Clinical trial results:
Phase 2, Open-Label Study to Investigate the Pharmacokinetics, Efficacy, Safety, and Tolerability of the Combination of Simeprevir (TMC435), Daclatasvir (BMS-790052) and Ribavirin (RBV) in Patients with Recurrent Chronic Hepatitis C Genotype 1b Infection after Orthotopic Liver Transplantation

Summary

EudraCT number	2013-002726-23
Trial protocol	ES IT
Global end of trial date	28 July 2015

Results information

Result version number	v1 (current)
This version publication date	03 July 2016
First version publication date	03 July 2016

Trial information

Trial identification

Sponsor protocol code	TMC435HPC3016

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01938625
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development NV
Sponsor organisation address	Turnhoutseweg 30, Beerse, Belgium, 2340
Public contact	Clinical Registry Group, Janssen Research & Development NV, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research & Development NV, ClinicalTrialsEU@its.jnj.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	28 July 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective was to evaluate the effect of steady-state Simeprevir (SMV) and Daclatasvir (DCV) on the steady-state pharmacokinetics of cyclosporine and tacrolimus when administered as a regimen containing SMV [150 milligram once a day (mg qd)] , DCV (60 mg qd) and Ribavirin (RBV) (1,000 to 1,200 mg per day) in post-orthotopic liver transplantation (OLT) subjects with recurrent hepatitis C virus (HCV) genotype 1b infection and to evaluate the efficacy of a 24-week treatment regimen containing SMV, DCV, and RBV with respect to the proportion of HCV genotype 1b infected post- OLT subjects achieving sustained virologic response 12 weeks after end of treatment (EOT) (SVR12).

Protection of trial subjects:

The trial was performed in accordance with the principles of good clinical practices [GCP] as outlined in 21 code of federal regulations [CFR] Parts 50, 56, and 312 and the Declaration of Helsinki and its subsequent revisions, and the European Union Clinical Trials Directive that are consistent with Good Clinical Practices and applicable regulatory requirements. During the study, various safety evaluations were performed at different timepoints like clinical laboratory assessments (hematology, serum chemistry and urinalysis), vital signs, 12-lead electrocardiograms (ECGs) and physical examination, all adverse events were reported from signing the informed consent until the follow-up visit.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 December 2013
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	Germany: 7
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Poland: 7
Worldwide total number of subjects	35
EEA total number of subjects	35

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)	26
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was conducted in 2 parts (Part 1 and Part 2). Total 21 subjects were included in Part 1 and 14 subjects were included in Part 2 of the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cyclosporine

Arm description:

Subjects received Cyclosporine as stable immunosuppressant therapy. The subjects also received Simeprevir (SMV) 150 milligram (mg) capsule administered once daily with food, Daclatasvir (DCV) 60 mg tablet once daily and Ribavirin (RBV) 1,000 or 1,200 mg/day (bid regimen) tablet (5/6 x 200 mg) with food for 24 weeks.

Arm type	Immunosuppressant therapy
Investigational medicinal product name	Cyclosporine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Cyclosporine as stable immunosuppressant therapy.

Investigational medicinal product name	Simeprevir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received Simeprevir (SMV) 150 milligram (mg) capsule administered once daily with food for 24 weeks.

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

Dosage and administration details:

Subjects received Daclatasvir (DCV) 60 mg tablet once daily for 24 weeks.

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

Dosage and administration details:

Subjects received Ribavirin (RBV) 1,000 or 1,200 mg/day (bid regimen) tablet (5/6 x 200 mg) with food for 24 weeks.

Arm title	Tacrolimus

Arm description:

Subjects received Tacrolimus as stable immunosuppressant therapy. The subjects also received Simeprevir (SMV) 150 milligram (mg) once daily capsule administered with food, Daclatasvir (DCV) 60 mg once daily tablet and Ribavirin (RBV) 1,000 or 1,200 mg/day (bid regimen) tablet (5/6 x 200 mg) with food for 24 weeks.

Arm type	Immunosuppressant therapy.
Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Tacrolimus as stable immunosuppressant therapy.

Investigational medicinal product name	Simeprevir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received Simeprevir (SMV) 150 milligram (mg) capsule administered once daily with food for 24 weeks.

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

Dosage and administration details:

Subjects received Daclatasvir (DCV) 60 mg tablet once daily for 24 weeks.

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

Dosage and administration details:

Subjects received Ribavirin (RBV) 1,000 or 1,200 mg/day (bid regimen) tablet (5/6 x 200 mg) with food for 24 weeks.

Number of subjects in period 1	Cyclosporine	Tacrolimus
Started	10	25
Completed	10	23
Not completed	0	2
Adverse event, serious fatal	-	1

Consent withdrawn by subject	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Cyclosporine
Reporting group description:	
Subjects received Cyclosporine as stable immunosuppressant therapy. The subjects also received Simeprevir (SMV) 150 milligram (mg) capsule administered once daily with food, Daclatasvir (DCV) 60 mg tablet once daily and Ribavirin (RBV) 1,000 or 1,200 mg/day (bid regimen) tablet (5/6 x 200 mg) with food for 24 weeks.	
Reporting group title	Tacrolimus
Reporting group description:	
Subjects received Tacrolimus as stable immunosuppressant therapy. The subjects also received Simeprevir (SMV) 150 milligram (mg) once daily capsule administered with food, Daclatasvir (DCV) 60 mg once daily tablet and Ribavirin (RBV) 1,000 or 1,200 mg/day (bid regimen) tablet (5/6 x 200 mg) with food for 24 weeks.	

Reporting group values	Cyclosporine	Tacrolimus	Total
Number of subjects	10	25	35
Title for AgeCategorical			
Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	7	19	26
From 65 to 84 years	3	6	9
85 years and over	0	0	0
Title for AgeContinuous			
Units: years			
median	64.5	61	
full range (min-max)	52 to 69	27 to 69	-
Title for Gender			
Units: subjects			
Female	4	9	13
Male	6	16	22

End points

End points reporting groups

Reporting group title	Cyclosporine

Reporting group description:

Subjects received Cyclosporine as stable immunosuppressant therapy. The subjects also received Simeprevir (SMV) 150 milligram (mg) capsule administered once daily with food, Daclatasvir (DCV) 60 mg tablet once daily and Ribavirin (RBV) 1,000 or 1,200 mg/day (bid regimen) tablet (5/6 x 200 mg) with food for 24 weeks.

Reporting group title	Tacrolimus

Reporting group description:

Subjects received Tacrolimus as stable immunosuppressant therapy. The subjects also received Simeprevir (SMV) 150 milligram (mg) once daily capsule administered with food, Daclatasvir (DCV) 60 mg once daily tablet and Ribavirin (RBV) 1,000 or 1,200 mg/day (bid regimen) tablet (5/6 x 200 mg) with food for 24 weeks.

Subject analysis set title	Simeprevir
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Pharmacokinetic (PK) population included all randomized subjects who received at least 1 dose of Simeprevir (Part 1 and Part 2) and with serial PK Blood samples.

Subject analysis set title	Daclatasvir
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Pharmacokinetic (PK) population included all randomized subjects who received at least 1 dose of Daclatasvir (Part 1 and Part 2) and with serial PK Blood samples.

Primary: Percentage of Subjects With A Sustained Virologic Response (SVR)12 Weeks After The End of Treatment

End point title	Percentage of Subjects With A Sustained Virologic Response (SVR)12 Weeks After The End of Treatment[1]

End point description:

Sustained Virologic Response (SVR) 12 is defined as the proportion of subjects (ITT analysis set) hepatitis C virus HCV RNA < 25 IU/mL detectable or undetectable at 12 weeks after the end of treatment. Intend to treat (ITT) population includes subjects who received at least 1 dose of investigational medication (SMV, DCV and/or RBV).

End point type	Primary

End point timeframe:

Week 36

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: Descriptive statistical analysis has been performed for this endpoint.

End point values	Cyclosporine	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	25		
Units: Percentage of subjects				
number (confidence interval 95%)	100 (69.2 to 100)	88 (68.8 to 97.5)		

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Observed Whole Blood Concentration (Cmax) of Cyclosporine (CsA)

End point title	Maximum Observed Whole Blood Concentration (Cmax) of Cyclosporine (CsA)[2][3]

End point description:

The Whole blood Concentration (Cmax) is defined as maximum observed analyte concentration. Pharmacokinetic (PK) population included all randomized subjects who received at least serial dose of the study drug and with 1 PK blood samples.

End point type	Primary

End point timeframe:

Pre-dose (within 15 minutes before the intake of study drug) and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose taken on Day -1 and Day 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: Descriptive statistical analysis has been performed for this endpoint.

[3] - 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: Descriptive statistical analysis has been performed for this endpoint..

End point values	Cyclosporine			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Cyclosporine (CsA): Day -1	487 (± 243)			
(CsA+ SMV+DCV+RBV)): Day 14	379 (± 198)			

Statistical analyses

No statistical analyses for this end point

Primary: Trough Whole Blood Concentration (Ctrough) of Cyclosporine

End point title	Trough Whole Blood Concentration (Ctrough) of

End point description:

The Ctrough is the whole blood concentration before dosing or at the end of the dosing interval of any dose other than the first dose in a multiple dosing regimen. Pharmacokinetic (PK) population included all randomized subjects who received at least 1 dose of the study drug and with 1 PK blood sample.

End point type	Primary

End point timeframe:

Pre-dose (within 15 minutes before the intake of study drug) sample taken on Day -1 and Day 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: Descriptive statistical analysis has been performed for this endpoint.

[5] - 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: Descriptive statistical analysis has been performed for this endpoint.

End point values	Cyclosporine			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: nanogram per milligram (ng/mL)				
arithmetic mean (standard deviation)				
Cyclosporine (CsA): Day -1	79.1 (± 44.2)			
(CsA+ SMV+DCV+RBV)): Day 14	99.9 (± 60.7)			

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Whole Blood Concentration-Time Curve From Time Zero to 24 Time (AUC[0-24]) of Cyclosporine

End point title	Area Under the Whole Blood Concentration-Time Curve From Time Zero to 24 Time (AUC[0-24]) of Cyclosporine[6][7]

End point description:

The AUC (0-24) is the area under the whole blood concentration-time curve during 24 hour time. Pharmacokinetic (PK) population included all randomized subjects who received at least 1 dose of the study drug and with serial PK blood samples. Here 'n' indicates the number of subjects analysed for this endpoint.

End point type	Primary

End point timeframe:

Pre-dose (within 15 minutes before the intake of study drug) and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on day -1 and day 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: Descriptive statistical analysis has been performed for this endpoint.

[7] - 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: Descriptive statistical analysis has been performed for this endpoint.

End point values	Cyclosporine			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: nanogram hour per milliliter (ng.h/mL)				
arithmetic mean (standard deviation)				
Cyclosporine (CsA): Day -1 (n=5)	4066 (± 2742)			
(CsA+ SMV+DCV+RBV)): Day 14 (n=7)	4141 (± 2594)			

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Observed Whole Blood Concentration (Cmax) of Tacrolimus (Tac)

End point title	Maximum Observed Whole Blood Concentration (Cmax) of

	Tacrolimus (Tac)[8][9]

End point description:

The whole blood concentration (Cmax) is defined as maximum observed analyte concentration. Pharmacokinetic (PK) population included all randomized subjects who received at least 1 dose of the study drug and with 1 PK blood sample. Here 'n' indicates number of subjects analysed for this endpoint.

End point type	Primary

End point timeframe:

Pre-dose (within 15 minutes before the intake of study drug) taken on Day -1 and Day 14

Notes:

[8] - 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: Descriptive statistical analysis has been performed for this endpoint.

[9] - 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: Descriptive statistical analysis has been performed for this endpoint.

End point values	Tacrolimus			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: nanogram per milligram (ng/mL)				
arithmetic mean (standard deviation)				
Part 1: Tac (Day-1: n=11)	10.5 (± 3.44)			
Part 1: Tac + SMV + DCV + RBV (Day 14: n=11)	7.52 (± 2.3)			
Part 2: Tac (Day -1: n=13)	10.9 (± 8.13)			
Part 2: Tac + SMV + DCV + RBV (Day 14: n=14)	9 (± 4.81)			

Statistical analyses

No statistical analyses for this end point

Primary: Trough Whole Blood Concentration (Ctrough) of Tacrolimus

End point title	Trough Whole Blood Concentration (Ctrough) of

End point description:

The Ctrough is the whole blood concentration before dosing or at the end of the dosing interval of any dose other than the first dose in a multiple dosing regimen. Pharmacokinetic (PK) population included all randomized subjects who received at least 1 dose of the study drug and with 1 PK blood sample. Here 'n' indicates number of subjects analysed for this endpoint.

End point type	Primary

End point timeframe:

Pre-dose (within 15 minutes before the intake of study drug) on Day -1 and Day 14.

Notes:

[10] - 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: Descriptive statistical analysis has been performed for this endpoint.

[11] - 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: Descriptive statistical analysis has been performed for this endpoint.

End point values	Tacrolimus			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: nanogram per milligram (ng/mL)				
arithmetic mean (standard deviation)				
Part 1: Tac (Day-1: n=9)	6.03 (± 2.03)			
Part 1: Tac + SMV + DCV + RBV (Day 14: n=11)	4.77 (± 2.01)			
Part 2: Tac (Day -1: n=13)	4.71 (± 2.08)			
Part 2: Tac + SMV + DCV + RBV (Day 14: n=14)	4.82 (± 1.82)			

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Whole Blood Concentration-Time Curve From Time Zero to 24 Hour Time (AUC[0-24h]) of Tacrolimus

End point title	Area Under the Whole Blood Concentration-Time Curve From Time Zero to 24 Hour Time (AUC[0-24h]) of Tacrolimus[12][13]

End point description:

The AUC (0-24 h) is the area under the whole blood concentration-time curve from during 24 hour time. Pharmacokinetic (PK) population included all randomized subjects who received at least 1 dose of the study drug and with serial PK blood samples. Here 'n' indicates number of subjects analysed for this endpoint.

End point type	Primary

End point timeframe:

Pre-dose (within 15 minutes before the intake of study drug) and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose taken on Day -1 and Day 14 after tacrolimus dose

Notes:

[12] - 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: Descriptive statistical analysis has been performed for this endpoint.

[13] - 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: Descriptive statistical analysis has been performed for this endpoint.

End point values	Tacrolimus			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: nanogram hour per milliliter (ng.h/mL)				
arithmetic mean (standard deviation)				
Part 1: Tac (Day-1: n=9)	177 (± 58.1)			
Part 1: Tac + SMV + DCV + RBV (Day 14: n=10)	129 (± 50.2)			
Part 2: Tac (Day -1: n=13)	147 (± 69)			
Part 2: Tac + SMV + DCV + RBV (Day 14: n=14)	144 (± 56.7)			

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Observed Plasma Concentration (Cmax) of Simeprevir (SMV) and Daclatasvir (DCV)

End point title	Maximum Observed Plasma Concentration (Cmax) of Simeprevir (SMV) and Daclatasvir (DCV)[14]

End point description:

The plasma concentration (Cmax) is defined as maximum observed analyte concentration. Pharmacokinetic (PK) population included all randomized subjects who received at least 1 dose of the study drug and with 1 PK blood sample. Here 'n' indicates number of subjects analysed for this endpoint.

End point type	Primary

End point timeframe:

Pre-dose (within 15 minutes before the intake of study drug) and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose taken on Day 14

Notes:

[14] - 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: Descriptive statistical analysis has been performed for this endpoint.

End point values	Simeprevir	Daclatasvir		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	13		
Units: nanogram per milligram (ng/mL)				
arithmetic mean (standard deviation)				
Part 1: CsA+SMV+DCV+RBV: Day 14 (n=10,10)	17640 (± 9365)	2532 (± 1736)		
Part 1: Tac+SMV+DCV+RBV: Day 14 (n=11,9)	6897 (± 4620)	1632 (± 589)		
Part 2: Tac+SMV+DCV+RBV: Day 14 (n=14,13)	7764 (± 5402)	1310 (± 779)		

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Plasma Concentration (Ctrough) of Simeprevir (SMV) And Daclatasvir (DCV)

End point title	Trough Plasma Concentration (Ctrough) of Simeprevir (SMV) And Daclatasvir (DCV)

End point description:

The Ctrough is the plasma concentration before dosing or at the end of the dosing interval of any dose other than the first dose in a multiple dosing regimen. Pharmacokinetic (PK) population included all randomized subjects who received at least 1 dose of the study drug and with 1 PK blood sample. Here 'n' indicates number of subjects analysed for this endpoint.

End point type	Secondary

End point timeframe:

Pre-dose (within 15 minutes before the intake of study drug) and taken on day 14, week 4, 8 and 12.

End point values	Simeprevir	Daclatasvir		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	13		
Units: nanogram per milligram (ng/mL)				
arithmetic mean (standard deviation)				
Part 1: CsA+SMV+DCV+RBV: Day 14 (n=10,10)	11653 (± 8338)	1368 (± 1319)		
Part 1: Tac+SMV+DCV+RBV: Day 14 (n=11,9)	2589 (± 3131)	564 (± 524)		
Part 2: Tac+SMV+DCV+RBV: Day 14 (n=14, 13)	3457 (± 3852)	468 (± 437)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Observed Plasma Concentration (Tmax) of Simeprevir (SMV) and Daclatasvir (DCV)

End point title	Time to Reach Maximum Observed Plasma Concentration (Tmax) of Simeprevir (SMV) and Daclatasvir (DCV)

End point description:

The Tmax is defined as actual sampling time to reach maximum observed analyte concentration. Pharmacokinetic (PK) population included all randomized subjects who received at least 1 dose of the study drug and with 1 PK blood sample. Here 'n' indicates number of subjects analysed for this endpoint.

End point type	Secondary

End point timeframe:

Pre-dose (within 15 minutes before the intake of study drug) and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on Week 2

End point values	Simeprevir	Daclatasvir		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	13		
Units: hour (h)				
median (full range (min-max))				
Part 1: CsA+SMV+DCV+RBV: Day 14 (n=10,10)	5 (4.92 to 9)	3.5 (1 to 6)		
Part 1: Tac+SMV+DCV+RBV: Day 14 (n=11,9)	5.58 (2 to 9.03)	2 (0.92 to 6)		
Part 2: Tac+SMV+DCV+RBV: Day 14 (n=14, 13)	6 (4 to 9)	3.92 (1 to 6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve From Time Zero to End of Dosing Interval (AUCtau) of Simeprevir (SMV) and Daclatasvir (DCV)

End point title	Area Under the Curve From Time Zero to End of Dosing Interval (AUCtau) of Simeprevir (SMV) and Daclatasvir (DCV)

End point description:

The AUCtau is the measure of the plasma drug concentration from time zero to end of dosing interval. It is used to characterize drug absorption. Pharmacokinetic (PK) population included all randomized subjects who received at least 1 dose of the study drug and with 1 PK blood sample. Here 'n' indicates number of subject analysed for this endpoint.

End point type	Secondary

End point timeframe:

Pre-dose (within 15 minutes before the intake of study drug) and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose taken on Day 14

End point values	Simeprevir	Daclatasvir		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	13		
Units: nanogram hour per milliliter (ng.h/mL)				
arithmetic mean (standard deviation)				
Part 1: CsA+SMV+DCV+RBV: Day 14 (n=10,10)	339848 (± 205582)	46114 (± 37087)		
Part 1: Tac+SMV+DCV+RBV: Day 14 (n=11,9)	107792 (± 89990)	22349 (± 11376)		
Part 2: Tac+SMV+DCV+RBV: Day 14 (n=14,13)	116242 (± 96234)	18441 (± 13379)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With A Sustained Virologic Response (SVR) 4 And 24 Weeks After The End of Treatment

End point title	Percentage of Subjects With A Sustained Virologic Response (SVR) 4 And 24 Weeks After The End of Treatment

End point description:

SVR 4 and SVR 24 are defined as the proportion of subjects with HCV RNA <25 IU/mL detectable or undetectable at the hepatitis C virus (HCV) ribonucleic acid (RNA) <25 IU/mL detectable or undetectable at week 4 or week 24 after the end of treatment, respectively. Intent to treat (ITT) population includes subjects who received at least 1 dose of investigational medication (SMV, DCV and/or RBV).

End point type	Secondary

End point timeframe:

Week 28 and 48

End point values	Cyclosporine	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	25		
Units: Percentage of subjects				
number (confidence interval 95%)				
SVR 4	100 (69.2 to 100)	88 (68.8 to 97.5)		
SVR 24	100 (69.2 to 100)	88 (68.8 to 97.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: On-Treatment Virologic Response With Undetectable HCV RNA (less than 25 IU/mL undetectable) and HCV RNA Detectable Less Than 25 IU/mL Detectable

End point title	On-Treatment Virologic Response With Undetectable HCV RNA (less than 25 IU/mL undetectable) and HCV RNA Detectable Less Than 25 IU/mL Detectable

End point description:

Rapid virologic response (RVR), defined as undetectable HCV RNA at Week 4 of treatment; extended rapid virologic response (eRVR), defined as undetectable HCV RNA at Week 4 and Week 12 of treatment and complete early virologic response (cEVR), defined as undetectable HCV RNA at Week 12. RVR signifies Rapid virologic response: undetectable HCV RNA at Week 4 while on treatment. cEVR signifies Complete early rapid virologic response: undetectable HCV RNA at Week 12 while on treatment. eRVR signifies extended Rapid Virologic Response: undetectable HCV RNA at Week 4 and Week 12 while on treatment. Intent to treat (ITT) population includes subjects who received at least 1 dose of investigational medication (SMV, DCV and/or RBV).

End point type	Secondary

End point timeframe:

Up to end of treatment (Weeks 2, 4, 12, and 24)

End point values	Cyclosporine	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	25		
Units: International Unit per milliliter(IU/mL)				
number (not applicable)				
Week 2 (<25 IU/mL detectable)	3	9		
Week 2 (<25 IU/mL undetectable)	1	3		
Week 4 (<25 IU/mL detectable)	3	6		
Week 4 (<25 IU/mL undetectable)(RVR)	7	17		

Week 12 (<25 IU/mL undetectable) (cEVR)	10	24		
Week 24 (<25 IU/mL undetectable)	10	21		
Week 4 and Week 12 (<25 IU/mL undetectable) (eRVR)	7	16		
EOT (<25 IU/mL undetectable)	10	22		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With On-Treatment Failure After Treatment With Regimen Simeprevir, Daclatasvir and RBV

End point title	Number of Subjects With On-Treatment Failure After Treatment With Regimen Simeprevir, Daclatasvir and RBV

End point description:

On-treatment failure is defined as HCV RNA level is greater than or equal to 25 IU/mL at end of treatment. Intent to treat (ITT) population includes subjects who received at least 1 dose of investigational medication (SMV, DCV and/or RBV).

End point type	Secondary

End point timeframe:

Screening, Baseline and Week 1 to 24

End point values	Cyclosporine	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	11		
Units: Number of subjects	0	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events

End point title	Number of Subjects With Adverse Events

End point description:

An AE is any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. An SAE is an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Safety population included all randomized subjects who received at least 1 dose of the study drug.

End point type	Secondary

End point timeframe:

Up to 48 Weeks

End point values	Cyclosporine	Tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	25		
Units: Number of Subjects	10	25		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Screening to Follow-up (up to 24 Weeks after actual end of treatment)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Cyclosporine

Reporting group description:

Subjects received Cyclosporine as stable immunosuppressant therapy. The subjects also received Simeprevir (SMV) 150 milligram (mg) capsule administered once daily with food, Daclatasvir (DCV) 60 mg tablet once daily and Ribavirin (RBV) 1,000 or 1,200 mg/day (bid regimen) tablet (5/6 x 200 mg) with food for 24 weeks.

Reporting group title	Tacrolimus

Reporting group description:

Subjects received Tacrolimus as stable immunosuppressant therapy. The subjects also received Simeprevir (SMV) 150 milligram (mg) capsule administered once daily with food, Daclatasvir (DCV) 60 mg tablet once daily and Ribavirin (RBV) 1,000 or 1,200 mg/day (bid regimen) tablet (5/6 x 200 mg) with food for 24 weeks.

Reporting group title	Overall

Reporting group description:

All the subjects received Simeprevir (SMV) 150 milligram (mg) capsule administered once daily with food, Daclatasvir (DCV) 60 mg tablet once daily and Ribavirin (RBV) 1,000 or 1,200 mg/day (bid regimen) tablet (5/6 x 200 mg) with food for 24 weeks.

Reporting group title	Cyclosporine Follow-Up

Reporting group description:

Subjects received Cyclosporine as stable immunosuppressant therapy. Follow-up Period after treatment with Simeprevir (SMV) 150 milligram (mg) capsule administered once daily with food, Daclatasvir (DCV) 60 mg tablet once daily and Ribavirin (RBV) 1,000 or 1,200 mg/day (bid regimen) tablet (5/6 x 200 mg)with food for 24 weeks after the treatment has been stopped.

Reporting group title	Tacrolimus Follow-Up

Reporting group description:

Subjects received tacrolimus as stable immunosuppressant therapy. Follow-up Period after treatment with Simeprevir (SMV) 150 milligram (mg) capsule administered once daily with food, Daclatasvir (DCV) 60 mg tablet once daily and Ribavirin (RBV) 1,000 or 1,200 mg/day (bid regimen) tablet (5/6 x 200 mg)with food for 24 weeks after the treatmant has been stopped.

Reporting group title	Overall Follow-Up

Reporting group description:

Follow-up Period after treatment with Simeprevir (SMV) 150 milligram (mg) capsule administered once daily with food, Daclatasvir (DCV) 60 mg tablet once daily and Ribavirin (RBV) 1,000 or 1,200 mg/day (bid regimen) tablet (5/6 x 200 mg) with food for 24 weeks after the treatment has been stopped.

Serious adverse events	Cyclosporine	Tacrolimus	Overall
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 10 (40.00%)	4 / 25 (16.00%)	8 / 35 (22.86%)
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)			
Lymphoma			
subjects affected / exposed	0 / 10 (0.00%)	1 / 25 (4.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	0 / 10 (0.00%)	1 / 25 (4.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 10 (0.00%)	1 / 25 (4.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 25 (4.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocytosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (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
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	3 / 10 (30.00%)	0 / 25 (0.00%)	3 / 35 (8.57%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (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
Abdominal pain upper			
subjects affected / exposed	0 / 10 (0.00%)	1 / 25 (4.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (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
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)	1 / 25 (4.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholestasis			

subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (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
Hyperbilirubinaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 25 (4.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Micturition disorder			
subjects affected / exposed	0 / 10 (0.00%)	1 / 25 (4.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Empyema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (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
Escherichia urinary tract infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Genital herpes			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis bacterial			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (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
Pneumonia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 25 (4.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (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
Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 25 (4.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cyclosporine Follow-Up	Tacrolimus Follow-Up	Overall Follow-Up
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)	3 / 25 (12.00%)	4 / 35 (11.43%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphoma			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (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			
Facial bones fracture			

subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (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
Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	0 / 10 (0.00%)	1 / 25 (4.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (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
Syncope			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (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 and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (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
Lymphocytosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 25 (4.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 25 (4.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 10 (0.00%)	1 / 25 (4.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (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
Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (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
Peritoneal haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 25 (4.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (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			
Prostatitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (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
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (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

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (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 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (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
Micturition disorder			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (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 impairment			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (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			
Empyema			
subjects affected / exposed	0 / 10 (0.00%)	1 / 25 (4.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (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
Genital herpes			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (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
Peritonitis bacterial			

subjects affected / exposed	0 / 10 (0.00%)	1 / 25 (4.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (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
Skin infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 25 (4.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (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	Cyclosporine	Tacrolimus	Overall
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	23 / 25 (92.00%)	33 / 35 (94.29%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 10 (0.00%)	3 / 25 (12.00%)	3 / 35 (8.57%)
occurrences (all)	0	3	3
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 10 (50.00%)	7 / 25 (28.00%)	12 / 35 (34.29%)
occurrences (all)	5	8	13
Fatigue			
subjects affected / exposed	2 / 10 (20.00%)	1 / 25 (4.00%)	3 / 35 (8.57%)
occurrences (all)	2	1	3
Gait disturbance			

subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
General physical health deterioration			
subjects affected / exposed	0 / 10 (0.00%)	2 / 25 (8.00%)	2 / 35 (5.71%)
occurrences (all)	0	2	2
Mucous membrane disorder			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Oedema peripheral			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Pyrexia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 25 (4.00%)	2 / 35 (5.71%)
occurrences (all)	5	2	7
Reproductive system and breast disorders			
Vulvovaginal pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 10 (20.00%)	3 / 25 (12.00%)	5 / 35 (14.29%)
occurrences (all)	3	3	6
Dysphonia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Dyspnoea			
subjects affected / exposed	2 / 10 (20.00%)	1 / 25 (4.00%)	3 / 35 (8.57%)
occurrences (all)	2	1	3
Productive cough			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Pulmonary hypertension			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Psychiatric disorders			

Anger			
subjects affected / exposed	1 / 10 (10.00%)	1 / 25 (4.00%)	2 / 35 (5.71%)
occurrences (all)	1	1	2
Hallucination, visual			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 10 (0.00%)	2 / 25 (8.00%)	2 / 35 (5.71%)
occurrences (all)	0	9	9
Hepatic enzyme increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Congenital, familial and genetic disorders			
Cataract congenital			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Headache			
subjects affected / exposed	1 / 10 (10.00%)	4 / 25 (16.00%)	5 / 35 (14.29%)
occurrences (all)	1	4	5
Restless legs syndrome			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 10 (70.00%)	11 / 25 (44.00%)	18 / 35 (51.43%)
occurrences (all)	17	16	33
Haemolytic anaemia			

subjects affected / exposed	0 / 10 (0.00%)	2 / 25 (8.00%)	2 / 35 (5.71%)
occurrences (all)	0	2	2
Leukopenia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 25 (4.00%)	2 / 35 (5.71%)
occurrences (all)	2	2	4
Thrombocytopenia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences (all)	2	0	2
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 10 (0.00%)	3 / 25 (12.00%)	3 / 35 (8.57%)
occurrences (all)	0	3	3
Eye disorders			
Ocular icterus			
subjects affected / exposed	1 / 10 (10.00%)	1 / 25 (4.00%)	2 / 35 (5.71%)
occurrences (all)	1	1	2
Visual acuity reduced			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Aphthous stomatitis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 25 (4.00%)	2 / 35 (5.71%)
occurrences (all)	1	1	2
Constipation			
subjects affected / exposed	1 / 10 (10.00%)	1 / 25 (4.00%)	2 / 35 (5.71%)
occurrences (all)	1	1	2
Diarrhoea			
subjects affected / exposed	1 / 10 (10.00%)	3 / 25 (12.00%)	4 / 35 (11.43%)
occurrences (all)	1	3	4
Haemorrhoids			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Lip dry			

subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Nausea			
subjects affected / exposed	1 / 10 (10.00%)	3 / 25 (12.00%)	4 / 35 (11.43%)
occurrences (all)	1	5	6
Tongue dry			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Vomiting			
subjects affected / exposed	1 / 10 (10.00%)	2 / 25 (8.00%)	3 / 35 (8.57%)
occurrences (all)	1	4	5
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Hyperbilirubinaemia			
subjects affected / exposed	2 / 10 (20.00%)	2 / 25 (8.00%)	4 / 35 (11.43%)
occurrences (all)	6	7	13
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 10 (0.00%)	2 / 25 (8.00%)	2 / 35 (5.71%)
occurrences (all)	0	2	2
Erythema			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Photosensitivity reaction			
subjects affected / exposed	1 / 10 (10.00%)	3 / 25 (12.00%)	4 / 35 (11.43%)
occurrences (all)	1	3	4
Pruritus			
subjects affected / exposed	1 / 10 (10.00%)	5 / 25 (20.00%)	6 / 35 (17.14%)
occurrences (all)	1	6	7
Rash			
subjects affected / exposed	1 / 10 (10.00%)	1 / 25 (4.00%)	2 / 35 (5.71%)
occurrences (all)	1	2	3
Renal and urinary disorders			

Renal failure			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 10 (0.00%)	2 / 25 (8.00%)	2 / 35 (5.71%)
occurrences (all)	0	2	2
Muscle spasms			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Myalgia			
subjects affected / exposed	1 / 10 (10.00%)	2 / 25 (8.00%)	3 / 35 (8.57%)
occurrences (all)	1	2	3
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	0 / 10 (0.00%)	2 / 25 (8.00%)	2 / 35 (5.71%)
occurrences (all)	0	2	2
Oral herpes			
subjects affected / exposed	1 / 10 (10.00%)	1 / 25 (4.00%)	2 / 35 (5.71%)
occurrences (all)	2	1	3
Urinary tract infection			
subjects affected / exposed	1 / 10 (10.00%)	2 / 25 (8.00%)	3 / 35 (8.57%)
occurrences (all)	1	2	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Hyperuricaemia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 25 (4.00%)	2 / 35 (5.71%)
occurrences (all)	1	1	2
Hyposideraemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cyclosporine Follow-Up	Tacrolimus Follow-Up	Overall Follow-Up
Total subjects affected by non-serious adverse events			

subjects affected / exposed	2 / 10 (20.00%)	3 / 25 (12.00%)	5 / 35 (14.29%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
General physical health deterioration			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Mucous membrane disorder			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Vulvovaginal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Dysphonia			

subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Productive cough			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Pulmonary hypertension			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anger			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Hallucination, visual			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Hepatic enzyme increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Congenital, familial and genetic disorders			
Cataract congenital			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Nervous system disorders			
Dysgeusia			

subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Restless legs syndrome			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Haemolytic anaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 25 (4.00%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Thrombocytopenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Ocular icterus			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Visual acuity reduced			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Aphthous stomatitis			

subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Lip dry			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Tongue dry			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Erythema			

subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Photosensitivity reaction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 10 (0.00%)	1 / 25 (4.00%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Rash			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Oral herpes			
subjects affected / exposed	0 / 10 (0.00%)	1 / 25 (4.00%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Hyperuricaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 25 (0.00%)	0 / 35 (0.00%)
occurrences (all)	0	0	0
Hyposideraemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 25 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 September 2013	The amendement included the addition of precautionary language on photosensitivity to the Prohibitions and Restrictions section of the protocol. As a follow-up to a recommendation by the US Food and Drug Administration (FDA), it was decided to reintroduce the recommendations with regard to photosensitivity, in all Simeprevir (SMV) studies in which subjects were still being dosed with SMV and in future SMV studies.
30 June 2014	The amendment included changes based on Day 14 pharmacokinetic results from subjects enrolled in Part 1 of the study, subjects who received cyclosporine as immunosuppressant therapy were excluded from Part 2 of the study. Repeat intensive pharmacokinetic sampling to be performed in those Part 1 subjects receiving cyclosporine and whose Simeprevir (SMV) doses were adjusted was added. Repeat intensive pharmacokinetic sampling for SMV and Daclatasvir (DCV) in Part 2 subjects was added in case revision to the dose and/or dosing regimen of SMV and/or DCV were made based on the Week 4 interim analyses. Given the fact that, after review of the Phase 3 data, elevations in direct and indirect bilirubin observed in Phase 3 clinical studies were not considered clinically relevant, specific management of grade 4 isolated bilirubin elevations was updated. Subjects with isolated grade 4 bilirubin elevation in absence of evidence of hepatic decompensation could continue intake of study medication with close monitoring of further increases in bilirubin, or discontinue, at the discretion of the investigator. In addition, rash management guidelines were clarified for photosensitivity conditions. Background information on the study drug was updated (replacement HPC2002 data with data from Phase 2 study AI-444-062) and marketing status of SMV was added (approval US and other regions and ongoing procedures worldwide). Definitions of SVR and treatment failure were revised as per Heath Authority recommendations. Clarification that the screening period of 4 weeks started from the time of signing the Informed Consent Form (ICF) was added. The possibility to have additional interim analyses for Health Authority submission and publication purpose was added. It was clarified that one hepatitis C virus (HCV RNA) retest had to be performed as soon as possible if Week 4 HCV RNA is >100 IU/mL and that subjects could continue study drug if HCV RNA is ≤100 International Unit per at the retest.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported