



## Clinical trial results:

### Antivirals for influenza Like Illness? An rCt of Clinical and Cost effectiveness in primary Care

#### Summary

|                          |                               |
|--------------------------|-------------------------------|
| EudraCT number           | 2014-004471-23                |
| Trial protocol           | HU BE IE GB SE CZ LT DK NL PL |
| Global end of trial date | 09 May 2018                   |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 26 July 2019 |
| First version publication date | 26 July 2019 |

#### Trial information

##### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | CB/ALICE/0010 |
|-----------------------|---------------|

##### Additional study identifiers

|                                    |                |
|------------------------------------|----------------|
| ISRCTN number                      | ISRCTN27908921 |
| ClinicalTrials.gov id (NCT number) | -              |
| WHO universal trial number (UTN)   | -              |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | University of Oxford   |
| Sponsor organisation address | Block 60 Churchill Hospital, Oxford, United Kingdom, OX3 7LE                               |
| Public contact               | Prof Chris Butler, University of Oxford, 0044 1865 289363, christopher.butler@phc.ox.ac.uk |
| Scientific contact           | Prof Chris Butler, University of Oxford, 0044 1865 289363, christopher.butler@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:

## Results analysis stage

|  |                   |
|--|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 24 September 2018 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 09 May 2018       |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 09 May 2018       |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

To determine whether adding antiviral treatment to best usual primary care is effective in reducing time to return to usual daily activity

Protection of trial subjects:

Patients were randomised to either usual care or usual care with oseltamivir treatment. Oseltamivir has a well recorded safety profile with minimal side effects and at the start of the trial was classified by the WHO as an essential medicine that had been stockpiled in many countries to treat and prevent seasonal and pandemic influenza.

The Primary Care Clinical Trials Unit (PC-CTU) at the Nuffield Department of Primary Care Health Sciences maintained a dedicated email, answer phone and fax line to allow reporting of all SAEs. Country Co-ordinators ensured the quick follow up of all SAEs within their country, and all SAEs were reported back to the PC-CTU for review by the sponsor and the IDMC.

The trial symptom diary was completed between day 0-14 by the trial participants or their legal guardians. This was a fairly significant burden on the participant, but essential to the trial. We made the diary as streamline and easy to complete as possible and only participants that have the time and ability, or where the legal guardian had the time and ability, to complete the diary were asked to join the trial.

Background therapy: -

Evidence for comparator:

General Practitioners in Europe usually advise patients who consult with ILI to take paracetamol or non-steroidal anti-inflammatory agents (NSAIDs), like ibuprofen, either when required or at regular intervals. They may also provide advice about over the counter remedies, maintaining fluids, bed rest and taking time off work. This broad approach is currently considered best practice for the empirical management of influenza like illness (ILI). ALIC4E included a 'best usual primary care' arm alone, and best usual primary care with oseltamivir treatment. This allowed the study to determine the added benefit of antiviral agents over and above current practice. This is necessary for answering the question about whether or not it is worth adding antiviral treatment to current practice in European primary care, which is important for informing: antiviral prescribing decisions, patients help seeking, self-care strategies and the provision and configuration of primary care services.

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 15 January 2016 |
| 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 | Netherlands: 63 |
| Country: Number of subjects enrolled | Norway: 55      |
| Country: Number of subjects enrolled | Poland: 632     |
| Country: Number of subjects enrolled | Spain: 508      |
| Country: Number of subjects enrolled | Sweden: 69      |

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | United Kingdom: 464 |
| Country: Number of subjects enrolled | Belgium: 609        |
| Country: Number of subjects enrolled | Czech Republic: 95  |
| Country: Number of subjects enrolled | Denmark: 68         |
| Country: Number of subjects enrolled | France: 49          |
| Country: Number of subjects enrolled | Hungary: 216        |
| Country: Number of subjects enrolled | Ireland: 48         |
| Country: Number of subjects enrolled | Lithuania: 239      |
| Country: Number of subjects enrolled | Greece: 125         |
| Country: Number of subjects enrolled | Switzerland: 26     |
| Worldwide total number of subjects   | 3266                |
| EEA total number of subjects         | 3240                |

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)  | 45   |
| Children (2-11 years)                     | 409  |
| Adolescents (12-17 years)                 | 172  |
| Adults (18-64 years)                      | 2431 |
| From 65 to 84 years                       | 204  |
| 85 years and over                         | 5    |

## Subject disposition

### Recruitment

Recruitment details:

21 networks covering 209 primary care practices in 15 European countries randomized 3266 participants over three consecutive influenza seasons: 495 in 2015-16, 1225 in 2016-17, and 1546 in 2017-18.

### Pre-assignment

Screening details:

This was a pragmatic trial with opportunistic recruitment during periods of high influenza. There was no initial screening or pre-assignment period but the participant had to satisfy the eligibility criteria before entering the study. 5501 assessed for eligibility, 2235 excluded and 3266 randomised.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | overall trial (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Not blinded                    |

### Arms

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

Arm description:

Usual care given by practitioners for treatment of ILI

|   |                 |
|---|-----------------|
| Arm type  | No intervention |
| No investigational medicinal product assigned in this arm |                 |

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | Usual care plus oseltamivir |
|------------------|-----------------------------|

Arm description:

This is usual care given by general practitioners plus treatment with oseltamivir

|  |                                     |
|--|-------------------------------------|
| Arm type                               | Active comparator                   |
| Investigational medicinal product name | Oseltamivir                         |
| Investigational medicinal product code | EU/1/02/222/001                     |
| Other name                             | Tamiflu                             |
| Pharmaceutical forms                   | Capsule, Powder for oral suspension |
| Routes of administration               | Oral use                            |

Dosage and administration details:

Adults and children weighing >40 kg who were randomized to intervention and able to swallow capsules were given 75 mg oral oseltamivir twice daily for five days. For those <13 years, oseltamivir was given in oral suspension, according to weight: 10-15 kg = 30 mg; >15-23 kg = 45 mg; >23-40 kg = 60 mg; >40 kg = 75 mg.

| Number of subjects in period 1 | Usual Care | Usual care plus oseltamivir |
|--------------------------------|------------|-----------------------------|
| Started                        | 1637       | 1629                        |
| Completed                      | 1526       | 1533                        |
| Not completed                  | 111        | 96                          |
| Consent withdrawn by subject   | 12         | 18                          |
| missing or conflicting data    | 5          | -                           |
| Lost to follow-up              | 91         | 72                          |

|                    |   |   |
|--------------------|---|---|
| Protocol deviation | 3 | 6 |
|--------------------|---|---|

## Baseline characteristics

### Reporting groups

|   |                             |
|---|-----------------------------|
| Reporting group title   | Usual Care                  |
| Reporting group description:  |                             |
| Usual care given by practitioners for treatment of ILI                            |                             |
| Reporting group title   | Usual care plus oseltamivir |
| Reporting group description:  |                             |
| This is usual care given by general practitioners plus treatment with oseltamivir |                             |

| Reporting group values              | Usual Care | Usual care plus oseltamivir | Total |
|-------------------------------------|------------|-----------------------------|-------|
| Number of subjects                  | 1637       | 1629                        | 3266  |
| Age categorical                     |            |                             |       |
| Units: Subjects                     |            |                             |       |
| 1 to 11 years                       | 223        | 225                         | 448   |
| 12 to 65 years                      | 1306       | 1296                        | 2602  |
| over 65 years                       | 106        | 103                         | 209   |
| Not recorded                        | 2          | 5                           | 7     |
| Age continuous                      |            |                             |       |
| Units: years                        |            |                             |       |
| arithmetic mean                     | 35.4       | 35.5                        |       |
| standard deviation                  | ± 18.7     | ± 18.7                      | -     |
| Gender categorical                  |            |                             |       |
| Units: Subjects                     |            |                             |       |
| Female                              | 904        | 915                         | 1819  |
| Male                                | 731        | 707                         | 1438  |
| Not recorded                        | 2          | 7                           | 9     |
| Use of antipyretics in last 4 hours |            |                             |       |
| Units: Subjects                     |            |                             |       |
| Yes                                 | 879        | 901                         | 1780  |
| No                                  | 756        | 717                         | 1473  |
| Missing                             | 2          | 11                          | 13    |
| Smoking                             |            |                             |       |
| Units: Subjects                     |            |                             |       |
| Yes                                 | 257        | 240                         | 497   |
| No                                  | 1312       | 1303                        | 2615  |
| Occasionally                        | 65         | 78                          | 143   |
| Missing                             | 3          | 8                           | 11    |
| Ethnicity                           |            |                             |       |
| Units: Subjects                     |            |                             |       |
| White                               | 1142       | 1146                        | 2288  |
| Black                               | 6          | 4                           | 10    |
| Hispanic                            | 70         | 75                          | 145   |
| Asian                               | 17         | 14                          | 31    |
| Arabic                              | 12         | 13                          | 25    |
| Other                               | 31         | 48                          | 79    |
| Missing                             | 359        | 329                         | 688   |
| Flu vaccine within 6 months         |            |                             |       |

|  |        |        |      |
|--|--------|--------|------|
| Units: Subjects                                |        |        |      |
| No   | 1477   | 1465   | 2942 |
| Yes  | 156    | 151    | 307  |
| Missing  | 4      | 13     | 17   |
| Co-morbidities                                 |        |        |      |
| Units: Subjects                                |        |        |      |
| No   | 1396   | 1373   | 2769 |
| Yes  | 239    | 251    | 490  |
| Missing  | 2      | 5      | 7    |
| Duration of symptoms                           |        |        |      |
| Duration of ILI symptoms before baseline visit |        |        |      |
| Units: Subjects                                |        |        |      |
| 0 - <=24 hours                                 | 454    | 448    | 902  |
| > 24 - <=48 hours                              | 633    | 616    | 1249 |
| >48 - <=72 hours                               | 548    | 560    | 1108 |
| Missing  | 2      | 5      | 7    |
| Severity of ILI symptoms                       |        |        |      |
| Clinician global severity rating               |        |        |      |
| Units: Subjects                                |        |        |      |
| Mild   | 353    | 340    | 693  |
| Moderate                                       | 985    | 983    | 1968 |
| Severe   | 297    | 301    | 598  |
| Missing  | 2      | 5      | 7    |
| Weight   |        |        |      |
| Units: Kg                                      |        |        |      |
| arithmetic mean                                | 68.1   | 67.2   |      |
| standard deviation                             | ± 24.4 | ± 24.3 | -    |
| Height   |        |        |      |
| Units: cm                                      |        |        |      |
| arithmetic mean                                | 162.4  | 162.1  |      |
| standard deviation                             | ± 22.7 | ± 22.9 | -    |
| Pulse rate                                     |        |        |      |
| Units: beats per minute                        |        |        |      |
| arithmetic mean                                | 87.4   | 87.7   |      |
| standard deviation                             | ± 15.1 | ± 16.1 | -    |
| Temperature                                    |        |        |      |
| Units: degrees celcius                         |        |        |      |
| arithmetic mean                                | 37.5   | 37.6   |      |
| standard deviation                             | ± 0.9  | ± 0.9  | -    |

## End points

### End points reporting groups

|   |                             |
|---|-----------------------------|
| Reporting group title   | Usual Care                  |
| Reporting group description:<br>Usual care given by practitioners for treatment of ILI                            |                             |
| Reporting group title   | Usual care plus oseltamivir |
| Reporting group description:<br>This is usual care given by general practitioners plus treatment with oseltamivir |                             |

### Primary: Model-based estimated mean number of days to recovery

|   |   |
|---|---|
| End point title   | Model-based estimated mean number of days to recovery |
| End point description:<br>The precision/dispersion type is Bayesian Credible Interval (BCI) |   |
| End point type  | Primary   |
| End point timeframe:<br>1 to 28 days  |   |

| End point values            | Usual Care      | Usual care plus oseltamivir |  |  |
|-----------------------------|-----------------|-----------------------------|--|--|
| Subject group type          | Reporting group | Reporting group             |  |  |
| Number of subjects analysed | 1526            | 1533                        |  |  |
| Units: days                 |                 |                             |  |  |
| number (not applicable)     | 6.73            | 5.71                        |  |  |

### Statistical analyses

|  |   |
|--|---|
| Statistical analysis title   | Bayesian piece-wise exponential time-to-event |
| Statistical analysis description:<br>The pre-specified primary analysis was based on a Bayesian piece-wise exponential time-to-event model. The model evaluated the benefit of oseltamivir in the overall intention-to-treat study population; the oseltamivir arm was declared superior if the Bayesian posterior probability that oseltamivir is better than usual care alone exceeded 0.975 |   |
| Comparison groups  | Usual Care v Usual care plus oseltamivir      |
| Number of subjects included in analysis  | 3059  |
| Analysis specification   | Pre-specified                                 |
| Analysis type  | superiority                                   |
| Parameter estimate   | Hazard ratio (HR)                             |
| Point estimate   | 1.29  |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided                                       |
| lower limit  | 1.2   |
| upper limit  | 1.39  |



| <div>Variability estimate</div> | <div>Standard error of the mean</div> |
|---------------------------------|---------------------------------------|
|---------------------------------|---------------------------------------|

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

All Serious Adverse Events (SAEs) occurring during the 28 days participants were enrolled on the trial were recorded.

Adverse event reporting additional description:

Oseltamivir has a well documented safety profile and is a commonly used medication in a primary care setting. As a result of this no non-serious adverse events were recorded in this study.

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

### Dictionary used

|                 |           |
|-----------------|-----------|
| Dictionary name | none used |
|-----------------|-----------|

|                    |   |
|--------------------|---|
| Dictionary version | 0 |
|--------------------|---|

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Usual Care |
|-----------------------|------------|

Reporting group description:

Usual care given by practitioners for treatment of ILI

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Usual care plus oseltamivir |
|-----------------------|-----------------------------|

Reporting group description:

This is usual care given by general practitioners plus treatment with oseltamivir

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Oseltamivir has a well documented safety profile and is a commonly used medication in a primary care setting. As a result of this no non-serious adverse events were recorded in this study.

| Serious adverse events                            | Usual Care  | Usual care plus oseltamivir |  |
|---|---|-----------------------------|--|
| Total subjects affected by serious adverse events |   |                             |  |
| subjects affected / exposed                       | 17 / 1635 (1.04%)   | 12 / 1624 (0.74%)           |  |
| number of deaths (all causes)                     | 0   | 0                           |  |
| number of deaths resulting from adverse events    | 0   | 0                           |  |
| Injury, poisoning and procedural complications    |   |                             |  |
| Overdose  | Additional description: paracetamol                             |                             |  |
| subjects affected / exposed                       | 1 / 1635 (0.06%)  | 0 / 1624 (0.00%)            |  |
| occurrences causally related to treatment / all   | 0 / 1   | 0 / 0                       |  |
| deaths causally related to treatment / all        | 0 / 0   | 0 / 0                       |  |
| Surgical and medical procedures                   |   |                             |  |
| Amputation  | Additional description: Ischaemic left leg requiring amputation |                             |  |
| subjects affected / exposed                       | 0 / 1635 (0.00%)  | 1 / 1624 (0.06%)            |  |
| occurrences causally related to treatment / all   | 0 / 0   | 1 / 1                       |  |
| deaths causally related to treatment / all        | 0 / 0   | 0 / 0                       |  |
| Lung operation                                    | Additional description: excision of lung carcinoma              |                             |  |

|   |  |                  |  |
|---|--|------------------|--|
| subjects affected / exposed                     | 1 / 1635 (0.06%)                                     | 0 / 1624 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Blood and lymphatic system disorders            |  |                  |  |
| Hypertension                                    |  |                  |  |
| subjects affected / exposed                     | 0 / 1635 (0.00%)                                     | 1 / 1624 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Immune system disorders                         |  |                  |  |
| Guillain-Barre syndrome                         |  |                  |  |
| subjects affected / exposed                     | 1 / 1635 (0.06%)                                     | 0 / 1624 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Social circumstances                            |  |                  |  |
| Hospitalisation                                 |  |                  |  |
|   | Additional description: planned visit                |                  |  |
| subjects affected / exposed                     | 0 / 1635 (0.00%)                                     | 1 / 1624 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Reproductive system and breast disorders        |  |                  |  |
| Ovarian cyst                                    |  |                  |  |
| subjects affected / exposed                     | 0 / 1635 (0.00%)                                     | 1 / 1624 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Respiratory, thoracic and mediastinal disorders |  |                  |  |
| Asthma  |  |                  |  |
| subjects affected / exposed                     | 2 / 1635 (0.12%)                                     | 0 / 1624 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2  | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Chest pain                                      |  |                  |  |
|   | Additional description: and shortness of breath      |                  |  |
| subjects affected / exposed                     | 0 / 1635 (0.00%)                                     | 1 / 1624 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Laryngospasm                                    |  |                  |  |
|   | Additional description: causing difficulty breathing |                  |  |

|   |  |                  |  |
|---|--|------------------|--|
| subjects affected / exposed                     | 1 / 1635 (0.06%)   | 0 / 1624 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Skin and subcutaneous tissue disorders          |  |                  |  |
| Hypersensitivity vasculitis                     | Additional description: Leukocytoclastic vasculitis      |                  |  |
| subjects affected / exposed                     | 1 / 1635 (0.06%)   | 0 / 1624 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Urticaria                                       |  |                  |  |
| subjects affected / exposed                     | 0 / 1635 (0.00%)   | 1 / 1624 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Musculoskeletal and connective tissue disorders |  |                  |  |
| Hip fracture                                    |  |                  |  |
| subjects affected / exposed                     | 0 / 1635 (0.00%)   | 1 / 1624 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Lower limb fracture                             | Additional description: broken leg after slipping on ice |                  |  |
| subjects affected / exposed                     | 1 / 1635 (0.06%)   | 0 / 1624 (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                     |  |                  |  |
| Otitis media                                    |  |                  |  |
| subjects affected / exposed                     | 1 / 1635 (0.06%)   | 0 / 1624 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Tonsillitis                                     |  |                  |  |
| subjects affected / exposed                     | 0 / 1635 (0.00%)   | 1 / 1624 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Influenza                                       |  |                  |  |
| subjects affected / exposed                     | 1 / 1635 (0.06%)   | 0 / 1624 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| Meningitis                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 1635 (0.00%) | 1 / 1624 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Meningitis viral                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 1635 (0.06%) | 0 / 1624 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peritonsillar abscess                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 1635 (0.06%) | 0 / 1624 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumonia                                       |                  |                  |  |
| subjects affected / exposed                     | 5 / 1635 (0.31%) | 3 / 1624 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

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

| <b>Non-serious adverse events</b>                     | Usual Care       | Usual care plus oseltamavir |  |
|---|------------------|-----------------------------|--|
| Total subjects affected by non-serious adverse events |                  |                             |  |
| subjects affected / exposed                           | 0 / 1635 (0.00%) | 0 / 1624 (0.00%)            |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 24 March 2015     | Removal of Nitazoxanide   |
| 26 May 2015       | Correction of Creatinine GFR unit in exclusion criteria, Clarification of SAE Reporting, Clarification of publication policy, Correction of country codes list  |
| 29 September 2015 | Correction of weight categories for children's medication   |
| 16 December 2015  | Changes to statistical analysis, change to primary end point for non-verbal children, addition of bacterial analysis for swabs, determination start of the influenza period, addition of OOH recruiting sites |
| 01 August 2016    | Change to statistics section – moving detail to SAP, change to sample size to 2500-4000, clarification of SAE reporting, UK Study Within A Trial (SWAT)   |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported