



Clinical trial results: Stratified Treatment OPTimisation for HCV-1 (STOPHCV-1) Summary

EudraCT number	2015-005004-28
Trial protocol	GB
Global end of trial date	04 April 2019

Results information

Result version number	v1 (current)
This version publication date	14 February 2020
First version publication date	14 February 2020

Trial information

Trial identification

Sponsor protocol code	15SM3025
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	London, London, United Kingdom,
Public contact	Helen Ainscough, MRC CTU at UCL, Institute of Clinical Trials and Methodology, +44 020 7670 4652,
Scientific contact	Helen Ainscough, MRC CTU at UCL, Institute of Clinical Trials and Methodology, +44 020 7670 4652,

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	15 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 April 2019
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:

1) To evaluate if short course HCV first line treatment (duration based on the viral load in the blood) followed by 12 weeks re-treatment of those failing therapy is non-inferior to a fixed duration of 8 weeks first line treatment followed by 12 weeks re-treatment of those failing therapy, looking at overall HCV cure in patients with minimal fibrosis and chronic HCV (type 1 and 4) infection.

2) To test the benefits and risks of adding adjunctive ribavirin with 4-8 weeks first line therapy.

Protection of trial subjects:

Retreatment was offered to all participants who failed on first-line treatment

Background therapy:

All participants took DAAs: either ombitasvir/paritaprevir/dasabuvir/ritonavir for genotype 1a or 1b participants, ombitasvir/paritaprevir/ritonavir for genotype 4 participants or glecaprevir/pibrentasvir for any genotype participants. All participants on retreatment took sofosbuvir/ledipasvir and ribavirin.

Evidence for comparator: -

Actual start date of recruitment	15 February 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	United Kingdom: 204
Worldwide total number of subjects	204
EEA total number of subjects	204

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)	197
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment was open from 15th March 2016 to 31st August 2018 in 15 sites within the UK. The first participant was recruited on 18th March 2016 and the last on 28th August 2018. 14 sites recruited at least one participant.

Pre-assignment

Screening details:

Eligibility criteria include aged 18 years or older, infected with HCV 1a or 1b or 4 for at least 6 months, no significant liver fibrosis, HCV VL <10,000,000 IU/ml, no previous DAA exposure for current infection, BMI 18 kg/m² or higher. If HIV co-infected, HIV VL <50 copies/ml for >24 weeks.

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?	No
Arm title	Variable duration

Arm description:

Participants randomised to receive variable duration treatment - the length of treatment is the intervention being tested

Arm type	Experimental
Investigational medicinal product name	Ombitasvir/paritaprevir/ritonavir
Investigational medicinal product code	
Other name	Viekirax
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received 4-7 weeks of treatment based on screening HCV viral load. Two tablets (12.5/75/50mg) to be taken once daily (total daily dose: 25/150/100mg). For all participants who are not taking glecaprevir/pibrentasvir.

Investigational medicinal product name	Dasabuvir
Investigational medicinal product code	
Other name	Exviera
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received 4-7 weeks of treatment based on screening HCV viral load. One 250mg tablet twice daily (total daily dosage: 500mg). Taken only by 1a and 1b participants who are also taking ombitasvir/paritaprevir/ritonavir

Investigational medicinal product name	Glecaprevir/pibrentasvir
Investigational medicinal product code	
Other name	Maviret
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received 4-7 weeks of treatment based on screening HCV viral load. Three tablets (100/40mg) taken once a day (total daily dose 300/120mg). Taken by all participants who are not taking ombitasvir/paritaprevir/ritonavir/(dasabuvir).

Arm title	Fixed duration
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Arm description:	
Participants randomised to receive fixed duration treatment	
Arm type	Active comparator
Investigational medicinal product name	Ombitasvir/paritaprevir/ritonavir
Investigational medicinal product code	
Other name	Viekirax
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Participants received 8 weeks of treatment. Two tablets (12.5/75/50mg) to be taken once daily (total daily dose: 25/150/100mg). For all participants who are not taking glecaprevir/pibrentasvir.	
Investigational medicinal product name	Dasabuvir
Investigational medicinal product code	
Other name	Exviera
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Participants received 8 weeks of treatment. One 250mg tablet twice daily (total daily dosage: 500mg). Taken only by 1a and 1b participants who are also taking ombitasvir/paritaprevir/ritonavir	
Investigational medicinal product name	Glecaprevir/pibrentasvir
Investigational medicinal product code	
Other name	Maviret
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Participants received 8 weeks of treatment. Three tablets (100/40mg) taken once a day (total daily dose 300/120mg). Taken by all participants who are not taking ombitasvir/paritaprevir/ritonavir/(dasabuvir).	
Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
For those randomised to ribavirin or those receiving retreatment, to be taken alongside DAAs. To be taken twice daily, dosing depending on weight and to be lowered in the case of AEs. For first-line treatment, 8 weeks. For retreatment, 12 weeks.	
Investigational medicinal product name	Sofosbuvir/ledipasvir
Investigational medicinal product code	
Other name	Harvoni
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Participants receiving retreatment only. One 400/90mg tablet to be taken once day for 12 weeks.	
Arm title	Ribavirin
Arm description:	
Participants randomised to receive ribavirin	
Arm type	Experimental

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

All participants on first-line and those receiving retreatment, to be taken alongside DAAs. To be taken twice daily, dosing depending on weight and to be lowered in the case of AEs. For first-line treatment, 4-7 or 8 weeks depending on duration randomisation allocation and screening HCV VL. For retreatment, 12 weeks.

Arm title	No ribavirin
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Arm description:

Participants randomised to receive no ribavirin

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

Number of subjects in period 1	Variable duration	Fixed duration	Ribavirin
Started	102	102	101
Completed	95	93	92
Not completed	7	9	9
Consent withdrawn by subject	1	-	-
Lost to follow-up	4	9	8
Randomised in error	2	-	1

Number of subjects in period 1	No ribavirin
Started	103
Completed	96
Not completed	7
Consent withdrawn by subject	1
Lost to follow-up	5
Randomised in error	1

Baseline characteristics

Reporting groups^[1]

Reporting group title	Overall trial
Reporting group description: -	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.

Justification: Two participants were randomised in error and withdrawn from the study before receiving study medication. As per the statistical analysis plan they have not been included in any analysis, including of the baseline characteristics

Reporting group values	Overall trial	Total	
Number of subjects	202	202	
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			
median	45.5		
inter-quartile range (Q1-Q3)	37.5 to 53.0	-	
Gender categorical			
Units: Subjects			
Female	62	62	
Male	140	140	
Ethnicity			
Units: Subjects			
White	176	176	
South Asian	1	1	
South East Asian	2	2	
Hispanic/Latino	9	9	
Black Caribbean/American	3	3	
Black African	2	2	
Mixed ethnic group	1	1	
Other	8	8	
HCV genotype/subgenotype			
Units: Subjects			
G1a	166	166	
G1b	34	34	
G4	2	2	
HIV coinfectd			
Units: Subjects			

Yes	68	68	
No	134	134	
IL28b genotype Units: Subjects			
CC	60	60	
CT	106	106	
TT	27	27	
No result	9	9	
Resistance associated substitution to any prescribed first-line drug Units: Subjects			
Yes	27	27	
No	161	161	
Unknown	14	14	
Ever spontaneously cleared and re- infected Units: Subjects			
Yes	6	6	
No	196	196	
Ever successfully treated and re-infected Units: Subjects			
Yes	10	10	
No	192	192	
Previously unsuccessfully treated with interferon Units: Subjects			
Yes	24	24	
No	178	178	
Current/recent alcoholism/alcohol abuse Units: Subjects			
Yes	13	13	
No	189	189	
Current/recent illicit substance abuse Units: Subjects			
Yes	64	64	
No	138	138	
Mode of HCV infection: no known risk factor Units: Subjects			
Yes	18	18	
No	179	179	
Not recorded	5	5	
Mode of HCV infection: injecting drug use Units: Subjects			
Yes	99	99	
No	101	101	
Not recorded	2	2	
Mode of HCV infection: blood/blood products Units: Subjects			
Yes	11	11	

No	186	186	
Not recorded	5	5	
Mode of HCV infection: perinatal exposure Units: Subjects			
Yes	4	4	
No	193	193	
Not recorded	5	5	
Mode of HCV infection: known HCV positive sexual partner Units: Subjects			
Yes	21	21	
No	176	176	
Not recorded	5	5	
Mode of HCV infection: born abroad Units: Subjects			
Yes	27	27	
No	170	170	
Not recorded	5	5	
Mode of HCV infection: high risk sexual partner Units: Subjects			
Yes	71	71	
No	130	130	
Not recorded	1	1	
Mode of HCV infection: tattoo Units: Subjects			
Yes	27	27	
No	170	170	
Not recorded	5	5	
Mode of HCV infection: healthcare exposure Units: Subjects			
Yes	19	19	
No	178	178	
Not recorded	5	5	
Mode of HCV infection: other Units: Subjects			
Yes	20	20	
No	176	176	
Not recorded	6	6	
BMI Units: kg/m ² median inter-quartile range (Q1-Q3)	24.9 22.2 to 27.2	-	
Screening HCV viral load Units: IU/ml median inter-quartile range (Q1-Q3)	711423 218776 to 1995262	-	
Enrolment HCV viral load Units: IU/ml median	741946		

inter-quartile range (Q1-Q3)	249097 to 1872136	-	
Fibroscan result			
Units: kPa			
median	4.9		
inter-quartile range (Q1-Q3)	4.2 to 5.8	-	
Haemoglobin			
Units: g/dl			
median	14.7		
inter-quartile range (Q1-Q3)	14.0 to 15.6	-	
ALT			
Units: IU/ml			
median	52		
inter-quartile range (Q1-Q3)	34 to 87	-	
AST			
Units: IU/ml			
median	38		
inter-quartile range (Q1-Q3)	30 to 57	-	
ALP			
Units: IU/ml			
median	72		
inter-quartile range (Q1-Q3)	59 to 91	-	
eGFR			
Units: ml/min			
median	109		
inter-quartile range (Q1-Q3)	93 to 131	-	
Bilirubin			
Units: umol/l			
median	9		
inter-quartile range (Q1-Q3)	6 to 12	-	

End points

End points reporting groups

Reporting group title	Variable duration
Reporting group description: Participants randomised to receive variable duration treatment - the length of treatment is the intervention being tested	
Reporting group title	Fixed duration
Reporting group description: Participants randomised to receive fixed duration treatment	
Reporting group title	Ribavirin
Reporting group description: Participants randomised to receive ribavirin	
Reporting group title	No ribavirin
Reporting group description: Participants randomised to receive no ribavirin	
Subject analysis set title	Per-protocol: variable duration group
Subject analysis set type	Per protocol
Subject analysis set description: Defined as those receiving >90% and <110% of the prescribed duration of first-line treatment based on prescription and temporary/permanent discontinuation, and where the difference between screening and enrolment HCV RNA values would have led to a difference of ≤ 2 days in allocated duration of DAAs had they been allocated to the varying duration group.	
Subject analysis set title	Per-protocol: fixed duration group
Subject analysis set type	Per protocol
Subject analysis set description: Defined as those receiving >90% and <110% of the prescribed duration of first-line treatment based on prescription and temporary/permanent discontinuation, and where the difference between screening and enrolment HCV RNA values would have led to a difference of ≤ 2 days in allocated duration of DAAs had they been allocated to the varying duration group.	
Subject analysis set title	All missing outcomes are failures: variable duration group
Subject analysis set type	Intention-to-treat
Subject analysis set description: All participants with missing data for SVR12 are considered as failing and not achieving SVR12 (sensitivity analysis, worst case scenario)	
Subject analysis set title	All missing outcomes are failures: fixed duration group
Subject analysis set type	Intention-to-treat
Subject analysis set description: All participants with missing SVR12 data are considered as failed and not achieving SVR12 (sensitivity analysis, worst case scenario)	
Subject analysis set title	All missing outcomes are cures: variable duration group
Subject analysis set type	Intention-to-treat
Subject analysis set description: All participants with missing SVR12 are considered as achieving SVR12 (sensitivity analysis, best case scenario)	
Subject analysis set title	All missing outcomes are cures: fixed duration group
Subject analysis set type	Intention-to-treat
Subject analysis set description: All participants with missing SVR12 data are considered as achieving SVR12 (sensitivity analysis, best case scenario)	
Subject analysis set title	Received VUS1: variable duration group
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants randomised before 1st April 2007 and receiving treatment that ranged between 4-6 weeks.	

Subject analysis set title	Received VUS1: fixed duration group
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants randomised before 1st April 2007 and would have received treatment that ranged between 4-6 weeks if randomised to variable duration	
Subject analysis set title	Received VUS2: variable duration group
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants randomised after 1st April 2007 and receiving treatment that ranged between 4-7 weeks.	
Subject analysis set title	Received VUS2: fixed duration group
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants randomised after 1st April 2007 and would have received treatment that ranged between 4-7 weeks if randomised to variable duration group.	
Subject analysis set title	Per-protocol: ribavirin group
Subject analysis set type	Per protocol
Subject analysis set description: Defined as those receiving >90% and <110% of the prescribed duration of first-line treatment based on prescription and temporary/permanent discontinuation, and where the difference between screening and enrolment HCV RNA values would have led to a difference of ≤2 days in allocated duration of DAAs had they been allocated to the varying duration group.	
Subject analysis set title	Per-protocol: no ribavirin group
Subject analysis set type	Per protocol
Subject analysis set description: Defined as those receiving >90% and <110% of the prescribed duration of first-line treatment based on prescription and temporary/permanent discontinuation, and where the difference between screening and enrolment HCV RNA values would have led to a difference of ≤2 days in allocated duration of DAAs had they been allocated to the varying duration group.	
Subject analysis set title	All missing outcomes are failures: ribavirin group
Subject analysis set type	Intention-to-treat
Subject analysis set description: All participants with missing SVR12 outcomes are considered as failing and not achieving SVR12 (sensitivity analysis, worst case scenario)	
Subject analysis set title	All missing outcomes are failures: no ribavirin group
Subject analysis set type	Intention-to-treat
Subject analysis set description: All participants with missing SVR12 outcomes are considered as failing and not achieving SVR12 (sensitivity analysis, worst case scenario)	
Subject analysis set title	All missing outcomes are cures: ribavirin group
Subject analysis set type	Intention-to-treat
Subject analysis set description: All participants with missing SVR12 outcomes are considered as cures and achieving SVR12 (sensitivity analysis, best case scenario)	
Subject analysis set title	All missing outcomes are cures: no ribavirin group
Subject analysis set type	Intention-to-treat
Subject analysis set description: All participants with missing SVR12 outcomes are considered as cures and achieving SVR12 (sensitivity analysis, best case scenario)	
Primary: SVR12 after first-line or retreatment (duration comparison)	
End point title	SVR12 after first-line or retreatment (duration comparison) ^[1]
End point description:	
End point type	Primary

End point timeframe:

12 weeks after first-line or any retreatment

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: SVR12 after first-line and retreatment is a primary outcome for the duration comparison but a secondary outcome for the ribavirin comparison. The outcome has been split for the two comparisons to reflect this

End point values	Variable duration	Fixed duration	Per-protocol: variable duration group	Per-protocol: fixed duration group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	97	100	69	71
Units: participants	97	100	69	71

End point values	All missing outcomes are failures: variable duration group	All missing outcomes are failures: fixed duration group	All missing outcomes are cures: variable duration group	All missing outcomes are cures: fixed duration group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	100	102	100	102
Units: participants	97	100	100	102

Statistical analyses

Statistical analysis title	Primary analysis: risk difference between groups
Comparison groups	Variable duration v Fixed duration
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[2]
Parameter estimate	Risk difference (RD)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.038
upper limit	0.037

Notes:

[2] - 4% non-inferiority margin

Statistical analysis title	Per-protocol: risk difference between groups
Statistical analysis description:	
Difference between groups limited to the per-protocol population	
Comparison groups	Per-protocol: variable duration group v Per-protocol: fixed duration group

Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[3]
Parameter estimate	Risk difference (RD)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.05

Notes:

[3] - 4% non-inferiority margin

Statistical analysis title	All missing=failures: difference between groups
Statistical analysis description:	
Difference between groups assuming all participants with missing SVR12 failed treatment	
Comparison groups	All missing outcomes are failures: variable duration group v All missing outcomes are failures: fixed duration group
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[4]
P-value	= 0.64
Method	Regression, binomial with identity link
Parameter estimate	Risk difference (RD)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.03

Notes:

[4] - 4% non-inferiority margin

Statistical analysis title	All missing=cured: difference between groups
Statistical analysis description:	
Difference between groups assuming all participants with missing SVR12 data achieved SVR12	
Comparison groups	All missing outcomes are cures: fixed duration group v All missing outcomes are cures: variable duration group
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[5]
Parameter estimate	Risk difference (RD)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.037
upper limit	0.036

Notes:

[5] - 4% non-inferiority margin

Primary: SVR12 after first-line only (ribavirin comparison)

End point title	SVR12 after first-line only (ribavirin comparison) ^[6]
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End point description:

End point type	Primary
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End point timeframe:

12 weeks after only first-line treatment only

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: SVR12 after first-line only is a primary outcome for the ribavirin comparison but a secondary outcome for the duration comparison. The outcome has been split for the two comparisons to reflect this

End point values	Ribavirin	No ribavirin	Per-protocol: ribavirin group	Per-protocol: no ribavirin group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	98	101	66	74
Units: participants	69	70	48	50

End point values	All missing outcomes are failures: ribavirin group	All missing outcomes are failures: no ribavirin group	All missing outcomes are cures: ribavirin group	All missing outcomes are cures: no ribavirin group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	100	102	100	102
Units: participants	69	70	71	71

Attachments (see zip file)	Forest plot of subgroup analysis: ribavirin/fs9ribsubgroup.pdf Suppressed VL by visit and VUS: ribavirin/fs7bsuppressribbyp.
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Statistical analyses

Statistical analysis title	Primary analysis: risk difference between groups
Comparison groups	No ribavirin v Ribavirin
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.48
Method	Regression, binomial with identity link
Parameter estimate	Risk difference (RD)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.06

Statistical analysis title	Per-protocol: difference between groups
Statistical analysis description:	
Difference between groups limited to the per-protocol population	
Comparison groups	Per-protocol: ribavirin group v Per-protocol: no ribavirin group
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.93
Method	Regression, binomial with identity link
Parameter estimate	Risk difference (RD)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.1

Statistical analysis title	All missing=failures: difference between groups
Statistical analysis description:	
Difference between groups assuming all participants with missing SVR12 data failed treatment	
Comparison groups	All missing outcomes are failures: ribavirin group v All missing outcomes are failures: no ribavirin group
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.37
Method	Regression, binomial with identity link
Parameter estimate	Risk difference (RD)
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.05

Statistical analysis title	All missing=cured: difference between groups
Statistical analysis description:	
Difference between groups assuming all participants with missing SVR12 data achieved SVR12	
Comparison groups	All missing outcomes are cures: no ribavirin group v All missing outcomes are cures: ribavirin group

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.48
Method	Regression, binomial with identity link
Parameter estimate	Risk difference (RD)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.06

Statistical analysis title	Suppressed viral load by visit
Comparison groups	Ribavirin v No ribavirin
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.82 ^[7]
Method	Regression, binomial GEE

Notes:

[7] - Global p-value is comparing ribavirin vs no ribavirin (VUS combined).

Time point p-values (chi-squared or Fisher exact): D3 p=0.33, D7 p=0.54, D14 p=0.57, D28 p=0.26, D42 p=0.74, EOT p=0.30, EOT+4 p=0.30, EOT+8 p=0.63, EOT+12 p=0.83, EOT+24 p=0.71

Secondary: SVR12 after first-line only (duration comparison)

End point title	SVR12 after first-line only (duration comparison) ^[8]
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End point description:

End point type	Secondary
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End point timeframe:

12 weeks after only first-line treatment

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: SVR12 after first-line only is a primary outcome for the ribavirin comparison but a secondary outcome for the duration comparison. The outcome has been split for the two comparisons to reflect this

End point values	Variable duration	Fixed duration	Per-protocol: variable duration group	Per-protocol: fixed duration group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	98	101	69	71
Units: participants	47	92	32	66

End point values	All missing outcomes are failures: variable	All missing outcomes are failures: fixed duration group	All missing outcomes are cures: variable duration group	All missing outcomes are cures: fixed duration group
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	duration group			
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	100	102	100	102
Units: participants	47	92	49	93

End point values	Received VUS1: variable duration group	Received VUS1: fixed duration group	Received VUS2: variable duration group	Received VUS2: fixed duration group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	66	67	32	34
Units: participants	24	62	23	30

Attachments (see zip file)	SVR by visit first suppressed/f3ctimesuppress.pdf Forest plot of subgroup analysis: duration/fs8dursubgroup.pdf Suppressed VL by visit: duration/fs6suppressdr.pdf
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Statistical analyses

Statistical analysis title	Primary analysis: difference between groups
Comparison groups	Fixed duration v Variable duration
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[9]
P-value	< 0.001
Method	Regression, binomial with identity link
Parameter estimate	Risk difference (RD)
Point estimate	-0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	-0.32

Notes:

[9] - 4% non-inferiority margin

Estimate is an average over both DAA strategies and taken from a model which includes an interaction between randomisation and DAA strategy (p=0.001).

Statistical analysis title	VUS1: difference between groups
Statistical analysis description:	
Difference between groups limited to participants randomised before 1st April 2017, when variable duration participants received between 4-6 weeks of treatment.	
Comparison groups	Received VUS1: fixed duration group v Received VUS1: variable duration group

Number of subjects included in analysis	133
Analysis specification	Post-hoc
Analysis type	non-inferiority ^[10]
P-value	< 0.001
Method	Regression, binomial with identity link
Parameter estimate	Risk difference (RD)
Point estimate	-0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.69
upper limit	-0.43

Notes:

[10] - 4% non-inferiority margin

Statistical analysis title	VUS2: difference between groups
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Statistical analysis description:

Difference between groups limited to participants randomised after 1st April 2017 when variable duration participants received 4-7 weeks of treatment

Comparison groups	Received VUS2: fixed duration group v Received VUS2: variable duration group
Number of subjects included in analysis	66
Analysis specification	Post-hoc
Analysis type	non-inferiority ^[11]
P-value	= 0.09
Method	Regression, binomial with identity link
Parameter estimate	Risk difference (RD)
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	0.03

Notes:

[11] - 4% non-inferiority margin

Statistical analysis title	Per-protocol: difference between groups
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Statistical analysis description:

Difference between groups limited to the per-protocol population

Comparison groups	Per-protocol: variable duration group v Per-protocol: fixed duration group
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[12]
P-value	< 0.001
Method	Regression, binomial with identity link
Parameter estimate	Risk difference (RD)
Point estimate	-0.46

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	-0.33

Notes:

[12] - 4% non-inferiority margin

Estimate is an average over both DAA strategies and taken from a model which includes an interaction between randomisation and DAA strategy (p=0.07).

Statistical analysis title	All missing=failures: difference between groups
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Statistical analysis description:

Difference between groups assuming all participants with missing SVR12 data failed treatment

Comparison groups	All missing outcomes are failures: variable duration group v All missing outcomes are failures: fixed duration group
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[13]
P-value	< 0.001
Method	Regression, binomial with identity link
Parameter estimate	Risk difference (RD)
Point estimate	-0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	-0.32

Notes:

[13] - 4% non-inferiority margin

Estimate is an average over both DAA strategies and taken from a model which includes an interaction between randomisation and DAA strategy (p=0.001).

Statistical analysis title	All missing=cured: difference between groups
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Statistical analysis description:

Difference between groups assuming all participants with missing SVR12 data achieved SVR12

Comparison groups	All missing outcomes are cures: fixed duration group v All missing outcomes are cures: variable duration group
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[14]
P-value	< 0.001
Method	Regression, binomial with identity link
Parameter estimate	Risk difference (RD)
Point estimate	-0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	-0.31

Notes:

[14] - 4% non-inferiority margin

Estimate is an average over both DAA strategies and taken from a model which includes an interaction between randomisation and DAA strategy (p=0.001).

Statistical analysis title	Suppressed VL by visit
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Comparison groups	Variable duration v Fixed duration
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001 ^[15]
Method	Regression, binomial GEE

Notes:

[15] - Global p-value comparing variable duration vs fixed duration.

p-values at each of the visits (chi-squared or Fisher exact): D3 p=0.53, D7 p=0.69, D14 p=0.39, D28 p=0.08, EOT p=0.28, EOT+4 p<0.001, EOT+8 p<0.001 EOT+12 p<0.001, EOT+24 p<0.001.

Secondary: SVR12 after first-line and retreatment (ribavirin comparison)

End point title	SVR12 after first-line and retreatment (ribavirin comparison) ^[16]
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End point description:

End point type	Secondary
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End point timeframe:

12 weeks after first-line and any retreatment

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: SVR12 after first-line and retreatment is a primary outcome for the duration comparison but a secondary outcome for the ribavirin comparison. The outcome has been split for the two comparisons to reflect this

End point values	Ribavirin	No ribavirin	Per-protocol: ribavirin group	Per-protocol: no ribavirin group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	97	100	66	74
Units: Participants	97	100	66	74

End point values	All missing outcomes are failures: ribavirin group	All missing outcomes are failures: no ribavirin group	All missing outcomes are cures: ribavirin group	All missing outcomes are cures: no ribavirin group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	100	102	100	102
Units: Participants	97	100	100	102

Statistical analyses

Statistical analysis title	Primary analysis: risk difference between groups
Comparison groups	No ribavirin v Ribavirin

Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.038
upper limit	0.037

Statistical analysis title	Per-protocol: difference between groups
Statistical analysis description:	
Difference between groups limited to the per-protocol population	
Comparison groups	Per-protocol: ribavirin group v Per-protocol: no ribavirin group
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.05

Statistical analysis title	All missing=failures: difference between groups
Statistical analysis description:	
Difference between groups assuming all participants with missing SVR12 data failed treatment	
Comparison groups	All missing outcomes are failures: no ribavirin group v All missing outcomes are failures: ribavirin group
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.64
Method	Regression, binomial with identity link
Parameter estimate	Risk difference (RD)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.03

Statistical analysis title	All missing=cured: difference between groups
Statistical analysis description:	
Difference between groups assuming that all participants with missing SVR12 data achieved SVR12	
Comparison groups	All missing outcomes are cures: no ribavirin group v All missing outcomes are cures: ribavirin group
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.037
upper limit	0.036

Secondary: SVR24 after first-line or retreatment

End point title	SVR24 after first-line or retreatment
End point description:	
End point type	Secondary
End point timeframe:	
24 weeks after first-line and any retreatment	

End point values	Variable duration	Fixed duration	Ribavirin	No ribavirin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	96	98	96	98
Units: Participants	96	98	96	98

Statistical analyses

Statistical analysis title	Duration comparison: difference between groups
Comparison groups	Fixed duration v Variable duration
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[17]
Parameter estimate	Risk difference (RD)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.038
upper limit	0.038

Notes:

[17] - 4% non-inferiority margin

Statistical analysis title	Ribavirin comparison: difference between groups
Comparison groups	No ribavirin v Ribavirin
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk difference (RD)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.038
upper limit	0.038

Secondary: SVR24 after first-line only

End point title	SVR24 after first-line only
End point description:	
End point type	Secondary
End point timeframe:	
24 weeks after only first-line treatment	

End point values	Variable duration	Fixed duration	Ribavirin	No ribavirin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	97	99	97	99
Units: Participants	46	88	68	66

End point values	Received VUS1: variable duration group	Received VUS1: fixed duration group	Received VUS2: variable duration group	Received VUS2: fixed duration group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	65	68	32	31
Units: Participants	23	61	23	27

Statistical analyses

Statistical analysis title	Duration comparison: difference between groups
Comparison groups	Fixed duration v Variable duration

Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[18]
P-value	< 0.001
Method	Regression, binomial with identity link
Parameter estimate	Risk difference (RD)
Point estimate	-0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	-0.31

Notes:

[18] - 4% non-inferiority margin

Estimate is an average over both DAA strategies and taken from a model which includes an interaction between randomisation and DAA strategy (p=0.001).

Statistical analysis title	VUS1 duration comparison: difference between group
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Statistical analysis description:

Difference between duration randomisation groups limited to participants randomised before 1st April 2017 when variable duration participants received between 4-6 weeks of treatment

Comparison groups	Received VUS1: fixed duration group v Received VUS1: variable duration group
Number of subjects included in analysis	133
Analysis specification	Post-hoc
Analysis type	non-inferiority ^[19]
P-value	< 0.001
Method	Regression, binomial with identity link
Parameter estimate	Risk difference (RD)
Point estimate	-0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	-0.41

Notes:

[19] - 4% non-inferiority margin

Statistical analysis title	VUS2 duration comparison: difference between group
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Statistical analysis description:

Difference between duration randomisation groups limited to participants randomised after 1st April 2017 when variable duration participants received between 4-7 weeks of treatment

Comparison groups	Received VUS2: variable duration group v Received VUS2: fixed duration group
Number of subjects included in analysis	63
Analysis specification	Post-hoc
Analysis type	non-inferiority ^[20]
P-value	= 0.13
Method	Regression, binomial with identity link
Parameter estimate	Risk difference (RD)
Point estimate	-0.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	0.04

Notes:

[20] - 4% non-inferiority margin

Statistical analysis title	Ribavirin comparison: difference between groups
Comparison groups	Ribavirin v No ribavirin
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.87
Method	Regression, binomial with identity link
Parameter estimate	Risk difference (RD)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.11

Secondary: Primary first-line treatment failure

End point title	Primary first-line treatment failure
End point description:	
Primary first-line treatment failure is defined as confirmed >1log10 increase in HCV VL above nadir on treatment and >2000 IU/ml	
End point type	Secondary
End point timeframe:	
While on first-line treatment and up to 24 weeks after completing first-line treatment or meeting a failure criteria	

End point values	Variable duration	Fixed duration	Ribavirin	No ribavirin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	100	102	100	102
Units: Participants	16	5	10	11

End point values	Received VUS1: variable duration group	Received VUS1: fixed duration group	Received VUS2: variable duration group	Received VUS2: fixed duration group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	68	68	32	34

Units: Participants	16	2	0	3
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Attachments (see zip file)	Cumulative incidence primary FL failure: duration/fs4bprimfail. Cumulative incidence primary FL failure: ribavirin/fs5bprimfail.
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Statistical analyses

Statistical analysis title	Duration comparison: difference between groups
Comparison groups	Fixed duration v Variable duration
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[21]
P-value	= 0.008
Method	Regression, binomial with identity link
Parameter estimate	Risk difference (RD)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.18

Notes:

[21] - 4% non-inferiority margin

Statistical analysis title	Duration comparison: HR between groups
Comparison groups	Variable duration v Fixed duration
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.01
Method	Regression, Cox
Parameter estimate	Cause-specific hazard ratio
Point estimate	3.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.33
upper limit	9.92

Statistical analysis title	VUS1 duration comparison: difference between group
Statistical analysis description:	
Difference between duration randomisation groups restricted to participants randomised before 1st April 2017 when variable duration participants received between 4-6 weeks of treatment	
Comparison groups	Received VUS1: variable duration group v Received VUS1:

	fixed duration group
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[22]
P-value	< 0.001
Method	Regression, binomial with identity link
Parameter estimate	Risk difference (RD)
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.31

Notes:

[22] - 4% non-inferiority margin

Statistical analysis title	VUS1 duration comparison: HR between groups
Comparison groups	Received VUS1: variable duration group v Received VUS1: fixed duration group
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.003
Method	Regression, Cox
Parameter estimate	Cause-specific hazard ratio
Point estimate	9.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.09
upper limit	39.54

Statistical analysis title	Ribavirin comparison: difference between groups
Comparison groups	No ribavirin v Ribavirin
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.84
Method	Regression, binomial with identity link
Parameter estimate	Risk difference (RD)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.08

Statistical analysis title	Ribavirin comparison: HR between groups
Comparison groups	Ribavirin v No ribavirin
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.83
Method	Regression, Cox
Parameter estimate	Cause specific hazard ratio
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	2.14

Secondary: HCV viral load rebound

End point title	HCV viral load rebound
End point description:	HCV VL rebound is defined as having confirmed detectable HCV VL after two consecutive visits of undetectable HCV VL, with the confirmatory VL >2000 IU/ml
End point type	Secondary
End point timeframe:	While on first-line treatment and up to 24 weeks after completing first-line treatment or until meeting failure criteria

End point values	Variable duration	Fixed duration	Ribavirin	No ribavirin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	100	102	100	102
Units: Participants	35	6	19	22

End point values	Received VUS1: variable duration group	Received VUS1: fixed duration group	Received VUS2: variable duration group	Received VUS2: fixed duration group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	68	68	32	34
Units: Participants	26	5	9	1

Attachments (see zip file)	Cumulative incidence HCV VL rebound: duration /fs4crebound. Cumulative incidence HCV VL rebound: ribavirin/fs5crebound.
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Statistical analyses

Statistical analysis title	Duration comparison: difference between groups
Comparison groups	Fixed duration v Variable duration
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[23]
P-value	< 0.001
Method	Regression, binomial with identity link
Parameter estimate	Risk difference (RD)
Point estimate	0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	0.39

Notes:

[23] - 4% non-inferiority margin

Statistical analysis title	Duration comparison: HR between groups
Comparison groups	Fixed duration v Variable duration
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[24]
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Cause specific hazard ratio
Point estimate	8.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.48
upper limit	22.73

Notes:

[24] - 4% non-inferiority margin

Statistical analysis title	VUS1 duration comparison: difference between group
Statistical analysis description:	
Difference between duration comparison groups limited to participants randomised before 1st April 2017 when variable duration participants received between 4-6 weeks of treatment	
Comparison groups	Received VUS1: variable duration group v Received VUS1: fixed duration group

Number of subjects included in analysis	136
Analysis specification	Post-hoc
Analysis type	non-inferiority ^[25]
P-value	< 0.001
Method	Regression, binomial with identity link
Parameter estimate	Risk difference (RD)
Point estimate	0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	0.44

Notes:

[25] - 4% non-inferiority margin

Statistical analysis title	VUS2 duration comparison: difference between group
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Statistical analysis description:

Difference between duration randomisation groups limited to participants randomised after 1st April 2017 when variable duration participants received between 4-7 weeks of treatment

Comparison groups	Received VUS2: variable duration group v Received VUS2: fixed duration group
Number of subjects included in analysis	66
Analysis specification	Post-hoc
Analysis type	non-inferiority ^[26]
P-value	= 0.004
Method	Regression, binomial with identity link
Parameter estimate	Risk difference (RD)
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	0.42

Notes:

[26] - 4% non-inferiority margin

Statistical analysis title	VUS1 duration comparison: HR between group
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Statistical analysis description:

Cause specific hazard ratio between duration randomisation groups limited to participants randomised before 1st April 2017 when variable duration participants received between 4-6 weeks of treatment

Comparison groups	Received VUS1: fixed duration group v Received VUS1: variable duration group
Number of subjects included in analysis	136
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Cause specific hazard ratio
Point estimate	8.21

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.86
upper limit	23.56

Statistical analysis title	VUS2 duration comparison: HR between groups
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Statistical analysis description:

Cause specific hazard ratio between duration randomisation groups limited to participants randomised before 1st April 2017 when variable duration participants received between 4-6 weeks of treatment

Comparison groups	Received VUS2: variable duration group v Received VUS2: fixed duration group
Number of subjects included in analysis	66
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.02
Method	Regression, Cox
Parameter estimate	Cause specific hazard ratio
Point estimate	11.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.42
upper limit	88.48

Statistical analysis title	Ribavirin comparison: difference between groups
Comparison groups	No ribavirin v Ribavirin
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.59
Method	Regression, binomial with identity link
Parameter estimate	Risk difference (RD)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.09

Statistical analysis title	Ribavirin comparison: HR between groups
Comparison groups	Ribavirin v No ribavirin

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.59
Method	Regression, Cox
Parameter estimate	Cause specific hazard ratio
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.56

Secondary: Detectable HCV VL 4 weeks after randomisation

End point title	Detectable HCV VL 4 weeks after randomisation
End point description:	
End point type	Secondary
End point timeframe:	
4 weeks after randomisation	

End point values	Variable duration	Fixed duration	Ribavirin	No ribavirin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	96	101	97	100
Units: Participants	15	26	17	24

Statistical analyses

Statistical analysis title	Duration comparison: difference between groups
Comparison groups	Fixed duration v Variable duration
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[27]
P-value	= 0.08
Method	Regression, binomial with identity link
Parameter estimate	Risk difference (RD)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	0.01

Notes:

[27] - 4% non-inferiority margin

Statistical analysis title	Ribavirin comparison: difference between groups
Comparison groups	No ribavirin v Ribavirin
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.26
Method	Regression, binomial with identity link
Parameter estimate	Risk difference (RD)
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.05

Secondary: Proportion with emergent RAVs to first-line treatment

End point title	Proportion with emergent RAVs to first-line treatment
End point description:	
RAVs=resistance associated variants	
End point type	Secondary
End point timeframe:	
After failing first-line treatment	

End point values	Variable duration	Fixed duration	Ribavirin	No ribavirin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46	10	27	29
Units: Participants	11	3	3	11

Statistical analyses

Statistical analysis title	Duration comparison: difference between groups
Comparison groups	Fixed duration v Variable duration
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[28]
P-value	= 0.77
Method	Regression, binomial with identity link
Parameter estimate	Risk difference (RD)
Point estimate	-0.05

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	0.27

Notes:

[28] - 4% non-inferiority margin

Statistical analysis title	Ribavirin comparison: difference between groups
Comparison groups	No ribavirin v Ribavirin
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Regression, binomial with identity link
Parameter estimate	Risk difference (RD)
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	-0.06

Secondary: Proportion with SAEs

End point title	Proportion with SAEs
End point description:	
End point type	Secondary
End point timeframe:	
Up until 24 weeks after completing first-line or any retreatment	

End point values	Variable duration	Fixed duration	Ribavirin	No ribavirin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	100	102	100	102
Units: Participants	5	5	5	5

Attachments (see zip file)	Kaplan-Meier plot of first SAE: duration/kmsae_first.pdf Kaplan-Meier plot of first SAE: ribavirin/kmsae_rib.pdf
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Statistical analyses

Statistical analysis title	Duration comparison: difference between groups
Comparison groups	Fixed duration v Variable duration
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Chi-squared

Statistical analysis title	Duration comparison: HR between groups
Comparison groups	Fixed duration v Variable duration
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.69
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	2.8

Statistical analysis title	Ribavirin comparison: difference between groups
Comparison groups	Ribavirin v No ribavirin
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Chi-squared

Statistical analysis title	Ribavirin comparison: HR between groups
Comparison groups	No ribavirin v Ribavirin
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.59
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	3.63

Secondary: Proportion with grade 3/4 AEs

End point title	Proportion with grade 3/4 AEs
End point description:	
End point type	Secondary
End point timeframe:	
Up to	

End point values	Variable duration	Fixed duration	Ribavirin	No ribavirin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	100	102	100	102
Units: Participants	9	5	9	5

Attachments (see zip file)	Kaplan-Meier plot of first G3/4 AE: duration/kmae_first.pdf
	Kaplan-Meier plot of first G3/4 AE: ribavirin/kmae_rib.pdf

Statistical analyses

Statistical analysis title	Duration comparison: difference between groups
Comparison groups	Fixed duration v Variable duration
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.28
Method	Chi-squared

Statistical analysis title	Duration comparison: HR between groups
Comparison groups	Fixed duration v Variable duration

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	5.24

Statistical analysis title	Ribavirin comparison: difference between groups
Comparison groups	Ribavirin v No ribavirin
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.28
Method	Chi-squared

Statistical analysis title	Ribavirin comparison: HR between groups
Comparison groups	Ribavirin v No ribavirin
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.59
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	5.72

Secondary: Proportion with grade 3/4 AEs judged definitely/probably related to first-line drugs

End point title	Proportion with grade 3/4 AEs judged definitely/probably related to first-line drugs
End point description:	
End point type	Secondary

End point timeframe:

Up until 24 weeks after completing first-line or any retreatment

End point values	Variable duration	Fixed duration	Ribavirin	No ribavirin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	100	102	100	102
Units: Participant	3	1	3	1

Statistical analyses

Statistical analysis title	Duration comparison: difference between groups
Comparison groups	Fixed duration v Variable duration
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.37
Method	Fisher exact

Statistical analysis title	Ribavirin comparison: difference between groups
Comparison groups	Ribavirin v No ribavirin
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.37
Method	Fisher exact

Secondary: Proportion with grade 3/4 AEs judged definitely/probably related to retreatment

End point title	Proportion with grade 3/4 AEs judged definitely/probably related to retreatment
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End point description:

End point type	Secondary
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End point timeframe:

Up until 24 weeks after completing first-line or any retreatment

End point values	Variable duration	Fixed duration	Ribavirin	No ribavirin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	100	102	100	102
Units: Participants	3	1	2	2

Statistical analyses

Statistical analysis title	Duration comparison: difference between groups
Comparison groups	Fixed duration v Variable duration
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.37
Method	Fisher exact

Statistical analysis title	Ribavirin comparison: difference between groups
Comparison groups	No ribavirin v Ribavirin
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

Secondary: Proportion with first-line drug changes due to AEs

End point title	Proportion with first-line drug changes due to AEs
End point description:	
End point type	Secondary
End point timeframe:	
Up until 24 weeks after completing first-line or any retreatment	

End point values	Variable duration	Fixed duration	Ribavirin	No ribavirin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	100	102	100	102
Units: Participants	3	1	4	0

Statistical analyses

Statistical analysis title	Duration comparison: difference between groups
Comparison groups	Fixed duration v Variable duration
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.37
Method	Fisher exact

Statistical analysis title	Ribavirin comparison: difference between groups
Comparison groups	No ribavirin v Ribavirin
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.058
Method	Fisher exact

Secondary: Proportion with retreatment drug changes due to AEs

End point title	Proportion with retreatment drug changes due to AEs
End point description:	
End point type	Secondary
End point timeframe:	
Up until 24 weeks after completing first-line or any retreatment	

End point values	Variable duration	Fixed duration	Ribavirin	No ribavirin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	100	102	100	102
Units: Participants	6	1	4	3

Statistical analyses

Statistical analysis title	Duration comparison: difference between groups
Comparison groups	Fixed duration v Variable duration
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06
Method	Fisher exact

Statistical analysis title	Ribavirin comparison: difference between groups
Comparison groups	Ribavirin v No ribavirin
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.72
Method	Fisher exact

Secondary: Proportion with grade 3/4 anaemias

End point title	Proportion with grade 3/4 anaemias
End point description:	
End point type	Secondary
End point timeframe:	
Up until 24 weeks after completing first-line or any retreatment	

End point values	Variable duration	Fixed duration	Ribavirin	No ribavirin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	100	102	100	102
Units: Participants	3	0	3	0

Statistical analyses

Statistical analysis title	Duration comparison: difference between groups
Comparison groups	Variable duration v Fixed duration
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	Fisher exact

Statistical analysis title	Ribavirin comparison: difference between groups
Comparison groups	No ribavirin v Ribavirin

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	Fisher exact

Other pre-specified: Change in safety lab values from randomisation to EOT+24

End point title	Change in safety lab values from randomisation to EOT+24
End point description:	
End point type	Other pre-specified
End point timeframe:	
While enrolled in the trial	

End point values	Variable duration	Fixed duration	Ribavirin	No ribavirin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	100	102	100	102
Units: Participants with EOT+24 measurements	45	83	63	65

Attachments (see zip file)	Change in Hb: duration/hbchange_first.pdf Change in ALT: duration/altchange_first.pdf Change in AST: duration/astchange_first.pdf Change in ALP: duration/alpchange_first.pdf Change in eGFR: duration/egfrchange_first.pdf Change in bilirubin: duration/brchange_first.pdf Change in Hb: ribavirin/hbchange_rib.pdf Change in ALT: ribavirin/altchange_rib.pdf Change in AST: ribavirin/astchange_rib.pdf Change in ALP: ribavirin/alpchange_rib.pdf Change in eGFR: ribavirin/egfrchange_rib.pdf Change in bilirubin: ribavirin/brchange_rib.pdf
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Statistical analyses

Statistical analysis title	Change in haemoglobin: duration comparison
Comparison groups	Fixed duration v Variable duration

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	other
P-value	= 18 ^[29]
Method	GEE

Notes:

[29] - Global p-value for change in Hb over time until EOT+24.

Time point p-values: D14 p=0.35, D28 p=0.11, EOT=0.20, EOT+12 p=0.42, EOT+24 p=0.36

Statistical analysis title	Change in ALT: duration comparison
Comparison groups	Fixed duration v Variable duration
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 ^[30]
Method	GEE

Notes:

[30] - Global p-value for change in ALT over time until EOT+24.

Time point p-values: D14: p=0.90, D28 p=0.15, EOT p=0.02, EOT+12 p=0.02, EOT+24 p=0.26

Statistical analysis title	Change in AST: duration comparison
Comparison groups	Variable duration v Fixed duration
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 ^[31]
Method	GEE

Notes:

[31] - Global p-value for change in AST over time until EOT+24.

Time point p-values: D14 p=0.40, D28 p=0.01, EOT p=0.01, EOT+12 p=0.004, EOT+24 p=0.008

Statistical analysis title	Change in ALP: duration comparison
Comparison groups	Fixed duration v Variable duration
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.68 ^[32]
Method	GEE

Notes:

[32] - Global p-value for change in ALP over time until EOT+24.

Time point p-values: D14 p=0.87, D28 p=0.73, EOT p=0.11, EOT+12 p=0.94, EOT+24 p=0.995

Statistical analysis title	Change in eGFR: duration comparison
Comparison groups	Variable duration v Fixed duration
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.23 ^[33]
Method	GEE

Notes:

[33] - Global p-value for change in eGFR over time until EOT+24.

Time point p-values: D14 p=0.62, D28 p=0.92, EOT p=0.41, EOT+12 p=0.89 EOT+24 p=0.31

Statistical analysis title	Change in bilirubin: duration comparison
Comparison groups	Fixed duration v Variable duration
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.86 ^[34]
Method	GEE

Notes:

[34] - Global p-value for change in bilirubin over time until EOT+24.

Time point p-values: D14 p=0.31, D28 p=0.63, EOT p=0.32, EOT+12 p=0.96, EOT+24 p=0.38

Statistical analysis title	Change in haemoglobin: ribavirin comparison
Comparison groups	Ribavirin v No ribavirin
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 ^[35]
Method	GEE

Notes:

[35] - Global p-value for change in Hb over time until EOT+24.

Time point p-values: D14 p<0.001, D28 p<0.001, EOT p<0.001, EOT+12 p=0.68, EOT+24 p=0.96

Statistical analysis title	Change in ALT: ribavirin comparison
Comparison groups	Ribavirin v No ribavirin
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.86 ^[36]
Method	GEE

Notes:

[36] - Global p-value for change in ALT over time until EOT+24.

Time point p-values: D14 p=0.56, D28 p=0.90, EOT p=0.84, EOT+12 p=0.62, EOT+24 p=0.35

Statistical analysis title	Change in AST: ribavirin comparison
Comparison groups	Ribavirin v No ribavirin
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.58 ^[37]
Method	GEE

Notes:

[37] - Global p-value for change in AST over time until EOT+24.

Time point p-values: D14 p=0.31, D28 p=0.85, EOT p=0.29, EOT+12 p=0.78, EOT+24 p=0.68

Statistical analysis title	Change in ALP: ribavirin comparison
Comparison groups	No ribavirin v Ribavirin
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.15 ^[38]
Method	GEE

Notes:

[38] - Global p-value for change in ALP over time until EOT+24.

Time point p-values: D14 p=0.75, D28 p=0.72, EOT p=0.12, EOT+12 p=0.13, EOT+24 p=0.73

Statistical analysis title	Change in eGFR: ribavirin comparison
Comparison groups	No ribavirin v Ribavirin
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.62 ^[39]
Method	GEE

Notes:

[39] - Global p-value for change in eGFR over time until EOT+24.

Time point p-values: D14 p=0.59, D28 p=0.25, EOT p=0.70, EOT+12 p=0.90, EOT+24 p=0.46

Statistical analysis title	Change in bilirubin: ribavirin comparison
Comparison groups	No ribavirin v Ribavirin
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 ^[40]
Method	GEE

Notes:

[40] - Global p-value for change in bilirubin over time until EOT+24.

Time point p-values: D14 p<0.001, D28 p<0.001, EOT p<0.001, EOT+12 p=0.23, EOT+24 p=0.93

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For an individual participant, the timeframe is from randomisation up to 24 weeks after completing their most recent treatment, either first-line or retreatment for those who started retreatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Variable duration
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Reporting group description:

All participants randomised to receive variable duration treatment

Reporting group title	Fixed duration
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Reporting group description:

All participants randomised to receive fixed duration

Reporting group title	Ribavirin group
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Reporting group description:

All participants randomised to receive ribavirin

Reporting group title	Without ribavirin group
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Reporting group description:

All participants randomised to not receive ribavirin

Serious adverse events	Variable duration	Fixed duration	Ribavirin group
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 100 (5.00%)	5 / 102 (4.90%)	5 / 100 (5.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Oesophageal adenocarcinoma			
subjects affected / exposed	0 / 100 (0.00%)	1 / 102 (0.98%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Thermal burn	Additional description: Burn to foot, degree unknown		
subjects affected / exposed	1 / 100 (1.00%)	0 / 102 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Pericarditis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 102 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Loss of consciousness	Additional description: Loss of consciousness due to (non-study) drug overdose		
subjects affected / exposed	1 / 100 (1.00%)	0 / 102 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain	Additional description: Musculoskeletal chest pain with radiation to left arm		
subjects affected / exposed	0 / 100 (0.00%)	1 / 102 (0.98%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 102 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 102 (0.98%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver abscess			
subjects affected / exposed	1 / 100 (1.00%)	0 / 102 (0.00%)	1 / 100 (1.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orchitis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 102 (0.98%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			

subjects affected / exposed	0 / 100 (0.00%)	1 / 102 (0.98%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Without ribavirin group		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 102 (4.90%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Oesophageal adenocarcinoma			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Thermal burn	Additional description: Burn to foot, degree unknown		
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Pericarditis			
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Loss of consciousness	Additional description: Loss of consciousness due to (non-study) drug overdose		
subjects affected / exposed	0 / 102 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain	Additional description: Musculoskeletal chest pain with radiation to left arm		
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infections and infestations Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 102 (0.00%) 0 / 0 0 / 0		
Urosepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 102 (0.98%) 0 / 1 0 / 0		
Liver abscess subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 102 (0.00%) 0 / 0 0 / 0		
Orchitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 102 (0.98%) 0 / 0 0 / 0		
Appendicitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 102 (0.98%) 0 / 1 0 / 0		

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

Non-serious adverse events	Variable duration	Fixed duration	Ribavirin group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 100 (15.00%)	15 / 102 (14.71%)	17 / 100 (17.00%)
Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 100 (1.00%)	1 / 102 (0.98%)	2 / 100 (2.00%)
occurrences (all)	1	1	2
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 100 (0.00%)	1 / 102 (0.98%)	0 / 100 (0.00%)
occurrences (all)	0	1	0

Vascular disorders Syncope subjects affected / exposed occurrences (all)	0 / 100 (0.00%) 0	1 / 102 (0.98%) 1	0 / 100 (0.00%) 0
Nervous system disorders Disturbance in attention subjects affected / exposed occurrences (all) Lethargy subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1 1 / 100 (1.00%) 1	0 / 102 (0.00%) 0 0 / 102 (0.00%) 0	1 / 100 (1.00%) 1 1 / 100 (1.00%) 1
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	6 / 100 (6.00%) 6	0 / 102 (0.00%) 0	3 / 100 (3.00%) 3
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1	0 / 102 (0.00%) 0	1 / 100 (1.00%) 1
Gastrointestinal disorders Inguinal hernia subjects affected / exposed occurrences (all) Mouth ulceration subjects affected / exposed occurrences (all) Stomatitis subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1 1 / 100 (1.00%) 1 1 / 100 (1.00%) 1	0 / 102 (0.00%) 0 0 / 102 (0.00%) 0 0 / 102 (0.00%) 0	1 / 100 (1.00%) 1 1 / 100 (1.00%) 1 1 / 100 (1.00%) 1
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all) Jaundice subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1 0 / 100 (0.00%) 0	0 / 102 (0.00%) 0 1 / 102 (0.98%) 1	0 / 100 (0.00%) 0 0 / 100 (0.00%) 0
Skin and subcutaneous tissue disorders			

Alopecia subjects affected / exposed occurrences (all)	0 / 100 (0.00%) 0	1 / 102 (0.98%) 1	1 / 100 (1.00%) 1
Psychiatric disorders Depressed mood subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1	0 / 102 (0.00%) 0	1 / 100 (1.00%) 1
Insomnia subjects affected / exposed occurrences (all)	3 / 100 (3.00%) 3	0 / 102 (0.00%) 0	3 / 100 (3.00%) 3
Suicidal ideation subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1	0 / 102 (0.00%) 0	1 / 100 (1.00%) 1
Infections and infestations			
Abscess limb subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1	0 / 102 (0.00%) 0	0 / 100 (0.00%) 0
Cellulitis subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1	1 / 102 (0.98%) 1	1 / 100 (1.00%) 1
Pyelonephritis subjects affected / exposed occurrences (all)	0 / 100 (0.00%) 0	1 / 102 (0.98%) 1	1 / 100 (1.00%) 1

Non-serious adverse events	Without ribavirin group		
Total subjects affected by non-serious adverse events subjects affected / exposed	13 / 102 (12.75%)		
Investigations Haemoglobin decreased subjects affected / exposed occurrences (all)	0 / 102 (0.00%) 0		
Injury, poisoning and procedural complications Alcohol poisoning subjects affected / exposed occurrences (all)	1 / 102 (0.98%) 1		
Vascular disorders			

Syncope subjects affected / exposed occurrences (all)	1 / 102 (0.98%) 1		
Nervous system disorders Disturbance in attention subjects affected / exposed occurrences (all)	0 / 102 (0.00%) 0		
Lethargy subjects affected / exposed occurrences (all)	0 / 102 (0.00%) 0		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	3 / 102 (2.94%) 3		
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	0 / 102 (0.00%) 0		
Gastrointestinal disorders Inguinal hernia subjects affected / exposed occurrences (all)	0 / 102 (0.00%) 0		
Mouth ulceration subjects affected / exposed occurrences (all)	0 / 102 (0.00%) 0		
Stomatitis subjects affected / exposed occurrences (all)	0 / 102 (0.00%) 0		
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)	1 / 102 (0.98%) 1		
Jaundice subjects affected / exposed occurrences (all)	1 / 102 (0.98%) 1		
Skin and subcutaneous tissue disorders			

Alopecia subjects affected / exposed occurrences (all)	0 / 102 (0.00%) 0		
Psychiatric disorders Depressed mood subjects affected / exposed occurrences (all)	0 / 102 (0.00%) 0		
Insomnia subjects affected / exposed occurrences (all)	0 / 102 (0.00%) 0		
Suicidal ideation subjects affected / exposed occurrences (all)	0 / 102 (0.00%) 0		
Infections and infestations			
Abscess limb subjects affected / exposed occurrences (all)	1 / 102 (0.98%) 1		
Cellulitis subjects affected / exposed occurrences (all)	1 / 102 (0.98%) 1		
Pyelonephritis subjects affected / exposed occurrences (all)	0 / 102 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 May 2017	After reviewing the data, the DMC recommended changing the duration of treatment for those receiving variable duration therapy from 4-6 weeks to 4-7 weeks.
19 October 2017	To help improve recruitment, genotype 4 patients were allowed to join the study (previously just 1a and 1b). The combination ombitasvir/paritaprevir/ritonavir was added to the protocol for genotype 4 patients. The combination glecaprevir/pibrentasvir was added to the protocol for all genotypes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported