Clinical trial results:
A Phase III, randomized, double-blind trial to evaluate the efficacy, safety and tolerability of TMC435 vs. telaprevir, both in combination with PegIFN-2a and ribavirin, in chronic hepatitis C genotype-1 infected subjects who were null or partial responders to prior PegIFN and ribavirin therapy

Summary

EudraCT number	2011-001180-53
Trial protocol	PT GR BE ES DE SE HU AT DK PL CZ NO GB IT BG
Global end of trial date	28 April 2014

Results information

Result version number	v2 (current)
This version publication date	23 June 2016
First version publication date	31 May 2015
Version creation reason	• Correction of full data set Review of data

Trial information

Trial identification

Sponsor protocol code	TMC435HPC3001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01485991
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Sciences
Sponsor organisation address	Eastgate Village, Eastgate, Little Island, Co. Cork, Ireland,
Public contact	Janssen R&D Ireland Eastgate Village, Eastgate Little Island, Co. Cork Ireland , Janssen Research & Development, Clinical Registry Group, ClinicalTrialsEU@its.jnj.com, + 353 21 4673500, ClinicalTrialsEU@its.jnj.com
Scientific contact	Janssen R&D Ireland Eastgate Village, Eastgate Little Island, Co. Cork Ireland , Janssen Research & Development, Clinical Registry Group, ClinicalTrialsEU@its.jnj.com, + 353 21 4673500, ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric	No

investigation plan (PIP)	
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 April 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to demonstrate the efficacy of TMC435 in combination with peginterferon (PegIFN) + ribavirin (RBV) by means of establishing its non- inferiority compared to an approved regimen of telaprevir + PegIFN + RBV in participants with chronic hepatitis C who have previously failed PegIFN.

Protection of trial subjects:

Table of AEs, incidence of AEs (regardless of severity or relation to study drugs), AEs of at least Grade 3 (regardless of relation to study drugs), and incidence of treatment-emergent graded laboratory abnormalities of interest over time will be reported.

Background therapy:

PegIFN + RBV

Evidence for comparator:

Telaprevir

Actual start date of recruitment	19 January 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 24
Country: Number of subjects enrolled	Australia: 15
Country: Number of subjects enrolled	Austria: 17
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Bulgaria: 32
Country: Number of subjects enrolled	Brazil: 46
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	Czech Republic: 39
Country: Number of subjects enrolled	Germany: 36

Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Spain: 40
Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	United Kingdom: 21
Country: Number of subjects enrolled	Greece: 15
Country: Number of subjects enrolled	Hungary: 29
Country: Number of subjects enrolled	Israel: 27
Country: Number of subjects enrolled	Italy: 49
Country: Number of subjects enrolled	Norway: 10
Country: Number of subjects enrolled	Poland: 91
Country: Number of subjects enrolled	Portugal: 19
Country: Number of subjects enrolled	Romania: 82
Country: Number of subjects enrolled	Sweden: 26
Country: Number of subjects enrolled	United States: 96
Worldwide total number of subjects	763
EEA total number of subjects	532

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)	730
From 65 to 84 years	33
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

771 participants were randomly assigned into two treatment groups,but only 763 of them received the study drug.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Telaprevir+Placebo+Peginterferon Alfa-2a+Ribavirin

Arm description:

2 Telaprevir (TVR) tablets, orally, 3 times a day along with TMC435 matched placebo capsule once daily for 12 weeks, in addition to peginterferon alfa-2a and ribavirin for 48 weeks.

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

Dosage and administration details:

2 Telaprevir (TVR) tablets, orally, 3 times a day along with 150 mg TMC435 matched placebo capsule once daily for 12 weeks, in addition to peginterferon alfa-2a and ribavirin for 48 weeks.

Arm title	Simeprevir+Placebo+Peginterferon Alfa-2a+Ribavirin

Arm description:

Simeprevir (TMC435) capsule, orally, once daily for 12 weeks, along with 2 telaprevir (TVR) matched placebo tablets 3 times a day for 12 weeks, and peginterferon alfa-2a and ribavirin for 48 weeks.

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

Dosage and administration details:

Simeprevir (TMC435) 150 milligram (mg) capsule, orally, once daily for 12 weeks, along with 2 telaprevir (TVR) matched placebo tablets 3 times a day for 12 weeks, and peginterferon alfa-2a and ribavirin for 48 weeks.

Number of subjects in period 1	Telaprevir+Placebo+ Peginterferon Alfa-2a+Ribavirin	Simeprevir+Placebo +Peginterferon Alfa-2a+Ribavirin
Started	384	379
Completed	350	353
Not completed	34	26
Consent withdrawn by subject	20	13
Adverse event	4	-
Lost to follow-up	10	13

Baseline characteristics

Reporting groups

Reporting group title	Telaprevir+Placebo+Peginterferon Alfa-2a+Ribavirin

Reporting group description:

2 Telaprevir (TVR) tablets, orally, 3 times a day along with TMC435 matched placebo capsule once daily for 12 weeks, in addition to peginterferon alfa-2a and ribavirin for 48 weeks.

Reporting group title	Simeprevir+Placebo+Peginterferon Alfa-2a+Ribavirin

Reporting group description:

Simeprevir (TMC435) capsule, orally, once daily for 12 weeks, along with 2 telaprevir (TVR) matched placebo tablets 3 times a day for 12 weeks, and peginterferon alfa-2a and ribavirin for 48 weeks.

Reporting group values	Telaprevir+Placebo+ Peginterferon Alfa-2a+Ribavirin	Simeprevir+Placebo +Peginterferon Alfa-2a+Ribavirin	Total
Number of subjects	384	379	763
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	364	366	730
From 65 to 84 years	20	13	33
85 years and over	0	0	0
Title for AgeContinuous Units: years			
median	52	50	
full range (min-max)	20 to 69	18 to 69	-
Title for Gender Units: subjects			
Female	161	136	297
Male	223	243	466

End points

End points reporting groups

Reporting group title	Telaprevir+Placebo+Peginterferon Alfa-2a+Ribavirin

Reporting group description:

2 Telaprevir (TVR) tablets, orally, 3 times a day along with TMC435 matched placebo capsule once daily for 12 weeks, in addition to peginterferon alfa-2a and ribavirin for 48 weeks.

Reporting group title	Simeprevir+Placebo+Peginterferon Alfa-2a+Ribavirin

Reporting group description:

Simeprevir (TMC435) capsule, orally, once daily for 12 weeks, along with 2 telaprevir (TVR) matched placebo tablets 3 times a day for 12 weeks, and peginterferon alfa-2a and ribavirin for 48 weeks.

Subject analysis set title	Intent-to-treat (ITT) population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intent-to-treat (ITT) population included all randomized participants who took at least 1 dose of study medication.

Primary: Percentage of Participants With Sustained Virologic Response 12 Weeks After the Planned End of Treatment (SVR12)

End point title	Percentage of Participants With Sustained Virologic Response 12 Weeks After the Planned End of Treatment (SVR12)

End point description:

Participants are considered to have reached SVR12 if both conditions below are met: 1) HCV RNA levels less than (<) 25 International unit per milliliter (IU/mL) undetectable (at the actual end of treatment); 2) HCV RNA levels <25 IU/mL undetectable or HCV RNA levels <25 IU/mL detectable 12 Weeks after Planned End of Treatment.

End point type	Primary

End point timeframe:

12 Weeks After the Planned End of Treatment (EOT: Week 48)

End point values	Telaprevir+Placebo+Peginterferon Alfa-2a+Ribavirin	Simeprevir+Placebo+Peginterferon Alfa-2a+Ribavirin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	384[1]	379[2]		
Units: percentage of participants				
number (not applicable)	54.7	53.6		

Notes:

[1] - ITT population

[2] - ITT population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Simeprevir+Placebo+Peginterferon Alfa-2a+Ribavirin v Telaprevir+Placebo+Peginterferon Alfa-2a+Ribavirin

Number of subjects included in analysis	763
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Stratified Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.8
upper limit	5.5

Secondary: Percentage of Participants With Sustained Virologic Response 24 Weeks After the Planned End of Treatment (SVR24)

End point title	Percentage of Participants With Sustained Virologic Response 24 Weeks After the Planned End of Treatment (SVR24)

End point description:

Participants are considered to have reached SVR24 if both conditions below are met: 1) HCV RNA levels less than <25 International unit per milliliter (IU/mL) undetectable (at the actual end of treatment);2) HCV RNA levels <25 IU/mL undetectable or HCV RNA levels <25 IU/mL detectable (24 weeks after the planned EOT).

End point type	Secondary

End point timeframe:

24 Weeks After the Planned EOT (Week 48)

End point values	Telaprevir+Placebo+Peginterferon Alfa-2a+Ribavirin	Simeprevir+Placebo+Peginterferon Alfa-2a+Ribavirin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	384[3]	379[4]		
Units: percentage of participants				
number (not applicable)	55.2	53.3		

Notes:

[3] - ITT population

[4] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Viral Relapse

End point title	Percentage of Participants With Viral Relapse

End point description:

Participants are considered to have a viral relapse if both conditions as specified are met: 1) <25 IU/mL undetectable HCV RNA at the actual end of study drug treatment; 2) confirmed HCV RNA greater than or equal to (>=) 25 IU/mL during follow-up.
'N' (number of participants analyzed) signifies those participants who were evaluable for this measure.
The incidence of viral relapse is only calculated for subjects with undetectable HCV RNA levels (or

unconfirmed detectable) at EOT and with at least one follow-up HCV RNA measurement.'

End point type	Secondary

End point timeframe:

End of Treatment (Week 48) up to Follow-up Period (until Week 72)

End point values	Telaprevir+Placebo+Peginterferon Alfa-2a+Ribavirin	Simeprevir+Placebo+Peginterferon Alfa-2a+Ribavirin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	246		
Units: percentage of participants				
number (not applicable)	16.4	17.9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to End of Treatment (EOT: Week 48)

Adverse event reporting additional description:

Out of four deaths reported, one death occurred in the follow up phase.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Telaprevir+Placebo+Peginterferon Alfa-2a+Ribavirin

Reporting group description:

2 Telaprevir tablets are taken 3 times a day together with 150 mg Simeprevir placebo capsule once daily for 12 weeks, in addition to peginterferon alfa-2a and ribavirin for 48 weeks

Reporting group title	Simeprevir+Placebo+Peginterferon Alfa-2a+Ribavirin

Reporting group description:

Simeprevir capsule (150 mg) is taken once daily in addition to 2 Telaprevir placebo tablets 3 times a day for 12 weeks, in addition to peginterferon alfa-2a and ribavirin for 48 weeks

Serious adverse events	Telaprevir+Placebo+Peginterferon Alfa-2a+Ribavirin	Simeprevir+Placebo+Peginterferon Alfa-2a+Ribavirin	
Total subjects affected by serious adverse events			
subjects affected / exposed	54 / 384 (14.06%)	22 / 379 (5.80%)	
number of deaths (all causes)	4	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic neoplasm malignant			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Hypertension			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 384 (0.26%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			

subjects affected / exposed	2 / 384 (0.52%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 384 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 384 (0.00%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 384 (0.00%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 384 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			

subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 384 (0.26%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 384 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Substance-induced psychotic disorder			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Chemical peritonitis			

subjects affected / exposed	0 / 384 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus lesion			
subjects affected / exposed	0 / 384 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 384 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 384 (0.00%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	0 / 384 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 384 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Critical illness polyneuropathy			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mononeuropathy			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
alternative assessment type: Systematic			
subjects affected / exposed	16 / 384 (4.17%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	20 / 22	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neutropenia			
subjects affected / exposed	3 / 384 (0.78%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 384 (0.26%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 384 (0.26%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic diathesis			
subjects affected / exposed	0 / 384 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 384 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic vein thrombosis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Visual impairment			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 384 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haemorrhoids			
subjects affected / exposed	0 / 384 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 384 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric vein thrombosis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Hepatic failure			
subjects affected / exposed	0 / 384 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	0 / 384 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug rash with eosinophilia and systemic symptoms			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash generalised			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle haemorrhage			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	4 / 384 (1.04%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			

subjects affected / exposed	1 / 384 (0.26%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			
subjects affected / exposed	0 / 384 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 384 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 384 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis infective			
subjects affected / exposed	0 / 384 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 384 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superinfection			
subjects affected / exposed	0 / 384 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candidiasis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impetigo			

subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia legionella			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Sepsis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			

subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Telaprevir+Placebo+Peginterferon Alfa-2a+Ribavirin	Simeprevir+Placebo+Peginterferon Alfa-2a+Ribavirin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	369 / 384 (96.09%)	349 / 379 (92.08%)	
Nervous system disorders			
Headache			
subjects affected / exposed	120 / 384 (31.25%)	103 / 379 (27.18%)	
occurrences (all)	177	140	
Dysgeusia			
subjects affected / exposed	36 / 384 (9.38%)	15 / 379 (3.96%)	
occurrences (all)	37	15	
Dizziness			
subjects affected / exposed	43 / 384 (11.20%)	26 / 379 (6.86%)	
occurrences (all)	53	28	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	155 / 384 (40.36%)	132 / 379 (34.83%)	
occurrences (all)	205	173	
Pyrexia			
subjects affected / exposed	101 / 384 (26.30%)	86 / 379 (22.69%)	
occurrences (all)	133	114	
Influenza like illness			
subjects affected / exposed	66 / 384 (17.19%)	64 / 379 (16.89%)	
occurrences (all)	69	69	
Asthenia			

subjects affected / exposed	69 / 384 (17.97%)	80 / 379 (21.11%)	
occurrences (all)	96	108	
Injection site erythema			
subjects affected / exposed	27 / 384 (7.03%)	14 / 379 (3.69%)	
occurrences (all)	27	15	
Chills			
subjects affected / exposed	40 / 384 (10.42%)	22 / 379 (5.80%)	
occurrences (all)	41	25	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	78 / 384 (20.31%)	82 / 379 (21.64%)	
occurrences (all)	236	259	
Anaemia			
subjects affected / exposed	157 / 384 (40.89%)	95 / 379 (25.07%)	
occurrences (all)	317	150	
Thrombocytopenia			
subjects affected / exposed	46 / 384 (11.98%)	40 / 379 (10.55%)	
occurrences (all)	91	81	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	110 / 384 (28.65%)	74 / 379 (19.53%)	
occurrences (all)	128	85	
Diarrhoea			
subjects affected / exposed	60 / 384 (15.63%)	51 / 379 (13.46%)	
occurrences (all)	72	58	
Dyspepsia			
subjects affected / exposed	29 / 384 (7.55%)	25 / 379 (6.60%)	
occurrences (all)	30	27	
Abdominal pain upper			
subjects affected / exposed	25 / 384 (6.51%)	24 / 379 (6.33%)	
occurrences (all)	30	28	
Vomiting			
subjects affected / exposed	36 / 384 (9.38%)	23 / 379 (6.07%)	
occurrences (all)	51	27	
Constipation			

subjects affected / exposed	10 / 384 (2.60%)	21 / 379 (5.54%)	
occurrences (all)	10	25	
Abdominal pain			
subjects affected / exposed	22 / 384 (5.73%)	11 / 379 (2.90%)	
occurrences (all)	23	14	
Anorectal discomfort			
subjects affected / exposed	32 / 384 (8.33%)	10 / 379 (2.64%)	
occurrences (all)	34	11	
Anal pruritus			
subjects affected / exposed	42 / 384 (10.94%)	9 / 379 (2.37%)	
occurrences (all)	42	10	
Dry mouth			
subjects affected / exposed	25 / 384 (6.51%)	11 / 379 (2.90%)	
occurrences (all)	25	11	
Haemorrhoids			
subjects affected / exposed	38 / 384 (9.90%)	6 / 379 (1.58%)	
occurrences (all)	43	6	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	53 / 384 (13.80%)	66 / 379 (17.41%)	
occurrences (all)	61	76	
Dyspnoea			
subjects affected / exposed	40 / 384 (10.42%)	30 / 379 (7.92%)	
occurrences (all)	47	31	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	100 / 384 (26.04%)	66 / 379 (17.41%)	
occurrences (all)	138	100	
Pruritus			
subjects affected / exposed	179 / 384 (46.61%)	142 / 379 (37.47%)	
occurrences (all)	244	182	
Dry skin			
subjects affected / exposed	30 / 384 (7.81%)	39 / 379 (10.29%)	
occurrences (all)	33	43	
Alopecia			

subjects affected / exposed	59 / 384 (15.36%)	33 / 379 (8.71%)	
occurrences (all)	60	34	
Psychiatric disorders			
Depression			
subjects affected / exposed	20 / 384 (5.21%)	35 / 379 (9.23%)	
occurrences (all)	26	42	
Insomnia			
subjects affected / exposed	73 / 384 (19.01%)	53 / 379 (13.98%)	
occurrences (all)	77	58	
Mood altered			
subjects affected / exposed	32 / 384 (8.33%)	35 / 379 (9.23%)	
occurrences (all)	35	37	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	63 / 384 (16.41%)	47 / 379 (12.40%)	
occurrences (all)	70	61	
Back pain			
subjects affected / exposed	30 / 384 (7.81%)	18 / 379 (4.75%)	
occurrences (all)	33	19	
Arthralgia			
subjects affected / exposed	45 / 384 (11.72%)	41 / 379 (10.82%)	
occurrences (all)	52	53	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	21 / 384 (5.47%)	12 / 379 (3.17%)	
occurrences (all)	25	12	
Metabolism and nutrition disorders			
Hyperuricaemia			
subjects affected / exposed	28 / 384 (7.29%)	3 / 379 (0.79%)	
occurrences (all)	32	3	
Decreased appetite			
subjects affected / exposed	64 / 384 (16.67%)	54 / 379 (14.25%)	
occurrences (all)	69	60	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 November 2011	The first amendment included change of primary efficacy endpoint SVR24 for ongoing and future SMV Phase 3 trials, to SVR12. Evaluation and updating the sustained virologic response definition and specific toxicities section. Additional tests for the urine dipstick analysis were listed. Upper age limit of 70 years for all participants was added, exclusion criteria 10 was revised. It was clarified that a liver biopsy was the required method for all subjects without a contraindication for this procedure. Clarifications were made to the disallowed concomitant medication section by adjusting the wording. Female subjects of male participants did not have to perform a pregnancy test. In the initial Clinical Trial Protocol HPC3001, it was previously required that female partners performed pregnancy tests regularly. An additional Skindex-16 questionnaire was added at the first unscheduled visit for rash management for subjects who presented with any rash. Comparison of treatments on severity and impact of rash in subjects who experienced rash was a secondary objective instead of an exploratory objective.
25 May 2012	In the second amendment CTPA-GEN-II,criterion related to the liver biopsy requirement (inclusion criterion 2) was updated and provided clarification about when and which alternative non-invasive methods were to be used. The definition of viral breakthrough and the on-treatment failure definition were clarified. Removal of erythropoiesis-stimulating agents from the list of disallowed medications to treat treatment-emergent anemia. Reduction in HCV RNA from baseline of <2 log10 IU/mL assessed after Week 12 until Week 24 was considered adequate for the identification of subjects with prior null response. The eligibility cut-off for alpha-fetoprotein (AFP) was increased from 50 to 100 ng/mL. A CT or MRI examination was mandatory for inclusion of cirrhotics with elevated AFP levels. Clarifications in the Pre study and Concomitant Therapy section, the Safety Evaluation section and the Study Medication Withdrawal section. Revision of the overall sampling schedule for pharmacokinetics evaluations following analysis of recent Phase 2 trials. Further recommendations were added related to female partners of male subjects who do not have to perform a pregnancy test because of privacy protection regulations. The Roche Cobas TaqMan HCV Test v2.0, for use with the High Pure System was used as the assay to determine HCV RNA levels. On request of Health Authorities, the key performance characteristics were added and the assay performance and validation documents were added to the reference list. The statistical methods were updated based on Health Authorities feedback regarding the primary endpoint, resulting in an update of the secondary endpoints. In addition, PROs were updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported