



Clinical trial results:

A Phase 3, Open-Label Study to Evaluate the Safety and Efficacy of TMC435 plus Pegylated Interferon alfa-2a and Ribavirin Administered for 12 Weeks in Treatment-Naïve Subjects with Chronic Genotype 1 or Genotype 4 HCV Infection

Summary

EudraCT number	2012-004905-29
Trial protocol	BE GB AT IT ES DE
Global end of trial date	31 August 2015

Results information

Result version number	v1 (current)
This version publication date	08 September 2016
First version publication date	08 September 2016

Trial information

Trial identification

Sponsor protocol code	TMC435HPC3014
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01846832
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Cilag International NV
Sponsor organisation address	Antwerpseweg 15-17, Beerse, Belgium, B-2340
Public contact	Clinical Registry Group, Janssen Cilag International NV, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Cilag International 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	31 August 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	31 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective was to determine the efficacy of simeprevir (SMV) plus pegylated interferon alpha-2a (PegIFNa-2a) and ribavirin (RBV) when administered for 12 weeks in treatment-naïve subjects with chronic genotype 1 hepatitis C virus (HCV) infection, as measured by the proportion of subjects with sustained virologic response 12 (SVR12) and to assess the safety and tolerability of SMV plus PegIFNa-2a and RBV when administered for 12 weeks in treatment-naïve subjects with chronic genotype 1 HCV infection.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Safety evaluations were based upon the type, incidence, and severity of AEs reported throughout the study, changes in clinical laboratory tests (hematology, biochemistry and urinalysis), vital sign measurements, 12-lead electrocardiograms (ECGs) and physical examination (including weight, height, and temperature).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 September 2013
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	Austria: 30
Country: Number of subjects enrolled	Belgium: 24
Country: Number of subjects enrolled	Germany: 28
Country: Number of subjects enrolled	Spain: 43
Country: Number of subjects enrolled	France: 50
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Italy: 27
Country: Number of subjects enrolled	Saudi Arabia: 17
Worldwide total number of subjects	230
EEA total number of subjects	213

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)	226
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 31 sites in 8 countries.

Pre-assignment

Screening details:

In total, 277 subjects were screened, of whom 230 were enrolled and treated. Two subjects were enrolled but not treated.

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

Arm title	Simeprevir 150 milligram 12 Weeks PR12/24
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Arm description:

Subjects received a 12-week triple therapy with Simeprevir (TMC435) 150 milligram (mg) plus pegylated interferon (PegIFNa-2a) and ribavirin (RBV) in treatment-naïve adult subjects with genotype 1 or genotype 4 chronic hepatitis C virus (HCV) infection and fibrosis stage equivalent to F0-F2. Treatment Extension up to 24/48 weeks total treatment duration was response-guided based on HCV RNA levels at Week 2, Week 4, and Week 8.

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:

Subjects received Simeprevir (TMC435) 150 milligram capsule orally once daily up to week 12.

Investigational medicinal product name	Pegylated Interferon-2a
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received pegylated interferon-2a 180 microgram (mcg) administered subcutaneous injection of 0.5 mL once weekly up to week 12.

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

Dosage and administration details:

Subjects received ribavirin 1000 mg or 1200 mg tablets administered orally twice daily as per subjects weight up to week 12.

Number of subjects in period 1	Simeprevir 150 milligram 12 Weeks PR12/24
Started	230
Completed	208
Not completed	22
Consent withdrawn by subject	7
Not specified	1
Subject entered another trial	3
Subject non-compliant	1
Lost to follow-up	10

Baseline characteristics

Reporting groups

Reporting group title	Simeprevir 150 milligram 12 Weeks PR12/24
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Reporting group description:

Subjects received a 12-week triple therapy with Simeprevir (TMC435) 150 milligram (mg) plus pegylated interferon (PegIFNa-2a) and ribavirin (RBV) in treatment-naïve adult subjects with genotype 1 or genotype 4 chronic hepatitis C virus (HCV) infection and fibrosis stage equivalent to F0-F2. Treatment Extension up to 24/48 weeks total treatment duration was response-guided based on HCV RNA levels at Week 2, Week 4, and Week 8.

Reporting group values	Simeprevir 150 milligram 12 Weeks PR12/24	Total	
Number of subjects	230	230	
Title for AgeCategorical Units: subjects			
Adults (18-64 years)	226	226	
From 65 to 84 years	4	4	
Title for AgeContinuous Units: years			
median	47		
full range (min-max)	19 to 68	-	
Title for Gender Units: subjects			
Female	91	91	
Male	139	139	

End points

End points reporting groups

Reporting group title	Simeprevir 150 milligram 12 Weeks PR12/24
Reporting group description: Subjects received a 12-week triple therapy with Simeprevir (TMC435) 150 milligram (mg) plus pegylated interferon (PegIFNa-2a) and ribavirin (RBV) in treatment-naïve adult subjects with genotype 1 or genotype 4 chronic hepatitis C virus (HCV) infection and fibrosis stage equivalent to F0-F2. Treatment Extension up to 24/48 weeks total treatment duration was response-guided based on HCV RNA levels at Week 2, Week 4, and Week 8.	
Subject analysis set title	Simeprevir 12Wks 150 mg PR12/24: Genotype 1
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subjects received a 12-week triple therapy with Simeprevir (TMC435) 150 milligram (mg) plus pegylated interferon (PegIFNa-2a) and ribavirin (RBV) in treatment-naïve adult subjects with genotype 1 chronic hepatitis C virus (HCV) infection and fibrosis stage equivalent to F0-F2. Treatment extension up to 24/48 weeks total treatment duration was response-guided based on HCV RNA levels at Week 2, Week 4, and Week 8.	
Subject analysis set title	Simeprevir 12Wks 150 mg PR12/24: Genotype 4
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subjects received a 12-week triple therapy with Simeprevir (TMC435) 150 milligram (mg) plus pegylated interferon (PegIFNa-2a) and ribavirin (RBV) in treatment-naïve adult subjects with genotype 4 chronic hepatitis C virus (HCV) infection and fibrosis stage equivalent to F0-F2. Treatment extension up to 24/48 weeks total treatment duration was response-guided based on HCV RNA levels at Week 2, Week 4, and Week 8.	

Primary: Percentage Of Subjects Infected With Genotype 1 hepatitis C virus (HCV) With A Sustained Virologic Response 12 Weeks (SVR12)

End point title	Percentage Of Subjects Infected With Genotype 1 hepatitis C virus (HCV) With A Sustained Virologic Response 12 Weeks (SVR12) ^[1]
End point description: Sustained Virologic Response (SVR) 12 is defined as the percentage of subjects (ITT analysis set) genotype 1 hepatitis C virus (HCV) ribonucleic acid (RNA) levels less than (<) 25 International unit per milliliter (IU/mL) detectable or undetectable at 12 weeks. The Intent to treat (ITT) population included all randomized subjects who received at least 1 dose of investigational medication (Simeprevir).	
End point type	Primary
End point timeframe: Up to Week 12	

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 reported for this endpoint based on the comparison of the response rate in the genotype 1-infected subjects who received a 12-week treatment with the minimally acceptable response rate of 80%.

End point values	Simeprevir 12Wks 150 mg PR12/24: Genotype 1			
Subject group type	Subject analysis set			
Number of subjects analysed	123			
Units: Percentage Of Subjects				
number (confidence interval 95%)	65.9 (57.47 to 74.23)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Subjects Infected With Genotype 4 HCV With A Sustained Virologic Response 12 Weeks (SVR12)

End point title	Percentage Of Subjects Infected With Genotype 4 HCV With A Sustained Virologic Response 12 Weeks (SVR12)
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End point description:

SVR 12 is defined as the percentage of subjects (ITT analysis set) genotype 4 HCV RNA levels < 25 IU/mL detectable or undetectable at 12 weeks. The ITT population included all randomized subjects who received at least 1 dose of investigational medication (Simeprevir).

End point type	Secondary
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End point timeframe:

Up to Week 12

End point values	Simeprevir 12Wks 150 mg PR12/24: Genotype 4			
Subject group type	Subject analysis set			
Number of subjects analysed	34			
Units: Percentage of Subjects				
number (confidence interval 95%)	97.1 (91.38 to 100)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Subjects Achieved Rapid Virologic Response (RVR)

End point title	Percentage Of Subjects Achieved Rapid Virologic Response (RVR)
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End point description:

Rapid virologic response (RVR) defined as HCV RNA < 25 IU/mL undetectable measured 4 weeks after start of treatment. The ITT population included all randomized subjects who received at least 1 dose of investigational medication (Simeprevir).

End point type	Secondary
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End point timeframe:

Up to Week 4

End point values	Simeprevir 12Wks 150 mg PR12/24: Genotype 1	Simeprevir 12Wks 150 mg PR12/24: Genotype 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	162 ^[2]	66 ^[3]		
Units: Subjects				
number (not applicable)				
12 Weeks Treatment	100	100		
> 12 (24/48) Weeks Treatment	12.8	75		

Notes:

[2] - Subjects enrolled are 123 up to week 12 and 39 for more than (>)12 (24/48) Weeks.

[3] - Subjects enrolled are 34 up to week 12 and 32 for more than (>)12 (24/48) Weeks.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Subjects Achieved Virologic Response At Week 2 (W2VR)

End point title	Percentage Of Subjects Achieved Virologic Response At Week 2 (W2VR)
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End point description:

Virologic response at Week 2 (W2VR) defined as HCV RNA < 25 IU/mL (detectable or undetectable) measured 2 weeks after start of treatment. The ITT population included all randomized subjects who received at least 1 dose of investigational medication (Simeprevir).

End point type	Secondary
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End point timeframe:

Up to Week 2

End point values	Simeprevir 12Wks 150 mg PR12/24: Genotype 1	Simeprevir 12Wks 150 mg PR12/24: Genotype 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	122	34		
Units: Percentage Of Subjects				
number (not applicable)				
< 25 undetectable: 12 weeks	41.8	94.1		
< 25 undetectable: >12 weeks	5.1	0		
< 25 detectable: 12 weeks	58.2	5.9		
< 25 detectable: >12 weeks	17.9	71		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Subjects With Sustained Virologic Response 24 Weeks After Planned End Of Treatment (SVR24)

End point title	Percentage Of Subjects With Sustained Virologic Response 24 Weeks After Planned End Of Treatment (SVR24)
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End point description:

SVR 24 is defined as the percentage of subjects (ITT analysis set) HCV RNA levels less than < 25 IU/mL detectable or undetectable at 24 weeks after the end of treatment. The ITT population included all randomized subjects who received at least 1 dose of investigational medication (Simeprevir).

End point type	Secondary
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End point timeframe:

Up to Week 48

End point values	Simeprevir 12Wks 150 mg PR12/24: Genotype 1	Simeprevir 12Wks 150 mg PR12/24: Genotype 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	163 ^[4]	67 ^[5]		
Units: Percentage of Subjects				
number (confidence interval 95%)				
12 Weeks Treatment	64.2 (55.76 to 72.7)	97.1 (91.38 to 100)		
> 12 (24/48) Weeks Treatment	52.5 (37.02 to 67.98)	81.8 (68.66 to 94.98)		

Notes:

[4] - Subjects enrolled are 123 up to week 12 and 40 for more than (>)12 (24/48) Weeks.

[5] - Subjects enrolled are 34 up to week 12 and 33 for more than (>)12 (24/48) Weeks.

Statistical analyses

No statistical analyses for this end point

Secondary: Hepatitis C Virus (HCV) RNA At Each Time Point

End point title	Hepatitis C Virus (HCV) RNA At Each Time Point
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End point description:

The ITT population included all randomized subjects who received at least 1 dose of investigational medication (Simeprevir). n is defined as number of subjects analysed for this endpoint at specific timepoint. EOT is defined as the end of treatment at week 48.

End point type	Secondary
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End point timeframe:

Up to Week 48

End point values	Simeprevir 12Wks 150 mg PR12/24: Genotype 1	Simeprevir 12Wks 150 mg PR12/24: Genotype 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	163	67		
Units: Number of Subjects				
arithmetic mean (standard deviation)				

Baseline (n=163, 67)	5201191 (± 6560084)	2892674 (± 4889401)		
Week 1 (n=162, 65)	4149.6 (± 50035.91)	245.3 (± 881.88)		
Week 2 (n=161, 65)	392.5 (± 3103.04)	6875.9 (± 55191.74)		
Week 4 (n=162, 66)	1124.9 (± 9931.98)	6693.4 (± 54281.9)		
Week 8 (n=154, 64)	9.3 (± 2.08)	9.2 (± 1.88)		
Week 12 (n=147, 61)	9 (± 0)	9 (± 0)		
Week 16 (n=29, 27)	13663.9 (± 73533.68)	9 (± 0)		
Week 20 (n=29, 26)	31767.3 (± 171023.7)	9 (± 0)		
Week 24 (n=26, 22)	9 (± 0)	9 (± 0)		
EOT (n=162, 66)	6806.3 (± 72951.22)	6692.1 (± 54282.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Subjects With Viral Breakthrough

End point title	Percentage Of Subjects With Viral Breakthrough
End point description:	
Viral breakthrough is a confirmed increase of more than (>) 1 log ₁₀ IU/mL in HCV RNA level from the lowest level reached, or a confirmed HCV RNA level of > 100 IU/mL in subjects whose HCV RNA levels had previously been below the limit of quantification (< 25 IU/mL detectable or undetectable) while on study treatment. The Viral Breakthrough during triple therapy or PR phase includes ITT Population with randomized subjects received at least 1 dose of study drug (Simeprevir).	
End point type	Secondary
End point timeframe:	
Up to Week 48	

End point values	Simeprevir 12Wks 150 mg PR12/24: Genotype 1	Simeprevir 12Wks 150 mg PR12/24: Genotype 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	163 ^[6]	67 ^[7]		
Units: Percentage of Subjects				
number (not applicable)				
12 Weeks Treatment	0	0		
>12 Weeks Treatment	10.3	3.1		

Notes:

[6] - Subjects enrolled are 123 up to week 12 and 40 for more than (>)12 (24/48) Weeks.

[7] - Subjects enrolled are 34 up to week 12 and 33 for more than (>)12 (24/48) Weeks.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Subjects With Viral Relapse

End point title	Percentage Of Subjects With Viral Relapse
End point description: Subjects considered to have a viral relapse if at actual end of treatment HCV RNA levels < 25 IU/mL undetectable, and during the follow-up period HCV RNA levels > or = 25 IU/mL. The ITT population included all randomized subjects who received at least 1 dose of study drug (Simeprevir).	
End point type	Secondary
End point timeframe: Up to Week 48	

End point values	Simeprevir 12Wks 150 mg PR12/24: Genotype 1	Simeprevir 12Wks 150 mg PR12/24: Genotype 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	163 ^[8]	67 ^[9]		
Units: Percentage of Subjects				
number (not applicable)				
12 Weeks Treatment	34.4	2.9		
> 12 Weeks Treatment	30	10		

Notes:

[8] - Subjects enrolled are 123 up to week 12 and 40 for more than (>)12 (24/48) Weeks.

[9] - Subjects enrolled are 34 up to week 12 and 33 for more than (>)12 (24/48) Weeks.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In The Hepatitis C Treatment Symptom and Impact Questionnaire (HCV SIQ) Symptom And Impact Scores

End point title	Change From Baseline In The Hepatitis C Treatment Symptom and Impact Questionnaire (HCV SIQ) Symptom And Impact Scores
End point description: The HCV SIQ asks subjects to rate 26 symptoms associated with HCV or its treatment and how symptoms impacted the subjects life during the prior week. Total Symptom Score [symptom items 1-26 were rescaled from 0 (none) to 100 (maximum severity/frequency) with a total score calculated from the mean of all symptoms] and Body System Scores [symptom items 1-26 were rescaled from 0 (none) to 100 (maximum severity/frequency) with domain scores calculated for each body system based on mean items scores within each domain. The overall body system score is then calculated as mean of the domain scores] were calculated and analyzed for HCV SIQ. The ITT population included all randomized subjects who received at least 1 dose of study drug (SMV) and completed 5 questionnaires during study visits at baseline, throughout treatment and follow-up to document changes. The value 99999 indicates standard deviation cannot be determined as only one subject analyzed at this time point.	
End point type	Secondary
End point timeframe: Day 1 and at each study visit up to Week 72	

End point values	Simeprevir 150 milligram 12 Weeks PR12/24			
Subject group type	Reporting group			
Number of subjects analysed	230			
Units: Number of Subjects				
arithmetic mean (standard deviation)				
Baseline (n=212)	8.9 (± 9.33)			
Week 1 (n=205)	13.8 (± 11.18)			
Week 2 (n=201)	15.6 (± 12.55)			
Week 4 (n=204)	20.1 (± 14.58)			
Week 8 (n=214)	23 (± 15.96)			
Week 12 (n=195)	25.5 (± 17.86)			
Week 16 (n=204)	16.6 (± 14.78)			
Week 20 (n=184)	14.8 (± 14.07)			
Week 24 (n=202)	14.1 (± 14.38)			
Week 28 (n=49)	13.3 (± 13.17)			
Week 36 (n=192)	9.1 (± 10.49)			
Week 48 (n=50)	8.5 (± 11.02)			
Week 52 (n=1)	4.8 (± 99999)			
Week 60 (n=1)	5.8 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In The Fatigue Severity Scale (FSS) Total Score

End point title	Change From Baseline In The Fatigue Severity Scale (FSS) Total Score
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End point description:

The FSS was used to document fatigue severity and impact of fatigue on subjects daily lives. Fatigue severity was measured using the FSS score, created as the mean of patient ratings for 9 items in the Fatigue Severity Scale. FSS scores have a range from 1 to 7 where higher scores indicate more severe fatigue. The ITT population included all randomized subjects who received at least 1 dose of investigational medication (Simeprevir) and completed 5 questionnaires during study visits at baseline, throughout treatment and follow-up to document changes. The data value 99999 indicate that standard deviation cannot be determined as only one subject analyzed at this time point. n is number of subjects analysed at specific timepoint.

End point type	Secondary
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End point timeframe:

Day 1 and at each study visit up to Week 72

End point values	Simeprevir 150 milligram 12 Weeks PR12/24			
Subject group type	Reporting group			
Number of subjects analysed	230			
Units: Number of Subjects				
arithmetic mean (standard deviation)				
Baseline (n=226)	2.733 (± 1.5692)			
Week 4 (n=219)	3.736 (± 1.8846)			
Week 8 (n=218)	3.916 (± 1.9206)			
Week 12 (n=208)	4.085 (± 1.9339)			
Week 16 (n=207)	3.153 (± 1.789)			
Week 20 (n=51)	3.903 (± 1.9175)			
Week 24 (n=196)	2.583 (± 1.5983)			
Week 36 (n=197)	2.443 (± 1.5463)			
Week 48 (n=52)	2.268 (± 1.5064)			
Week 60 (n=1)	3.778 (± 99999)			
Week 72 (n=1)	2.667 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In The Center For Epidemiologic Studies Depression Scale (CES-D) Score

End point title	Change From Baseline In The Center For Epidemiologic Studies Depression Scale (CES-D) Score
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End point description:

The Center For Epidemiologic Studies Depression Scale (CES-D) is the scores (0-3) for each of the 20 individual items are summed up to yield a total score (0 -60) with higher scores indicating more and/or more frequent experience of depressive symptoms during the past week. The scores of 16 to 22 indicate mild to moderate depressive illness and CES-D scores more than or equal to ($\geq$) 23 indicate probable major depressive illness (sensitivity: 0.95, specificity: 0.29). The ITT population included all randomized subjects who received at least 1 dose of investigational medication (Simeprevir) and completed 5 questionnaires during study visits at baseline, throughout treatment and follow-up to document changes. The data value 99999 indicate that standard deviation cannot be determined as only one subject analyzed at this time point. n is 'number of subjects' analysed in this endpoint at specific timepoint.

End point type	Secondary
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End point timeframe:

Day 1 and at each study visit up to Week 72

End point values	Simeprevir 150 milligram 12 Weeks PR12/24			
Subject group type	Reporting group			
Number of subjects analysed	230			
Units: Number of subjects				
arithmetic mean (standard deviation)				
Baseline (n=228)	11 ($\pm$ 7.79)			
Week 4 (n=218)	15.7 ($\pm$ 10.41)			
Week 8 (n=213)	15.8 ($\pm$ 10.45)			
Week 12 (n=213)	17.3 ($\pm$ 11.69)			
Week 16 (n=205)	12.5 ($\pm$ 10.37)			
Week 20 (n=50)	15.2 ($\pm$ 10.16)			
Week 24 (n=200)	10.8 ($\pm$ 8.94)			
Week 36 (n=192)	9.2 ($\pm$ 8.86)			
Week 48 (n=52)	9 ($\pm$ 7.8)			
Week 60 (n=1)	4 ($\pm$ 99999)			
Week 72 (n=1)	6 ($\pm$ 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In The Work Productivity And Activity Index (WPAI) For Hepatitis C Missed Work Time, Daily Activity Impairment And Productivity Scores

End point title	Change From Baseline In The Work Productivity And Activity Index (WPAI) For Hepatitis C Missed Work Time, Daily Activity Impairment And Productivity Scores
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End point description:

The Work Productivity And Activity Index (WPAI) was used to measure the impact of HCV on time missed from work (absenteeism), reduced performance while at work (productivity impairment), and impairment in daily activities without regard to employment status. The WPAI Productivity score has a possible range from 0% to 100% with higher scores indicating greater impairment in productivity. The ITT population included all randomized subjects who received at least 1 dose of investigational medication (Simeprevir) and completed 5 questionnaires during study visits at baseline, throughout treatment and follow-up to document changes. The data value 99999 indicate that standard deviation cannot be determined as only one subject analyzed at this time point. n is 'number of subjects' analysed for this endpoint at specific timepoints.

End point type	Secondary
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End point timeframe:

Day 1 and at each study visit up to Week 72

End point values	Simeprevir 150 milligram 12 Weeks PR12/24			
Subject group type	Reporting group			
Number of subjects analysed	230			
Units: Number of subjects				

arithmetic mean (standard deviation)				
Baseline (n=106)	8.3 (± 16.94)			
Week 4 (n=94)	32.3 (± 32.89)			
Week 8 (n=96)	30.1 (± 31.34)			
Week 12 (n=89)	37.9 (± 34.48)			
Week 16 (n=92)	22.7 (± 31.54)			
Week 20 (n=19)	35.8 (± 37.77)			
Week 24 (n=100)	13.8 (± 24.57)			
Week 36 (n=79)	8.9 (± 18.17)			
Week 48 (n=25)	7.2 (± 12.99)			
Week 60 (n=1)	0 (± 99999)			
Week 72 (n=1)	0 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In The EuroQol 5 Dimension (EQ5D) Visual Analog Scale (VAS) Valuation Index And Descriptive System Scores

End point title	Change From Baseline In The EuroQol 5 Dimension (EQ5D) Visual Analog Scale (VAS) Valuation Index And Descriptive System Scores
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End point description:

The EQ-5D questionnaire is an instrument designed to assess overall health status using 5 health dimension scores (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and a "thermometer" visual analog scale (VAS) ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The ITT population included all randomized subjects who received at least 1 dose of investigational medication (Simeprevir) and completed 5 questionnaires during study visits at baseline, throughout treatment and follow-up to document changes. The data value 99999 indicate that standard deviation cannot be determined as only one subject analyzed at this time point. n is 'number of subjects' analysed for this endpoint at specific timepoint.

End point type	Secondary
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End point timeframe:

Day 1 and at each study visit up to Week 72

End point values	Simeprevir 150 milligram 12 Weeks PR12/24			
Subject group type	Reporting group			
Number of subjects analysed	230			
Units: Number of subjects				
arithmetic mean (standard deviation)				
Baseline (n=197)	81.4 (± 16.41)			
Week 4 (n=189)	71.6 (± 20.06)			
Week 8 (n=193)	73.4 (± 17.7)			
Week 12 (n=201)	73.1 (± 19.5)			
Week 16 (n=200)	79.9 (± 17.43)			
Week 20 (n=47)	71.2 (± 20.08)			
Week 24 (n=192)	82 (± 16.01)			

Week 36 (n=191)	85.9 (± 14.62)			
Week 48 (n=47)	87.3 (± 10.72)			
Week 60 (n=1)	95 (± 99999)			
Week 72 (n=1)	95 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: The Percentage Of Subjects With Normalized Alanine Aminotransferase (ALT) Levels

End point title	The Percentage Of Subjects With Normalized Alanine Aminotransferase (ALT) Levels
End point description: The ITT population included all randomized subjects who received at least 1 dose of investigational medication (Simeprevir).	
End point type	Secondary
End point timeframe: Up to Week 48	

End point values	Simeprevir 150 milligram 12 Weeks PR12/24			
Subject group type	Reporting group			
Number of subjects analysed	115			
Units: Percentage of Subjects				
number (not applicable)	85.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Subjects With Sustained Virologic Response 12 Weeks After Planned End Of Treatment (SVR12)

End point title	Percentage Of Subjects With Sustained Virologic Response 12 Weeks After Planned End Of Treatment (SVR12)
End point description: SVR 12 is defined as the percentage of subjects (ITT analysis set) HCV RNA levels less than < 25 IU/mL detectable or undetectable at 12 weeks after the end of treatment. Subjects with HCV RNA <25 detectable or undetectable at 2 Weeks and <25 undetectable at 4 Weeks and <25 undetectable at 8 Weeks meet the Response Guided Treatment (RGT) criteria. Subjects that meet the RGT criteria have a planned treatment duration of 12 Weeks, whereas subjects who do not meet this rule have a planned treatment duration of 24 (or 48) weeks The ITT population included all randomized subjects who received at least 1 dose of investigational medication (Simeprevir). The value 000 or 999 indicates that no data evaluated at this timepoint.	
End point type	Secondary

End point timeframe:

Week 36

End point values	Simeprevir 12Wks 150 mg PR12/24: Genotype 1	Simeprevir 12Wks 150 mg PR12/24: Genotype 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	163 ^[10]	67 ^[11]		
Units: subjects				
number (confidence interval 95%)				
Met RGT criteria: 12 weeks Treatment	75.5 (0 to 999)	50.7 (0 to 999)		
SVR12: Met RGT criteria: >12 weeks Treatment	65.9 (57.47 to 74.23)	97.1 (91.38 to 100)		
Did not Met RGT criteria: 12 weeks treatment	23.3 (0 to 999)	46.3 (0 to 999)		
SVR12:Did not Met RGT criteria:>12 weeks treatment	55.3 (39.45 to 71.07)	83.9 (70.92 to 96.82)		

Notes:

[10] - N includes number of subjects analysed to evaluate RGT Criteria.

[11] - N includes number of subjects analysed to evaluate RGT Criteria.

Statistical analyses

No statistical analyses for this end point

Secondary: The Number Of Subjects Reporting Adverse Events

End point title	The Number Of Subjects Reporting Adverse Events
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End point description:

All subjects will be monitored throughout the study for the occurrence of adverse events including psychiatric symptoms, anemia, hyperglycemia (elevated glucose levels), disturbances in serum creatinine levels (a measure of renal [kidney] safety), decreased White Blood Cell (WBC) Count, decreased Platelet Count (ability of the blood to clot), and thyroid abnormalities. The ITT population included all randomized subjects who received at least 1 dose of investigational medication (Simeprevir).

End point type	Secondary
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End point timeframe:

Up to Week 48

End point values	Simeprevir 150 milligram 12 Weeks PR12/24			
Subject group type	Reporting group			
Number of subjects analysed	230			
Units: Number of Subjects				
SMV+PR Phase (n=230)	213			
PR Phase (n=62)	40			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 48 weeks

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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Reporting groups

Reporting group title	Simeprevir 150 milligram 12 Weeks PR12/24
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Reporting group description:

Subjects received a 12-week triple therapy with Simeprevir (TMC435) 150 milligram (mg) plus pegylated interferon (PegIFNa-2a) and ribavirin (RBV) in treatment-naïve adult subjects with genotype 1 or genotype 4 chronic hepatitis C virus (HCV) infection and fibrosis stage equivalent to F0-F2. Treatment Extension up to 24/48 weeks total treatment duration was response-guided based on HCV RNA levels at Week 2, Week 4, and Week 8.

Serious adverse events	Simeprevir 150 milligram 12 Weeks PR12/24		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 230 (3.48%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Vascular disorders			
Phlebitis			
subjects affected / exposed	1 / 230 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Testicular necrosis			
subjects affected / exposed	1 / 230 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 230 (0.43%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			

Alcohol withdrawal syndrome subjects affected / exposed	1 / 230 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychotic disorder subjects affected / exposed	1 / 230 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Acute sinusitis subjects affected / exposed	1 / 230 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Furuncle subjects affected / exposed	1 / 230 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pericoronitis subjects affected / exposed	1 / 230 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Simeprevir 150 milligram 12 Weeks PR12/24		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	204 / 230 (88.70%)		
Nervous system disorders			
Headache subjects affected / exposed	54 / 230 (23.48%)		
occurrences (all)	60		
Dizziness subjects affected / exposed	13 / 230 (5.65%)		
occurrences (all)	13		

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	59 / 230 (25.65%)		
occurrences (all)	64		
Influenza like illness			
subjects affected / exposed	71 / 230 (30.87%)		
occurrences (all)	85		
Asthenia			
subjects affected / exposed	57 / 230 (24.78%)		
occurrences (all)	61		
Pyrexia			
subjects affected / exposed	27 / 230 (11.74%)		
occurrences (all)	29		
Irritability			
subjects affected / exposed	15 / 230 (6.52%)		
occurrences (all)	16		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	48 / 230 (20.87%)		
occurrences (all)	80		
Anaemia			
subjects affected / exposed	26 / 230 (11.30%)		
occurrences (all)	28		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	12 / 230 (5.22%)		
occurrences (all)	13		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	24 / 230 (10.43%)		
occurrences (all)	26		
Nausea			
subjects affected / exposed	20 / 230 (8.70%)		
occurrences (all)	24		
Vomiting			

subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all)	13 / 230 (5.65%) 13 12 / 230 (5.22%) 12 12 / 230 (5.22%) 12		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	23 / 230 (10.00%) 23		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Erythema subjects affected / exposed occurrences (all) Alopecia subjects affected / exposed occurrences (all)	71 / 230 (30.87%) 80 33 / 230 (14.35%) 37 34 / 230 (14.78%) 44 12 / 230 (5.22%) 14 15 / 230 (6.52%) 15		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) Depression subjects affected / exposed occurrences (all) Sleep disorder	31 / 230 (13.48%) 31 20 / 230 (8.70%) 20		

subjects affected / exposed occurrences (all)	17 / 230 (7.39%) 18		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	21 / 230 (9.13%)		
occurrences (all)	23		
Myalgia			
subjects affected / exposed	18 / 230 (7.83%)		
occurrences (all)	23		
Back pain			
subjects affected / exposed	13 / 230 (5.65%)		
occurrences (all)	13		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	36 / 230 (15.65%)		
occurrences (all)	37		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 September 2013	The overall reason for the amendment was to implement comments received from ethics committees (EC) and Health authorities (HA) and to update the benefit-risk assessment with Phase 3 data that had become available.
28 October 2013	The overall reason for the amendment was to introduce precautionary language on photosensitivity.
02 December 2013	The overall reason for the amendment was to include subjects with genotype 4 hepatitis C virus (HCV) infection in the trial population.
16 June 2014	This amendment was created as an urgent safety measure because, in the ongoing study, a higher than expected relapse rate was observed in subjects infected with HCV genotype 1 and with a host interleukin-28B (IL28B) genotype CT or TT, who had detectable HCV Ribonucleic acid (RNA) at week 2.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported