



Clinical trial results:

A Phase 2, Open-Label Clinical Trial to Study the Efficacy and Safety of 12 weeks of the Combination Regimen of MK-3682 + Ruzasvir in Subjects with Chronic Hepatitis C Virus (HCV) Genotype 1, 2, 3, 4, 5 or 6 Infection

Summary

EudraCT number	2016-003227-37
Trial protocol	GB ES PL
Global end of trial date	05 March 2018

Results information

Result version number	v1 (current)
This version publication date	19 December 2018
First version publication date	19 December 2018

Trial information

Trial identification

Sponsor protocol code	3682-041
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02956629
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure,, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

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	05 March 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	05 March 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This is a nonrandomized, multi-site, open-label trial to evaluate a novel two-drug combination regimen (uprifosbuvir [MK-3682] 450 mg + ruzasvir [RZR; MK-8408] 180 mg once daily [q.d.] for 12 weeks) in male and female treatment-naïve (TN) or treatment experienced (TE) participants with chronic hepatitis C virus (HCV) infection genotype (GT) GT1, GT2, GT3, GT4, GT5, or GT6 who have not previously received HCV direct-acting antiviral (DAA) therapy. Cirrhotic (C) and non-cirrhotic (NC) participants with and without human immunodeficiency virus (HIV) co-infection will be enrolled. Any GT that meets virologic futility criteria will be given the option of extending treatment with uprifosbuvir + RZR to 16 weeks with ribavirin (RBV) added.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 November 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Canada: 40
Country: Number of subjects enrolled	Israel: 24
Country: Number of subjects enrolled	New Zealand: 14
Country: Number of subjects enrolled	Poland: 34
Country: Number of subjects enrolled	Russian Federation: 17
Country: Number of subjects enrolled	South Africa: 15
Country: Number of subjects enrolled	Spain: 28
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	United States: 86
Worldwide total number of subjects	282
EEA total number of subjects	81

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)	258
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Males and females of at least 18 years of age, with chronic Hepatitis C Virus (HCV) infection were enrolled in this study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	HCV Genotype (GT) 1

Arm description:

Male and female participants with HCV GT1a or GT1b infection take uprifosbuvir 450 mg + Ruzasvir (RZR) 180 mg for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Uprifosbuvir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants take 3 tablets each containing 150 mg uprifosbuvir orally once daily (q.d.) by mouth.

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ribavirin (RBV) 200 mg capsule will be taken orally according to package instructions for a maximum of 16 weeks for any GT that meets virologic futility rules on uprifosbuvir + RZR alone.

Investigational medicinal product name	Ruzasvir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants take 3 capsules each containing 60 mg RZR q.d. by mouth.

Arm title	HCV GT2
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Arm description:

Male and female participants with HCV GT2 infection take uprifosbuvir 450 mg + RZR 180 mg for 12 weeks.

Arm type	Experimental
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Investigational medicinal product name	Uprifosbuvir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants take 3 tablets each containing 150 mg uprifosbuvir orally (q.d.) by mouth.

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ribavirin (RBV) 200 mg capsule will be taken orally according to package instructions for a maximum of 16 weeks for any GT that meets virologic futility rules on uprifosbuvir + RZR alone.

Investigational medicinal product name	Ruzasvir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants take 3 capsules each containing 60 mg RZR q.d. by mouth.

Arm title	HCV GT3
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Arm description:

Male and female participants with HCV GT3 infection take uprifosbuvir 450 mg + RZR 180 mg for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Uprifosbuvir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants take 3 tablets each containing 150 mg uprifosbuvir orally (q.d.) by mouth.

Investigational medicinal product name	Ruzasvir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants take 3 capsules each containing 60 mg RZR q.d. by mouth.

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ribavirin (RBV) 200 mg capsule will be taken orally according to package instructions for a maximum of 16 weeks for any GT that meets virologic futility rules on uprifosbuvir + RZR alone.

Arm title	HCV GT4
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Arm description:

Male and female participants with HCV GT4 infection

take uprifosbuvir 450 mg + RZR 180 mg for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Uprifosbuvir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants take 3 tablets each containing 150 mg uprifosbuvir orally (q.d.) by mouth.

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ribavirin (RBV) 200 mg capsule will be taken orally according to package instructions for a maximum of 16 weeks for any GT that meets virologic futility rules on uprifosbuvir + RZR alone.

Investigational medicinal product name	Ruzasvir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants take 3 capsules each containing 60 mg RZR q.d. by mouth.

Arm title	HCV GT5
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Arm description:

Male and female participants with HCV GT5 infection take uprifosbuvir 450 mg + RZR 180 mg for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Uprifosbuvir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants take 3 tablets each containing 150 mg uprifosbuvir orally (q.d.) by mouth.

Investigational medicinal product name	Ruzasvir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants take 3 capsules each containing 60 mg RZR q.d. by mouth.

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ribavirin (RBV) 200 mg capsule will be taken orally according to package instructions for a maximum of 16 weeks for any GT that meets virologic futility rules on uprifosbuvir + RZR alone.

Arm title	HCV GT6
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Arm description:

Male and female participants with HCV GT6 infection take uprifosbuvir 450 mg + RZR 180 mg for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Uprifosbuvir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants take 3 tablets each containing 150 mg uprifosbuvir orally (q.d.) by mouth.

Investigational medicinal product name	Ruzasvir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants take 3 capsules each containing 60 mg RZR q.d. by mouth.

Investigational medicinal product name	Ribavirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ribavarin (RBV) 200 mg capsule will be taken orally according to package instructions for a maximum of 16 weeks for any GT that meets virologic futility rules on uprifosbuvir + RZR alone.

Number of subjects in period 1	HCV Genotype (GT) 1	HCV GT2	HCV GT3
Started	78	47	61
Completed	73	41	57
Not completed	5	6	4
Consent withdrawn by subject	3	1	-
Adverse event, non-fatal	-	-	1
Lost to follow-up	2	5	3

Number of subjects in period 1	HCV GT4	HCV GT5	HCV GT6
Started	56	18	22
Completed	55	18	21
Not completed	1	0	1
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	-	-
Lost to follow-up	1	-	1

Baseline characteristics

Reporting groups

Reporting group title	HCV Genotype (GT) 1
Reporting group description: Male and female participants with HCV GT1a or GT1b infection take uprifosbuvir 450 mg + Ruzasvir (RZR) 180 mg for 12 weeks.	
Reporting group title	HCV GT2
Reporting group description: Male and female participants with HCV GT2 infection take uprifosbuvir 450 mg + RZR 180 mg for 12 weeks.	
Reporting group title	HCV GT3
Reporting group description: Male and female participants with HCV GT3 infection take uprifosbuvir 450 mg + RZR 180 mg for 12 weeks.	
Reporting group title	HCV GT4
Reporting group description: Male and female participants with HCV GT4 infection take uprifosbuvir 450 mg + RZR 180 mg for 12 weeks.	
Reporting group title	HCV GT5
Reporting group description: Male and female participants with HCV GT5 infection take uprifosbuvir 450 mg + RZR 180 mg for 12 weeks.	
Reporting group title	HCV GT6
Reporting group description: Male and female participants with HCV GT6 infection take uprifosbuvir 450 mg + RZR 180 mg for 12 weeks.	

Reporting group values	HCV Genotype (GT) 1	HCV GT2	HCV GT3
Number of subjects	78	47	61
Age Categorical 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)	75	41	59
From 65-84 years	3	6	2
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	47.9	52.7	48.4
standard deviation	± 12.6	± 11.9	± 10.1
Gender Categorical Units: Subjects			
Female	35	24	27
Male	43	23	34

Reporting group values	HCV GT4	HCV GT5	HCV GT6
Number of subjects	56	18	22
Age Categorical 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)	51	12	20
From 65-84 years	5	6	2
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	46.4	57.4	53.3
standard deviation	± 13.0	± 12.4	± 11.0
Gender Categorical Units: Subjects			
Female	23	11	6
Male	33	7	16

Reporting group values	Total		
Number of subjects	282		
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)	258		
From 65-84 years	24		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical Units: Subjects			
Female	126		
Male	156		

End points

End points reporting groups

Reporting group title	HCV Genotype (GT) 1
Reporting group description: Male and female participants with HCV GT1a or GT1b infection take uprifosbuvir 450 mg + Ruzasvir (RZR) 180 mg for 12 weeks.	
Reporting group title	HCV GT2
Reporting group description: Male and female participants with HCV GT2 infection take uprifosbuvir 450 mg + RZR 180 mg for 12 weeks.	
Reporting group title	HCV GT3
Reporting group description: Male and female participants with HCV GT3 infection take uprifosbuvir 450 mg + RZR 180 mg for 12 weeks.	
Reporting group title	HCV GT4
Reporting group description: Male and female participants with HCV GT4 infection take uprifosbuvir 450 mg + RZR 180 mg for 12 weeks.	
Reporting group title	HCV GT5
Reporting group description: Male and female participants with HCV GT5 infection take uprifosbuvir 450 mg + RZR 180 mg for 12 weeks.	
Reporting group title	HCV GT6
Reporting group description: Male and female participants with HCV GT6 infection take uprifosbuvir 450 mg + RZR 180 mg for 12 weeks.	

Primary: Primary: Percentage of participants with sustained virologic response (SVR) 12 weeks after completing study therapy (SVR12)

End point title	Primary: Percentage of participants with sustained virologic response (SVR) 12 weeks after completing study therapy (SVR12) ^[1]
End point description: Plasma levels of hepatitis C virus (HCV) ribonucleic acid (RNA) were measured using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Test, v2.0 on blood samples drawn from participants. SVR12 is the absence of detectable RNA of the hepatitis C virus, (<lower limit of quantification [LLOQ] of 15 IU/mL) for at least 12 weeks after completing treatment. The population analyzed was all participants who were assigned to treatment, and received at least one dose of study medication.	
End point type	Primary
End point timeframe: 12 weeks after completing study therapy (Week 24)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical comparisons between treatment groups were neither planned nor performed for this primary endpoint.

End point values	HCV Genotype (GT) 1	HCV GT2	HCV GT3	HCV GT4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	78	47	61	56
Units: Percentage of participants				
number (confidence interval 95%)	92.3 (84.0 to 97.1)	91.5 (79.6 to 97.6)	73.8 (60.9 to 84.2)	98.2 (90.4 to 100.0)

End point values	HCV GT5	HCV GT6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	22		
Units: Percentage of participants				
number (confidence interval 95%)	100.0 (81.5 to 100.0)	90.9 (70.8 to 98.9)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants experiencing an adverse event (AE)

End point title	Percentage of participants experiencing an adverse event
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End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change infrequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an AE. The population analyzed was all participants who received at least one dose of study treatment.

End point type	Primary
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End point timeframe:

Up to Week 14

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical comparisons between treatment groups were neither planned nor performed for this primary endpoint.

End point values	HCV Genotype (GT) 1	HCV GT2	HCV GT3	HCV GT4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	78	47	61	56
Units: Percentage of participants				
number (not applicable)	60.3	61.7	57.4	55.4

End point values	HCV GT5	HCV GT6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	22		
Units: Percentage of participants				
number (not applicable)	77.8	77.3		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants experiencing an AE of clinical importance (ECI)

End point title	Percentage of participants experiencing an AE of clinical importance (ECI) ^[3]
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End point description:

Adverse events of clinical importance, excluding overdoses include, but is not limited to, significant changes in alanine aminotransferase, aspartate aminotransferase, blood creatinine, glomerular filtration rate or hepatitis B reactivation. The population analyzed was all participants who received at least one dose of study treatment.

End point type	Primary
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End point timeframe:

Up to Week 14

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical comparisons between treatment groups were neither planned nor performed for this primary endpoint.

End point values	HCV Genotype (GT) 1	HCV GT2	HCV GT3	HCV GT4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	78	47	61	56
Units: Percentage of participants				
number (not applicable)	1.3	2.1	1.6	3.6

End point values	HCV GT5	HCV GT6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	22		
Units: Percentage of participants				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants experiencing a serious adverse event (SAE)

End point title	Percentage of participants experiencing a serious adverse event (SAE) ^[4]
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End point description:

A serious adverse event (SAE) is any AE occurring at any dose or during any use of Sponsor's product that: results in death; is life threatening; results in persistent or significant disability/incapacity; results in or prolongs an existing inpatient hospitalization; is a congenital anomaly/birth defect; is another important medical event; is a cancer; is associated with an overdose. The population analyzed was all participants who received at least one dose of study treatment.

End point type	Primary
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End point timeframe:

Up to Week 14

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical comparisons between treatment groups were neither planned nor performed for this primary endpoint.

End point values	HCV Genotype (GT) 1	HCV GT2	HCV GT3	HCV GT4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	78	47	61	56
Units: Percentage of participants				
number (not applicable)	3.8	2.1	1.6	3.6

End point values	HCV GT5	HCV GT6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	22		
Units: Percentage of participants				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants experiencing a drug-related AE

End point title	Percentage of participants experiencing a drug-related AE ^[5]
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End point description:

An AE is defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change infrequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an AE. A drug-related AE is determined by the investigator to be related to the use of the drug. The population analyzed was all participants who received at least one dose of study treatment.

End point type	Primary
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End point timeframe:

Up to Week 14

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical comparisons between treatment groups were neither planned nor performed for this primary endpoint.

End point values	HCV Genotype (GT) 1	HCV GT2	HCV GT3	HCV GT4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	78	47	61	56
Units: Percentage of participants				
number (not applicable)	37.2	27.7	36.1	28.6

End point values	HCV GT5	HCV GT6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	22		
Units: Percentage of participants				
number (not applicable)	50.0	22.7		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants experiencing a drug-related SAE

End point title	Percentage of participants experiencing a drug-related SAE ^[6]
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End point description:

SAE is any AE occurring at any dose or during any use of Sponsor's product that: results in death; is life threatening; results in persistent or significant disability/incapacity; results in or prolongs an existing inpatient hospitalization; is a congenital anomaly/birth defect; is another important medical event; is a cancer; is associated with an overdose. A drug-related SAE is determined by the investigator to be related to the use of the drug. The population analyzed was all participants who received at least one dose of study treatment.

End point type	Primary
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End point timeframe:

Up to Week 14

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical comparisons between treatment groups were neither planned nor performed for this primary endpoint.

End point values	HCV Genotype (GT) 1	HCV GT2	HCV GT3	HCV GT4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	78	47	61	56
Units: Percentage of participants				
number (not applicable)	0	0	0	0

End point values	HCV GT5	HCV GT6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	22		
Units: Percentage of participants				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants discontinuing study therapy due to an AE

End point title	Percentage of participants discontinuing study therapy due to an AE ^[7]
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End point description:

An AE is defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change infrequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an AE. The population analyzed was all participants who received at least one dose of study treatment.

End point type	Primary
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End point timeframe:

Up to Week 12

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical comparisons between treatment groups were neither planned nor performed for this primary endpoint.

End point values	HCV Genotype (GT) 1	HCV GT2	HCV GT3	HCV GT4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	78	47	61	56
Units: Percentage of participants				
number (not applicable)	1.3	2.1	1.6	1.8

End point values	HCV GT5	HCV GT6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	22		
Units: Percentage of participants				
number (not applicable)	0	4.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with SVR 24 weeks after completing study therapy (SVR24)

End point title	Percentage of participants with SVR 24 weeks after completing study therapy (SVR24)
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End point description:

Plasma levels of HCV RNA were measured using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Test, v2.0 on blood samples drawn from participants. SVR24 is the absence of detectable RNA of the hepatitis C virus (<LLOQ of 15 IU/mL), for at least 24 weeks after completing treatment. The population analyzed was all participants who were assigned to treatment, and received at least one dose of study medication.

End point type	Secondary
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End point timeframe:

24 weeks after completing study therapy (Week 36)

End point values	HCV Genotype (GT) 1	HCV GT2	HCV GT3	HCV GT4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	78	47	61	56
Units: Percentage of participants				
number (confidence interval 95%)	89.7 (80.8 to 95.5)	85.1 (71.7 to 93.8)	72.1 (59.2 to 82.9)	96.4 (87.7 to 99.6)

End point values	HCV GT5	HCV GT6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	22		
Units: Percentage of participants				
number (confidence interval 95%)	100 (81.5 to 100)	81.8 (59.7 to 94.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with virologic failure

End point title	Percentage of participants with virologic failure
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End point description:

Virologic failure is the detection of HCV RNA among participants either due to non-response where HCV RNA is detected at end of treatment without HCV RNA <LLOQ having been achieved while on treatment; rebound defined as >1 log₁₀ IU/mL increase in HCV RNA from nadir while on treatment and confirmed from a separate blood draw within 2 weeks; or virologic breakthrough which is confirmed HCV RNA ≥LLOQ, after being <LLOQ previously while on treatment. Confirmation is defined as an HCV RNA ≥LLOQ from a separate blood draw repeated within 2 weeks; or relapse post-treatment, where there is a confirmed HCV RNA ≥LLOQ following end of all study therapy, after becoming undetectable at end of treatment. The population analyzed was participants who followed the protocol sufficiently to allow the analysis of the results.

End point type	Secondary
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End point timeframe:

Up to Week 24

End point values	HCV Genotype (GT) 1	HCV GT2	HCV GT3	HCV GT4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	78	47	61	56
Units: Percentage of participants				
number (not applicable)	3.8	2.1	23.0	0

End point values	HCV GT5	HCV GT6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	22		
Units: Percentage of participants				
number (not applicable)	0	13.6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 14

Adverse event reporting additional description:

All participants who received at least one dose of study treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	HCV GT1
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Reporting group description:

Male and female participants with HCV GT1a or GT1b infection take uprifosbuvir 450 mg + RZR 180 mg for 12 weeks.

Reporting group title	HCV GT2
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Reporting group description:

Male and female participants with HCV GT2 infection take uprifosbuvir 450 mg + RZR 180 mg for 12 weeks.

Reporting group title	HCV GT3
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Reporting group description:

Male and female participants with HCV GT3 infection take uprifosbuvir 450 mg + RZR 180 mg for 12 weeks.

Reporting group title	HCV GT4
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Reporting group description:

Male and female participants with HCV GT4 infection take uprifosbuvir 450 mg + RZR 180 mg for 12 weeks.

Reporting group title	HCV GT5
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Reporting group description:

Male and female participants with HCV GT5 infection take uprifosbuvir 450 mg + RZR 180 mg for 12 weeks.

Reporting group title	HCV GT6
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Reporting group description:

Male and female participants with HCV GT6 infection take uprifosbuvir 450 mg + RZR 180 mg for 12 weeks.

Serious adverse events	HCV GT1	HCV GT2	HCV GT3
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 78 (3.85%)	1 / 47 (2.13%)	1 / 61 (1.64%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Ammonia increased			

subjects affected / exposed	0 / 78 (0.00%)	0 / 47 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 78 (0.00%)	0 / 47 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 78 (0.00%)	0 / 47 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 78 (0.00%)	0 / 47 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 78 (1.28%)	0 / 47 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 78 (0.00%)	0 / 47 (0.00%)	0 / 61 (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
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 78 (0.00%)	1 / 47 (2.13%)	0 / 61 (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
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	0 / 78 (0.00%)	0 / 47 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	0 / 78 (0.00%)	0 / 47 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 78 (0.00%)	0 / 47 (0.00%)	0 / 61 (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
Cellulitis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 47 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 47 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	HCV GT4	HCV GT5	HCV GT6
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 56 (3.57%)	0 / 18 (0.00%)	0 / 22 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Ammonia increased			
subjects affected / exposed	0 / 56 (0.00%)	0 / 18 (0.00%)	0 / 22 (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
Blood creatinine increased			

subjects affected / exposed	0 / 56 (0.00%)	0 / 18 (0.00%)	0 / 22 (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
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 56 (0.00%)	0 / 18 (0.00%)	0 / 22 (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
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 56 (0.00%)	0 / 18 (0.00%)	0 / 22 (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
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 56 (0.00%)	0 / 18 (0.00%)	0 / 22 (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
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 56 (1.79%)	0 / 18 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 56 (0.00%)	0 / 18 (0.00%)	0 / 22 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 56 (0.00%)	0 / 18 (0.00%)	0 / 22 (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
Musculoskeletal and connective tissue disorders			

Rhabdomyolysis			
subjects affected / exposed	0 / 56 (0.00%)	0 / 18 (0.00%)	0 / 22 (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
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 56 (1.79%)	0 / 18 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 56 (0.00%)	0 / 18 (0.00%)	0 / 22 (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
Sinusitis			
subjects affected / exposed	0 / 56 (0.00%)	0 / 18 (0.00%)	0 / 22 (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

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

Non-serious adverse events	HCV GT1	HCV GT2	HCV GT3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 78 (35.90%)	20 / 47 (42.55%)	30 / 61 (49.18%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 78 (0.00%)	0 / 47 (0.00%)	0 / 61 (0.00%)
occurrences (all)	0	0	0
Blood pressure increased			
subjects affected / exposed	0 / 78 (0.00%)	0 / 47 (0.00%)	0 / 61 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	2 / 78 (2.56%)	0 / 47 (0.00%)	0 / 61 (0.00%)
occurrences (all)	3	0	0
Contusion			

subjects affected / exposed occurrences (all)	1 / 78 (1.28%) 1	1 / 47 (2.13%) 1	0 / 61 (0.00%) 0
Joint injury subjects affected / exposed occurrences (all)	0 / 78 (0.00%) 0	0 / 47 (0.00%) 0	0 / 61 (0.00%) 0
Meniscus injury subjects affected / exposed occurrences (all)	0 / 78 (0.00%) 0	0 / 47 (0.00%) 0	0 / 61 (0.00%) 0
Traumatic haemorrhage subjects affected / exposed occurrences (all)	0 / 78 (0.00%) 0	0 / 47 (0.00%) 0	0 / 61 (0.00%) 0
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	3 / 78 (3.85%) 3	0 / 47 (0.00%) 0	4 / 61 (6.56%) 4
Headache subjects affected / exposed occurrences (all)	7 / 78 (8.97%) 9	5 / 47 (10.64%) 6	10 / 61 (16.39%) 13
Somnolence subjects affected / exposed occurrences (all)	0 / 78 (0.00%) 0	0 / 47 (0.00%) 0	0 / 61 (0.00%) 0
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	5 / 78 (6.41%) 5	1 / 47 (2.13%) 1	6 / 61 (9.84%) 6
Fatigue subjects affected / exposed occurrences (all)	14 / 78 (17.95%) 15	5 / 47 (10.64%) 5	5 / 61 (8.20%) 5
Oedema peripheral subjects affected / exposed occurrences (all)	0 / 78 (0.00%) 0	0 / 47 (0.00%) 0	1 / 61 (1.64%) 1
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	1 / 78 (1.28%) 1	1 / 47 (2.13%) 1	1 / 61 (1.64%) 1
Constipation			

subjects affected / exposed	2 / 78 (2.56%)	1 / 47 (2.13%)	1 / 61 (1.64%)
occurrences (all)	2	1	1
Diarrhoea			
subjects affected / exposed	3 / 78 (3.85%)	2 / 47 (4.26%)	2 / 61 (3.28%)
occurrences (all)	3	2	2
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 78 (1.28%)	0 / 47 (0.00%)	0 / 61 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	7 / 78 (8.97%)	1 / 47 (2.13%)	4 / 61 (6.56%)
occurrences (all)	9	1	5
Toothache			
subjects affected / exposed	1 / 78 (1.28%)	1 / 47 (2.13%)	0 / 61 (0.00%)
occurrences (all)	5	1	0
Vomiting			
subjects affected / exposed	4 / 78 (5.13%)	0 / 47 (0.00%)	2 / 61 (3.28%)
occurrences (all)	4	0	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 78 (2.56%)	0 / 47 (0.00%)	1 / 61 (1.64%)
occurrences (all)	2	0	1
Oropharyngeal pain			
subjects affected / exposed	1 / 78 (1.28%)	2 / 47 (4.26%)	1 / 61 (1.64%)
occurrences (all)	1	3	1
Rhinitis allergic			
subjects affected / exposed	0 / 78 (0.00%)	0 / 47 (0.00%)	0 / 61 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 78 (0.00%)	0 / 47 (0.00%)	1 / 61 (1.64%)
occurrences (all)	0	0	1
Psoriasis			
subjects affected / exposed	0 / 78 (0.00%)	0 / 47 (0.00%)	0 / 61 (0.00%)
occurrences (all)	0	0	0
Rash			

subjects affected / exposed occurrences (all)	0 / 78 (0.00%) 0	3 / 47 (6.38%) 4	3 / 61 (4.92%) 3
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 78 (0.00%)	0 / 47 (0.00%)	1 / 61 (1.64%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	0 / 78 (0.00%)	1 / 47 (2.13%)	3 / 61 (4.92%)
occurrences (all)	0	1	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 78 (3.85%)	0 / 47 (0.00%)	1 / 61 (1.64%)
occurrences (all)	3	0	1
Muscle spasms			
subjects affected / exposed	1 / 78 (1.28%)	0 / 47 (0.00%)	1 / 61 (1.64%)
occurrences (all)	1	0	1
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 78 (0.00%)	0 / 47 (0.00%)	0 / 61 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 47 (0.00%)	0 / 61 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 78 (2.56%)	3 / 47 (6.38%)	2 / 61 (3.28%)
occurrences (all)	3	3	2
Urinary tract infection			
subjects affected / exposed	3 / 78 (3.85%)	1 / 47 (2.13%)	0 / 61 (0.00%)
occurrences (all)	3	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 78 (3.85%)	2 / 47 (4.26%)	3 / 61 (4.92%)
occurrences (all)	3	2	3
Hyperkalaemia			
subjects affected / exposed	0 / 78 (0.00%)	0 / 47 (0.00%)	0 / 61 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	HCV GT4	HCV GT5	HCV GT6
Total subjects affected by non-serious adverse events subjects affected / exposed	22 / 56 (39.29%)	14 / 18 (77.78%)	10 / 22 (45.45%)
Investigations			
Blood creatine phosphokinase increased subjects affected / exposed	1 / 56 (1.79%)	3 / 18 (16.67%)	0 / 22 (0.00%)
occurrences (all)	1	3	0
Blood pressure increased subjects affected / exposed	0 / 56 (0.00%)	1 / 18 (5.56%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Accidental overdose subjects affected / exposed	2 / 56 (3.57%)	1 / 18 (5.56%)	0 / 22 (0.00%)
occurrences (all)	2	1	0
Contusion subjects affected / exposed	1 / 56 (1.79%)	1 / 18 (5.56%)	0 / 22 (0.00%)
occurrences (all)	1	1	0
Joint injury subjects affected / exposed	0 / 56 (0.00%)	1 / 18 (5.56%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Meniscus injury subjects affected / exposed	0 / 56 (0.00%)	1 / 18 (5.56%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Traumatic haemorrhage subjects affected / exposed	0 / 56 (0.00%)	1 / 18 (5.56%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness subjects affected / exposed	3 / 56 (5.36%)	0 / 18 (0.00%)	0 / 22 (0.00%)
occurrences (all)	4	0	0
Headache subjects affected / exposed	8 / 56 (14.29%)	2 / 18 (11.11%)	1 / 22 (4.55%)
occurrences (all)	10	2	1
Somnolence			

subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	1 / 18 (5.56%) 1	0 / 22 (0.00%) 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 56 (0.00%)	0 / 18 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	4 / 56 (7.14%)	0 / 18 (0.00%)	1 / 22 (4.55%)
occurrences (all)	4	0	1
Oedema peripheral			
subjects affected / exposed	0 / 56 (0.00%)	1 / 18 (5.56%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 56 (3.57%)	2 / 18 (11.11%)	1 / 22 (4.55%)
occurrences (all)	2	2	1
Constipation			
subjects affected / exposed	1 / 56 (1.79%)	0 / 18 (0.00%)	2 / 22 (9.09%)
occurrences (all)	1	0	2
Diarrhoea			
subjects affected / exposed	3 / 56 (5.36%)	2 / 18 (11.11%)	1 / 22 (4.55%)
occurrences (all)	3	2	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 56 (0.00%)	1 / 18 (5.56%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	5 / 56 (8.93%)	1 / 18 (5.56%)	1 / 22 (4.55%)
occurrences (all)	6	1	1
Toothache			
subjects affected / exposed	0 / 56 (0.00%)	0 / 18 (0.00%)	2 / 22 (9.09%)
occurrences (all)	0	0	2
Vomiting			
subjects affected / exposed	1 / 56 (1.79%)	1 / 18 (5.56%)	1 / 22 (4.55%)
occurrences (all)	1	1	1
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	2 / 56 (3.57%) 2	0 / 18 (0.00%) 0	2 / 22 (9.09%) 2
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	0 / 18 (0.00%) 0	2 / 22 (9.09%) 3
Rhinitis allergic subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	1 / 18 (5.56%) 1	0 / 22 (0.00%) 0
Skin and subcutaneous tissue disorders			
Pruritus subjects affected / exposed occurrences (all)	2 / 56 (3.57%) 2	0 / 18 (0.00%) 0	2 / 22 (9.09%) 2
Psoriasis subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	1 / 18 (5.56%) 1	0 / 22 (0.00%) 0
Rash subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	0 / 18 (0.00%) 0	0 / 22 (0.00%) 0
Psychiatric disorders			
Depression subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	1 / 18 (5.56%) 1	0 / 22 (0.00%) 0
Insomnia subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	1 / 18 (5.56%) 1	0 / 22 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	2 / 56 (3.57%) 3	2 / 18 (11.11%) 3	0 / 22 (0.00%) 0
Muscle spasms subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	2 / 18 (11.11%) 2	0 / 22 (0.00%) 0
Infections and infestations			
Influenza			

subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	1 / 18 (5.56%) 1	0 / 22 (0.00%) 0
Rhinitis subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3	0 / 18 (0.00%) 0	0 / 22 (0.00%) 0
Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 56 (3.57%) 2	3 / 18 (16.67%) 3	1 / 22 (4.55%) 2
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	1 / 18 (5.56%) 1	1 / 22 (4.55%) 1
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	1 / 18 (5.56%) 1	0 / 22 (0.00%) 0
Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	1 / 18 (5.56%) 1	0 / 22 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 September 2016	Amendment 1: Added stopping criteria and rescue treatment option based on USA Food and Drug Administration (FDA) feedback
02 November 2016	Amendment 2: The study design was changed to include a rescue regimen in the event that virologic futility criteria are met. Also added anti hepatitis B core antibody (anti-HBc) testing.
07 December 2016	Amendment 4: Incorporated all changes from Amendment 3 to make this language available to all countries. Further refined the laboratory testing criteria for Hepatitis B virus (HBV). Additionally, added an Event of Clinical Interest related to HBV reactivation, based on the results from this monitoring.
06 December 2017	Amendment 5: The 3-year long-term follow-up period was removed from the trial. This change was made to due to a strategic decision to discontinue the development of the investigational product.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
05 March 2018	This study was terminated by the Sponsor based on a review of available Phase 2 efficacy data.	-

Notes:

Limitations and caveats

None reported