary endpoint.	
Arm type	Placebo
Investigational medicinal product name	ingenol disoxate gel vehicle
Investigational medicinal product code	LEO 43204 gel vehicle
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:
For description see 0.018% cohort.

Arm title	Part 2 - 0.037%
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Arm description:

Based on the general tolerability profile observed in Part 1 - Dose escalation, it was decided to move forward with the two doses 0.05% and 0.037% in Part 2.

See more information under Part 1 - Primary endpoint.

Arm type	Experimental
Investigational medicinal product name	ingenol disoxate gel 0.037%
Investigational medicinal product code	LEO 43204 gel 0.037%
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

For description see 0.018% cohort.

Arm title	Part 2 - 0.05%
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Arm description:

Based on the general tolerability profile observed in Part 1 - Dose escalation, it was decided to move forward with the two doses 0.05% and 0.037% in Part 2.

See more information under Part 1 - Primary endpoint.

Arm type	Experimental
Investigational medicinal product name	ingenol disoxate gel 0.5%
Investigational medicinal product code	LEO 43204 gel 0.5%
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

For description see 0.018% cohort.

Number of subjects in period 1	Part 1 - 0.018% cohort	Part 1 - 0.025% cohort	Part 1 - 0.037% cohort
Started	10	11	12
Completed	10	11	12
Not completed	0	0	0
Adverse event, non-fatal	-	-	-

Number of subjects in period 1	Part 1 - 0.05% cohort	Part 1 - 0.075% cohort	Part 2 - Vehicle
Started	12	12	32
Completed	12	12	32
Not completed	0	0	0
Adverse event, non-fatal	-	-	-

Number of subjects in period 1	Part 2 - 0.037%	Part 2 - 0.05%
Started	64	67

Completed	64	66
Not completed	0	1
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Part 1 - 0.018% cohort
Reporting group description:	
Part 1 - Dose escalation	
Reporting group title	Part 1 - 0.025% cohort
Reporting group description:	
Part 1 - Dose escalation	
Reporting group title	Part 1 - 0.037% cohort
Reporting group description:	
Part 1 - Dose escalation	
Reporting group title	Part 1 - 0.05% cohort
Reporting group description:	
Part 1 - Dose escalation	
Reporting group title	Part 1 - 0.075% cohort
Reporting group description:	
Part 1 - Dose escalation	
Reporting group title	Part 2 - Vehicle
Reporting group description:	
Based on the general tolerability profile observed in Part 1 - Dose escalation, it was decided to move forward with the two doses 0.05% and 0.037% in Part 2.	
See more information under Part 1 - Primary endpoint.	
Reporting group title	Part 2 - 0.037%
Reporting group description:	
Based on the general tolerability profile observed in Part 1 - Dose escalation, it was decided to move forward with the two doses 0.05% and 0.037% in Part 2.	
See more information under Part 1 - Primary endpoint.	
Reporting group title	Part 2 - 0.05%
Reporting group description:	
Based on the general tolerability profile observed in Part 1 - Dose escalation, it was decided to move forward with the two doses 0.05% and 0.037% in Part 2.	
See more information under Part 1 - Primary endpoint.	

Reporting group values	Part 1 - 0.018% cohort	Part 1 - 0.025% cohort	Part 1 - 0.037% cohort
Number of subjects	10	11	12
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	2	3	4
From 65-84 years	7	7	8
85 years and over	1	1	0

Gender categorical			
Units: Subjects			
Female	0	0	0
Male	10	11	12

Reporting group values	Part 1 - 0.05% cohort	Part 1 - 0.075% cohort	Part 2 - Vehicle
Number of subjects	12	12	32
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	4	2	9
From 65-84 years	8	10	21
85 years and over	0	0	2
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	12	12	32

Reporting group values	Part 2 - 0.037%	Part 2 - 0.05%	Total
Number of subjects	64	67	220
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	9	14	47
From 65-84 years	52	50	163
85 years and over	3	3	10
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	64	67	220

End points

End points reporting groups

Reporting group title	Part 1 - 0.018% cohort
Reporting group description:	
Part 1 - Dose escalation	
Reporting group title	Part 1 - 0.025% cohort
Reporting group description:	
Part 1 - Dose escalation	
Reporting group title	Part 1 - 0.037% cohort
Reporting group description:	
Part 1 - Dose escalation	
Reporting group title	Part 1 - 0.05% cohort
Reporting group description:	
Part 1 - Dose escalation	
Reporting group title	Part 1 - 0.075% cohort
Reporting group description:	
Part 1 - Dose escalation	
Reporting group title	Part 2 - Vehicle
Reporting group description:	
Based on the general tolerability profile observed in Part 1 - Dose escalation, it was decided to move forward with the two doses 0.05% and 0.037% in Part 2. See more information under Part 1 - Primary endpoint.	
Reporting group title	Part 2 - 0.037%
Reporting group description:	
Based on the general tolerability profile observed in Part 1 - Dose escalation, it was decided to move forward with the two doses 0.05% and 0.037% in Part 2. See more information under Part 1 - Primary endpoint.	
Reporting group title	Part 2 - 0.05%
Reporting group description:	
Based on the general tolerability profile observed in Part 1 - Dose escalation, it was decided to move forward with the two doses 0.05% and 0.037% in Part 2. See more information under Part 1 - Primary endpoint.	

Primary: Part 1: Identify the maximum tolerated dose (MTD) of LEO 43204 after once daily treatment for 2 consecutive days

End point title	Part 1: Identify the maximum tolerated dose (MTD) of LEO 43204 after once daily treatment for 2 consecutive days ^{[1][2]}
End point description:	
The MTD was defined as the highest dose level with less than 4 out of 12 subjects experiencing a dose-limiting toxicity (DLT).	
DLT is defined as:	
<ul style="list-style-type: none">- Erosion/ulceration Grade 4 on the LSR scale- Other clinically relevant signs or symptoms observed, which the International Co-ordinating Investigator judges to be counted as a DLT.	
End point type	Primary
End point timeframe:	
Day 1 to Day 8	

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: No subjects met the predefined criteria for DLT. However, there was a dose dependent increase in the number and severity of AEs. In cohort 0.075%, 3 out of 12 subjects experienced severe application site burning or pain, and 2 of them discontinued treatment. Based on the general tolerability profile observed in this cohort, the dose escalation committee decided to stop dose escalation and appoint 0.075% as the MTD.

It was decided to move forward with the two doses 0.05% and 0.037% in Part 2

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As per trial design, MTD of LEO 43204 after once daily treatment for 2 consecutive days was investigated in Part 1 of the trial.

End point values	Part 1 - 0.018% cohort	Part 1 - 0.025% cohort	Part 1 - 0.037% cohort	Part 1 - 0.05% cohort
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	11	12	12
Units: subjects				
number (not applicable)				
DLT	0	0	0	0

End point values	Part 1 - 0.075% cohort			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: subjects				
number (not applicable)				
DLT	0			

Statistical analyses

No statistical analyses for this end point

Primary: Part 2: Percent reduction in AK count from baseline to Week 8

End point title	Part 2: Percent reduction in AK count from baseline to Week
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End point description:

End point type	Primary
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End point timeframe:

Baseline to Week 8

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As per trial design, percent reduction in AK count from baseline to Week 8 was investigated in Part 2 of the trial.

End point values	Part 2 - Vehicle	Part 2 - 0.037%	Part 2 - 0.05%	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	64	67	
Units: percent reduction				
number (confidence interval 95%)	12.6 (9.5 to 30.3)	72.7 (66.9 to 77.5)	78.5 (73.7 to 82.5)	

Statistical analyses

Statistical analysis title	Reduction in AK count at Week 8
Statistical analysis description: Negative binominal regression with log baseline count as offset variable and treatment group and analysis site as factors.	
Comparison groups	Part 2 - 0.037% v Part 2 - 0.05%
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Negative binomial regression
Parameter estimate	AK count ratio
Point estimate	0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	0.42

Statistical analysis title	Reduction in AK count at Week 8
Statistical analysis description: Negative binominal regression with log baseline count as offset variable and treatment group and analysis site as factors.	
Comparison groups	Part 2 - 0.05% v Part 2 - Vehicle
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Negative binomial regression
Parameter estimate	AK count ratio
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	0.33

Statistical analysis title	Reduction in AK count at Week 8
Statistical analysis description: Negative binominal regression with log baseline count as offset variable and treatment group and analysis site as factors.	
Comparison groups	Part 2 - 0.05% v Part 2 - 0.037%
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.096
Method	Negative binomial regression
Parameter estimate	AK count ratio
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.04

Secondary: Part 1: Evaluate safety of LEO 43204 in escalating doses after once daily treatment for 2 consecutive days

End point title	Part 1: Evaluate safety of LEO 43204 in escalating doses after once daily treatment for 2 consecutive days ^[4]
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End point description:

Analysis:

All dose cohorts had subjects with AEs, most AEs were related to treatment and relatively few AEs were of severe intensity. The number and intensity of administration site reactions (MedDRA high level group term) increased with increasing dose and all severe administration site reactions were observed in the 0.05% and 0.075% cohorts.

End point type	Secondary
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End point timeframe:

Day 1 to end of Part 1 - dose escalation

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: As per trial design, safety of LEO 43204 in escalating doses after once daily treatment for 2 consecutive days was investigated in Part 1 of the trial.

End point values	Part 1 - 0.018% cohort	Part 1 - 0.025% cohort	Part 1 - 0.037% cohort	Part 1 - 0.05% cohort
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	11	12	12
Units: NA				
number (not applicable)	0	0	0	0

End point values	Part 1 - 0.075% cohort			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: NA				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Complete clearance at Week 8

End point title	Part 2: Complete clearance at Week 8 ^[5]
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End point description:

End point type	Secondary
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End point timeframe:

Baseline to Week 8

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: As per trial design, complete clearance at Week 8 was investigated in Part 2 of the trial.

End point values	Part 2 - Vehicle	Part 2 - 0.037%	Part 2 - 0.05%	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	64	67	
Units: percent				
number (confidence interval 95%)				
Cleared	3.1 (0.1 to 16.2)	21.9 (12.5 to 34)	29.9 (19.3 to 42.3)	

Statistical analyses

Statistical analysis title	Complete clearance at Week 8
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Statistical analysis description:

Ratio of clearance rates.

Log binomial regression with treatment group as factor and baseline AK count included as covariate.

Comparison groups	Part 2 - 0.037% v Part 2 - Vehicle
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Log binomial regression
Parameter estimate	Risk ratio (RR)
Point estimate	7.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.53
upper limit	124

Statistical analysis title	Complete clearance at Week 8
Statistical analysis description:	
Ratio of clearance rates.	
Log binomial regression with treatment group as factor and baseline AK count included as covariate.	
Comparison groups	Part 2 - 0.05% v Part 2 - Vehicle
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	= 0.001
Method	Log binomial regression
Parameter estimate	Risk ratio (RR)
Point estimate	8.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.99
upper limit	154.5

Notes:

[6] - Ratio of clearance rates

Statistical analysis title	Complete clearance at Week 8
Statistical analysis description:	
Ratio of clearance rates.	
Log binomial regression with treatment group as factor and baseline AK count included as covariate.	
Comparison groups	Part 2 - 0.05% v Part 2 - 0.037%
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.43
Method	Log binomial regression
Parameter estimate	Risk ratio (RR)
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	2.31

Secondary: Part 2: Partial clearance of AKs at Week 8

End point title	Part 2: Partial clearance of AKs at Week 8 ^[7]
End point description:	
Partial clearance of AKs at Week 8 is defined as at least 75% reduction from baseline in AK count.	
End point type	Secondary
End point timeframe:	
Baseline to Week 8	

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: As per trial design, partial clearance of AKs at Week 8 was investigated in Part 2 of the trial.

End point values	Part 2 - Vehicle	Part 2 - 0.037%	Part 2 - 0.05%	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	64	67	
Units: NA				
number (confidence interval 95%)	6.3 (0.8 to 20.8)	54.7 (41.77 to 67.2)	59.7 (47 to 71.5)	

Statistical analyses

Statistical analysis title	Partial clearance of AKs at Week 8
Comparison groups	Part 2 - 0.037% v Part 2 - Vehicle
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Log binomial regression
Parameter estimate	Risk ratio (RR)
Point estimate	8.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.93
upper limit	51.66

Statistical analysis title	Partial clearance of AKs at Week 8
Comparison groups	Part 2 - 0.05% v Part 2 - Vehicle
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Log binomial regression
Parameter estimate	Risk ratio (RR)
Point estimate	9.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.22
upper limit	56.4

Statistical analysis title	Partial clearance of AKs at Week 8
Comparison groups	Part 2 - 0.05% v Part 2 - 0.037%
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.55
Method	Log binomial regression
Parameter estimate	Risk ratio (RR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.49

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to End of trial for both part 1 and part 2

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.1
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Reporting groups

Reporting group title	Part 1 - 0.018% cohort
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Reporting group description: -

Reporting group title	Part 1 - 0.025% cohort
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Reporting group description: -

Reporting group title	Part 1 - 0.037% cohort
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Reporting group description: -

Reporting group title	Part 1 - 0.05% cohort
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Reporting group description: -

Reporting group title	Part 1 - 0.075% cohort
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Reporting group description: -

Reporting group title	Part 2 - Vehicle
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Reporting group description: -

Reporting group title	Part 2 - 0.037%
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Reporting group description: -

Reporting group title	Part 2 - 0.05%
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Reporting group description: -

Serious adverse events	Part 1 - 0.018% cohort	Part 1 - 0.025% cohort	Part 1 - 0.037% cohort
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 12 (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)			
Brain neoplasm			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 12 (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			
Atrial flutter			

subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 12 (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
Acute myocardial infarction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 12 (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
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 12 (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			
Nephrolithiasis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 12 (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
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 12 (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	Part 1 - 0.05% cohort	Part 1 - 0.075% cohort	Part 2 - Vehicle
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 32 (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)			
Brain neoplasm			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 32 (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			

Atrial flutter			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 32 (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
Acute myocardial infarction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 32 (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
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 32 (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			
Nephrolithiasis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 32 (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
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 32 (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	Part 2 - 0.037%	Part 2 - 0.05%	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 64 (3.13%)	3 / 67 (4.48%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain neoplasm			
subjects affected / exposed	0 / 64 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Atrial flutter			
subjects affected / exposed	1 / 64 (1.56%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 64 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 64 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 64 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Part 1 - 0.018% cohort	Part 1 - 0.025% cohort	Part 1 - 0.037% cohort
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 10 (70.00%)	7 / 11 (63.64%)	12 / 12 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Squamous cell carcinoma of skin			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Vascular disorders			
Peripheral artery aneurysm subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Hypertension subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Surgical and medical procedures			
Cholecystectomy subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
General disorders and administration site conditions			
Application site pruritus subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 3	3 / 11 (27.27%) 3	7 / 12 (58.33%) 7
Application site pain subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 3	4 / 11 (36.36%) 5	12 / 12 (100.00%) 18
Application site paraesthesia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Application site discomfort subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Application site discharge subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Application site hyperaesthesia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Application site oedema subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Fatigue			

subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Chills			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Asthenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Feeling abnormal			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Discomfort			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Nasal oedema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Sinus congestion			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Sleep disorder			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Confusional state			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Investigations			
Electrocardiogram abnormal			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram t wave abnormal			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram u-wave abnormality			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Blood urine present			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Laceration			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Head injury subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Injury subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Procedural pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Tooth fracture subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Accidental exposure subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Nervous system disorders Tension headache subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 11 (9.09%) 1	2 / 12 (16.67%) 2
Hyperaesthesia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Convulsion subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	1 / 12 (8.33%) 1
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	1 / 12 (8.33%) 1
Eye disorders			

Periorbital oedema subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 11 (9.09%) 1	2 / 12 (16.67%) 2
Lacrimation increased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Eyelid oedema subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Conjunctivitis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Retinal detachment subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Xerophthalmia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Toothache subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Skin and subcutaneous tissue disorders			
Scar subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Circumoral oedema subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Skin irritation			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Skin lesion subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Intervertebral disc protrusion subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 11 (9.09%) 1	0 / 12 (0.00%) 0
Hordeolum subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 11 (9.09%) 1	0 / 12 (0.00%) 0
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Oral herpes subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Herpes zoster subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Herpes simplex subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Influenza subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Onychomycosis			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Visceral larva migrans subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Folliculitis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Gastroenteritis viral subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0
Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 12 (0.00%) 0

Non-serious adverse events	Part 1 - 0.05% cohort	Part 1 - 0.075% cohort	Part 2 - Vehicle
Total subjects affected by non-serious adverse events subjects affected / exposed	10 / 12 (83.33%)	12 / 12 (100.00%)	4 / 32 (12.50%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Skin papilloma subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Squamous cell carcinoma of skin subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Vascular disorders Peripheral artery aneurysm subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0

Hypertension subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Surgical and medical procedures Cholecystectomy subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
General disorders and administration site conditions			
Application site pruritus subjects affected / exposed occurrences (all)	5 / 12 (41.67%) 5	9 / 12 (75.00%) 10	1 / 32 (3.13%) 1
Application site pain subjects affected / exposed occurrences (all)	9 / 12 (75.00%) 16	12 / 12 (100.00%) 17	2 / 32 (6.25%) 2
Application site paraesthesia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 12 (8.33%) 2	1 / 32 (3.13%) 1
Application site discomfort subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Application site discharge subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Application site hyperaesthesia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Application site oedema subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Fatigue subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Chills subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Asthenia			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Feeling abnormal subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Pain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Discomfort subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Oedema peripheral subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Cough subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Nasal oedema subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Sinus congestion subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	4 / 12 (33.33%) 4	0 / 32 (0.00%) 0
Sleep disorder			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Confusional state subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Investigations			
Electrocardiogram abnormal subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Electrocardiogram t wave abnormal subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Electrocardiogram u-wave abnormality subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Blood urine present subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	1 / 32 (3.13%) 1
Injury, poisoning and procedural complications			
Laceration subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1	0 / 32 (0.00%) 0
Head injury subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Injury subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Procedural pain			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Tooth fracture subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Accidental exposure subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Nervous system disorders Tension headache subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1	0 / 32 (0.00%) 0
Hyperaesthesia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Convulsion subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Eye disorders Periorbital oedema subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Lacrimation increased subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 12 (8.33%) 2	0 / 32 (0.00%) 0
Eyelid oedema			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Conjunctivitis subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Retinal detachment subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Xerophthalmia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1	0 / 32 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Toothache subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Skin and subcutaneous tissue disorders Scar subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Circumoral oedema subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Skin irritation subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Skin lesion subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Hordeolum			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Oral herpes			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Herpes simplex			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Onychomycosis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Visceral larva migrans subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0
Folliculitis subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	1 / 32 (3.13%) 1
Gastroenteritis viral subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	1 / 32 (3.13%) 1
Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	0 / 32 (0.00%) 0

Non-serious adverse events	Part 2 - 0.037%	Part 2 - 0.05%	
Total subjects affected by non-serious adverse events subjects affected / exposed	47 / 64 (73.44%)	50 / 67 (74.63%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Skin papilloma subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 1	0 / 67 (0.00%) 0	
Squamous cell carcinoma of skin subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 1	0 / 67 (0.00%) 0	
Vascular disorders Peripheral artery aneurysm subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0	1 / 67 (1.49%) 1	
Hypertension subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 1	0 / 67 (0.00%) 0	
Surgical and medical procedures Cholecystectomy subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0	1 / 67 (1.49%) 1	

General disorders and administration site conditions			
Application site pruritus			
subjects affected / exposed	16 / 64 (25.00%)	18 / 67 (26.87%)	
occurrences (all)	18	18	
Application site pain			
subjects affected / exposed	31 / 64 (48.44%)	38 / 67 (56.72%)	
occurrences (all)	42	51	
Application site paraesthesia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Application site discomfort			
subjects affected / exposed	1 / 64 (1.56%)	3 / 67 (4.48%)	
occurrences (all)	1	3	
Application site discharge			
subjects affected / exposed	0 / 64 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Application site hyperaesthesia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Application site oedema			
subjects affected / exposed	0 / 64 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	0 / 64 (0.00%)	0 / 67 (0.00%)	
occurrences (all)	0	0	
Chills			
subjects affected / exposed	2 / 64 (3.13%)	4 / 67 (5.97%)	
occurrences (all)	2	4	
Asthenia			
subjects affected / exposed	1 / 64 (1.56%)	1 / 67 (1.49%)	
occurrences (all)	1	1	
Feeling abnormal			
subjects affected / exposed	1 / 64 (1.56%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Pain			

subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 1	1 / 67 (1.49%) 1	
Discomfort subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0	1 / 67 (1.49%) 1	
Oedema peripheral subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0	1 / 67 (1.49%) 1	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 1	0 / 67 (0.00%) 0	
Cough subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 1	1 / 67 (1.49%) 1	
Nasal oedema subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 1	0 / 67 (0.00%) 0	
Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 1	0 / 67 (0.00%) 0	
Sinus congestion subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 1	0 / 67 (0.00%) 0	
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0	1 / 67 (1.49%) 1	
Sleep disorder subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 1	2 / 67 (2.99%) 2	
Confusional state subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 1	0 / 67 (0.00%) 0	
Investigations			

Electrocardiogram abnormal subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 1	0 / 67 (0.00%) 0	
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0	1 / 67 (1.49%) 1	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0	1 / 67 (1.49%) 1	
Electrocardiogram t wave abnormal subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0	1 / 67 (1.49%) 1	
Electrocardiogram u-wave abnormality subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0	1 / 67 (1.49%) 1	
Blood urine present subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0	0 / 67 (0.00%) 0	
Injury, poisoning and procedural complications			
Laceration subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0	0 / 67 (0.00%) 0	
Head injury subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 1	0 / 67 (0.00%) 0	
Injury subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 1	0 / 67 (0.00%) 0	
Procedural pain subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 1	0 / 67 (0.00%) 0	
Tooth fracture subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 1	0 / 67 (0.00%) 0	
Accidental exposure			

subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0	1 / 67 (1.49%) 1	
Nervous system disorders			
Tension headache			
subjects affected / exposed	0 / 64 (0.00%)	0 / 67 (0.00%)	
occurrences (all)	0	0	
Headache			
subjects affected / exposed	6 / 64 (9.38%)	5 / 67 (7.46%)	
occurrences (all)	7	5	
Hyperaesthesia			
subjects affected / exposed	0 / 64 (0.00%)	2 / 67 (2.99%)	
occurrences (all)	0	2	
Convulsion			
subjects affected / exposed	0 / 64 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 64 (1.56%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 64 (0.00%)	0 / 67 (0.00%)	
occurrences (all)	0	0	
Eye disorders			
Periorbital oedema			
subjects affected / exposed	3 / 64 (4.69%)	4 / 67 (5.97%)	
occurrences (all)	3	5	
Lacrimation increased			
subjects affected / exposed	0 / 64 (0.00%)	0 / 67 (0.00%)	
occurrences (all)	0	0	
Eyelid oedema			
subjects affected / exposed	1 / 64 (1.56%)	0 / 67 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 67 (1.49%)	
occurrences (all)	0	1	
Retinal detachment			

subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0	1 / 67 (1.49%) 1	
Xerophthalmia subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0	1 / 67 (1.49%) 1	
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 1	0 / 67 (0.00%) 0	
Vomiting subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0	0 / 67 (0.00%) 0	
Toothache subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 1	0 / 67 (0.00%) 0	
Skin and subcutaneous tissue disorders			
Scar subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 1	0 / 67 (0.00%) 0	
Circumoral oedema subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0	1 / 67 (1.49%) 1	
Skin irritation subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0	1 / 67 (1.49%) 1	
Skin lesion subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0	1 / 67 (1.49%) 1	
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	2 / 64 (3.13%) 2	0 / 67 (0.00%) 0	
Intervertebral disc protrusion subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 1	0 / 67 (0.00%) 0	
Infections and infestations			

Gastroenteritis		
subjects affected / exposed	0 / 64 (0.00%)	0 / 67 (0.00%)
occurrences (all)	0	0
Hordeolum		
subjects affected / exposed	0 / 64 (0.00%)	0 / 67 (0.00%)
occurrences (all)	0	0
Nasopharyngitis		
subjects affected / exposed	2 / 64 (3.13%)	6 / 67 (8.96%)
occurrences (all)	2	6
Oral herpes		
subjects affected / exposed	2 / 64 (3.13%)	0 / 67 (0.00%)
occurrences (all)	2	0
Herpes zoster		
subjects affected / exposed	1 / 64 (1.56%)	0 / 67 (0.00%)
occurrences (all)	1	0
Herpes simplex		
subjects affected / exposed	0 / 64 (0.00%)	1 / 67 (1.49%)
occurrences (all)	0	1
Influenza		
subjects affected / exposed	1 / 64 (1.56%)	0 / 67 (0.00%)
occurrences (all)	1	0
Onychomycosis		
subjects affected / exposed	1 / 64 (1.56%)	0 / 67 (0.00%)
occurrences (all)	1	0
Upper respiratory tract infection		
subjects affected / exposed	1 / 64 (1.56%)	0 / 67 (0.00%)
occurrences (all)	1	0
Urinary tract infection		
subjects affected / exposed	1 / 64 (1.56%)	0 / 67 (0.00%)
occurrences (all)	1	0
Visceral larva migrans		
subjects affected / exposed	1 / 64 (1.56%)	0 / 67 (0.00%)
occurrences (all)	1	0
Folliculitis		
subjects affected / exposed	0 / 64 (0.00%)	0 / 67 (0.00%)
occurrences (all)	0	0

Gastroenteritis viral subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0	0 / 67 (0.00%) 0	
Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 1	0 / 67 (0.00%) 0	

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