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
Arm title	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

Arm title	Usual care plus oseltmavir

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 oseltmavir
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 oseltmavir
Reporting group description:	
This is usual care given by general practitioners plus treatment with oseltamivir	

Reporting group values	Usual Care	Usual care plus oseltmavir	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:	
Usual care given by practitioners for treatment of ILI	
Reporting group title	Usual care plus oseltmavir
Reporting group description:	
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:	
The precision/dispersion type is Bayesian Credible Interval (BCI)	
End point type	Primary
End point timeframe:	
1 to 28 days	

End point values	Usual Care	Usual care plus oseltmavir		
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:	
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 oseltmavir
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

Variability estimate	Standard error of the mean

Adverse events

Adverse events information[1]

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 oseltmavir

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 oseltmavir	
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: paracetemol		
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 %

Non-serious adverse events	Usual Care	Usual care plus oseltmavir	
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:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported