



## Clinical trial results:

### The early use of Antibiotics for at Risk CHildren with Influenza in primary care

### (ARCHIE): a double-blind randomised placebo-controlled trial

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2013-002822-21 |
| Trial protocol           | GB             |
| Global end of trial date | 15 August 2019 |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 05 March 2020 |
| First version publication date | 05 March 2020 |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | ARCHIE001 |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |                |
|------------------------------------|----------------|
| ISRCTN number                      | ISRCTN70714783 |
| ClinicalTrials.gov id (NCT number) | -              |
| WHO universal trial number (UTN)   | -              |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | University of Oxford  |
| Sponsor organisation address | Joint Research Office, 1 st floor, Boundary Brook House, Churchill Drive, Headington, Oxford, United Kingdom, OX3 7GB |
| Public contact               | Prof Anthony Harnden, University of Oxford, 44 01865 289314, anthony.harnden@phc.ox.ac.uk                             |
| Scientific contact           | Prof Anthony Harnden, University of Oxford, 44 01865 289314, anthony.harnden@phc.ox.ac.uk                             |

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:

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**Results analysis stage**

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|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 16 December 2019 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 15 March 2019    |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 15 August 2019   |
| Was the trial ended prematurely?                     | No               |

Notes:

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**General information about the trial**

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Main objective of the trial:

To determine whether early treatment with co-amoxiclav reduces the likelihood of re-consultation due to clinical deterioration in 'at risk' children with influenza/influenza-like illness (ILI) within 28 days of study entry.

Protection of trial subjects:

We consulted with groups representing both patients and parents when designing the trial and had representatives of on our steering committee. A full risk assessment was conducted before commencing the trial and this was reviewed throughout. Informed consent from every participant's parent/guardian was obtained and the trial was reviewed and approved by a Research Ethics Committee (NRES Committee North West - Liverpool East 13/NW/0621).

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 01 November 2013 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | United Kingdom: 271 |
| Worldwide total number of subjects   | 271                 |
| EEA total number of subjects         | 271                 |

Notes:

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**Subjects enrolled per age group**

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|   |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 89  |
| Children (2-11 years)                     | 179 |
| Adolescents (12-17 years)                 | 3   |
| Adults (18-64 years)                      | 0   |
| From 65 to 84 years                       | 0   |

|                   |   |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

## Subject disposition

### Recruitment

Recruitment details:

Recruitment opened on 11th Feb 2015 and closed 20th April 2018 (seasonal recruitment only running from Oct – end of ILI season following spring). An additional winter season (2017-2018) was added after an extension from the funder. Follow up was completed by 31st July 2019. The trial was not stopped early.

### Pre-assignment

Screening details:

756 patients were screened for eligibility. Of these, 485 were not eligible and 115 were eligible but declined to consent

### Period 1

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

### Arms

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

Arm description:

Co-amoxiclav 400mg/57mg/5ml Sugar Free Powder for Oral Suspension (70ml)

|  |                            |
|--|----------------------------|
| Arm type                               | Experimental               |
| Investigational medicinal product name | Co-amoxiclav               |
| Investigational medicinal product code |                            |
| Other name                             |                            |
| Pharmaceutical forms                   | Powder for oral suspension |
| Routes of administration               | Oral use                   |

Dosage and administration details:

Dosage was given following British National Formulary Guidelines

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Placebo contains the same excipients as the test product. In order to match the test product for fill weight, bulk density, and viscosity, tests were carried out with different excipients ratios in order to identify the most comparable formulation.

|  |                          |
|--|--------------------------|
| Arm type                               | Placebo                  |
| Investigational medicinal product name | Placebo                  |
| Investigational medicinal product code |                          |
| Other name                             |                          |
| Pharmaceutical forms                   | Powder for oral solution |
| Routes of administration               | Oral use                 |

Dosage and administration details:

Dosage was given following British National Formulary Guidelines

| <b>Number of subjects in period 1</b> | Co-amoxiclav | Placebo |
|---------------------------------------|--------------|---------|
| Started                               | 136          | 135     |
| Completed                             | 134          | 135     |
| Not completed                         | 2            | 0       |
| Consent withdrawn by subject          | 1            | -       |
| Physician decision                    | 1            | -       |

## Baseline characteristics

### Reporting groups

|  |              |
|--|--------------|
| Reporting group title  | Co-amoxiclav |
| Reporting group description:   |              |
| Co-amoxiclav 400mg/57mg/5ml Sugar Free Powder for Oral Suspension (70ml)   |              |
| Reporting group title  | Placebo      |
| Reporting group description:   |              |
| Placebo contains the same excipients as the test product. In order to match the test product for fill weight, bulk density, and viscosity, tests were carried out with different excipients ratios in order to identify the most comparable formulation. |              |

| Reporting group values  | Co-amoxiclav | Placebo  | Total |
|---|--------------|----------|-------|
| Number of subjects  | 136          | 135      | 271   |
| 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)  | 45           | 44       | 89    |
| Children (2-11 years)   | 89           | 90       | 179   |
| Adolescents (12-17 years)   | 2            | 1        | 3     |
| Adults (18-64 years)  | 0            | 0        | 0     |
| From 65-84 years  | 0            | 0        | 0     |
| 85 years and over   | 0            | 0        | 0     |
| Age continuous  |              |          |       |
| Units: months   |              |          |       |
| median  | 41           | 36       |       |
| inter-quartile range (Q1-Q3)  | 19 to 86     | 21 to 71 | -     |
| Gender categorical  |              |          |       |
| Units: Subjects   |              |          |       |
| Female  | 53           | 55       | 108   |
| Male  | 83           | 80       | 163   |
| Region  |              |          |       |
| Region A: Thames Valley & South Midlands, West Midlands, North Thames, North West London, South London; Region B: West of England, South West Peninsula, Cardiff & Vale University Health Board, Aneurin Bevan University Health Board, Abertawe Bro Morgannwg University Health Board; Region C: Greater Manchester, North East and North Cumbria, North West Coast, Yorkshire & Humber; Region D: Kent Surrey & Sussex, Wessex & Region E: Eastern, East Midlands |              |          |       |
| Units: Subjects   |              |          |       |
| Region A  | 45           | 44       | 89    |
| Region B  | 32           | 30       | 62    |
| Region C  | 25           | 25       | 50    |
| Region D  | 23           | 24       | 47    |
| Region E  | 11           | 12       | 23    |
| Current seasonal influenza vaccination  |              |          |       |
| Received this season's seasonal influenza vaccination?  |              |          |       |
| Units: Subjects   |              |          |       |
| Yes   | 45           | 45       | 90    |

|  |     |     |     |
|--|-----|-----|-----|
| No   | 88  | 86  | 174 |
| Don't know   | 3   | 4   | 7   |
| Last year seasonal influenza vaccination                       |     |     |     |
| Received last season's seasonal influenza vaccination?         |     |     |     |
| Units: Subjects  |     |     |     |
| Yes  | 48  | 41  | 89  |
| No   | 63  | 72  | 135 |
| Don't know   | 25  | 21  | 46  |
| Missing  | 0   | 1   | 1   |
| Household smoking status                                       |     |     |     |
| Units: Subjects  |     |     |     |
| Non-Smoking  | 113 | 107 | 220 |
| Smoking  | 21  | 27  | 48  |
| Missing  | 2   | 1   | 3   |
| Antibiotics prescribed in the 3 months preceding randomisation |     |     |     |
| Units: Subjects  |     |     |     |
| Yes  | 33  | 25  | 58  |
| No   | 95  | 105 | 200 |
| Unknown  | 5   | 2   | 7   |
| Missing  | 3   | 3   | 6   |
| Antivirals taken during current episode                        |     |     |     |
| Units: Subjects  |     |     |     |
| Yes  | 0   | 0   | 0   |
| No   | 133 | 135 | 268 |
| Unknown  | 2   | 0   | 2   |
| Missing  | 1   | 0   | 1   |
| Antipyretics taken during current episode                      |     |     |     |
| Units: Subjects  |     |     |     |
| Yes  | 115 | 118 | 233 |
| No   | 19  | 15  | 34  |
| Unknown  | 2   | 2   | 4   |
| Other medications taken during current episode                 |     |     |     |
| Units: Subjects  |     |     |     |
| Yes  | 80  | 71  | 151 |
| No   | 55  | 64  | 119 |
| Unknown  | 1   | 0   | 1   |
| Hib Vaccination Status   |     |     |     |
| Units: Subjects  |     |     |     |
| Yes  | 124 | 124 | 248 |
| No   | 8   | 5   | 13  |
| Unknown  | 1   | 3   | 4   |
| Missing  | 3   | 3   | 6   |
| PCV Vaccination Received                                       |     |     |     |
| Units: Subjects  |     |     |     |
| Yes  | 122 | 122 | 244 |
| No   | 10  | 6   | 16  |
| Unknown  | 1   | 4   | 5   |
| Missing  | 3   | 3   | 6   |
| Any acute consultations in the 12 month                        |     |     |     |

|   |     |     |     |
|---|-----|-----|-----|
| period before entering the study          |     |     |     |
| Units: Subjects                           |     |     |     |
| Yes                                       | 123 | 119 | 242 |
| No  | 8   | 12  | 20  |
| Unknown                                   | 2   | 1   | 3   |
| Missing                                   | 3   | 3   | 6   |
| Any Influenza strain                      |     |     |     |
| Units: Subjects                           |     |     |     |
| Yes                                       | 21  | 16  | 37  |
| No  | 115 | 119 | 234 |
| Influenza strains                         |     |     |     |
| Units: Subjects                           |     |     |     |
| Influenza A                               | 3   | 1   | 4   |
| Influenza A/H1-2009                       | 1   | 3   | 4   |
| Influenza A/H3                            | 7   | 6   | 13  |
| Other                                     | 125 | 125 | 250 |
| Influenza B                               |     |     |     |
| Units: Subjects                           |     |     |     |
| Yes                                       | 10  | 7   | 17  |
| No  | 126 | 128 | 254 |
| Any Parainfluenza strain                  |     |     |     |
| Other respiratory infections (nasal swab) |     |     |     |
| Units: Subjects                           |     |     |     |
| Yes                                       | 10  | 16  | 26  |
| No  | 126 | 119 | 245 |
| Adenovirus                                |     |     |     |
| Other respiratory infections (nasal swab) |     |     |     |
| Units: Subjects                           |     |     |     |
| Yes                                       | 8   | 15  | 23  |
| No  | 128 | 120 | 248 |
| Coronavirus                               |     |     |     |
| Other respiratory infections (nasal swab) |     |     |     |
| Units: Subjects                           |     |     |     |
| Yes                                       | 15  | 11  | 26  |
| No  | 121 | 124 | 245 |
| Human Metapneumovirus                     |     |     |     |
| Other respiratory infections (nasal swab) |     |     |     |
| Units: Subjects                           |     |     |     |
| Yes                                       | 8   | 9   | 17  |
| No  | 128 | 126 | 254 |
| Rhinovirus/Enterovirus                    |     |     |     |
| Other respiratory infections (nasal swab) |     |     |     |
| Units: Subjects                           |     |     |     |
| Yes                                       | 55  | 64  | 119 |
| No  | 81  | 71  | 152 |
| Respiratory Syncytial Virus               |     |     |     |
| Other respiratory infections (nasal swab) |     |     |     |
| Units: Subjects                           |     |     |     |
| Yes                                       | 24  | 24  | 48  |
| No  | 112 | 111 | 223 |
| Bordetella pertussis                      |     |     |     |



|   |       |       |     |
|---|-------|-------|-----|
| Other respiratory infections (nasal swab)   |       |       |     |
| Units: Subjects                             |       |       |     |
| Yes   | 0     | 0     | 0   |
| No  | 136   | 135   | 271 |
| Mycoplasma pneumoniae                       |       |       |     |
| Other respiratory infections (nasal swab)   |       |       |     |
| Units: Subjects                             |       |       |     |
| Yes   | 3     | 1     | 4   |
| No  | 133   | 134   | 267 |
| Chlamydomphila pneumoniae                   |       |       |     |
| Other respiratory infections (nasal swab)   |       |       |     |
| Units: Subjects                             |       |       |     |
| Yes   | 0     | 2     | 2   |
| No  | 136   | 133   | 269 |
| Risk category - Respiratory                 |       |       |     |
| At risk categories (not mutually exclusive) |       |       |     |
| Units: Subjects                             |       |       |     |
| Yes   | 99    | 99    | 198 |
| No  | 37    | 36    | 73  |
| Risk category - Neurological                |       |       |     |
| At risk categories (not mutually exclusive) |       |       |     |
| Units: Subjects                             |       |       |     |
| Yes   | 6     | 9     | 15  |
| No  | 130   | 126   | 256 |
| Risk category - Cardiac                     |       |       |     |
| At risk categories (not mutually exclusive) |       |       |     |
| Units: Subjects                             |       |       |     |
| Yes   | 12    | 4     | 16  |
| No  | 124   | 131   | 255 |
| Risk category - Renal                       |       |       |     |
| At risk categories (not mutually exclusive) |       |       |     |
| Units: Subjects                             |       |       |     |
| Yes   | 3     | 0     | 3   |
| No  | 133   | 135   | 268 |
| Risk category - Immunodeficiency            |       |       |     |
| At risk categories (not mutually exclusive) |       |       |     |
| Units: Subjects                             |       |       |     |
| Yes   | 1     | 0     | 1   |
| No  | 135   | 135   | 270 |
| Heart rate (beats/minute)                   |       |       |     |
| (n=267)                                     |       |       |     |
| Units: beats/minute                         |       |       |     |
| arithmetic mean                             | 115   | 117   |     |
| standard deviation                          | ± 22  | ± 23  | -   |
| Respiratory rate                            |       |       |     |
| (n=268)                                     |       |       |     |
| Units: breaths/minute                       |       |       |     |
| arithmetic mean                             | 27.6  | 28.3  |     |
| standard deviation                          | ± 9.1 | ± 9.9 | -   |
| Temperature                                 |       |       |     |
| (n=270)                                     |       |       |     |

|  |                |              |   |
|--|----------------|--------------|---|
| Units: Degrees Celsius<br>arithmetic mean<br>standard deviation                      | 37<br>± 0.8    | 37<br>± 0.9  | - |
| Total number of acute consultations in the 12 month period before entering the study |                |              |   |
| (n=202)  |                |              |   |
| Units: units<br>median<br>inter-quartile range (Q1-Q3)                               | 6.0<br>3 to 10 | 5<br>3 to 9  | - |
| Duration of illness  |                |              |   |
| Medical history (n=271)  |                |              |   |
| Units: days<br>arithmetic mean<br>standard deviation                                 | 2.7<br>± 1.2   | 2.7<br>± 1.2 | - |
| Duration of fever  |                |              |   |
| Medical history (n=266)  |                |              |   |
| Units: days<br>arithmetic mean<br>standard deviation                                 | 1.9<br>± 1.2   | 2.2<br>± 1.2 | - |

## End points

### End points reporting groups

|  |              |
|--|--------------|
| Reporting group title  | Co-amoxiclav |
| Reporting group description:   |              |
| Co-amoxiclav 400mg/57mg/5ml Sugar Free Powder for Oral Suspension (70ml)   |              |
| Reporting group title  | Placebo      |
| Reporting group description:   |              |
| Placebo contains the same excipients as the test product. In order to match the test product for fill weight, bulk density, and viscosity, tests were carried out with different excipients ratios in order to identify the most comparable formulation. |              |

### Primary: Proportion of children re-consulting due to clinical deterioration

|  |  |
|--|--|
| End point title  | Proportion of children re-consulting due to clinical deterioration |
| End point description:   |  |
| Re-consultation was defined as any subsequent visit to a primary care or other equivalent ambulatory care setting within 28 days of entering the trial.  |  |
| Clinical deterioration was defined as any of: worsening symptoms, development of new symptoms or development of a complication requiring medication or hospitalisation after randomisation. This definition is based on that used by the GRACE (Genomics to combat Resistance against Antibiotics in Community-acquired lower respiratory tract infection in Europe) consortium in relation to lower respiratory tract infections (Little et al., 2013). |  |
| Date of study entry was defined as the date of randomisation.  |  |
| End point type   | Primary  |
| End point timeframe:   |  |
| within 28 days of study entry  |  |

| End point values            | Co-amoxiclav    | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 133             | 132             |  |  |
| Units: re-consultations     |                 |                 |  |  |
| Yes                         | 33              | 28              |  |  |
| No                          | 100             | 104             |  |  |

### Statistical analyses

|   |                          |
|---|--------------------------|
| Statistical analysis title  | Primary Outcome Analysis |
| Statistical analysis description:   |                          |
| The primary analysis of the primary outcome (i.e. proportion of participants having a re-consultation) was conducted using a log binomial regression model. The model adjusted for region, age (as a continuous variable rather than categorised as per the minimisation criteria) and current seasonal influenza vaccination status (yes, no/unknown). The treatment effect is reported as a relative risk and 95% confidence interval with a corresponding P-value. |                          |
| Comparison groups   | Placebo v Co-amoxiclav   |

|   |                               |
|---|-------------------------------|
| Number of subjects included in analysis | 265                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority                   |
| P-value                                 | = 0.513                       |
| Method                                  | log binomial regression model |
| Parameter estimate                      | Risk ratio (RR)               |
| Point estimate                          | 1.16                          |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | 0.75                          |
| upper limit                             | 1.8                           |

## Secondary: Duration of fever (days)

|   |                          |
|---|--------------------------|
| End point title   | Duration of fever (days) |
| End point description:  |                          |
| A fever was defined as a temperature equal to or above 37.5C. If the temperature was not recorded on any day, and there were not 2 consecutive days of temperature below 37.5C, this outcome was classed as missing. Duration of fever was defined as the number of days from randomisation until the last day the temperature was recorded as $\geq 37.5$ C, followed by being recorded as less than 37.5C for two consecutive days. |                          |
| End point type  | Secondary                |
| End point timeframe:  |                          |
| The child's temperature was recorded each day for 28 days or until it had been below 37.5C for 2 consecutive days.  |                          |

| End point values                      | Co-amoxiclav    | Placebo         |  |  |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type                    | Reporting group | Reporting group |  |  |
| Number of subjects analysed           | 71              | 65              |  |  |
| Units: days                           |                 |                 |  |  |
| median (inter-quartile range (Q1-Q3)) | 0 (0 to 1)      | 0 (0 to 1)      |  |  |

## Statistical analyses

|   |                        |
|---|------------------------|
| Statistical analysis title  | Wilcoxon rank sum test |
| Statistical analysis description:   |                        |
| The data for this outcome followed a skewed distribution and could not be transformed to Normality. Therefore, medians and IQRs are presented and a Wilcoxon rank sum test applied to the data. As the Wilcoxon test is a non-parametric univariate test, no adjustment was possible for stratification/minimisation factors. |                        |
| Comparison groups   | Co-amoxiclav v Placebo |

|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 136                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.614                 |
| Method                                  | Wilcoxon (Mann-Whitney) |

## Secondary: Duration of Cough

|                 |                   |
|-----------------|-------------------|
| End point title | Duration of Cough |
|-----------------|-------------------|

End point description:

Duration of cough was computed as the number of days from randomisation until the last day the symptom was recorded as >0, followed by being recorded as 0 (normal/not affected) for two consecutive days.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Cough was scored each day for 28 days from 0-6 (0 being normal/not affected and 6 being as bad as it could be). Once all symptoms were scored 0 for 2 consecutive days recording was stopped

| End point values                      | Co-amoxiclav    | Placebo         |  |  |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type                    | Reporting group | Reporting group |  |  |
| Number of subjects analysed           | 50              | 47              |  |  |
| Units: days                           |                 |                 |  |  |
| median (inter-quartile range (Q1-Q3)) | 8 (5 to 13)     | 11 (7 to 14)    |  |  |

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Wilcoxon rank sum test |
|----------------------------|------------------------|

Statistical analysis description:

The data for this outcome followed a skewed distribution and could not be transformed to Normality. Therefore, medians and IQRs are presented and a Wilcoxon rank sum test applied to the data. As the Wilcoxon test is a non-parametric univariate test, no adjustment was possible for stratification/minimisation factors.

|   |                         |
|---|-------------------------|
| Comparison groups                       | Co-amoxiclav v Placebo  |
| Number of subjects included in analysis | 97                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.199                 |
| Method                                  | Wilcoxon (Mann-Whitney) |

## Secondary: Duration of Phlegm

|                 |                    |
|-----------------|--------------------|
| End point title | Duration of Phlegm |
|-----------------|--------------------|

End point description:

Duration of phlegm was computed as the number of days from randomisation until the last day the symptom was recorded as >0, followed by being recorded as 0 (normal/not affected) for two

consecutive days.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Phlegm was scored each day for 28 days from 0-6 (0 being normal/not affected and 6 being as bad as it could be). Once all symptoms were scored 0 for 2 consecutive days recording was stopped

|                                       |                 |                 |  |  |
|---------------------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>               | Co-amoxiclav    | Placebo         |  |  |
| Subject group type                    | Reporting group | Reporting group |  |  |
| Number of subjects analysed           | 57              | 55              |  |  |
| Units: days                           |                 |                 |  |  |
| median (inter-quartile range (Q1-Q3)) | 6 (3 to 9)      | 6 (3 to 10)     |  |  |

## Statistical analyses

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Wilcoxon rank sum test |
|-----------------------------------|------------------------|

Statistical analysis description:

The data for this outcome followed a skewed distribution and could not be transformed to Normality. Therefore, medians and IQRs are presented and a Wilcoxon rank sum test applied to the data. As the Wilcoxon test is a non-parametric univariate test, no adjustment was possible for stratification/minimisation factors.

|   |                         |
|---|-------------------------|
| Comparison groups                       | Co-amoxiclav v Placebo  |
| Number of subjects included in analysis | 112                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.513                 |
| Method                                  | Wilcoxon (Mann-Whitney) |

## Secondary: Duration of Shortness of breath

|                 |                                 |
|-----------------|---------------------------------|
| End point title | Duration of Shortness of breath |
|-----------------|---------------------------------|

End point description:

Duration of Shortness of breath was computed as the number of days from randomisation until the last day the symptom was recorded as >0, followed by being recorded as 0 (normal/not affected) for two consecutive days.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Shortness of breath was scored each day for 28 days from 0-6 (0 being normal/not affected and 6 being as bad as it could be). Once all symptoms were scored 0 for 2 consecutive days recording was stopped

| End point values                      | Co-amoxiclav    | Placebo         |  |  |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type                    | Reporting group | Reporting group |  |  |
| Number of subjects analysed           | 66              | 58              |  |  |
| Units: days                           |                 |                 |  |  |
| median (inter-quartile range (Q1-Q3)) | 3 (1 to 6)      | 5 (2 to 7)      |  |  |

## Statistical analyses

| Statistical analysis title | Wilcoxon rank sum test |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

The data for this outcome followed a skewed distribution and could not be transformed to Normality. Therefore, medians and IQRs are presented and a Wilcoxon rank sum test applied to the data. As the Wilcoxon test is a non-parametric univariate test, no adjustment was possible for stratification/minimisation factors.

|   |                         |
|---|-------------------------|
| Comparison groups                       | Co-amoxiclav v Placebo  |
| Number of subjects included in analysis | 124                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.119                 |
| Method                                  | Wilcoxon (Mann-Whitney) |

## Secondary: Duration of Disturbed sleep

|                 |                             |
|-----------------|-----------------------------|
| End point title | Duration of Disturbed sleep |
|-----------------|-----------------------------|

End point description:

Duration of disturbed sleep was computed as the number of days from randomisation until the last day the symptom was recorded as >0, followed by being recorded as 0 (normal/not affected) for two consecutive days.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Disturbed sleep was scored each day for 28 days from 0-6 (0 being normal/not affected and 6 being as bad as it could be). Once all symptoms were scored 0 for 2 consecutive days recording was stopped

| End point values                      | Co-amoxiclav    | Placebo         |  |  |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type                    | Reporting group | Reporting group |  |  |
| Number of subjects analysed           | 59              | 55              |  |  |
| Units: days                           |                 |                 |  |  |
| median (inter-quartile range (Q1-Q3)) | 4 (2 to 6)      | 7 (3 to 11)     |  |  |

## Statistical analyses

| Statistical analysis title | Wilcoxon rank sum test |
|----------------------------|------------------------|
|----------------------------|------------------------|

---

**Statistical analysis description:**

The data for this outcome followed a skewed distribution and could not be transformed to Normality. Therefore, medians and IQRs are presented and a Wilcoxon rank sum test applied to the data. As the Wilcoxon test is a non-parametric univariate test, no adjustment was possible for stratification/minimisation factors.

|   |                         |
|---|-------------------------|
| Comparison groups                       | Co-amoxiclav v Placebo  |
| Number of subjects included in analysis | 114                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.021                 |
| Method                                  | Wilcoxon (Mann-Whitney) |

---

**Secondary: Duration of Feeling generally unwell**

|                 |                                      |
|-----------------|--------------------------------------|
| End point title | Duration of Feeling generally unwell |
|-----------------|--------------------------------------|

**End point description:**

Duration of Feeling generally unwell was computed as the number of days from randomisation until the last day the symptom was recorded as >0, followed by being recorded as 0 (normal/not affected) for two consecutive days.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

**End point timeframe:**

Feeling generally unwell was scored each day for 28 days from 0-6 (0 being normal/not affected and 6 being as bad as it could be). Once all symptoms were scored 0 for 2 consecutive days recording was stopped

---

|                                       |                 |                 |  |  |
|---------------------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>               | Co-amoxiclav    | Placebo         |  |  |
| Subject group type                    | Reporting group | Reporting group |  |  |
| Number of subjects analysed           | 65              | 55              |  |  |
| Units: days                           |                 |                 |  |  |
| median (inter-quartile range (Q1-Q3)) | 5 (3 to 8)      | 7 (4 to 8)      |  |  |

---

**Statistical analyses**

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Wilcoxon rank sum test |
|-----------------------------------|------------------------|

**Statistical analysis description:**

The data for this outcome followed a skewed distribution and could not be transformed to Normality. Therefore, medians and IQRs are presented and a Wilcoxon rank sum test applied to the data. As the Wilcoxon test is a non-parametric univariate test, no adjustment was possible for stratification/minimisation factors.

|                   |                        |
|-------------------|------------------------|
| Comparison groups | Co-amoxiclav v Placebo |
|-------------------|------------------------|



|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 120                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.231                 |
| Method                                  | Wilcoxon (Mann-Whitney) |

## Secondary: Duration of Interference with normal activities ratings

|                 |   |
|-----------------|---|
| End point title | Duration of Interference with normal activities ratings |
|-----------------|---|

End point description:

Duration of Interference with normal activities ratings was computed as the number of days from randomisation until the last day the symptom was recorded as >0, followed by being recorded as 0 (normal/not affected) for two consecutive days.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Interference with normal activities ratings was scored each day for 28 days from 0-6 (0 being normal/not affected and 6 being as bad as it could be). Once all symptoms were scored 0 for 2 consecutive days recording was stopped

| End point values                      | Co-amoxiclav    | Placebo         |  |  |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type                    | Reporting group | Reporting group |  |  |
| Number of subjects analysed           | 65              | 61              |  |  |
| Units: days                           |                 |                 |  |  |
| median (inter-quartile range (Q1-Q3)) | 4 (2 to 6)      | 6 (3 to 8)      |  |  |

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Wilcoxon rank sum test |
|----------------------------|------------------------|

Statistical analysis description:

The data for this outcome followed a skewed distribution and could not be transformed to Normality. Therefore, medians and IQRs are presented and a Wilcoxon rank sum test applied to the data. As the Wilcoxon test is a non-parametric univariate test, no adjustment was possible for stratification/minimisation factors.

|   |                         |
|---|-------------------------|
| Comparison groups                       | Co-amoxiclav v Placebo  |
| Number of subjects included in analysis | 126                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.096                 |
| Method                                  | Wilcoxon (Mann-Whitney) |

## Secondary: Medication or further investigations required

|                 |   |
|-----------------|---|
| End point title | Medication or further investigations required |
|-----------------|---|

End point description:

From case notes review, information on whether the child was prescribed antibiotics, other treatments

or investigations at re-consultation episode or hospital admission was used to generate a binary variable to indicate medication or further investigations (Yes/No)

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

All medications and investigations had to be within 28 days from randomisation

| End point values            | Co-amoxiclav    | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 133             | 132             |  |  |
| Units: number               |                 |                 |  |  |
| Yes                         | 41              | 33              |  |  |
| No                          | 92              | 99              |  |  |

## Statistical analyses

|                            |                                  |
|----------------------------|----------------------------------|
| Statistical analysis title | Adjusted log-binomial regression |
|----------------------------|----------------------------------|

Statistical analysis description:

The analysis was carried out using a log-Binomial regression model adjusted for region, age and current vaccination status

|   |                               |
|---|-------------------------------|
| Comparison groups                       | Placebo v Co-amoxiclav        |
| Number of subjects included in analysis | 265                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority                   |
| P-value                                 | = 0.274                       |
| Method                                  | log binomial regression model |
| Parameter estimate                      | Risk ratio (RR)               |
| Point estimate                          | 1.24                          |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | 0.84                          |
| upper limit                             | 1.83                          |

## Secondary: Hospitalisation or death within 28 days

|                 |   |
|-----------------|---|
| End point title | Hospitalisation or death within 28 days |
|-----------------|---|

End point description:

'Hospitalised' was defined as admitted to a hospital ward or intensive care unit for at least one overnight stay. The child has a positive response for this outcome if any of the following were recorded as 'yes':

- o Admitted to intensive care unit with an overnight stay and this occurred within 28 days of study entry.
- o The participant had an acute hospital admission episodes, when he or she has had to spend one or more nights in hospital and the admission occurred within 28 days of study entry.
- o The participant died and the death occurred within 28 days of study entry.

If the date of the event was missing, the CRF was reviewed and followed up in order to attempt to fill in the missing data. If the start date could not be established, the event was not included in the analysis.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:  
Within 28 days of study entry

|                             |                 |                 |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>     | Co-amoxiclav    | Placebo         |  |  |
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 133             | 132             |  |  |
| Units: number               |                 |                 |  |  |
| Yes                         | 7               | 7               |  |  |
| No                          | 126             | 125             |  |  |

### Statistical analyses

|  |                                  |
|--|----------------------------------|
| <b>Statistical analysis title</b>  | Adjusted log-binomial regression |
| Statistical analysis description:<br>The analysis was carried out using a log-Binomial regression model on treatment group, adjusted for age and current vaccination status only |                                  |
| Comparison groups  | Co-amoxiclav v Placebo           |
| Number of subjects included in analysis  | 265                              |
| Analysis specification   | Pre-specified                    |
| Analysis type  | superiority                      |
| P-value  | = 0.997                          |
| Method   | Log-binomial regression          |
| Parameter estimate   | Risk ratio (RR)                  |
| Point estimate   | 1                                |
| Confidence interval  |                                  |
| level  | 95 %                             |
| sides  | 2-sided                          |
| lower limit  | 0.36                             |
| upper limit  | 2.77                             |

### Secondary: Adverse event occurred within 28 days

|   |                                       |
|---|---------------------------------------|
| End point title   | Adverse event occurred within 28 days |
| End point description:                                  |                                       |
| End point type  | Secondary                             |
| End point timeframe:<br>Within 28 days from study entry |                                       |

| End point values            | Co-amoxiclav    | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 136             | 135             |  |  |
| Units: Number of events     |                 |                 |  |  |
| Yes                         | 32              | 22              |  |  |
| No                          | 104             | 113             |  |  |

## Statistical analyses

| Statistical analysis title   | Adjusted log-binomial regression |
|--|----------------------------------|
| Statistical analysis description:  |                                  |
| The analysis was carried out using a log-Binomial regression model adjusted for region, age and current vaccination status |                                  |
| Comparison groups  | Co-amoxiclav v Placebo           |
| Number of subjects included in analysis  | 271                              |
| Analysis specification   | Pre-specified                    |
| Analysis type  | superiority                      |
| P-value  | = 0.131                          |
| Method   | Log-binomial regression          |
| Parameter estimate   | Risk ratio (RR)                  |
| Point estimate   | 1.45                             |
| Confidence interval  |                                  |
| level  | 95 %                             |
| sides  | 2-sided                          |
| lower limit  | 0.9                              |
| upper limit  | 2.34                             |

## Secondary: Adverse event occurred within 28 days (Including AE information for the participant with no AE start date)

|                               |  |
|-------------------------------|--|
| End point title               | Adverse event occurred within 28 days (Including AE information for the participant with no AE start date) |
| End point description:        |  |
| End point type                | Secondary  |
| End point timeframe:          |  |
| Within 28 days of study entry |  |

| End point values            | Co-amoxiclav    | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 136             | 135             |  |  |
| Units: Number of events     |                 |                 |  |  |
| Yes                         | 32              | 23              |  |  |
| No                          | 104             | 112             |  |  |

## Statistical analyses

|   |                                  |
|---|----------------------------------|
| <b>Statistical analysis title</b>   | Adjusted log-binomial regression |
| Statistical analysis description:   |                                  |
| The SAP specified that if no adverse event start date was indicated, then the AE should not be counted as it is not known if it commenced within 28 days of randomisation. In this additional analysis, one participant with an AE but no AE start date is counted as having an AE. The analysis was carried out using a log-Binomial regression model adjusted for region, age and current vaccination status. |                                  |
| Comparison groups   | Co-amoxiclav v Placebo           |
| Number of subjects included in analysis   | 271                              |
| Analysis specification  | Pre-specified                    |
| Analysis type   | superiority                      |
| P-value   | = 0.194                          |
| Method  | Log-binomial regression          |
| Parameter estimate  | Risk ratio (RR)                  |
| Point estimate  | 1.37                             |
| Confidence interval   |                                  |
| level   | 95 %                             |
| sides   | 2-sided                          |
| lower limit   | 0.85                             |
| upper limit   | 2.18                             |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All AEs occurring in participants within 28 days of study entry observed by the investigator or reported by the participant, whether or not attributed to study medication, will be recorded on the CRF

Adverse event reporting additional description:

Co-amoxiclav is a licensed medication whose most common side-effects are mucocutaneous candidosis (thrush), diarrhoea, nausea, vomiting and rash (occurrence  $\geq 1/100$  to  $< 1/10$ ) (GlaxoSmithKline UK 2012). If these occur and are non-serious and of mild to moderate severity (based on clinician's assessment), they will not be recorded

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 17.0   |

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Co-amoxiclav |
|-----------------------|--------------|

Reporting group description:

Subjects randomised to receive co-amoxiclav

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects randomised to receive Placebo

| Serious adverse events                            | Co-amoxiclav    | Placebo         |  |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events |                 |                 |  |
| subjects affected / exposed                       | 8 / 134 (5.97%) | 7 / 135 (5.19%) |  |
| number of deaths (all causes)                     | 0               | 0               |  |
| number of deaths resulting from adverse events    | 0               | 0               |  |
| Nervous system disorders                          |                 |                 |  |
| Lethargy  |                 |                 |  |
| subjects affected / exposed                       | 0 / 134 (0.00%) | 1 / 135 (0.74%) |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                        |                 |                 |  |
| Vomiting  |                 |                 |  |
| subjects affected / exposed                       | 1 / 134 (0.75%) | 1 / 135 (0.74%) |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders   |                 |                 |  |
| Asthma  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 134 (0.00%) | 1 / 135 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspnoea  |                 |                 |  |
| subjects affected / exposed                     | 3 / 134 (2.24%) | 4 / 135 (2.96%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoxia   |                 |                 |  |
| subjects affected / exposed                     | 3 / 134 (2.24%) | 5 / 135 (3.70%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonitis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 134 (0.75%) | 0 / 135 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tachypnoea                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 134 (0.75%) | 0 / 135 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wheezing  |                 |                 |  |
| subjects affected / exposed                     | 2 / 134 (1.49%) | 3 / 135 (2.22%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Musculoskeletal chest pain                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 134 (0.75%) | 0 / 135 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Bronchiolitis                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 134 (0.00%) | 1 / 135 (0.74%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Lower respiratory tract infection<br>subjects affected / exposed                          | 3 / 134 (2.24%) | 3 / 135 (2.22%) |  |
| occurrences causally related to<br>treatment / all  | 0 / 3           | 0 / 3           |  |
| deaths causally related to<br>treatment / all   | 0 / 0           | 0 / 0           |  |
| Pharyngitis<br>subjects affected / exposed  | 1 / 134 (0.75%) | 0 / 135 (0.00%) |  |
| occurrences causally related to<br>treatment / all  | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all   | 0 / 0           | 0 / 0           |  |
| Pneumonia<br>subjects affected / exposed  | 0 / 134 (0.00%) | 1 / 135 (0.74%) |  |
| occurrences causally related to<br>treatment / all  | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all   | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders<br>Fluid intake reduced<br>subjects affected / exposed | 0 / 134 (0.00%) | 1 / 135 (0.74%) |  |
| occurrences causally related to<br>treatment / all  | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all   | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>  | Co-amoxiclav      | Placebo           |  |
|--|-------------------|-------------------|--|
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed                      | 32 / 134 (23.88%) | 23 / 135 (17.04%) |  |
| Injury, poisoning and procedural<br>complications<br>Vaccination complication<br>subjects affected / exposed | 1 / 134 (0.75%)   | 0 / 135 (0.00%)   |  |
| occurrences (all)  | 1                 | 0                 |  |
| Surgical and medical procedures<br>Oxygen supplementation<br>subjects affected / exposed                     | 0 / 134 (0.00%)   | 1 / 135 (0.74%)   |  |
| occurrences (all)  | 0                 | 1                 |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed  | 1 / 134 (0.75%)   | 0 / 135 (0.00%)   |  |
| occurrences (all)  | 1                 | 0                 |  |
| Lethargy   |                   |                   |  |



|   |                      |                      |  |
|---|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)                              | 0 / 134 (0.00%)<br>0 | 1 / 135 (0.74%)<br>1 |  |
| Psychomotor hyperactivity<br>subjects affected / exposed<br>occurrences (all) | 0 / 134 (0.00%)<br>0 | 1 / 135 (0.74%)<br>1 |  |
| General disorders and administration<br>site conditions                       |                      |                      |  |
| Adverse drug reaction<br>subjects affected / exposed<br>occurrences (all)     | 3 / 134 (2.24%)<br>3 | 0 / 135 (0.00%)<br>0 |  |
| Discomfort<br>subjects affected / exposed<br>occurrences (all)                | 1 / 134 (0.75%)<br>1 | 0 / 135 (0.00%)<br>0 |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)                   | 3 / 134 (2.24%)<br>3 | 0 / 135 (0.00%)<br>0 |  |
| Ear and labyrinth disorders   |                      |                      |  |
| Ear Pain<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 134 (0.75%)<br>1 | 0 / 135 (0.00%)<br>0 |  |
| Gastrointestinal disorders  |                      |                      |  |
| Anal fissure<br>subjects affected / exposed<br>occurrences (all)              | 0 / 134 (0.00%)<br>0 | 1 / 135 (0.74%)<br>1 |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)              | 1 / 134 (0.75%)<br>1 | 0 / 135 (0.00%)<br>0 |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                 | 4 / 134 (2.99%)<br>4 | 1 / 135 (0.74%)<br>1 |  |
| Vomitting<br>subjects affected / exposed<br>occurrences (all)                 | 3 / 134 (2.24%)<br>3 | 3 / 135 (2.22%)<br>3 |  |
| Respiratory, thoracic and mediastinal<br>disorders                            |                      |                      |  |
| Asthma<br>subjects affected / exposed<br>occurrences (all)                    | 2 / 134 (1.49%)<br>2 | 1 / 135 (0.74%)<br>1 |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| Cough                                  |                 |                 |  |
| subjects affected / exposed            | 1 / 134 (0.75%) | 0 / 135 (0.00%) |  |
| occurrences (all)                      | 1               | 0               |  |
| Dyspnoea                               |                 |                 |  |
| subjects affected / exposed            | 1 / 134 (0.75%) | 2 / 135 (1.48%) |  |
| occurrences (all)                      | 1               | 2               |  |
| Epistaxis                              |                 |                 |  |
| subjects affected / exposed            | 0 / 134 (0.00%) | 1 / 135 (0.74%) |  |
| occurrences (all)                      | 0               | 1               |  |
| Hypoxia                                |                 |                 |  |
| subjects affected / exposed            | 1 / 134 (0.75%) | 4 / 135 (2.96%) |  |
| occurrences (all)                      | 1               | 4               |  |
| Rhinorrhoea                            |                 |                 |  |
| subjects affected / exposed            | 2 / 134 (1.49%) | 0 / 135 (0.00%) |  |
| occurrences (all)                      | 2               | 0               |  |
| Wheezing                               |                 |                 |  |
| subjects affected / exposed            | 1 / 134 (0.75%) | 1 / 135 (0.74%) |  |
| occurrences (all)                      | 1               | 1               |  |
| Skin and subcutaneous tissue disorders |                 |                 |  |
| Dermatitis allergic                    |                 |                 |  |
| subjects affected / exposed            | 1 / 134 (0.75%) | 0 / 135 (0.00%) |  |
| occurrences (all)                      | 1               | 0               |  |
| Dermatitis diaper                      |                 |                 |  |
| subjects affected / exposed            | 1 / 134 (0.75%) | 0 / 135 (0.00%) |  |
| occurrences (all)                      | 1               | 0               |  |
| Rash                                   |                 |                 |  |
| subjects affected / exposed            | 4 / 134 (2.99%) | 3 / 135 (2.22%) |  |
| occurrences (all)                      | 4               | 3               |  |
| Rash generalised                       |                 |                 |  |
| subjects affected / exposed            | 0 / 134 (0.00%) | 1 / 135 (0.74%) |  |
| occurrences (all)                      | 0               | 1               |  |
| Rash macular                           |                 |                 |  |
| subjects affected / exposed            | 1 / 134 (0.75%) | 0 / 135 (0.00%) |  |
| occurrences (all)                      | 1               | 0               |  |
| Rash papular                           |                 |                 |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 0 / 134 (0.00%)<br>0 | 1 / 135 (0.74%)<br>1 |  |
| Swelling face<br>subjects affected / exposed<br>occurrences (all)  | 0 / 134 (0.00%)<br>0 | 1 / 135 (0.74%)<br>1 |  |
| Psychiatric disorders<br>Delirium<br>subjects affected / exposed<br>occurrences (all)                                      | 1 / 134 (0.75%)<br>1 | 0 / 135 (0.00%)<br>0 |  |
| Irritability<br>subjects affected / exposed<br>occurrences (all)   | 0 / 134 (0.00%)<br>0 | 1 / 135 (0.74%)<br>1 |  |
| Musculoskeletal and connective tissue disorders<br>Myalgia intercostal<br>subjects affected / exposed<br>occurrences (all) | 1 / 134 (0.75%)<br>1 | 0 / 135 (0.00%)<br>0 |  |
| Infections and infestations<br>Bronchiolitis<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 134 (0.00%)<br>0 | 1 / 135 (0.74%)<br>1 |  |
| Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)   | 1 / 134 (0.75%)<br>1 | 1 / 135 (0.74%)<br>1 |  |
| Ear Infection<br>subjects affected / exposed<br>occurrences (all)  | 1 / 134 (0.75%)<br>1 | 2 / 135 (1.48%)<br>2 |  |
| hand-foot -and-mouth disease<br>subjects affected / exposed<br>occurrences (all)   | 0 / 134 (0.00%)<br>0 | 1 / 135 (0.74%)<br>1 |  |
| Infection<br>subjects affected / exposed<br>occurrences (all)  | 0 / 134 (0.00%)<br>0 | 1 / 135 (0.74%)<br>1 |  |
| Lower respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                                      | 3 / 134 (2.24%)<br>3 | 1 / 135 (0.74%)<br>1 |  |
| Otitis externa   |                      |                      |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed             | 1 / 134 (0.75%) | 0 / 135 (0.00%) |  |
| occurrences (all)                       | 1               | 0               |  |
| Pneumonia                               |                 |                 |  |
| subjects affected / exposed             | 1 / 134 (0.75%) | 1 / 135 (0.74%) |  |
| occurrences (all)                       | 1               | 1               |  |
| Pneumonia viral                         |                 |                 |  |
| subjects affected / exposed             | 1 / 134 (0.75%) | 0 / 135 (0.00%) |  |
| occurrences (all)                       | 1               | 0               |  |
| Rhinitis                                |                 |                 |  |
| subjects affected / exposed             | 1 / 134 (0.75%) | 0 / 135 (0.00%) |  |
| occurrences (all)                       | 1               | 0               |  |
| Scarlet fever                           |                 |                 |  |
| subjects affected / exposed             | 0 / 134 (0.00%) | 1 / 135 (0.74%) |  |
| occurrences (all)                       | 0               | 1               |  |
| Tonsillitis                             |                 |                 |  |
| subjects affected / exposed             | 1 / 134 (0.75%) | 0 / 135 (0.00%) |  |
| occurrences (all)                       | 1               | 0               |  |
| Viral infection                         |                 |                 |  |
| subjects affected / exposed             | 0 / 134 (0.00%) | 1 / 135 (0.74%) |  |
| occurrences (all)                       | 0               | 1               |  |
| Viral rash                              |                 |                 |  |
| subjects affected / exposed             | 2 / 134 (1.49%) | 0 / 135 (0.00%) |  |
| occurrences (all)                       | 2               | 0               |  |
| Viral upper respiratory tract infection |                 |                 |  |
| subjects affected / exposed             | 1 / 134 (0.75%) | 0 / 135 (0.00%) |  |
| occurrences (all)                       | 1               | 0               |  |
| Influenza                               |                 |                 |  |
| subjects affected / exposed             | 0 / 134 (0.00%) | 1 / 135 (0.74%) |  |
| occurrences (all)                       | 0               | 1               |  |
| Respiratory tract infection             |                 |                 |  |
| subjects affected / exposed             | 0 / 134 (0.00%) | 1 / 135 (0.74%) |  |
| occurrences (all)                       | 0               | 1               |  |
| Metabolism and nutrition disorders      |                 |                 |  |
| Fluid intake reduced                    |                 |                 |  |
| subjects affected / exposed             | 0 / 134 (0.00%) | 1 / 135 (0.74%) |  |
| occurrences (all)                       | 0               | 1               |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 13 June 2017      | <ol style="list-style-type: none"><li>1. Addition of investigator and updating of contact details</li><li>2. Clarified dosing regime based on BNF guidelines and addition of advice if child under 6kg</li><li>3. Clarified data collected during telephone follow up calls including compliance data</li><li>4. Addition of vaccination data collection in trial design summary as previously omitted in error</li><li>5. Modified eligibility criteria to:<ol style="list-style-type: none"><li>a. Remove requirement that children should be registered at a GP surgery in England and replaced with requirement that child should be registered at a GP surgery in UK.</li><li>b. Clarify that exclusion criterion relating to antibiotic use within the last 72 hours refers specifically to use of antibiotics for treatment of acute infection.</li><li>c. Clarify exclusion criteria relating to hospitalisation.</li></ol></li><li>6. Addition of hospitalization with pneumonia as a potential risk category</li><li>7. Clarify recruitment and screening &amp; eligibility processes to allow flexibility across different sites and site types.</li><li>8. Removal of term 'high' in reference to nasal swabs to better reflect actual procedure</li><li>9. Addition of availability of emergency randomization procedures</li><li>10. Changed reference to trial SOP's to working instructions to reflect PC CTU internal policy that the term SOP's should be used to refer to general and trial procedures while work instructions should be used to refer to trial specific procedures.</li><li>11. Clarified SAE reporting procedures</li><li>12. Clarified extension of planned trial period to May 2019.</li></ol> |
| 12 September 2018 | <ol style="list-style-type: none"><li>1. Change of Chief Investigator (CI)</li><li>2. Addition of investigators</li><li>3. Clarification that end of trial is considered to be the date of the last data capture of the last trial participant.</li><li>4. Gift vouchers to be offered to children participating in the follow up swab sub study</li><li>5. Change of Principal Investigators at CRN's with open sites where former CI has acted as regional PI.</li></ol>  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported