



Clinical trial results:

A randomized, vehicle controlled, active comparator, parallel group study to evaluate safety, tolerability and preliminary efficacy of topical LFX453 formulations in patients with actinic keratosis

Summary

EudraCT number	2014-003613-28
Trial protocol	AT IS DE DK GB
Global end of trial date	27 January 2016

Results information

Result version number	v1 (current)
This version publication date	12 February 2017
First version publication date	12 February 2017

Trial information

Trial identification

Sponsor protocol code	CLFX453X2201
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02404389
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 January 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	27 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the study were i) to assess tolerability and safety of LFX453 in patients with actinic keratosis (AK) and ii) to assess efficacy of LFX453 compared to vehicle in patients with actinic keratosis.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 March 2015
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	Austria: 6
Country: Number of subjects enrolled	Denmark: 15
Country: Number of subjects enrolled	Germany: 41
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Iceland: 19
Worldwide total number of subjects	82
EEA total number of subjects	82

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)	18
From 65 to 84 years	64
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 82 patients, male and female of non-childbearing potential aged 18-75 years, with Actinic Keratosis (AK) on the face or balding scalp were enrolled in the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	LFX453 0.1% NMC

Arm description:

LFX453 0.1% nanomedicinal cream (NMC) Twice daily applications

Arm type	Experimental
Investigational medicinal product name	LFX453
Investigational medicinal product code	LFX453
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

LFX453 nanomedicinal cream (NMC) 0.1% apply twice daily topically

Arm title	LFX453 0.15% LCC
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Arm description:

LFX453 0.15% liquid crystal cream (LCC) Twice daily applications

Arm type	Experimental
Investigational medicinal product name	LFX453
Investigational medicinal product code	LFX453
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

LFX453 liquid crystal cream (LCC) 0.15% apply twice daily topically

Arm title	Vehicle to NMC
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Arm description:

Vehicle to nanomedicinal cream (NMC) Twice daily applications

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	LFX453
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

vehicle to nanomedicinal cream (NMC) apply twice daily topically

Arm title	Vehicle to LCC
Arm description: Vehicle to liquid crystal cream (LCC) Twice daily applications	
Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	LFX453
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

vehicle to liquid crystal cream (LCC) apply twice daily topically

Arm title	Aldara
Arm description: Aldara cream 3 applications per week	
Arm type	Active comparator
Investigational medicinal product name	imiquimod
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

Aldara® 5% cream apply 3 days per week topically

Number of subjects in period 1	LFX453 0.1% NMC	LFX453 0.15% LCC	Vehicle to NMC
Started	20	20	11
Completed	18	20	10
Not completed	2	0	1
Adverse event, non-fatal	1	-	1
Subject/guardian decision	1	-	-

Number of subjects in period 1	Vehicle to LCC	Aldara
Started	10	21
Completed	9	18
Not completed	1	3
Adverse event, non-fatal	-	2
Subject/guardian decision	1	1

Baseline characteristics

Reporting groups

Reporting group title	LFX453 0.1% NMC
Reporting group description:	LFX453 0.1% nanomedicinal cream (NMC) Twice daily applications
Reporting group title	LFX453 0.15% LCC
Reporting group description:	LFX453 0.15% liquid crystal cream (LCC) Twice daily applications
Reporting group title	Vehicle to NMC
Reporting group description:	Vehicle to nanomedicinal cream (NMC) Twice daily applications
Reporting group title	Vehicle to LCC
Reporting group description:	Vehicle to liquid crystal cream (LCC) Twice daily applications
Reporting group title	Aldara
Reporting group description:	Aldara cream 3 applications per week

Reporting group values	LFX453 0.1% NMC	LFX453 0.15% LCC	Vehicle to NMC
Number of subjects	20	20	11
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)	7	4	2
From 65-84 years	13	16	9
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	67.7	68.6	68.3
standard deviation	± 5.23	± 6.25	± 6.66
Gender, Male/Female			
Units: Subjects			
Female	5	2	0
Male	15	18	11

Reporting group values	Vehicle to LCC	Aldara	Total
Number of subjects	10	21	82
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)	1	4	18
From 65-84 years	9	17	64
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	70.2	68.6	
standard deviation	± 4.32	± 5.61	-
Gender, Male/Female			
Units: Subjects			
Female	2	0	9
Male	8	21	73

Subject analysis sets

Subject analysis set title	Combined Vehicle
Subject analysis set type	Full analysis

Subject analysis set description:

Vehicle to nanomedicinal cream (NMC) and Vehicle to liquid crystal cream (LCC) Twice daily applications

Reporting group values	Combined Vehicle		
Number of subjects	21		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	3		
From 65-84 years	18		
85 years and over	0		
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	±		
Gender, Male/Female			
Units: Subjects			
Female	2		
Male	19		

End points

End points reporting groups

Reporting group title	LFX453 0.1% NMC
Reporting group description:	LFX453 0.1% nanomedicinal cream (NMC) Twice daily applications
Reporting group title	LFX453 0.15% LCC
Reporting group description:	LFX453 0.15% liquid crystal cream (LCC) Twice daily applications
Reporting group title	Vehicle to NMC
Reporting group description:	Vehicle to nanomedicinal cream (NMC) Twice daily applications
Reporting group title	Vehicle to LCC
Reporting group description:	Vehicle to liquid crystal cream (LCC) Twice daily applications
Reporting group title	Aldara
Reporting group description:	Aldara cream 3 applications per week
Subject analysis set title	Combined Vehicle
Subject analysis set type	Full analysis
Subject analysis set description:	Vehicle to nanomedicinal cream (NMC) and Vehicle to liquid crystal cream (LCC) Twice daily applications

Primary: Number of adverse events (AE)/Serious Adverse Events (SAE) as a measure of safety and tolerability up to 20 weeks

End point title	Number of adverse events (AE)/Serious Adverse Events (SAE) as a measure of safety and tolerability up to 20 weeks ^[1]
End point description:	Number of participants with at least one AE/SAE in the category up to 20 weeks
End point type	Primary
End point timeframe:	20 weeks

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 statistical analysis was planned for this primary outcome.

End point values	LFX453 0.1% NMC	LFX453 0.15% LCC	Vehicle to NMC	Vehicle to LCC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	20	11	10
Units: participants				
Adverse Events (AEs)	10	15	9	8
Serious Adverse Events (SAEs)	1	1	1	1

End point values	Aldara			
Subject group type	Reporting group			
Number of subjects analysed	21			

Units: participants				
Adverse Events (AEs)	18			
Serious Adverse Events (SAEs)	1			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants that had Complete clearance of Actinic keratosis (AK) at 8 weeks after the end of treatment (Week 20) for LFX453 compared to vehicle groups combined

End point title	Number of Participants that had Complete clearance of Actinic keratosis (AK) at 8 weeks after the end of treatment (Week 20) for LFX453 compared to vehicle groups combined ^[2]
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End point description:

Complete clearance of Actinic keratosis (AK), defined as the number of patients with a count of zero lesions in the treated area, evaluated 8 weeks after the end of treatment (Week 20) for LFX453 compared to vehicle groups combined

End point type	Primary
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End point timeframe:

Week 20

Notes:

[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: End point was provided for the arms that were part of this objective and not all baseline period arms

End point values	LFX453 0.1% NMC	LFX453 0.15% LCC	Combined Vehicle	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	20	20	21	
Units: participants	1	1	1	

Statistical analyses

Statistical analysis title	LFX453 0.1% NMC versus Combined Vehicle
Comparison groups	LFX453 0.1% NMC v Combined Vehicle
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[3]
P-value	= 0.515
Method	Posterior mean
Parameter estimate	Mean difference (net)
Point estimate	0
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.12
upper limit	0.12

Variability estimate	Standard deviation
Dispersion value	0.07

Notes:

[3] - There was no difference in the posterior mean in the complete clearance rate between LFX453 NMC and the combined vehicle group, since the posterior distribution for the difference in complete clearance rate did not reach a 90% chance of being positive (probability =0.515).

Statistical analysis title	LFX453 0.15% LCC versus Combined Vehicle
Comparison groups	LFX453 0.15% LCC v Combined Vehicle
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[4]
P-value	= 0.517
Method	posterior mean
Parameter estimate	Mean difference (net)
Point estimate	0
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.12
upper limit	0.13
Variability estimate	Standard deviation
Dispersion value	0.07

Notes:

[4] - There was no difference in the posterior mean in the complete clearance rate between LFX453 LCC and the combined vehicle group, since the posterior distribution for the difference in complete clearance rate did not reach a 90% chance of being positive (probability =0.517).

Primary: Reduction rate (percent) of Actinic keratosis (AK) lesion count at 8 weeks after the end of treatment (Week 20) for LFX453 compared to vehicle groups combined

End point title	Reduction rate (percent) of Actinic keratosis (AK) lesion count at 8 weeks after the end of treatment (Week 20) for LFX453 compared to vehicle groups combined ^[5] ^[6]
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End point description:

Reduction rate (percent) of Actinic keratosis (AK) lesion count at 8 weeks after the end of treatment (Week 20) for LFX453 compared to vehicle groups combined

End point type	Primary
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End point timeframe:

Week 20

Notes:

[5] - 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 statistical analysis was planned for this primary outcome.

[6] - 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: End point was provided for the arms that were part of this objective and not all baseline period arms

End point values	LFX453 0.1% NMC	LFX453 0.15% LCC	Combined Vehicle	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	20	20	21	
Units: lesion count				
arithmetic mean (standard deviation)	33.2 (± 31.19)	34.5 (± 33.2)	34.3 (± 33.31)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants that had Complete clearance of Actinic keratosis (AK) at Week 8 and Week 16 for LFX453 compared to vehicle groups combined

End point title	Number of Participants that had Complete clearance of Actinic keratosis (AK) at Week 8 and Week 16 for LFX453 compared to vehicle groups combined ^[7]
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End point description:

Complete clearance of Actinic keratosis (AK), defined as the number of patients with a count of zero lesions in the treated area, evaluated at week 8 and Week 16 for LFX453 compared to vehicle groups combined

End point type	Secondary
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End point timeframe:

week 8, week 16

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: End point was provided for the arms that were part of this objective and not all baseline period arms

End point values	LFX453 0.1% NMC	LFX453 0.15% LCC	Combined Vehicle	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	20	20	21	
Units: participants				
Week 8	0	0	1	
Week 16	1	1	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants that had Partial clearance of Actinic keratosis (AK) at 8 weeks after the end of treatment (Week 20) for LFX453 compared to vehicle groups combined

End point title	Number of Participants that had Partial clearance of Actinic keratosis (AK) at 8 weeks after the end of treatment (Week 20) for LFX453 compared to vehicle groups combined ^[8]
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End point description:

Partial clearance of Actinic keratosis (AK), the defined as proportion of patients with at least 75% reduction in the number of AK lesion count compared to baseline, evaluated at 8 weeks after the end of treatment (Week 20 = EOS visit) for LFX453 compared to vehicle groups combined

End point type	Secondary
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End point timeframe:

Week 20

Notes:

[8] - 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: End point was provided for the arms that were part of this objective and not all baseline period arms

End point values	LFX453 0.1% NMC	LFX453 0.15% LCC	Combined Vehicle	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	20	20	21	
Units: participants	1	2	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants that Partial clearance of Actinic keratosis (AK) at at Week 8 and Week 16 for LFX453 compared to vehicle groups combined

End point title	Number of Participants that Partial clearance of Actinic keratosis (AK) at at Week 8 and Week 16 for LFX453 compared to vehicle groups combined ^[9]
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End point description:

Partial clearance of Actinic keratosis (AK), the defined as proportion of patients with at least 75% reduction in the number of AK lesion count compared to baseline, evaluated at week 8 and Week 16 for LFX453 compared to vehicle groups combined

End point type	Secondary
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End point timeframe:

week 8, week 16

Notes:

[9] - 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: End point was provided for the arms that were part of this objective and not all baseline period arms

End point values	LFX453 0.1% NMC	LFX453 0.15% LCC	Combined Vehicle	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	20	20	21	
Units: participants				
Week 8	1	0	3	
Week 16	3	4	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction rate (percent) of Actinic keratosis (AK) lesion count at Week 8 for LFX453 compared to vehicle groups combined

End point title	Reduction rate (percent) of Actinic keratosis (AK) lesion count at Week 8 for LFX453 compared to vehicle groups combined ^[10]
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End point description:

Reduction rate (percent) of Actinic keratosis (AK) lesion count at Week 8 for LFX453 compared to vehicle groups combined

End point type	Secondary
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End point timeframe:

Week 8

Notes:

[10] - 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: End point was provided for the arms that were part of this objective and not all baseline period arms

End point values	LFX453 0.1% NMC	LFX453 0.15% LCC	Combined Vehicle	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	20	20	21	
Units: lesion count				
arithmetic mean (standard deviation)	21.9 (± 36.18)	21.9 (± 28.91)	32.3 (± 33.55)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	LFX453 0.1% NMC
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Reporting group description:

LFX453 0.1% NMC

Reporting group title	LFX453 0.15% LCC
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Reporting group description:

LFX453 0.15% LCC

Reporting group title	Vehicle NMC
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Reporting group description:

Vehicle NMC

Reporting group title	Vehicle LCC
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Reporting group description:

Vehicle LCC

Reporting group title	Aldara
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Reporting group description:

Aldara

Serious adverse events	LFX453 0.1% NMC	LFX453 0.15% LCC	Vehicle NMC
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	1 / 11 (9.09%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
FEMORAL NECK FRACTURE			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 11 (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 FIBRILLATION			

subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
CEREBRAL INFARCTION			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL HERNIA			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 11 (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
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 11 (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
Serious adverse events			
Vehicle LCC			
Aldara			
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)	1 / 21 (4.76%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
FEMORAL NECK FRACTURE			
subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ATRIAL FIBRILLATION			

subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CEREBRAL INFARCTION			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL HERNIA			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	1 / 10 (10.00%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	LFX453 0.1% NMC	LFX453 0.15% LCC	Vehicle NMC
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 20 (50.00%)	14 / 20 (70.00%)	9 / 11 (81.82%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BASAL CELL CARCINOMA			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
SEBORRHOEIC KERATOSIS			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0

Vascular disorders			
HAEMATOMA			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
HYPERTENSION			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
THROMBOSIS			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
APPLICATION SITE COLDNESS			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
APPLICATION SITE ERYTHEMA			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
APPLICATION SITE PRURITUS			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
APPLICATION SITE SCAB			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
CHILLS			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
FATIGUE			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
HYPOTHERMIA			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
NON-CARDIAC CHEST PAIN			

subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 20 (0.00%) 0	0 / 11 (0.00%) 0
Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 20 (5.00%) 1	0 / 11 (0.00%) 0
RHINITIS ALLERGIC subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 20 (0.00%) 0	0 / 11 (0.00%) 0
Psychiatric disorders AGITATION subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 20 (0.00%) 0	0 / 11 (0.00%) 0
BURNOUT SYNDROME subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 20 (5.00%) 1	0 / 11 (0.00%) 0
Investigations ANTIPSYCHOTIC DRUG LEVEL INCREASED subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 20 (0.00%) 0	0 / 11 (0.00%) 0
BLOOD CREATININE INCREASED subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 20 (0.00%) 0	1 / 11 (9.09%) 1
GAMMA-GLUTAMYLTRANSFERASE INCREASED subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 20 (0.00%) 0	0 / 11 (0.00%) 0
LYMPHOCYTE COUNT DECREASED subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 20 (0.00%) 0	0 / 11 (0.00%) 0
Injury, poisoning and procedural complications CONTUSION subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 20 (5.00%) 1	0 / 11 (0.00%) 0
CORNEAL ABRASION			

subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
EYELID INJURY			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
HEAD INJURY			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
LACERATION			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
MUSCLE RUPTURE			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
PERIORBITAL HAEMATOMA			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
RIB FRACTURE			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
AUTONOMIC NERVOUS SYSTEM IMBALANCE			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
BURNING SENSATION			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
DIZZINESS			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
HEADACHE			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	2
POLYNEUROPATHY			

subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
POOR QUALITY SLEEP			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
SCIATICA			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
HAEMOLYTIC ANAEMIA			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
INCREASED TENDENCY TO BRUISE			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
VESTIBULAR DISORDER			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
BLEPHARITIS			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
APHTHOUS ULCER			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
APICAL GRANULOMA			

subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
DIARRHOEA			
subjects affected / exposed	0 / 20 (0.00%)	3 / 20 (15.00%)	0 / 11 (0.00%)
occurrences (all)	0	3	0
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
NAUSEA			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
TOOTHACHE			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
CHOLELITHIASIS			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
BLISTER			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
DRY SKIN			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
ECZEMA			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
ERYTHEMA			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
PAIN OF SKIN			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
SKIN EXFOLIATION			

subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 20 (0.00%) 0	0 / 11 (0.00%) 0
Renal and urinary disorders RENAL CYST subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 20 (0.00%) 0	1 / 11 (9.09%) 1
Musculoskeletal and connective tissue disorders ARTHRALGIA subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 20 (5.00%) 1	0 / 11 (0.00%) 0
BACK PAIN subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 20 (5.00%) 1	1 / 11 (9.09%) 1
MUSCLE SPASMS subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 20 (0.00%) 0	0 / 11 (0.00%) 0
MYALGIA subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	1 / 20 (5.00%) 1	0 / 11 (0.00%) 0
MYOSCLEROSIS subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 20 (0.00%) 0	0 / 11 (0.00%) 0
NECK PAIN subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 20 (0.00%) 0	0 / 11 (0.00%) 0
OSTEOARTHRITIS subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 20 (5.00%) 1	0 / 11 (0.00%) 0
PAIN IN EXTREMITY subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	1 / 20 (5.00%) 1	1 / 11 (9.09%) 2
PERIARTHRITIS subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 20 (5.00%) 1	0 / 11 (0.00%) 0
Infections and infestations			

BRONCHITIS			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
CYSTITIS			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
EYE INFECTION			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
GASTROENTERITIS			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
INFLUENZA			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
NASOPHARYNGITIS			
subjects affected / exposed	1 / 20 (5.00%)	5 / 20 (25.00%)	3 / 11 (27.27%)
occurrences (all)	1	6	3
ORAL HERPES			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
PNEUMONIA			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
RELAPSING FEVER			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
SINUSITIS			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
TINEA PEDIS			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
HYPOKALAEMIA			

subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Vehicle LCC	Aldara	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 10 (80.00%)	17 / 21 (80.95%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BASAL CELL CARCINOMA			
subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	2	
SEBORRHOEIC KERATOSIS			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
HAEMATOMA			
subjects affected / exposed	1 / 10 (10.00%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
HYPERTENSION			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
THROMBOSIS			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
APPLICATION SITE COLDNESS			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
APPLICATION SITE ERYTHEMA			
subjects affected / exposed	0 / 10 (0.00%)	5 / 21 (23.81%)	
occurrences (all)	0	6	
APPLICATION SITE PRURITUS			
subjects affected / exposed	1 / 10 (10.00%)	2 / 21 (9.52%)	
occurrences (all)	1	2	
APPLICATION SITE SCAB			
subjects affected / exposed	0 / 10 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	3	

CHILLS			
subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
FATIGUE			
subjects affected / exposed	0 / 10 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
HYPOTHERMIA			
subjects affected / exposed	1 / 10 (10.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	0 / 10 (0.00%)	3 / 21 (14.29%)	
occurrences (all)	0	3	
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
RHINITIS ALLERGIC			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
AGITATION			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
BURNOUT SYNDROME			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Investigations			
ANTIPSYCHOTIC DRUG LEVEL INCREASED			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
BLOOD CREATININE INCREASED			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	

GAMMA-GLUTAMYLTRANSFERASE INCREASED	subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	
	occurrences (all)	0	1	
	LYMPHOCYTE COUNT DECREASED			
	subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
	occurrences (all)	0	0	
Injury, poisoning and procedural complications				
CONTUSION				
	subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
	occurrences (all)	0	0	
CORNEAL ABRASION				
	subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
	occurrences (all)	0	0	
EYELID INJURY				
	subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
	occurrences (all)	0	0	
HEAD INJURY				
	subjects affected / exposed	1 / 10 (10.00%)	1 / 21 (4.76%)	
	occurrences (all)	1	1	
LACERATION				
	subjects affected / exposed	1 / 10 (10.00%)	0 / 21 (0.00%)	
	occurrences (all)	1	0	
MUSCLE RUPTURE				
	subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
	occurrences (all)	0	0	
PERIORBITAL HAEMATOMA				
	subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
	occurrences (all)	0	0	
RIB FRACTURE				
	subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	
	occurrences (all)	0	1	
Nervous system disorders				
AUTONOMIC NERVOUS SYSTEM IMBALANCE				
	subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
	occurrences (all)	0	0	

BURNING SENSATION			
subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
DIZZINESS			
subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
HEADACHE			
subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	2	
POLYNEUROPATHY			
subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
POOR QUALITY SLEEP			
subjects affected / exposed	1 / 10 (10.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
SCIATICA			
subjects affected / exposed	1 / 10 (10.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
HAEMOLYTIC ANAEMIA			
subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
INCREASED TENDENCY TO BRUISE			
subjects affected / exposed	1 / 10 (10.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
VESTIBULAR DISORDER			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Eye disorders			
BLEPHARITIS			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			

ABDOMINAL PAIN			
subjects affected / exposed	1 / 10 (10.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
APHTHOUS ULCER			
subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
APICAL GRANULOMA			
subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
DIARRHOEA			
subjects affected / exposed	1 / 10 (10.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
GASTROESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
NAUSEA			
subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
TOOTHACHE			
subjects affected / exposed	1 / 10 (10.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
CHOLELITHIASIS			
subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
BLISTER			
subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
DRY SKIN			
subjects affected / exposed	1 / 10 (10.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
ECZEMA			

subjects affected / exposed	1 / 10 (10.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
ERYTHEMA			
subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
PAIN OF SKIN			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
SKIN EXFOLIATION			
subjects affected / exposed	1 / 10 (10.00%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Renal and urinary disorders			
RENAL CYST			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
BACK PAIN			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
MUSCLE SPASMS			
subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
MYALGIA			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
MYOSCLEROSIS			
subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
NECK PAIN			
subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
OSTEOARTHRITIS			

subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
PERIARTHROSITIS			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
CYSTITIS			
subjects affected / exposed	1 / 10 (10.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
EYE INFECTION			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
GASTROENTERITIS			
subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
INFLUENZA			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
NASOPHARYNGITIS			
subjects affected / exposed	1 / 10 (10.00%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
ORAL HERPES			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
PNEUMONIA			
subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
RELAPSING FEVER			
subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	

SINUSITIS			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
TINEA PEDIS			
subjects affected / exposed	0 / 10 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
HYPOKALAEMIA			
subjects affected / exposed	1 / 10 (10.00%)	0 / 21 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 September 2014	Amendment 1 (issued before patient enrollment started) was generated as a result of a change in the storage conditions of the study drug. The major change to the protocol was the description of study drug handling when administered to the patient in Protocol Section 3.1. Minor typos were corrected and imiquimod 5% cream specified to Aldara® to reflect actual plans. The changes included in this amendment did not influence the population or design of the study.
27 January 2015	Amendment 2 was generated to implement requests received from Health Authorities (HAs) and ethics committees (ECs) primarily to repeat pregnancy tests throughout the treatment period of the study, ensure that patients included were not under any influence from study staff, and included information to instruct patients to minimize exposure of the treated areas to UV light or sunlight. The changes included in this amendment did not influence the patient safety or scientific value of this study. The amendment was considered to be non-substantial.
15 September 2015	Amendment 3 was developed to clarify the analyses time point considered for the interim and final analysis of the primary and secondary endpoints given the fact that patients could achieve complete clearance already at the end of the first of 4-week treatment. The specific length of treatment duration (2 cycles of 4-week treatment) was removed to allow patients with complete clearance after one treatment cycle to be included in the analysis. The opportunity was also taken to clarify the exclusion criterion #7 and the location of biopsies. The frequent association of Bowen's disease in these patients was not foreseen and therefore could constitute an exclusion criterion based on the previous wording of exclusion criterion #7. The exclusion criterion #7 was revised to clarify that patients with Bowen's disease shall not be excluded, similarly to patients with basal cell carcinoma of the skin or in-situ cervical cancer. The changes described in this amended protocol were substantial and required IRB/IEC approval prior to implementation. In addition, if the changes herein affected the Informed Consent, sites were required to update and submit for approval a revised Informed Consent that took into account the changes described in this amended protocol. These amendments were not considered to have affected the interpretation of study results as they were minor and occurred prior to study unblinding.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported