



## Clinical trial results:

**A double blind, placebo controlled, randomised dose escalation trial to investigate the safety and efficacy of topical salbutamol in the improvement of scar appearance when applied to approximated wound margins in healthy volunteers.**

**Short title: A trial to assess the safety and efficacy of topical salbutamol in healthy volunteers**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2017-003118-15 |
| Trial protocol           | GB             |
| Global end of trial date | 01 July 2019   |

### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 06 January 2021 |
| First version publication date | 06 January 2021 |

### Trial information

#### Trial identification

|                       |       |
|-----------------------|-------|
| Sponsor protocol code | 97807 |
|-----------------------|-------|

#### Additional study identifiers

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

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | University Hospitals of Leicester - NHS Trust                                   |
| Sponsor organisation address | Leicester Royal Infirmary, Infirmary Square, Leicester, United Kingdom, LE1 5WW |
| Public contact               | David Fairlamb, ProTherax Ltd, +44 1274561815, davidfairlamb@protherax.com      |
| Scientific contact           | David Fairlamb, ProTherax Ltd, +44 1274561815, davidfairlamb@protherax.com      |

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |              |
|--|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 23 June 2020 |
| Is this the analysis of the primary completion data? | Yes          |
| Primary completion date                              | 01 July 2019 |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 01 July 2019 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study is to assess the safety and tolerance of topically applied salbutamol gel, when applied topically to the approximated wound margins of male and female subjects following surgical incisions.

Protection of trial subjects:

Trial subjects were recruited sequentially in escalating dose groups, and escalation of salbutamol concentrations (2.5mM, 5.0mM, and 10.0mM) was based on an assessment by an independent Data Safety Monitoring Committee (DSMC) which assessed safety of the IMP after the last patient of each group had reached Day 14

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 09 October 2017 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | Yes             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 45 |
| Worldwide total number of subjects   | 45                 |
| EEA total number of subjects         | 45                 |

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)                      | 45 |

|                     |   |
|---------------------|---|
| From 65 to 84 years | 0 |
| 85 years and over   | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Subjects recruited to the study were healthy volunteers, recruited between Jan 2018 and 01 July 2018. Last subject completed follow-up in 01 July 2019. All subjects were recruited in the UK.

### Pre-assignment

Screening details:

Healthy volunteers aged 18-50, who provided written informed consent, registered on The Over Volunteering Prevention System (TOPS), had a BMI of 15.0-35.0 kg/m<sup>2</sup> and who had acceptable clinical laboratory tests. Total number of subjects screened was 51.

### Period 1

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

Blinding implementation details:

This study was a double-blind trial using a placebo (vehicle) gel without salbutamol as the comparator. There was no visual, tactile or odour differences between the two gel products. All subjects, investigators and staff involved in trial related assessments were blinded to study treatment administered to each incision site.

### Arms

|                              |                                 |
|------------------------------|---------------------------------|
| Are arms mutually exclusive? | Yes                             |
| <b>Arm title</b>             | Salbutamol Gel 2.5mM vs placebo |

Arm description:

Within patient study, in which an incision on one arm was dosed with Salbutamol Gel 2.5mM and one arm was dosed with placebo.

|  |                      |
|--|----------------------|
| Arm type                               | IMP vs Placebo       |
| Investigational medicinal product name | Salbutamol Gel 2.5mM |
| Investigational medicinal product code |                      |
| Other name                             |                      |
| Pharmaceutical forms                   | Gel                  |
| Routes of administration               | Cutaneous use        |

Dosage and administration details:

1mL administered to the incisional wound site every day for 60 days

|  |               |
|--|---------------|
| Investigational medicinal product name | Placebo       |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Gel           |
| Routes of administration               | Cutaneous use |

Dosage and administration details:

1mL administered to the incisional wound site daily for 60 days

|                  |                                 |
|------------------|---------------------------------|
| <b>Arm title</b> | Salbutamol Gel 5.0mM vs Placebo |
|------------------|---------------------------------|

Arm description:

Within subject comparison of salbutamol Gel 5.0mM administered to a wound on one arm compared with Placebo Gel administered to the contralateral arm

|          |                |
|----------|----------------|
| Arm type | IMP vs Placebo |
|----------|----------------|

|   |                                |
|---|--------------------------------|
| Investigational medicinal product name  | Salbutamol Gel 5.0mM           |
| Investigational medicinal product code  |                                |
| Other name  |                                |
| Pharmaceutical forms  | Gel                            |
| Routes of administration  | Cutaneous use                  |
| Dosage and administration details:  |                                |
| 1mL administered to the incisional wound site daily for 60 days.  |                                |
| Investigational medicinal product name  | Placebo                        |
| Investigational medicinal product code  |                                |
| Other name  |                                |
| Pharmaceutical forms  | Gel                            |
| Routes of administration  | Cutaneous use                  |
| Dosage and administration details:  |                                |
| 1mL administered to the incisional wound site daily for 60 days   |                                |
| <b>Arm title</b>  | Salbutamol Gel 10mM vs placebo |
| Arm description:  |                                |
| Within subject comparison in which Salbutamol Gel 10mM was administered to one arm and placebo gel to the contralateral arm |                                |
| Arm type  | IMP vs Placebo                 |
| Investigational medicinal product name  | Salbutamol 10mM Gel            |
| Investigational medicinal product code  |                                |
| Other name  |                                |
| Pharmaceutical forms  | Gel                            |
| Routes of administration  | Cutaneous use                  |
| Dosage and administration details:  |                                |
| 1mL administered to the incisional wound site daily for 60 days   |                                |
| Investigational medicinal product name  | Placebo                        |
| Investigational medicinal product code  |                                |
| Other name  |                                |
| Pharmaceutical forms  | Gel                            |
| Routes of administration  | Cutaneous use                  |
| Dosage and administration details:  |                                |
| 1mL administered to the incisional wound site daily for 60 days   |                                |

| Number of subjects in period 1 | Salbutamol Gel 2.5mM vs placebo | Salbutamol Gel 5.0mM vs Placebo | Salbutamol Gel 10mM vs placebo |
|--------------------------------|---------------------------------|---------------------------------|--------------------------------|
| Started                        | 15                              | 15                              | 15                             |
| Completed                      | 15                              | 15                              | 15                             |

## Baseline characteristics

### Reporting groups

|  |                                 |
|--|---------------------------------|
| Reporting group title  | Salbutamol Gel 2.5mM vs placebo |
| Reporting group description:<br>Within patient study, in which an incision on one arm was dosed with Salbutamol Gel 2.5mM and one arm was dosed with placebo.                        |                                 |
| Reporting group title  | Salbutamol Gel 5.0mM vs Placebo |
| Reporting group description:<br>Within subject comparison of salbutamol Gel 5.0mM administered to a wound on one arm compared with Placebo Gel administered to the contralateral arm |                                 |
| Reporting group title  | Salbutamol Gel 10mM vs placebo  |
| Reporting group description:<br>Within subject comparison in which Salbutamol Gel 10mM was administered to one arm and placebo gel to the contralateral arm                          |                                 |

| Reporting group values                             | Salbutamol Gel 2.5mM vs placebo | Salbutamol Gel 5.0mM vs Placebo | Salbutamol Gel 10mM vs placebo |
|--|---------------------------------|---------------------------------|--------------------------------|
| Number of subjects                                 | 15                              | 15                              | 15                             |
| Age categorical                                    |                                 |                                 |                                |
| Units: Subjects                                    |                                 |                                 |                                |
| In utero   |                                 |                                 |                                |
| Preterm newborn infants (gestational age < 37 wks) |                                 |                                 |                                |
| Newborns (0-27 days)                               |                                 |                                 |                                |
| Infants and toddlers (28 days-23 months)           |                                 |                                 |                                |
| Children (2-11 years)                              |                                 |                                 |                                |
| Adolescents (12-17 years)                          |                                 |                                 |                                |
| Adults (18-64 years)                               |                                 |                                 |                                |
| From 65-84 years                                   |                                 |                                 |                                |
| 85 years and over                                  |                                 |                                 |                                |
| Age continuous                                     |                                 |                                 |                                |
| Subject Age  |                                 |                                 |                                |
| Units: years                                       |                                 |                                 |                                |
| arithmetic mean                                    | 21.7                            | 22.6                            | 27.2                           |
| standard deviation                                 | ± 2.6                           | ± 2.2                           | ± 8.3                          |
| Gender categorical                                 |                                 |                                 |                                |
| Units: Subjects                                    |                                 |                                 |                                |
| Female   | 7                               | 6                               | 10                             |
| Male   | 8                               | 9                               | 5                              |
| Fitzpatrick Skin Scale                             |                                 |                                 |                                |
| Fitzpatrick skin type of subjects                  |                                 |                                 |                                |
| Units: Subjects                                    |                                 |                                 |                                |
| I-   | 6                               | 8                               | 4                              |
| II-  | 8                               | 5                               | 8                              |
| III-IV   | 1                               | 0                               | 1                              |
| V-VI   | 0                               | 2                               | 2                              |

| Reporting group values | Total |  |  |
|------------------------|-------|--|--|
| Number of subjects     | 45    |  |  |

|   |    |  |  |
|---|----|--|--|
| Age categorical                                       |    |  |  |
| Units: Subjects                                       |    |  |  |
| In utero  | 0  |  |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0  |  |  |
| Newborns (0-27 days)                                  | 0  |  |  |
| Infants and toddlers (28 days-23<br>months)           | 0  |  |  |
| Children (2-11 years)                                 | 0  |  |  |
| Adolescents (12-17 years)                             | 0  |  |  |
| Adults (18-64 years)                                  | 0  |  |  |
| From 65-84 years                                      | 0  |  |  |
| 85 years and over                                     | 0  |  |  |
| Age continuous  |    |  |  |
| Subject Age   |    |  |  |
| Units: years  |    |  |  |
| arithmetic mean                                       |    |  |  |
| standard deviation                                    | -  |  |  |
| Gender categorical                                    |    |  |  |
| Units: Subjects                                       |    |  |  |
| Female  | 23 |  |  |
| Male  | 22 |  |  |
| Fitzpatrick Skin Scale                                |    |  |  |
| Fitzpatrick skin type of subjects                     |    |  |  |
| Units: Subjects                                       |    |  |  |
| I-  | 18 |  |  |
| II-   | 21 |  |  |
| III-IV  | 2  |  |  |
| V-VI  | 4  |  |  |

## End points

### End points reporting groups

|  |                                 |
|--|---------------------------------|
| Reporting group title  | Salbutamol Gel 2.5mM vs placebo |
| Reporting group description:<br>Within patient study, in which an incision on one arm was dosed with Salbutamol Gel 2.5mM and one arm was dosed with placebo.                        |                                 |
| Reporting group title  | Salbutamol Gel 5.0mM vs Placebo |
| Reporting group description:<br>Within subject comparison of salbutamol Gel 5.0mM administered to a wound on one arm compared with Placebo Gel administered to the contralateral arm |                                 |
| Reporting group title  | Salbutamol Gel 10mM vs placebo  |
| Reporting group description:<br>Within subject comparison in which Salbutamol Gel 10mM was administered to one arm and placebo gel to the contralateral arm                          |                                 |

### Primary: Proportion of patients achieving salbutamol PK <30mg/mL

|   |  |
|---|--|
| End point title   | Proportion of patients achieving salbutamol PK <30mg/mL <sup>[1]</sup> |
| End point description:<br>Pharmacokinetic analysis was summarised for each time of the sample time points. These data were used to calculate the C <sub>max</sub> , T <sub>max</sub> , T <sub>1/2</sub> and AUC <sub>24</sub> hours for the cutaneous route of administration. The proportion of individuals with Salbutamol peak plasma concentration less than 30ng/ml for the 24 hours following gel application at day 0 were also summarised for each dose |  |
| End point type  | Primary  |
| End point timeframe:<br>Day 0   |  |

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: As a pilot safety study, the number and percentage of participants in each dose group with the primary outcome (i.e. Salbutamol peak plasma concentration in the 24 hours following gel administration at day 0 greater than 30ng/ml), are presented but no statistical tests were performed.

| End point values            | Salbutamol Gel 2.5mM vs placebo | Salbutamol Gel 5.0mM vs Placebo | Salbutamol Gel 10mM vs placebo |  |
|-----------------------------|---------------------------------|---------------------------------|--------------------------------|--|
| Subject group type          | Reporting group                 | Reporting group                 | Reporting group                |  |
| Number of subjects analysed | 15                              | 15                              | 15                             |  |
| Units: Subjects             | 15                              | 15                              | 15                             |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Proportion of patients achieving salbutamol PK <30mg/mL

|                        |  |
|------------------------|--|
| End point title        | Proportion of patients achieving salbutamol PK <30mg/mL <sup>[2]</sup> |
| End point description: |  |
| End point type         | Primary  |



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End point timeframe:

Day 10- to 11

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Notes:

[2] - 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: As a pilot safety study, the number and percentage of participants in each dose group with the primary outcome (i.e. Salbutamol peak plasma concentration in the 24 hours following gel administration at day 0 greater than 30ng/ml), are presented but no statistical tests were performed.

| <b>End point values</b>     | Salbutamol Gel<br>2.5mM vs<br>placebo | Salbutamol Gel<br>5.0mM vs<br>Placebo | Salbutamol Gel<br>10mM vs<br>placebo |  |
|-----------------------------|---------------------------------------|---------------------------------------|--------------------------------------|--|
| Subject group type          | Reporting group                       | Reporting group                       | Reporting group                      |  |
| Number of subjects analysed | 13                                    | 15                                    | 15                                   |  |
| Units: Subjects             | 13                                    | 15                                    | 15                                   |  |

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

12 Months

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |    |
|--------------------|----|
| Dictionary version | 23 |
|--------------------|----|

### Reporting groups

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Salbutamol Gel 2.5mM vs placebo |
|-----------------------|---------------------------------|

Reporting group description:

Within patient study, in which an incision on one arm was dosed with Salbutamol Gel 2.5mM and one arm was dosed with placebo.

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Salbutamol Gel 5.0mM vs Placebo |
|-----------------------|---------------------------------|

Reporting group description:

Within subject comparison of salbutamol Gel 5.0mM administered to a wound on one arm compared with Placebo Gel administered to the contralateral arm

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Salbutamol Gel 10mM vs placebo |
|-----------------------|--------------------------------|

Reporting group description:

Within subject comparison in which Salbutamol Gel 10mM was administered to one arm and placebo gel to the contralateral arm

| Serious adverse events                            | Salbutamol Gel 2.5mM vs placebo | Salbutamol Gel 5.0mM vs Placebo | Salbutamol Gel 10mM vs placebo |
|---|---------------------------------|---------------------------------|--------------------------------|
| Total subjects affected by serious adverse events |                                 |                                 |                                |
| subjects affected / exposed                       | 1 / 15 (6.67%)                  | 0 / 15 (0.00%)                  | 0 / 15 (0.00%)                 |
| number of deaths (all causes)                     | 0                               | 0                               | 0                              |
| number of deaths resulting from adverse events    | 0                               | 0                               | 0                              |
| Reproductive system and breast disorders          |                                 |                                 |                                |
| Haemorrhagic ovarian cyst                         |                                 |                                 |                                |
| subjects affected / exposed                       | 1 / 15 (6.67%)                  | 0 / 15 (0.00%)                  | 0 / 15 (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                          |

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

| Non-serious adverse events                            | Salbutamol Gel 2.5mM vs placebo | Salbutamol Gel 5.0mM vs Placebo | Salbutamol Gel 10mM vs placebo |
|---|---------------------------------|---------------------------------|--------------------------------|
| Total subjects affected by non-serious adverse events |                                 |                                 |                                |
| subjects affected / exposed                           | 6 / 15 (40.00%)                 | 6 / 15 (40.00%)                 | 10 / 15 (66.67%)               |
| Injury, poisoning and procedural complications        |                                 |                                 |                                |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| Blister<br>subjects affected / exposed<br>occurrences (all)   | 1 / 15 (6.67%)<br>0 | 0 / 15 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 |
| Contusion<br>subjects affected / exposed<br>occurrences (all)   | 0 / 15 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1 | 0 / 15 (0.00%)<br>0 |
| Ankle fracture<br>subjects affected / exposed<br>occurrences (all)  | 0 / 15 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1 | 0 / 15 (0.00%)<br>0 |
| Vascular disorders<br>Neurogenic shock<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 15 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1 |
| Surgical and medical procedures<br>Wisdom teeth removal<br>subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1 |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 15 (6.67%)<br>1 | 1 / 15 (6.67%)<br>1 | 0 / 15 (0.00%)<br>0 |
| Syncope<br>subjects affected / exposed<br>occurrences (all)   | 1 / 15 (6.67%)<br>1 | 0 / 15 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)         | 1 / 15 (6.67%)<br>1 | 0 / 15 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 |
| Gastrointestinal disorders<br>Tooth impacted<br>subjects affected / exposed<br>occurrences (all)            | 0 / 15 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1 |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)  | 1 / 15 (6.67%)<br>1 | 0 / 15 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1 |
| Reproductive system and breast disorders  |                     |                     |                     |

|  |                      |                     |                      |
|--|----------------------|---------------------|----------------------|
| Polycystic ovaries<br>subjects affected / exposed<br>occurrences (all) | 1 / 15 (6.67%)<br>0  | 0 / 15 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0  |
| Skin and subcutaneous tissue disorders                                 |                      |                     |                      |
| Erythema<br>subjects affected / exposed<br>occurrences (all)           | 2 / 15 (13.33%)<br>2 | 1 / 15 (6.67%)<br>1 | 1 / 15 (6.67%)<br>1  |
| Dermatitis<br>subjects affected / exposed<br>occurrences (all)         | 0 / 15 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0 | 3 / 15 (20.00%)<br>3 |
| Urticaria<br>subjects affected / exposed<br>occurrences (all)          | 0 / 15 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0 | 2 / 15 (13.33%)<br>0 |
| Acne<br>subjects affected / exposed<br>occurrences (all)               | 0 / 15 (0.00%)<br>0  | 1 / 15 (6.67%)<br>1 | 0 / 15 (0.00%)<br>0  |
| Psychiatric disorders  |                      |                     |                      |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)            | 1 / 15 (6.67%)<br>1  | 0 / 15 (0.00%)<br>0 | 0 / 15 (0.00%)<br>0  |
| Musculoskeletal and connective tissue disorders                        |                      |                     |                      |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)         | 0 / 15 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1  |
| Foot fracture<br>subjects affected / exposed<br>occurrences (all)      | 0 / 15 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1  |
| Infections and infestations  |                      |                     |                      |
| Infected bite<br>subjects affected / exposed<br>occurrences (all)      | 0 / 15 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1  |
| Viral rash<br>subjects affected / exposed<br>occurrences (all)         | 0 / 15 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1  |
| Bacterial vaginosis  |                      |                     |                      |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| subjects affected / exposed             | 0 / 15 (0.00%) | 2 / 15 (13.33%) | 0 / 15 (0.00%) |
| occurrences (all)                       | 0              | 2               | 0              |
| Conjunctivitis                          |                |                 |                |
| subjects affected / exposed             | 1 / 15 (6.67%) | 0 / 15 (0.00%)  | 0 / 15 (0.00%) |
| occurrences (all)                       | 1              | 0               | 0              |
| Ear infection                           |                |                 |                |
| subjects affected / exposed             | 0 / 15 (0.00%) | 1 / 15 (6.67%)  | 0 / 15 (0.00%) |
| occurrences (all)                       | 0              | 1               | 0              |
| Lower respiratory tract infection       |                |                 |                |
| subjects affected / exposed             | 0 / 15 (0.00%) | 0 / 15 (0.00%)  | 1 / 15 (6.67%) |
| occurrences (all)                       | 0              | 0               | 1              |
| Tinea infection                         |                |                 |                |
| subjects affected / exposed             | 0 / 15 (0.00%) | 0 / 15 (0.00%)  | 1 / 15 (6.67%) |
| occurrences (all)                       | 0              | 0               | 1              |
| Tooth abscess                           |                |                 |                |
| subjects affected / exposed             | 0 / 15 (0.00%) | 0 / 15 (0.00%)  | 1 / 15 (6.67%) |
| occurrences (all)                       | 0              | 0               | 1              |
| Tooth infection                         |                |                 |                |
| subjects affected / exposed             | 0 / 15 (0.00%) | 0 / 15 (0.00%)  | 1 / 15 (6.67%) |
| occurrences (all)                       | 0              | 0               | 1              |
| Viral upper respiratory tract infection |                |                 |                |
| subjects affected / exposed             | 1 / 15 (6.67%) | 1 / 15 (6.67%)  | 0 / 15 (0.00%) |
| occurrences (all)                       | 1              | 1               | 0              |
| Metabolism and nutrition disorders      |                |                 |                |
| Vitamin D deficiency                    |                |                 |                |
| subjects affected / exposed             | 1 / 15 (6.67%) | 0 / 15 (0.00%)  | 0 / 15 (0.00%) |
| occurrences (all)                       | 1              | 0               | 0              |

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported