



## 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 |
|-----------------------|--------------|

#### 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, Carer, Data analyst, Assessor |

### Arms

|                              |                 |
|------------------------------|-----------------|
| Are arms mutually exclusive? | Yes             |
| <b>Arm title</b>             | 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

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | LFX453 0.15% LCC |
|------------------|------------------|

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

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Vehicle to NMC |
|------------------|----------------|

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

|                                                                                    |                |
|------------------------------------------------------------------------------------|----------------|
| <b>Arm title</b>                                                                   | Vehicle to LCC |
| Arm description:<br>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

|                                                          |                   |
|----------------------------------------------------------|-------------------|
| <b>Arm title</b>                                         | Aldara            |
| Arm description:<br>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

| <b>Number of subjects in period 1</b> | 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               | -                | -              |

| <b>Number of subjects in period 1</b> | 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:<br>LFX453 0.1% nanomedicinal cream (NMC) Twice daily applications                                               |                  |
| Reporting group title                                                                                                                        | LFX453 0.15% LCC |
| Reporting group description:<br>LFX453 0.15% liquid crystal cream (LCC) Twice daily applications                                             |                  |
| Reporting group title                                                                                                                        | Vehicle to NMC   |
| Reporting group description:<br>Vehicle to nanomedicinal cream (NMC) Twice daily applications                                                |                  |
| Reporting group title                                                                                                                        | Vehicle to LCC   |
| Reporting group description:<br>Vehicle to liquid crystal cream (LCC) Twice daily applications                                               |                  |
| Reporting group title                                                                                                                        | Aldara           |
| Reporting group description:<br>Aldara cream 3 applications per week                                                                         |                  |
| Subject analysis set title                                                                                                                   | Combined Vehicle |
| Subject analysis set type                                                                                                                    | Full analysis    |
| Subject analysis set description:<br>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 <sup>[1]</sup> |
| End point description:<br>Number of participants with at least one AE/SAE in the category up to 20 weeks |                                                                                                                                  |
| End point type                                                                                           | Primary                                                                                                                          |
| End point timeframe:<br>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 <sup>[2]</sup> |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

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 |
|----------------|---------|

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

|                                         |                                         |
|-----------------------------------------|-----------------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[3]</sup>          |
| 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).

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[4]</sup>           |
| 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 <sup>[5]</sup> <sup>[6]</sup> |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

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 |
|----------------|---------|

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

|                                      |                 |                  |                      |  |
|--------------------------------------|-----------------|------------------|----------------------|--|
| <b>End point values</b>              | 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 <sup>[7]</sup> |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|

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 |
|----------------|-----------|

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 <sup>[8]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

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 |
|----------------|-----------|

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 <sup>[9]</sup> |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|

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 |
|----------------|-----------|

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 <sup>[10]</sup> |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------|

---

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 |
|----------------|-----------|

---

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

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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 |
|-----------------|------------|

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 18.1   |

### Reporting groups

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | LFX453 0.1% NMC |
|-----------------------|-----------------|

Reporting group description:

LFX453 0.1% NMC

|                       |                  |
|-----------------------|------------------|
| Reporting group title | LFX453 0.15% LCC |
|-----------------------|------------------|

Reporting group description:

LFX453 0.15% LCC

|                       |             |
|-----------------------|-------------|
| Reporting group title | Vehicle NMC |
|-----------------------|-------------|

Reporting group description:

Vehicle NMC

|                       |             |
|-----------------------|-------------|
| Reporting group title | Vehicle LCC |
|-----------------------|-------------|

Reporting group description:

Vehicle LCC

|                       |        |
|-----------------------|--------|
| Reporting group title | Aldara |
|-----------------------|--------|

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          |
| <b>Serious adverse events</b>                     |                 |                |                |
| 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<br>occurrences (all)                                                                | 0 / 20 (0.00%)<br>0 | 0 / 20 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0 |
| Respiratory, thoracic and mediastinal disorders<br>COUGH<br>subjects affected / exposed<br>occurrences (all)    | 0 / 20 (0.00%)<br>0 | 1 / 20 (5.00%)<br>1 | 0 / 11 (0.00%)<br>0 |
| RHINITIS ALLERGIC<br>subjects affected / exposed<br>occurrences (all)                                           | 1 / 20 (5.00%)<br>1 | 0 / 20 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0 |
| Psychiatric disorders<br>AGITATION<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 20 (5.00%)<br>1 | 0 / 20 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0 |
| BURNOUT SYNDROME<br>subjects affected / exposed<br>occurrences (all)                                            | 0 / 20 (0.00%)<br>0 | 1 / 20 (5.00%)<br>1 | 0 / 11 (0.00%)<br>0 |
| Investigations<br>ANTIPSYCHOTIC DRUG LEVEL INCREASED<br>subjects affected / exposed<br>occurrences (all)        | 1 / 20 (5.00%)<br>1 | 0 / 20 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0 |
| BLOOD CREATININE INCREASED<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 20 (0.00%)<br>0 | 0 / 20 (0.00%)<br>0 | 1 / 11 (9.09%)<br>1 |
| GAMMA-GLUTAMYLTRANSFERASE INCREASED<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 20 (5.00%)<br>1 | 0 / 20 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0 |
| LYMPHOCYTE COUNT DECREASED<br>subjects affected / exposed<br>occurrences (all)                                  | 1 / 20 (5.00%)<br>1 | 0 / 20 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0 |
| Injury, poisoning and procedural complications<br>CONTUSION<br>subjects affected / exposed<br>occurrences (all) | 0 / 20 (0.00%)<br>0 | 1 / 20 (5.00%)<br>1 | 0 / 11 (0.00%)<br>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<br>occurrences (all)                                                                  | 0 / 20 (0.00%)<br>0 | 0 / 20 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0 |
| Renal and urinary disorders<br>RENAL CYST<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 20 (0.00%)<br>0 | 0 / 20 (0.00%)<br>0 | 1 / 11 (9.09%)<br>1 |
| Musculoskeletal and connective tissue disorders<br>ARTHRALGIA<br>subjects affected / exposed<br>occurrences (all) | 0 / 20 (0.00%)<br>0 | 1 / 20 (5.00%)<br>1 | 0 / 11 (0.00%)<br>0 |
| BACK PAIN<br>subjects affected / exposed<br>occurrences (all)                                                     | 0 / 20 (0.00%)<br>0 | 1 / 20 (5.00%)<br>1 | 1 / 11 (9.09%)<br>1 |
| MUSCLE SPASMS<br>subjects affected / exposed<br>occurrences (all)                                                 | 0 / 20 (0.00%)<br>0 | 0 / 20 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0 |
| MYALGIA<br>subjects affected / exposed<br>occurrences (all)                                                       | 1 / 20 (5.00%)<br>1 | 1 / 20 (5.00%)<br>1 | 0 / 11 (0.00%)<br>0 |
| MYOSCLEROSIS<br>subjects affected / exposed<br>occurrences (all)                                                  | 0 / 20 (0.00%)<br>0 | 0 / 20 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0 |
| NECK PAIN<br>subjects affected / exposed<br>occurrences (all)                                                     | 0 / 20 (0.00%)<br>0 | 0 / 20 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0 |
| OSTEOARTHRITIS<br>subjects affected / exposed<br>occurrences (all)                                                | 0 / 20 (0.00%)<br>0 | 1 / 20 (5.00%)<br>1 | 0 / 11 (0.00%)<br>0 |
| PAIN IN EXTREMITY<br>subjects affected / exposed<br>occurrences (all)                                             | 1 / 20 (5.00%)<br>1 | 1 / 20 (5.00%)<br>1 | 1 / 11 (9.09%)<br>2 |
| PERIARTHRITIS<br>subjects affected / exposed<br>occurrences (all)                                                 | 0 / 20 (0.00%)<br>0 | 1 / 20 (5.00%)<br>1 | 0 / 11 (0.00%)<br>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              |

| <b>Non-serious adverse events</b>                                   | 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<br>occurrences (all)                                                                  | 1 / 10 (10.00%)<br>1 | 0 / 21 (0.00%)<br>0 |  |
| ERYTHEMA<br>subjects affected / exposed<br>occurrences (all)                                                      | 0 / 10 (0.00%)<br>0  | 1 / 21 (4.76%)<br>1 |  |
| PAIN OF SKIN<br>subjects affected / exposed<br>occurrences (all)                                                  | 0 / 10 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0 |  |
| SKIN EXFOLIATION<br>subjects affected / exposed<br>occurrences (all)                                              | 1 / 10 (10.00%)<br>1 | 1 / 21 (4.76%)<br>1 |  |
| Renal and urinary disorders<br>RENAL CYST<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 10 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0 |  |
| Musculoskeletal and connective tissue disorders<br>ARTHRALGIA<br>subjects affected / exposed<br>occurrences (all) | 0 / 10 (0.00%)<br>0  | 1 / 21 (4.76%)<br>1 |  |
| BACK PAIN<br>subjects affected / exposed<br>occurrences (all)                                                     | 0 / 10 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0 |  |
| MUSCLE SPASMS<br>subjects affected / exposed<br>occurrences (all)                                                 | 0 / 10 (0.00%)<br>0  | 1 / 21 (4.76%)<br>1 |  |
| MYALGIA<br>subjects affected / exposed<br>occurrences (all)                                                       | 0 / 10 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0 |  |
| MYOSCLEROSIS<br>subjects affected / exposed<br>occurrences (all)                                                  | 0 / 10 (0.00%)<br>0  | 1 / 21 (4.76%)<br>1 |  |
| NECK PAIN<br>subjects affected / exposed<br>occurrences (all)                                                     | 0 / 10 (0.00%)<br>0  | 1 / 21 (4.76%)<br>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