Clinical trial results:
Response guided therapy with sofosbuvir and velpatasvir for 12 or 24 weeks in patients with genotype 3 chronic hepatitis C virus: is longer therapy worthwhile?

Summary

EudraCT number	2016-000599-87
Trial protocol	GB
Global end of trial date	04 April 2019

Results information

Result version number	v1 (current)
This version publication date	29 March 2020
First version publication date	29 March 2020

Trial information

Trial identification

Sponsor protocol code	011094

Additional study identifiers

ISRCTN number	ISRCTN16857338
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Queen Mary University of London
Sponsor organisation address	Joint Research Management Office, 5 Walden Street, Queen Mary Innovation Centre , London , United Kingdom, E1 2EF
Public contact	Dr Sally Burtles, Queen Mary University of London, 44 02078827260, sponsorsrep@bartshealth.nhs.uk
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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	26 July 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 April 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This trial will study the treatment effectiveness of sofosbuvir/velpatasvir for 12 or 24 weeks, in patients infected with genotype 3 hepatitis C virus (HCV), with advanced liver disease (cirrhosis), who are slow responders to treatment with persistent virus after the first two weeks of treatment.

This trial will answer if identifying patients by their viral response during treatment (whether the virus is cleared after the first two weeks) can guide the duration of therapy required to achieve cure.

Protection of trial subjects:

The main trial intervention is the allocation of different durations of the treatment sofosbuvir/velpatasvir to patients. Other trial procedures (such as blood tests and clinical examination) are in line with standard clinical practice.

Regarding the drug treatment, the 12 week duration is standard of care while the 24 week duration is the test treatment. Available data has not shown any significant increase in adverse events in patients taking longer durations of treatment.

For patients who have decompensated cirrhosis (that is, the most advanced stage of liver cirrhosis), the standard of care treatment is 12 weeks of sofosbuvir/ velpatasvir, plus an additional drug ribavirin, which has been shown to improve likelihood of viral cure. For this trial, patients with decompensated cirrhosis are invited to participate only if their clinicians deem them unsuitable for ribavirin use, since it is unclear if the trial treatment (12 or 24 weeks of sofosbuvir/velpatasvir without ribavirin)

Background therapy:

Sofosbuvir/velpatsvir is a combined oral tablet of two medicines. The trial supply is purchased from the manufacturer Gilead. Sofosbuvir/velpatasvir is licensed in the EU for the treatment of all genotypes (subtypes) of chronic HCV infection. In most patients the licensed duration of treatment is 12 weeks. In genotype 3 HCV infection, which this trial investigates, the license recommendation is to consider the addition of ribavirin in patients with compensated cirrhosis, and to add ribavirin in patients with decompensated cirrhosis.

This study investigates ribavirin-free treatments in genotype 3 HCV-infected patients, to reduce the side effect burden of therapy which is associated with ribavirin use. Sofosbuvir/velpatasvir is used in two durations - 12 weeks, which is considered the standard of care treatment, and 24 weeks, which is considered the test treatment.

No other drugs or therapies are used within this trial.

Evidence for comparator:

The comparator arm in this trial is the standard of care treatment for genotype 3 HCV infected patients, which is 12 weeks of sofosbuvir/velpatasvir. Given the evidence for the benefits of clearing HCV in patients with advanced liver disease, it is unethical to use placebo.

The test treatment is 24 weeks of sofosbvuir/velpatasvir. This duration has been evaluated in a phase III trial showing no increased adverse events compared to the 12 week duration, but the 24 week regimen has not been recommended by license as it was not associated with significantly improved efficacy. However the study was not powered to detect significant differences in efficacy, and the 2016 international guidelines from EASL recommended that patients with genotype 3 HCV who have contraindications or poor tolerance to the use of ribaviirn should receive 24 weeks of sofosbuvir/velpatasvir alone.

Actual start date of recruitment	02 January 2017
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: 25
Worldwide total number of subjects	25
EEA total number of subjects	25

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)	21
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial opened on 22 May 2017 and closed on 1 Oct 2018, following 2 extensions to the recruitment window. The trial also increased the number of sites from 5 to 6. The final recruit was 25 patients out of the intended 60.

Pre-assignment

Screening details:

The trial screened and recruited patients who exhibited a slow viral response after the first 2 weeks of sofosbuvir/velpatasvir treatment. Therefore all patients in whom clinicians preferred to add ribavirin were ineligible. The proportion of patients with slow viral response was roughly x. There were no screen failures.

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:

There was no blinding to the participant or investigator of the allocated trial intervention.

Arms

Are arms mutually exclusive?	Yes
Arm title	12 weeks sofosbuvir/velpatasvir

Arm description:

standard of care treatment arm

Arm type	Active comparator
Investigational medicinal product name	sofosbuvir/velpatasvir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet contains 400mg sofosbuvir and 100mg velpatasvir, taken orally 1 tablet per day with or without food.

Arm title	24 weeks sofosbuvir/velpatasvir

Arm description:

The extended use of sofosbuvir/velpatasvir from week 13-24 is considered the investigational medicinal product (IMP). The product itself is the licensed, commercially available form.

Arm type	Experimental
Investigational medicinal product name	sofosbuvir/velpatasvir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet contains 400mg sofosbuvir and 100mg velpatasvir, taken orally 1 tablet per day with or without food.

Number of subjects in period 1	12 weeks sofosbuvir/velpatasvir	24 weeks sofosbuvir/velpatasvir
Started	12	13
Completed	11	11
Not completed	1	2
Adverse event, serious fatal	-	1
Consent withdrawn by subject	1	-
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	12 weeks sofosbuvir/velpatasvir
Reporting group description:	
standard of care treatment arm	
Reporting group title	24 weeks sofosbuvir/velpatasvir
Reporting group description:	
The extended use of sofosbuvir/velpatasvir from week 13-24 is considered the investigational medicinal product (IMP). The product itself is the licensed, commercially available form.	

Reporting group values	12 weeks sofosbuvir/velpatasvir	24 weeks sofosbuvir/velpatasvir	Total
Number of subjects	12	13	25
Age categorical			
Adult patients aged >18 were eligible			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	9	12	21
From 65-84 years	3	1	4
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	53.7	50.8	
full range (min-max)	30 to 84	31 to 78	-
Gender categorical			
Units: Subjects			
Female	7	6	13
Male	5	7	12
Ethnicity			
self-reported ethnicity group			
Units: Subjects			
Caucasian	3	5	8
Asian	8	8	16
others/ mixed	1	0	1
HCV treatment history			
Units: Subjects			
treatment naive	9	13	22
peg-interferon/ribavirin	2	0	2
others	1	0	1
hepatic decompensation (past or current)			
Units: Subjects			

yes	1	1	2
no	11	12	23

HCV load			
Units: iu/mL			
arithmetic mean	2977293	2186396	
full range (min-max)	12977 to 12882500	178000 to 5816224	-
week 2 HCV load			
Units: iu/mL			
arithmetic mean	170	58	
full range (min-max)	36 to 365	31 to 124	-
Haemoglobin			
Units: g/L			
arithmetic mean	131	137	
full range (min-max)	112 to 169	107 to 183	-
platelet count			
Units: x10^9/L			
arithmetic mean	148	176	
full range (min-max)	56 to 301	76 to 324	-
sodium			
Units: mmol/L			
arithmetic mean	140.3	139.1	
full range (min-max)	136 to 143	126 to 143	-
creatinine			
Units: umol/L			
arithmetic mean	62.4	72.2	
full range (min-max)	47 to 88	50 to 101	-
alanine aminotransferase (ALT)			
Units: iu/L			
arithmetic mean	92.2	109.7	
full range (min-max)	28 to 304	25 to 245	-
bilirubin			
Units: umol/L			
arithmetic mean	20.6	14.7	
full range (min-max)	7 to 82	3 to 32	-
albumin			
Units: g/L			
arithmetic mean	37.9	37.9	
full range (min-max)	31 to 46	29 to 51	-
MELD			
Units: points			
arithmetic mean	7.5	7.1	
full range (min-max)	6 to 16	6 to 11	-

Subject analysis sets

Subject analysis set title	12 week sofosbuvir/velpatasvir (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This analysis set includes all patients recruited into the trial who randomised to the 12 week (control) treatment arm

Subject analysis set title	24 week sofosbuvir/velpatasvir (ITT)

Subject analysis set type	Intention-to-treat

Subject analysis set description:

This analysis set includes all patients recruited into the trial who randomised to the 24 week (test) treatment arm

Subject analysis set title	12 weeks sof/vel (mITT)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The mITT analysis population excluded patients without available primary endpoint (SVR12) data

Subject analysis set title	24 weeks sof/vel (mITT)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

the mITT analysis population excluded patients without available primary endpoint (SVR12) data

Reporting group values	12 week sofosbuvir/velpatasvir (ITT)	24 week sofosbuvir/velpatasvir (ITT)	12 weeks sof/vel (mITT)
Number of subjects	12	13	12
Age categorical			
Adult patients aged >18 were eligible			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	9	12	9
From 65-84 years	3	1	3
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	53.7	50.8	53.7
full range (min-max)	30 to 84	31 to 78	30 to 84
Gender categorical			
Units: Subjects			
Female	7	6	
Male	5	7	
Ethnicity			
self-reported ethnicity group			
Units: Subjects			
Caucasian	3	5	
Asian	8	8	
others/ mixed	1	0	
HCV treatment history			
Units: Subjects			
treatment naive	9	13	
peg-interferon/ribavirin	2	0	
others	1	0	
hepatic decompensation (past or current)			
Units: Subjects			

yes	1	1	1
no	11	12	11

HCV load			
Units: iu/mL			
arithmetic mean	2977293	2186396	
full range (min-max)	12977 to 12882500	178000 to 5816224	
week 2 HCV load			
Units: iu/mL			
arithmetic mean	170	58	
full range (min-max)	36 to 365	31 to 124	
Haemoglobin			
Units: g/L			
arithmetic mean	131	137	
full range (min-max)	112 to 169	107 to 183	
platelet count			
Units: x10^9/L			
arithmetic mean	148	176	
full range (min-max)	56 to 301	76 to 324	
sodium			
Units: mmol/L			
arithmetic mean	140.3	139.1	
full range (min-max)	136 to 143	126 to 143	
creatinine			
Units: umol/L			
arithmetic mean	62.4	72.2	
full range (min-max)	47 to 88	50 to 101	
alanine aminotransferase (ALT)			
Units: iu/L			
arithmetic mean	92.2	109.7	
full range (min-max)	28 to 304	25 to 245	
bilirubin			
Units: umol/L			
arithmetic mean	20.6	14.7	
full range (min-max)	7 to 82	3 to 32	
albumin			
Units: g/L			
arithmetic mean	37.9	37.9	
full range (min-max)	31 to 46	29 to 51	
MELD			
Units: points			
arithmetic mean	7.5	7.1	
full range (min-max)	6 to 16	6 to 11	

Reporting group values	24 weeks sof/vel (mITT)		
Number of subjects	11		
Age categorical			
Adult patients aged >18 were eligible			
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)	11		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	48.5		
full range (min-max)	31 to 59		
Gender categorical			
Units: Subjects			
Female			
Male			
Ethnicity			
self-reported ethnicity group			
Units: Subjects			
Caucasian			
Asian			
others/ mixed			
HCV treatment history			
Units: Subjects			
treatment naive			
peg-interferon/ribavirin			
others			
hepatic decompensation (past or current)			
Units: Subjects			
yes	1		
no	10		
HCV load			
Units: iu/mL			
arithmetic mean			
full range (min-max)			
week 2 HCV load			
Units: iu/mL			
arithmetic mean			
full range (min-max)			
Haemoglobin			
Units: g/L			
arithmetic mean			
full range (min-max)			
platelet count			
Units: x10^9/L			
arithmetic mean			
full range (min-max)			
sodium			
Units: mmol/L			

arithmetic mean full range (min-max)			
creatinine Units: umol/L arithmetic mean full range (min-max)			
alanine aminotransferase (ALT) Units: iu/L arithmetic mean full range (min-max)			
bilirubin Units: umol/L arithmetic mean full range (min-max)			
albumin Units: g/L arithmetic mean full range (min-max)			
MELD Units: points arithmetic mean full range (min-max)			

End points

End points reporting groups

Reporting group title	12 weeks sofosbuvir/velpatasvir
Reporting group description: standard of care treatment arm	
Reporting group title	24 weeks sofosbuvir/velpatasvir
Reporting group description: The extended use of sofosbuvir/velpatasvir from week 13-24 is considered the investigational medicinal product (IMP). The product itself is the licensed, commercially available form.	
Subject analysis set title	12 week sofosbuvir/velpatasvir (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description: This analysis set includes all patients recruited into the trial who randomised to the 12 week (control) treatment arm	
Subject analysis set title	24 week sofosbuvir/velpatasvir (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description: This analysis set includes all patients recruited into the trial who randomised to the 24 week (test) treatment arm	
Subject analysis set title	12 weeks sof/vel (mITT)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: The mITT analysis population excluded patients without available primary endpoint (SVR12) data	
Subject analysis set title	24 weeks sof/vel (mITT)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: the mITT analysis population excluded patients without available primary endpoint (SVR12) data	

Primary: proportion achieving SVR12 (undetectable HCV in serum at 12 weeks post treatment end)

End point title	proportion achieving SVR12 (undetectable HCV in serum at 12 weeks post treatment end)
End point description: undetectable HCV is defined as RNA below limit of quantification up to 15iu/mL	
End point type	Primary
End point timeframe: SVR outcome is collected from 12 weeks up to 16 weeks post treatment end.	

End point values	12 weeks sofosbuvir/velpatasvir	24 weeks sofosbuvir/velpatasvir	12 week sofosbuvir/velpatasvir (ITT)	24 week sofosbuvir/velpatasvir (ITT)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	12	13	12	13
Units: subjects				
number (not applicable)				
SVR12	8	11	8	11
non-SVR12	4	2	4	2

End point values	12 weeks sof/vel (mITT)	24 weeks sof/vel (mITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12[1]	11[2]		
Units: subjects				
number (not applicable)				
SVR12	8	11		
non-SVR12	4	11		

Notes:

[1] - one patient withdrew before study end after treatment failure (HCV relapse) was included

[2] - 2 patients without primary endpoint data were excluded

Attachments (see zip file)	treatment outcomes.png svr barcharts.png itt v mitt SVR.png

Statistical analyses

Statistical analysis title	SVR12 - ITT
Statistical analysis description:	
proportion of patients achieving SVR12 between the 12 and 24 week treatment arms (all randomised patients analysed)	
Comparison groups	12 week sofosbuvir/velpatasvir (ITT) v 24 week sofosbuvir/velpatasvir (ITT)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	SVR12 - mITT
Statistical analysis description:	
proportion of patients achieving SVR12 in both treatment arms (mITT - only patients with available SVR12 data included)	
Comparison groups	12 week sofosbuvir/velpatasvir (ITT) v 24 week sofosbuvir/velpatasvir (ITT)

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	2-sided

Secondary: proportion of patients requiring treatment discontinuation

End point title	proportion of patients requiring treatment discontinuation

End point description:

End point type	Secondary

End point timeframe:

study start to end of planned treatment

End point values	12 weeks sofosbuvir/velpatasvir	24 weeks sofosbuvir/velpatasvir	12 week sofosbuvir/velpatasvir (ITT)	24 week sofosbuvir/velpatasvir (ITT)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	12	13	12	13
Units: subjects				
number (not applicable)				
yes	0	0	0	0
no	12	13	12	13

Statistical analyses

No statistical analyses for this end point

Secondary: proportion of patients with serious adverse events

End point title	proportion of patients with serious adverse events

End point description:

serious adverse events are defined as a medical event which results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect

End point type	Secondary

End point timeframe:

study start to study end

End point values	12 weeks sofosbuvir/velpatasvir	24 weeks sofosbuvir/velpatasvir	12 week sofosbuvir/velpatasvir (ITT)	24 week sofosbuvir/velpatasvir (ITT)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	12	13	12	13
Units: subjects				
number (not applicable)				
yes	2	3	2	3
no	10	10	10	10

Attachments (see zip file)	saes.png

Statistical analyses

Statistical analysis title	proportion of patients with SAEs by treatment grow
Comparison groups	12 week sofosbuvir/velpatasvir (ITT) v 24 week sofosbuvir/velpatasvir (ITT)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Fisher exact
Parameter estimate	Odds ratio (OR)

Secondary: quality of life - SF36 scores - physical component summary

End point title	quality of life - SF36 scores - physical component summary

End point description:

For each treatment arm, group mean scores at both timepoints, as well as the change from end of treatment to post treatment, will be analysed

End point type	Secondary

End point timeframe:

the first survey timepoint is at the end of treatment (week 12 or 24 depending on treatment arm) and at 3 months post treatment end

End point values	12 weeks sofosbuvir/velpatasvir	24 weeks sofosbuvir/velpatasvir	12 weeks sof/vel (mITT)	24 weeks sof/vel (mITT)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: score				
end of treatment	41	50	41	50
3 months post treatment	36	48	36	48

Statistical analyses

No statistical analyses for this end point

Secondary: quality of life - SF36 scores - mental component summary

End point title	quality of life - SF36 scores - mental component summary

End point description:

For each treatment arm, group mean scores at both timepoints, as well as the change from end of treatment to post treatment, will be analysed

End point type	Secondary

End point timeframe:

the first survey timepoint is at the end of treatment (week 12 or 24 depending on treatment arm) and at 3 months post treatment end

End point values	12 weeks sofosbuvir/velpatasvir	24 weeks sofosbuvir/velpatasvir	12 weeks sof/vel (mITT)	24 weeks sof/vel (mITT)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	11	11	11	11
Units: score				
end of treatment	43	44	43	44
3 months post treatment end	38	47	38	47

Attachments (see zip file)	Sf36 /sf36.png

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

start of sofosbuvir/velpatasivr treatment to end of follow up (3 months post treatment end). This trial recruits patients who have taken at least 2 weeks of treatment as standard of care. AEs which occurred before recruitment are retrospectively assessed.

Adverse event reporting additional description:

Week 12-24 of sofosbuvir/velpatasvir is considered the investigational medicinal product (IMP) in this trial, therefore only AEs associated with IMP use (until the end of follow up) are reported to the MHRA.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	12 weeks sofosbuvir/velpatasvir (control arm)
Reporting group description: -	
Reporting group title	24 weeks sofosbuvir/velpatasvir (test arm)

Reporting group description: -

Serious adverse events	12 weeks sofosbuvir/velpatasvir (control arm)	24 weeks sofosbuvir/velpatasvir (test arm)	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 12 (16.67%)	3 / 13 (23.08%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Blood and lymphatic system disorders			
Deep vein thrombosis	Additional description: distal femoral deep vein thrombosis (associated with cellulitis)		
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death	Additional description: cause of death not established but not felt related to treatment given patient's age and comorbidities		
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatobiliary disorders			
Hepatocellular carcinoma			

subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Removal of external fixation	Additional description: removal of screws from left lower limb		
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis	Additional description: left leg cellulitis		
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	12 weeks sofosbuvir/velpatasvir (control arm)	24 weeks sofosbuvir/velpatasvir (test arm)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 12 (75.00%)	12 / 13 (92.31%)	
General disorders and administration site conditions			
Lethargy			
subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Fatigue			

subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Immune system disorders			
Rhinitis allergic	Additional description: hay fever		
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract infection	Additional description: 2 patients from the test arm reported coryzal symptoms		
subjects affected / exposed	0 / 12 (0.00%)	5 / 13 (38.46%)	
occurrences (all)	0	5	
Lower respiratory tract infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Sinusitis	Additional description: sinus infection		
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Overdose	Additional description: accidental overdose of study medication		
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache	Additional description: one patient on the test arm reported heaviness of head		
subjects affected / exposed	0 / 12 (0.00%)	3 / 13 (23.08%)	
occurrences (all)	0	3	
Blood and lymphatic system disorders			

Neutropenia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	1 / 12 (8.33%)	2 / 13 (15.38%)	
occurrences (all)	1	2	
Ear and labyrinth disorders			
Discharge	Additional description: itchy & discharging middle ear		
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Ear discomfort			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Dizziness	Additional description: one participant on the standard of care arm reported light headedness		
subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Rectal haemorrhage			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	2 / 12 (16.67%)	1 / 13 (7.69%)	
occurrences (all)	2	1	
Vomiting			
subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	
occurrences (all)	2	1	
Haematemesis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Constipation			

subjects affected / exposed	0 / 12 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Dyspepsia	Additional description: bloating		
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	3 / 12 (25.00%)	3 / 13 (23.08%)	
occurrences (all)	3	3	
Hepatobiliary disorders			
Scan abdomen abnormal			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 12 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Dermatitis allergic			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Mouth ulceration			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Pruritus	Additional description: itchy skin		
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Pyuria			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Renal impairment			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Endocrine disorders			

Hypothyroidism			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 12 (8.33%)	2 / 13 (15.38%)	
occurrences (all)	1	2	
Gout			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Arthralgia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Pain in extremity	Additional description: posterior lower leg pain		
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Paresis	Additional description: weakness of arms and legs		
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	2	
Eye infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Folate deficiency			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Iron deficiency			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Vitamin D deficiency			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	

Gynaecomastia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 13 (7.69%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 July 2017	change in research site (St Mary's Hospital, London to Royal Sussex County Hospital, Brighton) and addition of one extra site (North Manchester General Hospital) making a total of 6
11 December 2017	change in research site (Royal Sussex County Hospital, Brighton to Chelsea & Westminster Hospital, London)

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.

The trial was terminated early prior to reaching the recruitment target. The total recruit was 25 patients out of planned 60. The study showed improved SVR in the test arm compared stop standard of care but the study has limited power.

Notes: