Clinical trial results:
Favipiravir, lopinavir/ritonavir or combination therapy: a randomised, double blind, 2x2 factorial placebo-controlled trial of early antiviral therapy in COVID-19

Summary

EudraCT number	2020-002106-68
Trial protocol	GB
Global end of trial date	10 January 2022

Results information

Result version number	v1 (current)
This version publication date	26 January 2023
First version publication date	26 January 2023

Trial information

Trial identification

Sponsor protocol code	CTU/2020/354

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04499677
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Gower Street,, London, United Kingdom, WC1E 6BT
Public contact	CCTU enquires, The Comprehensive Clinical Trials Unit, University College London , 44 0207907466, cctu.enquires@ucl.ac.uk
Scientific contact	CCTU enquires, The Comprehensive Clinical Trials Unit, University College London , 44 02079074669, cctu.enquires@ucl.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	03 December 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 December 2021
Global end of trial reached?	Yes
Global end of trial date	10 January 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial is to assess whether early antiviral therapy with either favipiravir + LPV/r, LPV/r or favipiravir is associated with a decrease in viral load in the upper respiratory tract after 5 days of therapy, compared with placebo.

Protection of trial subjects:

The trial was conducted in compliance with the approved protocol, the Declaration of Helsinki (2008),the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the Human Tissue (Quality and Safety for Human Application) Regulations 2007, the UK Data Protection Act, and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF). Participants were provided trial treatment for a 7-day period , and remained on the trial for a total of 28 days. Averse Events were collected throughout the trial and treated accordingly. As participation was voluntary, participants were free to discontinue at any given time without giving reason and without it affecting their normal standard of care.

Background therapy:

N/A

Evidence for comparator: -

Actual start date of recruitment	24 July 2020
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: 240
Worldwide total number of subjects	240
EEA total number of subjects	0

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)	236
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants aged between 18 and 70 years who had recently (within the last 5 days) developed symptoms of COVID-19, or who had tested positive for SARS-CoV-2 by polymerase chain reaction (PCR) and were within 7 days of symptom onset, or who were asymptomatic but had tested positive by PCR within the previous 48 hours, were recruited in 2 UK sites.

Pre-assignment

Screening details:

A pre-screening visit (usually by telephone) briefly assessed eligibility and collected the following information: study site, age , sex, height and weight, symptomatic or asymptomatic, current smoking status, ethnicity, previous COVID-19 specific vaccination, and presence/absence of the following comorbidities

Pre-assignment period milestones

Number of subjects started	1215[1]
Number of subjects completed	240

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 637
Reason: Number of subjects	Ineligible: 338

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The pre-assignment period is the screening phase on this trial. Patients are considered enrolled when they are randomised to a treatment after being deemed eligible..

Period 1

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

Blinding implementation details:

Trial medication kits, prepared by RenaClinical, were coded to maintain double blinding (investigators and participants). Kits contained favipiravir or colour and size matched placebo 200-mg tablets supplied by Fujifilm Toyama Chemical Co. and lopinavir-ritonavir 200-mg/50-mg tablets (AbbVie) or colour and size matched placebos (RenaClinical).

Arms

Are arms mutually exclusive?	Yes
Arm title	Favipiravir+LPV/r

Arm description: -

Arm type	Experimental
Investigational medicinal product name	favipiravir and lopinavir/ritonavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral favipiravir 1800 mg twice daily on Day 1, followed by 400 mg four (4) times daily from Day 2 to Day 7 PLUS Lopinavir/ritonavir (LPV/r) at 400mg/100 mg twice daily on Day 1 followed by 200mg/50mg four (4) times daily from Day 2 to Day 7.

Arm title	Favipiravir+Placebo
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	favipiravir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral favipiravir, 1800 mg twice daily on Day 1, followed by 400 mg four (4) times daily from Day 2 to Day 7 PLUS Lopinavir/ritonavir (LPV/r) matched placebo at 400mg/100 mg twice daily on Day 1, followed by 200mg/50mg four (4) times daily from Day 2 to Day 7.

Arm title	LPV/r+Placebo
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	lopinavir/ritonavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral favipiravir matched placebo 1800 mg twice daily on Day 1, followed by 400 mg four (4) times daily from Day 2 to Day 7 PLUS Lopinavir/ritonavir (LPV/r) at 400mg/100 mg twice daily on Day 1, followed by 200mg/50mg four (4) times daily from Day 2 to Day 7.

Arm title	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	favipiravir placebo and lopinavir/ritonavir placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral favipiravir matched placebo 1800 mg twice daily on Day 1, followed by 400 mg four (4) times daily from Day 2 to Day 7 PLUS Lopinavir/ritonavir (LPV/r) matched placebo at 400mg/100 mg twice daily on Day 1 followed by 200mg/50mg four (4) times daily from Day 2 to Day 7.

Number of subjects in period 1	Favipiravir+LPV/r	Favipiravir+Placebo	LPV/r+Placebo
Started	61	59	60
Completed	55	56	55
Not completed	6	3	5
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	5	2	3
Missing primary outcome	1	1	-
Lost to follow-up	-	-	1

Number of subjects in period 1	Placebo

Started	60
Completed	58
Not completed	2
Consent withdrawn by subject	-
Adverse event, non-fatal	-
Missing primary outcome	1
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Favipiravir+LPV/r
Reporting group description: -	
Reporting group title	Favipiravir+Placebo
Reporting group description: -	
Reporting group title	LPV/r+Placebo
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Favipiravir+LPV/r	Favipiravir+Placebo	LPV/r+Placebo
Number of subjects	61	59	60
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	40.3	40.3	38.6
standard deviation	± 13.1	± 12.1	± 11.5
Gender categorical Units: Subjects			
Female	30	27	31
Male	31	32	29
Site Units: Subjects			
Royal Free	56	55	55
UCLH	5	4	5
Age Units: Subjects			
≤ 55 years	53	52	55
> 55 years	8	7	5
Ethnicity Units: Subjects			
Caucasian	50	49	49
Other	11	10	11
BMI Units: Subjects			

<30	51	49	50
≥30	10	10	10
Symptomatic disease Units: Subjects			
Yes	61	59	60
No	0	0	0
Current smoker Units: Subjects			
Yes	6	7	7
No	55	52	53
Vaccinated Units: Subjects			
Yes	32	30	31
No	29	29	29
Comorbidity Units: Subjects			
Present	11	9	8
Absent	50	50	52

Reporting group values	Placebo	Total	
Number of subjects	60	240	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	40.6		
standard deviation	± 12.2	-	
Gender categorical Units: Subjects			
Female	29	117	
Male	31	123	
Site Units: Subjects			
Royal Free	55	221	
UCLH	5	19	
Age Units: Subjects			
≤ 55 years	55	215	
> 55 years	5	25	
Ethnicity Units: Subjects			

Caucasian	49	197	
Other	11	43	
BMI Units: Subjects			
<30	50	200	
≥30	10	40	
Symptomatic disease Units: Subjects			
Yes	59	239	
No	1	1	
Current smoker Units: Subjects			
Yes	7	27	
No	53	213	
Vaccinated Units: Subjects			
Yes	30	123	
No	30	117	
Comorbidity Units: Subjects			
Present	8	36	
Absent	52	204	

End points

End points reporting groups	
Reporting group title	Favipiravir+LPV/r
Reporting group description: -	
Reporting group title	Favipiravir+Placebo
Reporting group description: -	
Reporting group title	LPV/r+Placebo
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Viral load	
End point title	Viral load
End point description:	
End point type	Primary
End point timeframe:	
Measured at baseline (Day 1) and at Day 5.	

End point values	Favipiravir+LPV/r	Favipiravir+Placebo	LPV/r+Placebo	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	55	56	55	58
Units: log 10				
arithmetic mean (standard deviation)	2.5 (± 2.1)	1.9 (± 2.0)	2.5 (± 2.0)	2.7 (± 2.2)

Statistical analyses

Statistical analysis title	Primary outcome analysis
Comparison groups	Placebo v Favipiravir+Placebo
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Slope
Point estimate	-0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.21
upper limit	0.07

Statistical analysis title	Primary outcome analysis
Comparison groups	Placebo v LPV/r+Placebo
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Slope
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.82
upper limit	0.46

Statistical analysis title	Primary outcome analysis
Comparison groups	Placebo v Favipiravir+LPV/r
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Slope
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	1.5

Secondary: Undetected viral load	
End point title	Undetected viral load
End point description:	

End point type	Secondary
End point timeframe:	
At Day 5.	

End point values	Favipiravir+LPV/r	Favipiravir+Placebo	LPV/r+Placebo	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	51	51	51
Units: Patients				
Yes	20	25	17	14
No	34	26	34	37

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Comparison groups	Placebo v Favipiravir+Placebo
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	5.65

Statistical analysis title	Secondary outcome analysis
Comparison groups	Placebo v LPV/r+Placebo
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	3

Statistical analysis title	Secondary outcome analysis
Comparison groups	Placebo v Favipiravir+LPV/r

Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	1.66

Other pre-specified: Viral load - adjusted for minimisation factors

End point title	Viral load - adjusted for minimisation factors
End point description:	

End point type	Other pre-specified
End point timeframe:	
From Day 1 to Day 5.	

End point values	Favipiravir+LPV/r	Favipiravir+Placebo	LPV/r+Placebo	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56	56	55	58
Units: log 10				
arithmetic mean (standard deviation)	2.6 (± 2.1)	1.9 (± 2.0)	2.5 (± 2.0)	2.7 (± 2.2)

Statistical analyses

Statistical analysis title	Sensitivity analysis
Comparison groups	Placebo v Favipiravir+Placebo
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Slope
Point estimate	-0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.16
upper limit	0.02

Statistical analysis title	Sensitivity analysis
Comparison groups	Placebo v LPV/r+Placebo
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Log risk ratio
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.73
upper limit	0.45

Statistical analysis title	Sensitivity analysis
Comparison groups	Placebo v Favipiravir+LPV/r
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Slope
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	1.46

Other pre-specified: Viral load - mITT population	
End point title	Viral load - mITT population
End point description:	

End point type	Other pre-specified
End point timeframe:	
From Day 1 to Day 5.	

End point values	Favipiravir+LPV/r	Favipiravir+Placebo	LPV/r+Placebo	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	51	51	52
Units: log 10				
arithmetic mean (standard deviation)	2.6 (± 2.1)	2.1 (± 2.0)	2.7 (± 2.0)	3.0 (± 2.1)

Statistical analyses

Statistical analysis title	Sensitivity analysis - mitt population
Comparison groups	Placebo v Favipiravir+Placebo
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Slope
Point estimate	-0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.29
upper limit	0.11

Statistical analysis title	Sensitivity analysis - mitt population
Comparison groups	LPV/r+Placebo v Placebo
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Slope
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.87
upper limit	0.51

Statistical analysis title	Sensitivity analysis - mitt population
Comparison groups	Favipiravir+LPV/r v Placebo

Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Slope
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	1.63

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From Day 1 to Day 28.	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	5

Reporting groups	
Reporting group title	Favipravir + LPV/r
Reporting group description: -	
Reporting group title	Favipravir + Placebo
Reporting group description: -	
Reporting group title	LPV/r + Placebo
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Favipravir + LPV/r	Favipravir + Placebo	LPV/r + Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 61 (1.64%)	1 / 59 (1.69%)	1 / 60 (1.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 59 (1.69%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia viral			
subjects affected / exposed	1 / 61 (1.64%)	0 / 59 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 60 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from			

adverse events			
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia viral			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Favipravir + LPV/r	Favipravir + Placebo	LPV/r + Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 61 (90.16%)	38 / 59 (64.41%)	59 / 60 (98.33%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 61 (9.84%)	1 / 59 (1.69%)	1 / 60 (1.67%)
occurrences (all)	6	1	1
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 61 (6.56%)	0 / 59 (0.00%)	1 / 60 (1.67%)
occurrences (all)	4	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 61 (9.84%)	7 / 59 (11.86%)	4 / 60 (6.67%)
occurrences (all)	6	7	4
Anosmia			
subjects affected / exposed	5 / 61 (8.20%)	3 / 59 (5.08%)	8 / 60 (13.33%)
occurrences (all)	5	3	9
Dysgeusia			
subjects affected / exposed	3 / 61 (4.92%)	4 / 59 (6.78%)	6 / 60 (10.00%)
occurrences (all)	3	4	6
Dizziness			

subjects affected / exposed	4 / 61 (6.56%)	1 / 59 (1.69%)	6 / 60 (10.00%)
occurrences (all)	4	1	6
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 61 (6.56%)	4 / 59 (6.78%)	7 / 60 (11.67%)
occurrences (all)	4	4	7
Non-cardiac chest pain			
subjects affected / exposed	4 / 61 (6.56%)	0 / 59 (0.00%)	1 / 60 (1.67%)
occurrences (all)	4	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	38 / 61 (62.30%)	8 / 59 (13.56%)	44 / 60 (73.33%)
occurrences (all)	41	8	47
Nausea			
subjects affected / exposed	16 / 61 (26.23%)	12 / 59 (20.34%)	28 / 60 (46.67%)
occurrences (all)	16	13	28
Vomiting			
subjects affected / exposed	8 / 61 (13.11%)	1 / 59 (1.69%)	6 / 60 (10.00%)
occurrences (all)	8	1	6
Abdominal pain			
subjects affected / exposed	2 / 61 (3.28%)	3 / 59 (5.08%)	2 / 60 (3.33%)
occurrences (all)	2	3	2
Dyspepsia			
subjects affected / exposed	3 / 61 (4.92%)	0 / 59 (0.00%)	2 / 60 (3.33%)
occurrences (all)	3	0	2
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	5 / 61 (8.20%)	6 / 59 (10.17%)	7 / 60 (11.67%)
occurrences (all)	5	6	7
Cough			
subjects affected / exposed	2 / 61 (3.28%)	4 / 59 (6.78%)	4 / 60 (6.67%)
occurrences (all)	2	5	4
Nasal congestion			
subjects affected / exposed	1 / 61 (1.64%)	3 / 59 (5.08%)	1 / 60 (1.67%)
occurrences (all)	1	3	1
Rhinorrhea			

subjects affected / exposed	2 / 61 (3.28%)	0 / 59 (0.00%)	0 / 60 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	2 / 61 (3.28%)	4 / 59 (6.78%)	1 / 60 (1.67%)
occurrences (all)	2	4	1
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	3 / 61 (4.92%)	2 / 59 (3.39%)	1 / 60 (1.67%)
occurrences (all)	3	2	1
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	2 / 61 (3.28%)	1 / 59 (1.69%)	7 / 60 (11.67%)
occurrences (all)	2	1	7

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 60 (65.00%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 60 (10.00%)		
occurrences (all)	6		
Anosmia			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	5		
Dysgeusia			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		
Dizziness			

subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 60 (10.00%)		
occurrences (all)	7		
Non-cardiac chest pain			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	2		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	10 / 60 (16.67%)		
occurrences (all)	10		
Nausea			
subjects affected / exposed	6 / 60 (10.00%)		
occurrences (all)	6		
Vomiting			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	2		
Abdominal pain			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	5		
Dyspepsia			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	6 / 60 (10.00%)		
occurrences (all)	6		
Cough			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	5		
Nasal congestion			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	2		
Rhinorrhea			

subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 3		
Skin and subcutaneous tissue disorders Rash maculo-papular subjects affected / exposed occurrences (all)	 2 / 60 (3.33%) 2		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	 3 / 60 (5.00%) 3		
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	 2 / 60 (3.33%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 October 2020	Broadening the entry criteria from key workers and their household contacts to all adults aged 18-70 years as the population at risk has expanded. Specifying that participants can attend for recruitment visits in a designated area of the hospital site (with appropriate precautions), rather than only as a home visit. Specifying a maximum recommended paracetamol dose of 3g daily, as recommended by the manufacturers of favipiravir. Amending some details relating to the laboratory processing of samples for pharmacokinetic analysis specifying that sample inactivation should be with ethanol rather than heat, and that storage temperature can be at -20 C or below. Updating the statistical analysis methods with no changes to the participant numbers, endpoints or the running of the trial.
26 January 2021	• Change to the eligibility criteria to exclude participants who have received COVID-19 vaccination • Clarification that participants will not undergo safety blood tests at their Day 14 visit if no significantly abnormal results are observed for safety bloods tests taken at Day 7. This change is intended to limit the number of blood tests required of participants and therefore to facilitate an increase in the number of those consenting by removing one potential barrier (as venepuncture is often unpopular with trial participants). This change poses no increased risk to participant's safety. • Addition of flexibility windows to the trial visits in order to accommodate sites where the research staff do not work during weekends • Removal of collection of serum for storage and stool samples at Day 14 visit • Updated secondary outcomes to reflect changes at Day 14 visit • Addition of guidance for sites where unused trial medication cannot be destroyed or disposed by Pharmacy as part of the site local policy for COVID-19 trials. • Clarification regarding participants who start Day 1 of dosing but are deemed ineligible following results from safety bloods collected at Screening/Baseline visit. • Addition of guidance for sites contacting participants lost to follow-up • Clarification to when the participants will be considered as fully randomised

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.

13 participants withdrew from the trial and a further 28 discontinued medication but provided samples for analysis.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33685502

http://www.ncbi.nlm.nih.gov/pubmed/36260627