Clinical trial results:
Ingenol Mebutate Gel, 0.015% Repeat Use for Multiple Actinic Keratoses on Face and Scalp

Summary

EudraCT number	2011-005018-13
Trial protocol	GB DE
Global end of trial date	05 February 2014

Results information

Result version number	v1 (current)
This version publication date	19 February 2016
First version publication date	22 July 2015

Trial information

Trial identification

Sponsor protocol code	LP0041-22

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01600014
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	LEO Pharma A/S
Sponsor organisation address	Industriparken 55, Ballerup, Denmark,
Public contact	Clinical Trial Disclosure Manager, LEO Pharma A/S, +45 44 94 58 88, ctr.disclosure@leo-pharma.com
Scientific contact	Clinical Trial Disclosure Manager, LEO Pharma A/S, +45 44 94 58 88, ctr.disclosure@leo-pharma.com
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Scientific contact	Clinical Trial Disclosure Manager, LEO Pharma A/S, +45 44945888, 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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 February 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 February 2014
Global end of trial reached?	Yes
Global end of trial date	05 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that ingenol mebutate gel is efficacious in treating AKs present 8 weeks after initial field treatment (field recalcitrant) or emerging in a previously cleared field (field recurrent).

Efficacy will be evaluated separately for the two sub-groups of "field recalcitrant" and "field recurrent".

Protection of trial subjects:	
Not Applicable	
Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	04 June 2012
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	France: 115
Country: Number of subjects enrolled	United Kingdom: 92
Country: Number of subjects enrolled	Germany: 91
Country: Number of subjects enrolled	Canada: 91
Country: Number of subjects enrolled	Australia: 61
Worldwide total number of subjects	450
EEA total number of subjects	298

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)	86
From 65 to 84 years	338
85 years and over	26

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 463 subjects were enrolled in the trial, 13 of whom were screening failures. The remaining 450 subjects were allocated to open-label treatment with ingenol mebutate gel.

Period 1

Period 1 title	Initial treatment and Observation period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Ingenol mebutate gel 0.015% - Complete AK clearance at week 8
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Ingenol mebutate 0.015%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Cutaneous use

Dosage and administration details:

Treatment with ingenol mebutate gel 0.015% in the selected treatment area (STA) for 3 consecutive days (Day 1-3)

Number of subjects in period 1[1]	Ingenol mebutate gel 0.015% - Complete AK clearance at week 8
Started	450
Completed	162
Not completed	288
Adverse event, non-fatal	6
Other	27
Transferred to other arm/group	203
Site closure due to protocol deviation	6
Voluntary (and no other reason)	24
Lost to follow-up	8
Exclusion criteria emerging during the study	14

Notes:

[1] - The number of subjects transferring in and out of the arms in the period are not the same. It is expected the net number of transfers in and out of the arms in a period, will be zero.
Justification: In the first treatment cycle (Day 1 to Week 8), all eligible subjects were to be treated with ingenol mebutate gel, 0.015% in the STA for 3 consecutive days (Day 1-3). At 8 weeks (Day 57) following first application with ingenol mebutate gel subjects not completely cleared in the STA were randomised 2:1 to ingenol mebutate gel or vehicle gel. The first unit dose of trial medication was applied on the same day, corresponding to Day 1 in the second treatment cycle.

Period 2

Period 2 title	Second treatment cycle Week 8-Week 52
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Ingenol mebutate gel 0.015% field recalcitrant subgroup

Arm description: -

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

Dosage and administration details:

Treatment with ingenol mebutate gel 0.015% in the STA for 3 consecutive days (Day 1-3)

Arm title	Vehicle gel field recalcitrant subgroup

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Vehicle gel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Cutaneous use

Dosage and administration details:

The investigational product was applied once daily for 3 consecutive days in the STA in patients with recalcitrant disease on the face or scalp.

Number of subjects in period 2[2]	Ingenol mebutate gel 0.015% field recalcitrant subgroup	Vehicle gel field recalcitrant subgroup
Started	92	49
Completed	80	39
Not completed	12	10
Death	1	2
Other	1	3
Site closure due to protocol deviation	5	-

Voluntary (and no other reason)	2	1
Lost to follow-up	1	3
Exclusion criteria emerging during the study	1	1
Lack of efficacy	1	-

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Second Treatment Cycle (Period of 8 weeks: From either Week 26 or 44):
At Day 1 in the second treatment cycle, subjects who were not completely cleared in the STA were randomised 2:1 to treatment with ingenol mebutate gel or vehicle gel.
Follow-up Period (Week 16 or 34 to Week 52): The follow-up period was only applicable for subjects who had completed the second treatment cycle (8 weeks after randomisation), and the period continued until trial completion at Week 52.

Period 3

Period 3 title	Second treatment cycle Week 26 or 44-52
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Ingenol mebutate gel 0.015% field recurrent subgroup

Arm description: -

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

Dosage and administration details:

Treatment with ingenol mebutate gel 0.015% in the STA for 3 consecutive days (Day 1-3)

Arm title	Vehicle gel field recurrent subgroup

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Vehicle gel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Cutaneous use

Dosage and administration details:

The investigational product was applied once daily for 3 consecutive days in the STA in patients with recalcitrant disease on the face or scalp.

Number of subjects in period 3[3]	Ingenol mebutate gel 0.015% field recurrent subgroup	Vehicle gel field recurrent subgroup
Started	42	20
Completed	39	20
Not completed	3	0
Adverse event, non-fatal	1	-
Voluntary (and no other reason)	1	-
Lost to follow-up	1	-

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Second Treatment Cycle (Period of 8 weeks: From either Week 26 or 44):
At Day 1 in the second treatment cycle, subjects who were not completely cleared in the STA were randomised 2:1 to treatment with ingenol mebutate gel or vehicle gel.
Follow-up Period (Week 34 to Week 52): The follow-up period was only applicable for subjects who had completed the second treatment cycle (8 weeks after randomisation), and the period continued until trial completion at Week 52.

Baseline characteristics

Reporting groups	
Reporting group title	Ingenol mebutate gel 0.015% - Complete AK clearance at week 8

Reporting group description: -

Reporting group values	Ingenol mebutate gel 0.015% - Complete AK clearance at week 8	Total	
Number of subjects	450	450	
Age categorical Units: Subjects			
Adults (18-64 years)	86	86	
From 65-84 years	338	338	
85 years and over	26	26	
Age continuous Units: years			
arithmetic mean	71.7		
standard deviation	± 8.7	-	
Gender categorical Units: Subjects			
Female	53	53	
Male	397	397	

End points

End points reporting groups

Reporting group title	Ingenol mebutate gel 0.015% - Complete AK clearance at week 8
Reporting group description: -	
Reporting group title	Ingenol mebutate gel 0.015% field recalcitrant subgroup
Reporting group description: -	
Reporting group title	Vehicle gel field recalcitrant subgroup
Reporting group description: -	
Reporting group title	Ingenol mebutate gel 0.015% field recurrent subgroup
Reporting group description: -	
Reporting group title	Vehicle gel field recurrent subgroup
Reporting group description: -	

Primary: Complete clearance of AKs, defined as no clinically visible AKs in the STA, 8 weeks after randomisation

End point title	Complete clearance of AKs, defined as no clinically visible AKs in the STA, 8 weeks after randomisation
End point description:	
End point type	Primary
End point timeframe:	
8 weeks after randomisation	

End point values	Ingenol mebutate gel 0.015% field recalcitrant subgroup	Vehicle gel field recalcitrant subgroup	Ingenol mebutate gel 0.015% field recurrent subgroup	Vehicle gel field recurrent subgroup
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	92	49	42	20
Units: AK count	43	9	25	5

Statistical analyses

Statistical analysis title	AK clearance, Week 8 field recalcitrant subgroup
Statistical analysis description:	
Cochran-Mantel-Haenszel ratio of clearance rates (Ingenol mebutate relative to Vehicle) adjusted for anatomical location and country.	
Comparison groups	Ingenol mebutate gel 0.015% field recalcitrant subgroup v Vehicle gel field recalcitrant subgroup

Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [1]
Method	Cochran-Mantel-Haenszel

Notes:

[1] - The complete clearance rate in the field recalcitrant subgroup was statistically significantly higher in the ingenol mebutate group (46.7%) compared to the vehicle group (18.4%).

Statistical analysis title	Week 8 field recurrent subgroup

Statistical analysis description:

Cochran-Mantel-Haenszel ratio of clearance rates (Ingenol mebutate relative to Vehicle) adjusted for anatomical location and week of randomisation.

Comparison groups	Ingenol mebutate gel 0.015% field recurrent subgroup v Vehicle gel field recurrent subgroup
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013 [2]
Method	Cochran-Mantel-Haenszel

Notes:

[2] - The complete clearance rate in the field recurrent subgroup was statistically significantly higher in the ingenol mebutate group (59.5%) compared to the vehicle group (25.0%) (p=0.013).

Secondary: Complete clearance through to Month 12, defined as no clinically visible AKs and no lesions treated in the STA at any time from last treatment cycle through to Month 12

End point title	Complete clearance through to Month 12, defined as no clinically visible AKs and no lesions treated in the STA at any time from last treatment cycle through to Month 12

End point description:

The complete clearance through to Month 12 was defined as no clinically visible lesions at any time from the last treatment cycle through to month 12. The analysis was done separately for the field recalcitrant and the field recurrent subgroups.

Repeat use regimen:
The complete clearance through to Month 12 of the repeat use regimen was defined as no clinically visible lesions at any time from the last treatment cycle through to month 12. The overall estimate of 12 months clearance includes subjects not randomised to a second treatment cycle. Subjects randomised to vehicle were not included in the estimate, instead the subjects randomised to ingenol mebutate were given higher weights to reflect the hypothetical scenario where all subjects were given active treatment during the second treatment cycle. For the full analysis set, depending on the imputation method used, the complete clearance through to Month 12 of the repeat use
regimen ranged from 37.8% to 61.6%.

End point type	Secondary

End point timeframe:

The complete clearance through month 12

End point values	Ingenol mebutate gel 0.015% field recalcitrant subgroup	Vehicle gel field recalcitrant subgroup	Ingenol mebutate gel 0.015% field recurrent subgroup	Vehicle gel field recurrent subgroup
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	92	49	42	20
Units: Number of subjects	17	2	13	3

Statistical analyses

Statistical analysis title	Clearance Month 12 field recalcitrant, frequency

Statistical analysis description:

Cochran-Mantel-Haenszel ratio of clearance rates (Ingenol mebutate relative to Vehicle) adjusted for anatomical location and country.

Comparison groups	Ingenol mebutate gel 0.015% field recalcitrant subgroup v Vehicle gel field recalcitrant subgroup
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016 [3]
Method	Cochran-Mantel-Haenszel

Notes:

[3] - The complete clearance rate through to Month 12 in the field recalcitrant subgroup was statistically significantly higher in the ingenol mebutate group (18.5%) compared to the vehicle group (4.1%)

Statistical analysis title	Clearance Month 12 field recurrent, frequency
Comparison groups	Ingenol mebutate gel 0.015% field recurrent subgroup v Vehicle gel field recurrent subgroup
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1 [4]
Method	Cochran-Mantel-Haenszel

Notes:

[4] - The complete clearance rate through to Month 12 in the field recurrent subgroup was higher in the ingenol mebutate group (31.0%) compared to the vehicle group (15.0%). This difference was not statistically significant (p=0.10).

Secondary: The change in AK count from randomisation to 8 weeks after randomisation

End point title	The change in AK count from randomisation to 8 weeks after randomisation

End point description:

The change in AK count from randomisation to 8 weeks after randomisation was determined for the field recalcitrant and the field recurrent subgroups.

End point type	Secondary

End point timeframe:

From randomisation to Week 8

End point values	Ingenol mebutate gel 0.015% field recalcitrant subgroup	Vehicle gel field recalcitrant subgroup	Ingenol mebutate gel 0.015% field recurrent subgroup	Vehicle gel field recurrent subgroup
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	92	49	42	20
Units: Change in AK count				
arithmetic mean (standard deviation)	-1.41 (± 1.49)	-0.51 (± 1.65)	-1.52 (± 1.49)	-0.85 (± 0.99)

Statistical analyses

Statistical analysis title	Analysis 1

Statistical analysis description:

Analysed using ANCOVA adjusted for anatomical location, country and AK count at randomisation.

Comparison groups	Ingenol mebutate gel 0.015% field recalcitrant subgroup v Vehicle gel field recalcitrant subgroup
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [5]
Method	ANCOVA

Notes:

[5] - At 8 weeks after randomisation, using baseline observation carried forward (BOCF) as the imputation method, there was a statistically significant difference in the adjusted mean AK count between the ingenol mebutate and vehicle groups of -0.88.

Statistical analysis title	Analysis 2

Statistical analysis description:

sensitivity analysis using complete cases,

Comparison groups	Ingenol mebutate gel 0.015% field recalcitrant subgroup v Vehicle gel field recalcitrant subgroup
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [6]
Method	ANCOVA

Notes:

[6] - The difference was -1.01

Statistical analysis title	Analysis 3
Comparison groups	Ingenol mebutate gel 0.015% field recurrent subgroup v Vehicle gel field recurrent subgroup
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008 [7]
Method	ANCOVA

Notes:

[7] - At 8 weeks after randomisation, using BOCF as the imputation method, the difference in the adjusted mean AK count between the ingenol mebutate and vehicle groups was -0.69.

Statistical analysis title	Analysis 4
Comparison groups	Ingenol mebutate gel 0.015% field recurrent subgroup v Vehicle gel field recurrent subgroup
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [8]
Method	ANCOVA

Notes:

[8] - In a sensitivity analysis using complete cases, this difference was -0.77.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were recorded up to and including Week 8 of the first treatment cycle and second treatment cycle. In the observation period and follow-up period, all AEs within the STA, all SAEs, and all SCC or BCC outside the STA were to be recorded

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	First treatment cycle and observation period

Reporting group description:

All AEs reported up to Week 8 of the first treatment cycle.

Reporting group title	Second treatment cycle and follow-up period

Reporting group description:

All AEs reported up to Week 8 of the second treatment cycle.
During the follow-up period, only the following was to be recorded: all AEs within the selected treatment area, all SAEs, and all occurrences of SCC or BCC outside the selected treatment area.

Serious adverse events	First treatment cycle and observation period	Second treatment cycle and follow-up period	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 450 (4.22%)	16 / 203 (7.88%)	
number of deaths (all causes)	0	3	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	3 / 450 (0.67%)	3 / 203 (1.48%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carcinoma in situ of skin			
subjects affected / exposed	1 / 450 (0.22%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			

subjects affected / exposed	2 / 450 (0.44%)	2 / 203 (0.99%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 450 (0.00%)	3 / 203 (1.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carcinoma in situ			
subjects affected / exposed	0 / 450 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basosquamous carcinoma of skin			
subjects affected / exposed	0 / 450 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangioma			
subjects affected / exposed	0 / 450 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm skin			
subjects affected / exposed	0 / 450 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease			
subjects affected / exposed	0 / 450 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratoacanthoma			
subjects affected / exposed	1 / 450 (0.22%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			

subjects affected / exposed	1 / 450 (0.22%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	2 / 450 (0.44%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorder			
subjects affected / exposed	0 / 450 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Sciatica			
subjects affected / exposed	1 / 450 (0.22%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalamic infarction			
subjects affected / exposed	1 / 450 (0.22%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 450 (0.22%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 450 (0.22%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 450 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatism			
subjects affected / exposed	1 / 450 (0.22%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Lung disorder			
subjects affected / exposed	1 / 450 (0.22%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 450 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin and subcutaneous tissue disorders			
Aktinic keratosis			
subjects affected / exposed	0 / 450 (0.00%)	2 / 203 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 450 (0.22%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 450 (0.00%)	2 / 203 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			

Completed suicide			
subjects affected / exposed	0 / 450 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Musculoskeletal and connective tissue disorders			
Polymyalgia rheumatica			
subjects affected / exposed	1 / 450 (0.22%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Herpes virus infection			
subjects affected / exposed	0 / 450 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyelonephritis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 450 (0.22%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary tract infection			
subjects affected / exposed	1 / 450 (0.22%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	First treatment cycle and observation period	Second treatment cycle and follow-up period	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	265 / 450 (58.89%)	105 / 203 (51.72%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	46 / 450 (10.22%)	22 / 203 (10.84%)	
occurrences (all)	67	43	
Bowen's disease			
subjects affected / exposed	7 / 450 (1.56%)	8 / 203 (3.94%)	
occurrences (all)	11	10	
Squamous cell carcinoma of skin			
subjects affected / exposed	14 / 450 (3.11%)	13 / 203 (6.40%)	
occurrences (all)	15	22	
Seborrhoeic keratosis			
subjects affected / exposed	10 / 450 (2.22%)	0 / 203 (0.00%)	
occurrences (all)	15	0	
Nervous system disorders			
Headache			
subjects affected / exposed	21 / 450 (4.67%)	0 / 203 (0.00%)	
occurrences (all)	24	0	
General disorders and administration site conditions			
Application site pain			
subjects affected / exposed	62 / 450 (13.78%)	15 / 203 (7.39%)	
occurrences (all)	71	19	
Application site pruritus			
subjects affected / exposed	20 / 450 (4.44%)	0 / 203 (0.00%)	
occurrences (all)	20	0	
Eye disorders			

Eyelid oedema subjects affected / exposed occurrences (all) Periorbital oedema subjects affected / exposed occurrences (all)	17 / 450 (3.78%) 18 15 / 450 (3.33%) 16	0 / 203 (0.00%) 0 0 / 203 (0.00%) 0	
Skin and subcutaneous tissue disorders Actinic keratosis subjects affected / exposed occurrences (all)	60 / 450 (13.33%) 87	39 / 203 (19.21%) 67	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	12 / 450 (2.67%) 12	0 / 203 (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