Clinical trial results:
Anti-viral prophylaxis for prevention of cytomegalovirus (CMV) reactivation in immunocompetent patients in critical care.

Summary

EudraCT number	2010-024646-30
Trial protocol	GB
Global end of trial date	19 January 2017

Results information

Result version number	v1 (current)
This version publication date	28 December 2019
First version publication date	28 December 2019
Summary attachment (see zip file)	Antiviral drugs suppress CMV reactivation in critically ill adults JAMA Int Med 2017 (CMV reactivation suppression in critically ill adults JAMA-IM 2017.pdf) CMV suppression trial statistical report (4C statistical report FINAL March 10th 2015.pdf)

Trial information

Trial identification

Sponsor protocol code	CCCC_CMV_protocol

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01503918
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospitals Birmingham
Sponsor organisation address	Edgbaston, Birmingham, United Kingdom, B15 2TH
Public contact	Professor Julian Bion, University of Birmingham, 0044 (0)1213716816, J.F.Bion@bham.ac.uk
Scientific contact	Professor Julian Bion, University of Birmingham, 0044 (0)1213716816, J.F.Bion@bham.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	19 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 January 2014
Global end of trial reached?	Yes
Global end of trial date	19 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Does the use of antiviral prophylaxis using valganciclovir or valaciclovir effectively and safely suppress cytomegalovirus reactivation in critically ill patients in intensive care?

Protection of trial subjects:

Patients were critically ill, undergoing mechanical ventilation in an intensive care unit. They received 24/7 1:1 nursing care with a minimum of twice daily consultant review.
During the study we observed an imbalance in hospital mortality rates, with an unexpectedly low mortality rate in the controls, and high in the group assigned to aciclovir. We undertook an independent blinded case record review and could find no explanation for the mortality difference other than severity of illness: all deaths were expected. After discussion with the Data Monitoring Committee we suspended further recruitment to the aciclovir arm, continuing recruitment to the ganciclovir group.

Background therapy:

All patients received life supporting treatments and drugs as part of their standard care in the ICU.

Evidence for comparator:

Patients were randomly assigned to continue standard intensive care treatments, or to standard treatments with the addition of either aciclovir or ganciclovir.

Actual start date of recruitment	30 January 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 124
Worldwide total number of subjects	124
EEA total number of subjects	124

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	80
From 65 to 84 years	42
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Informed consent was obtained from patient representatives using a two-stage procedure, first for sampling to determine CMV status, and then for those who were CMV antibody negative, consent to participate in the trial of antiviral prophylaxis. Accruals started in January 2012 and finished in January 2014.

Pre-assignment

Screening details:

Patients were eligible for the study if they were seropositive for CMV, already in the ICU for more than 24 hours, and mechanically ventilated, with the ICU stay and mechanical ventilation anticipated to continue for at least 48 hours.

Period 1

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

Blinding implementation details:

Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Control

Arm description:

Standard care

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Intervention Goups: Valaciclovir/acyclovir or valganciclovir

Arm description:

Patients randomized to the valacyclovir hydrochloride arm received2g4times a day by the enteral route. Patients unable to receive enteral medication received intravenous aciclovir sodium, 10 mg/kg of ideal body weight, 3 times a day until they were able to receive enteral medication.

Patients randomized to the valganciclovir hydrochloride arm received 450mg once a day by the enteral route. Patients in this group who were unable to receive enteral medication received intravenous ganciclovir sodium, 2.5mg/kg ideal body weight, once a day until they were able to receive enteral medication

Arm type	Experimental
Investigational medicinal product name	Valaciclovir/acyclovir
Investigational medicinal product code	n/a
Other name	
Pharmaceutical forms	Tablet, Injection
Routes of administration	Intravascular use , Enteral use

Dosage and administration details:

Patients randomized to the valacyclovir hydrochloride arm received2g4times a day by the enteral route. Patients unable to receive enteral medication received intravenous aciclovir sodium, 10 mg/kg of ideal body weight, 3 times a day until they were able to receive enteral medication.

Investigational medicinal product name	Valganciclovir hydrochloride
Investigational medicinal product code	n/a
Other name	

Pharmaceutical forms	Injection, Tablet
Routes of administration	Enteral use , Intravascular use

Dosage and administration details:

Patients randomized to the valganciclovir hydrochloride arm received 450mg once a day by the enteral route.
Patients in this group who were unable to receive enteral medication received intravenous ganciclovir sodium,
2.5mg/kg ideal body weight, once a day until they were able to receive enteral medication.

Number of subjects in period 1	Control	Intervention Goups: Valaciclovir/acyclovir or valganciclovir
Started	44	80
Completed	44	80

Baseline characteristics

Reporting groups	
Reporting group title	Control
Reporting group description: Standard care	
Reporting group title	Intervention Goups: Valaciclovir/acyclovir or valganciclovir
Reporting group description: Patients randomized to the valacyclovir hydrochloride arm received2g4times a day by the enteral route. Patients unable to receive enteral medication received intravenous aciclovir sodium, 10 mg/kg of ideal body weight, 3 times a day until they were able to receive enteral medication. Patients randomized to the valganciclovir hydrochloride arm received 450mg once a day by the enteral route. Patients in this group who were unable to receive enteral medication received intravenous ganciclovir sodium, 2.5mg/kg ideal body weight, once a day until they were able to receive enteral medication	

Reporting group values	Control	Intervention Goups: Valaciclovir/acyclovir or valganciclovir	Total
Number of subjects	44	80	124
Age categorical Units: Subjects			
Adults 18-64 years	32	48	80
Adults 65-84 years	11	31	42
Adults 85 years and over	1	1	2
Age continuous Units: years			
arithmetic mean	55	58	
standard deviation	± 17	± 16.8	-
Gender categorical Units: Subjects			
Female	21	25	46
Male	23	55	78

End points

End points reporting groups

Reporting group title	Control
Reporting group description:	
Standard care	
Reporting group title	Intervention Goups: Valaciclovir/acyclovir or valganciclovir
Reporting group description:	
Patients randomized to the valacyclovir hydrochloride arm received2g4times a day by the enteral route. Patients unable to receive enteral medication received intravenous aciclovir sodium, 10 mg/kg of ideal body weight, 3 times a day until they were able to receive enteral medication. Patients randomized to the valganciclovir hydrochloride arm received 450mg once a day by the enteral route. Patients in this group who were unable to receive enteral medication received intravenous ganciclovir sodium, 2.5mg/kg ideal body weight, once a day until they were able to receive enteral medication	

Primary: time to first reactivation ofCMVin blood (defined as above the lower limit of the qPCR assay[20 copies/mL])

End point title	time to first reactivation ofCMVin blood (defined as above the lower limit of the qPCR assay[20 copies/mL])
End point description:	
End point type	Primary
End point timeframe:	
28 days or until hospital discharge if earlier	

End point values	Control	Intervention Goups: Valaciclovir/acyclovir or valganciclovir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	80		
Units: >20 copies/mL]				
number (not applicable)	12	1		

Statistical analyses

Statistical analysis title	Analysis
Statistical analysis description:	
All analyses were performed on an intention-totreat principle, whereby patients included in the analysiswere analyzed according to the treatment group to which theywere randomized regardless of whether they received this treatment. As the primary outcome of the study was to measure the efficacy of antiviral drugs to preventCMVreactivation, patientswere excluded fromthe analyses ofCMVviral load if viral reactivation had already taken place before initiation of the	

study drug on the day

Comparison groups	Control v Intervention Goups: Valaciclovir/acyclovir or valganciclovir
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Confidence interval	
level	95 %
sides	1-sided
Variability estimate	Standard deviation

Notes:

[1] - All analyses were performed on an intention-totreat principle, whereby patients included in the analysiswere analyzed according to the treatment group to which theywere randomized regardless of whether they received this treatment. As the primary outcome of the study was to measure the efficacy of antiviral drugs to preventCMVreactivation, patientswere excluded fromthe analyses ofCMVviral load if viral reactivation had already taken place before initiation of the study drug on the day of

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Up to 28 days following recruitment

Adverse event reporting additional description:

Recruitment into the valacyclovir arm stopped prematurely in September2013, following an interim analysis presented to the independentDataMonitoringCommittee, which advised that this arm be closed because of significantly higher mortality in this group.

Assessment type	Systematic

Dictionary used

Dictionary name	Study-specific
Dictionary version	1

Reporting groups

Reporting group title	Control
Reporting group description: -	
Reporting group title	Valaciclovir
Reporting group description: -	
Reporting group title	Valganciclovir
Reporting group description: -	

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: Please refer to the publication.

Serious adverse events	Control	Valaciclovir	Valganciclovir
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 44 (15.91%)	10 / 34 (29.41%)	16 / 46 (34.78%)
number of deaths (all causes)	7	14	10
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Mortality	Additional description: See description of increased mortality in aciclovir group		
subjects affected / exposed	7 / 44 (15.91%)	10 / 34 (29.41%)	16 / 46 (34.78%)
occurrences causally related to treatment / all	4 / 7	9 / 10	15 / 16
deaths causally related to treatment / all	2 / 7	2 / 14	3 / 10

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Control	Valaciclovir	Valganciclovir
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 44 (0.00%)	0 / 34 (0.00%)	0 / 46 (0.00%)

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 September 2013	Recruitment into the valacyclovir arm stopped prematurely in September2013, following an interim analysis presentedto the independentDataMonitoringCommittee, which advised that this arm be closed because of significantly higher mortality in this group.At this point, 34 participantshadbeen recruitedinto the valacyclovir arm, 14 (41.2%;95%CI, 24.6%-57.7%)ofwhom had died by 28 days, comparedwith 5 of 37 participants (13.5%; 95% CI, 2.5%-24.5%) in the control arm and 7 of 34 participants (20.6%; 95%CI, 7.0%-34.2%) in the valganciclovir arm. To investigate potential associations between valacyclovir and cause of death, an independent case record review was performed. Reviewers were intensive care physicians independent of the study team; each set of case notes was examined by 2 reviewers blinded to groupallocation.Thereviewers identified all deaths as expected and attributable to the underlying disease. By the end of the study, mortality in the control group increased from13.5%to 15.9%(7 of 44 participants) for 28-day mortality and to 20.5% (9 of 44 participants) for inhospital mortality.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This is a pilot proof of principle study undetaken to determine whether it would be appropriate to undertake a large-scale RCT.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28437539