Clinical trial results:
A Phase 2, Open-Label Study of Daclatasvir (BMS-790052) and TMC435 in Combination With or Without Ribavirin (RBV) For Treatment-Naive Subjects or Null Responders to Prior Peginterferon Alfa (PegIFN)/RBV Therapy with Genotype 1 Chronic Hepatitis C

Summary

EudraCT number	2012-000070-28
Trial protocol	HU DE ES
Global end of trial date	21 November 2013

Results information

Result version number	v1 (current)
This version publication date	16 February 2017
First version publication date	16 February 2017

Trial information

Trial identification

Sponsor protocol code	AI444-062

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01628692
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb International Corporation, clinical.trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb International Corporation, clinical.trials@bms.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	21 November 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess efficacy of daclatasvir and TMC435 with and without ribavirin, as determined by the proportion of subjects with sustained virologic response at post-treatment follow-up Week 12 (SVR12), defined as hepatitis C virus (HCV) ribonucleic acid (RNA) < lower limit of quantitation (LLOQ) at post-treatment Week 12.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 June 2012
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	Argentina: 18
Country: Number of subjects enrolled	United States: 48
Country: Number of subjects enrolled	Spain: 29
Country: Number of subjects enrolled	France: 75
Country: Number of subjects enrolled	Germany: 35
Country: Number of subjects enrolled	Hungary: 25
Worldwide total number of subjects	230
EEA total number of subjects	164

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)	185
From 65 to 84 years	45
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 25 sites in 6 countries.

Pre-assignment

Screening details:

A total of 230 subjects were enrolled and 168 were treated. 62 subjects were enrolled, but did not enter the treatment period. Reasons for non-treatment include 54 subjects no longer met the study entry criteria, 6 subjects withdrew consent, and 2 subjects were lost to follow-up.

Period 1

Period 1 title	Treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Genotype 1b: Daclatasvir + Simeprevir (Naive)

Arm description:

Subjects with no prior treatment of hepatitis C virus genotype 1b. Received daclatasvir 30 mg with or without food and simeprevir 150 mg with a light to standard meal once daily (QD), for a period of 12 weeks or 24 weeks based on re-randomization and continued into a post-treatment follow-up period.

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

Dosage and administration details:

Subjects received Daclatasvir orally 30-mg tablets once daily (QD). Daclatasvir was administered as 1 tablet with or without food for the duration of assigned treatment. mg=milligram

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

Dosage and administration details:

Subjects received Simeprevir orally 150-mg gelatin capsule once daily (QD). Simeprevir was administered as 1 gelatin capsule with a light to standard meal for the duration of assigned treatment. mg=milligram

Arm title	Genotype 1b: Daclatasvir + Simeprevir (Null)

Arm description:

Subjects with hepatitis C virus genotype 1b, and who never attained ≥2 log10 decline in hepatitis C virus RNA levels after at least 12 weeks of prior therapy with peginterferon/ribavirin. Received daclatasvir 30 mg with or without food and simeprevir 150 mg with a light to standard meal QD, for a period of 12 or 24 weeks based on re-randomization and continued into post-treatment follow-up.

Arm type	Experimental

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

Dosage and administration details:

Subjects received Daclatasvir orally 30-mg tablets once daily (QD). Daclatasvir was administered as 1 tablet with or without food for the duration of assigned treatment. mg=milligram

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

Dosage and administration details:

Subjects received Simeprevir orally 150-mg gelatin capsule once daily (QD). Simeprevir was administered as 1 gelatin capsule with a light to standard meal for the duration of assigned treatment. mg=milligram

Arm title	Genotype 1b: Daclatasvir + Simeprevir + Ribavirin (Naive)

Arm description:

Subjects with no prior treatment of hepatitis C virus genotype 1b. Received daclatasvir 30 mg with or without food, simeprevir 150 mg with a light to standard meal QD, and weight stratified (1000/1200 mg for participants weighing <75/>= 75 kg, respectively) ribavirin twice daily (BID) for a period of 12 or 24 weeks based on re-randomization and continued into post-treatment follow-up.

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

Dosage and administration details:

Subjects received Daclatasvir orally 30-mg tablets once daily (QD). Daclatasvir was administered as 1 tablet with or without food for the duration of assigned treatment. mg=milligram

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

Dosage and administration details:

Subjects received Simeprevir orally 150-mg gelatin capsule once daily (QD). Simeprevir was administered as 1 gelatin capsule with a light to standard meal for the duration of assigned treatment. mg=milligram

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 administered at a daily weight stratified dose of 1,000 to 1,200 mg orally in 2 divided doses. Subjects received either 400 mg (2 tablets for subjects < 75 kg) or 600 mg (3 tablets for subjects ≥ 75 kg) of Ribavirin in the morning with food and 600 mg (3 tablets) of RBV in the evening with food. mg=milligram; kg=kilogram

Arm title	Genotype 1b: Daclatasvir + Simeprevir + Ribavirin (Null)

Arm description:

Subjects with hepatitis C virus genotype 1b, who never attained ≥2 log10 decline in hepatitis C virus RNA level after at least 12 weeks of prior therapy with peginterferon/ribavirin. Received daclatasvir 30

mg with or without food, simeprevir 150 mg with a light to standard meal QD, and weight stratified (1000/1200 mg for participants weighing <75/>=75 kg, respectively) ribavirin BID were continued to receive treatment for a period of 12 or 24 weeks based on re-randomization and continued into post-treatment follow-up period.

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

Dosage and administration details:

Subjects received Daclatasvir orally 30-mg tablets once daily (QD). Daclatasvir was administered as 1 tablet with or without food for the duration of assigned treatment. mg=milligram

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

Dosage and administration details:

Subjects received Simeprevir orally 150-mg gelatin capsule once daily (QD). Simeprevir was administered as 1 gelatin capsule with a light to standard meal for the duration of assigned treatment. mg=milligram

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 administered at a daily weight stratified dose of 1,000 to 1,200 mg orally in 2 divided doses. Subjects received either 400 mg (2 tablets for subjects < 75 kg) or 600 mg (3 tablets for subjects ≥ 75 kg) of Ribavirin in the morning with food and 600 mg (3 tablets) of RBV in the evening with food. mg=milligram; kg=kilogram

Arm title	Genotype 1a: Daclatasvir + Simeprevir + Ribavirin (Naive)

Arm description:

Subjects with no prior treatment of hepatitis C virus genotype 1a. Received daclatasvir 30 mg with or without food, simeprevir 150 mg with a light to standard meal QD, and weight stratified (1000/1200 mg for participants weighing <75/>=75 kg, respectively) ribavirin BID for a period of 24 weeks and continued into post-treatment follow-up period of 24 weeks.

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

Dosage and administration details:

Subjects received Daclatasvir orally 30-mg tablets once daily (QD). Daclatasvir was administered as 1 tablet with or without food for the duration of assigned treatment. mg=milligram

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

Dosage and administration details:

Subjects received Simeprevir orally 150-mg gelatin capsule once daily (QD). Simeprevir was administered as 1 gelatin capsule with a light to standard meal for the duration of assigned treatment. mg=milligram

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 administered at a daily weight stratified dose of 1,000 to 1,200 mg orally in 2 divided doses. Subjects received either 400 mg (2 tablets for subjects < 75 kg) or 600 mg (3 tablets for subjects ≥ 75 kg) of Ribavirin in the morning with food and 600 mg (3 tablets) of RBV in the evening with food. mg=milligram; kg=kilogram

Arm title	Genotype 1a: Daclatasvir + Simeprevir + Ribavirin (Null)

Arm description:

Subjects with hepatitis C virus genotype 1a, who never attained ≥2 log10 decline in hepatitis C virus RNA level after at least 12 weeks of prior therapy. Received daclatasvir 30 mg with or without food, simeprevir 150 mg with a light to standard meal QD, and weight stratified (1000/1200 mg for participants weighing <75/>=75 kg, respectively) ribavirin BID for a period of 24 weeks and continued into post-treatment follow-up period of 24 weeks.

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

Dosage and administration details:

Subjects received Daclatasvir orally 30-mg tablets once daily (QD). Daclatasvir was administered as 1 tablet with or without food for the duration of assigned treatment. mg=milligram

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

Dosage and administration details:

Subjects received Simeprevir orally 150-mg gelatin capsule once daily (QD). Simeprevir was administered as 1 gelatin capsule with a light to standard meal for the duration of assigned treatment. mg=milligram

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 administered at a daily weight stratified dose of 1,000 to 1,200 mg orally in 2 divided doses. Subjects received either 400 mg (2 tablets for subjects < 75 kg) or 600 mg (3 tablets for subjects ≥ 75 kg) of Ribavirin in the morning with food and 600 mg (3 tablets) of RBV in the evening with food. mg=milligram; kg=kilogram

Number of subjects in period 1[1]	Genotype 1b: Daclatasvir + Simeprevir (Naive)	Genotype 1b: Daclatasvir + Simeprevir (Null)	Genotype 1b: Daclatasvir + Simeprevir + Ribavirin (Naive)
Started	53	23	51
Completed	46	17	43
Not completed	7	6	8
Withdrawl by Subject	-	1	1
Adverse Event	2	-	2
Poor compliance/noncompliance	1	-	-
Death	-	1	-
Administrative Reason by Sponsor	-	-	-
Completed 12 Week only	-	-	-
Lack of efficacy	4	4	5

Number of subjects in period 1[1]	Genotype 1b: Daclatasvir + Simeprevir + Ribavirin (Null)	Genotype 1a: Daclatasvir + Simeprevir + Ribavirin (Naive)	Genotype 1a: Daclatasvir + Simeprevir + Ribavirin (Null)
Started	20	12	9
Completed	19	8	0
Not completed	1	4	9
Withdrawl by Subject	-	-	-
Adverse Event	-	-	-
Poor compliance/noncompliance	-	-	-
Death	-	-	-
Administrative Reason by Sponsor	-	-	1
Completed 12 Week only	-	-	1
Lack of efficacy	1	4	7

Notes:

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

Justification: Out of 230 subjects who were enrolled, 168 subjects received at least 1 dose of study therapy.

Period 2

Period 2 title	Follow-up Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No

Arm title	Genotype 1b: Daclatasvir + Simeprevir (Naive)

Arm description:

Post-treatment follow-up for either 24 or 36 weeks depending on the duration of treatment assigned for subjects with no prior treatment of hepatitis C virus genotype 1b. Received daclatasvir 30 mg with or without food and simeprevir 150 mg with a light to standard meal once daily (QD), for a period of 12 weeks or 24 weeks based on re-randomization and continued into a post-treatment follow-up period.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Genotype 1b: Daclatasvir + Simeprevir (Null)

Arm description:

Post-treatment follow-up for either 24 or 36 weeks depending on the duration of treatment assigned for subjects with hepatitis C virus genotype 1b, and who never attained ≥2 log10 decline in hepatitis C virus RNA levels after at least 12 weeks of prior therapy with peginterferon/ribavirin. Received daclatasvir 30 mg with or without food and simeprevir 150 mg with a light to standard meal QD, for a period of 12 or 24 weeks based on re-randomization and continued into post-treatment follow-up.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Genotype 1b: Daclatasvir + Simeprevir + Ribavirin (Naive)

Arm description:

Post-treatment follow-up for either 24 or 36 weeks depending on the duration of treatment assigned for subjects with no prior treatment of hepatitis C virus genotype 1b. Received daclatasvir 30 mg with or without food, simeprevir 150 mg with a light to standard meal QD, and weight stratified (1000/1200 mg for participants weighing <75/>= 75 kg, respectively) ribavirin twice daily (BID) for a period of 12 or 24 weeks based on re-randomization and continued into post-treatment follow-up.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Genotype 1b: Daclatasvir + Simeprevir + Ribavirin (Null)

Arm description:

Post-treatment follow-up for either 24 or 36 weeks depending on the duration of treatment assigned for subjects with hepatitis C virus genotype 1b, who never attained ≥2 log10 decline in hepatitis C virus RNA level after at least 12 weeks of prior therapy with peginterferon/ribavirin. Received daclatasvir 30 mg with or without food, simeprevir 150 mg with a light to standard meal QD, and weight stratified (1000/1200 mg for participants weighing <75/>=75 kg, respectively) ribavirin BID were continued to receive treatment for a period of 12 or 24 weeks based on re-randomization and continued into post-treatment follow-up period.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Genotype 1a: Daclatasvir + Simeprevir + Ribavirin (Naive)

Arm description:

Post-treatment follow-up for 24 weeks for subjects with no prior treatment of hepatitis C virus genotype 1a. Received daclatasvir 30 mg with or without food, simeprevir 150 mg with a light to standard meal QD, and weight stratified (1000/1200 mg for participants weighing <75/>=75 kg, respectively) ribavirin BID for a period of 24 weeks and continued into post-treatment follow-up period of 24 weeks.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Genotype 1a: Daclatasvir + Simeprevir + Ribavirin (Null)

Arm description:

Post-treatment follow-up for 24 weeks for subjects with hepatitis C virus genotype 1a, who never attained ≥2 log10 decline in hepatitis C virus RNA level after at least 12 weeks of prior therapy. Received daclatasvir 30 mg with or without food, simeprevir 150 mg with a light to standard meal QD, and weight stratified (1000/1200 mg for participants weighing <75/>=75 kg, respectively) ribavirin BID for a period of 24 weeks and continued into post-treatment follow-up period of 24 weeks.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Genotype 1b: Daclatasvir + Simeprevir (Naive)	Genotype 1b: Daclatasvir + Simeprevir (Null)	Genotype 1b: Daclatasvir + Simeprevir + Ribavirin (Naive)
Started	46	17	43
Completed	51	21	44
Not completed	0	0	3
Consent withdrawn by subject	-	-	1
Death	-	-	1
Lost to follow-up	-	-	1
Joined	5	4	4
Did not complete treatment, but joined follow up	5	4	4

Number of subjects in period 2	Genotype 1b: Daclatasvir + Simeprevir + Ribavirin (Null)	Genotype 1a: Daclatasvir + Simeprevir + Ribavirin (Naive)	Genotype 1a: Daclatasvir + Simeprevir + Ribavirin (Null)
Started	19	8	2
Completed	20	10	2
Not completed	0	0	0
Consent withdrawn by subject	-	-	-
Death	-	-	-
Lost to follow-up	-	-	-
Joined	1	2	0
Did not complete treatment, but joined follow up	1	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Genotype 1b: Daclatasvir + Simeprevir (Naive)
Reporting group description:	
Subjects with no prior treatment of hepatitis C virus genotype 1b. Received daclatasvir 30 mg with or without food and simeprevir 150 mg with a light to standard meal once daily (QD), for a period of 12 weeks or 24 weeks based on re-randomization and continued into a post-treatment follow-up period.	
Reporting group title	Genotype 1b: Daclatasvir + Simeprevir (Null)
Reporting group description:	
Subjects with hepatitis C virus genotype 1b, and who never attained ≥2 log10 decline in hepatitis C virus RNA levels after at least 12 weeks of prior therapy with peginterferon/ribavirin. Received daclatasvir 30 mg with or without food and simeprevir 150 mg with a light to standard meal QD, for a period of 12 or 24 weeks based on re-randomization and continued into post-treatment follow-up.	
Reporting group title	Genotype 1b: Daclatasvir + Simeprevir + Ribavirin (Naive)
Reporting group description:	
Subjects with no prior treatment of hepatitis C virus genotype 1b. Received daclatasvir 30 mg with or without food, simeprevir 150 mg with a light to standard meal QD, and weight stratified (1000/1200 mg for participants weighing <75/>= 75 kg, respectively) ribavirin twice daily (BID) for a period of 12 or 24 weeks based on re-randomization and continued into post-treatment follow-up.	
Reporting group title	Genotype 1b: Daclatasvir + Simeprevir + Ribavirin (Null)
Reporting group description:	
Subjects with hepatitis C virus genotype 1b, who never attained ≥2 log10 decline in hepatitis C virus RNA level after at least 12 weeks of prior therapy with peginterferon/ribavirin. Received daclatasvir 30 mg with or without food, simeprevir 150 mg with a light to standard meal QD, and weight stratified (1000/1200 mg for participants weighing <75/>=75 kg, respectively) ribavirin BID were continued to receive treatment for a period of 12 or 24 weeks based on re-randomization and continued into post-treatment follow-up period.	
Reporting group title	Genotype 1a: Daclatasvir + Simeprevir + Ribavirin (Naive)
Reporting group description:	
Subjects with no prior treatment of hepatitis C virus genotype 1a. Received daclatasvir 30 mg with or without food, simeprevir 150 mg with a light to standard meal QD, and weight stratified (1000/1200 mg for participants weighing <75/>=75 kg, respectively) ribavirin BID for a period of 24 weeks and continued into post-treatment follow-up period of 24 weeks.	
Reporting group title	Genotype 1a: Daclatasvir + Simeprevir + Ribavirin (Null)
Reporting group description:	
Subjects with hepatitis C virus genotype 1a, who never attained ≥2 log10 decline in hepatitis C virus RNA level after at least 12 weeks of prior therapy. Received daclatasvir 30 mg with or without food, simeprevir 150 mg with a light to standard meal QD, and weight stratified (1000/1200 mg for participants weighing <75/>=75 kg, respectively) ribavirin BID for a period of 24 weeks and continued into post-treatment follow-up period of 24 weeks.	

Reporting group values	Genotype 1b: Daclatasvir + Simeprevir (Naive)	Genotype 1b: Daclatasvir + Simeprevir (Null)	Genotype 1b: Daclatasvir + Simeprevir + Ribavirin (Naive)
Number of subjects	53	23	51
Age categorical			
Units: Subjects			
< 21 years	0	0	0
Between 21 and 64 years	41	19	42
>=65 years	12	4	9
Age continuous			
Units: years			
arithmetic mean	53.6	53.8	53
standard deviation	± 12.98	± 11.26	± 11.29

Gender categorical Units: Subjects			
Female	31	11	26
Male	22	12	25
Hepatitis C Virus RNA Distribution Units: Subjects			
<800,000 IU/mL	12	3	11
≥800,000 IU/mL	41	20	40
Randomization Stratum Units: Subjects			
Hepatitis C Virus Genotype 1b	53	23	51
Hepatitis C Virus Genotype 1a	0	0	0

Reporting group values	Genotype 1b: Daclatasvir + Simeprevir + Ribavirin (Null)	Genotype 1a: Daclatasvir + Simeprevir + Ribavirin (Naive)	Genotype 1a: Daclatasvir + Simeprevir + Ribavirin (Null)
Number of subjects	20	12	9
Age categorical Units: Subjects			
< 21 years	1	1	0
Between 21 and 64 years	11	11	9
>=65 years	8	0	0
Age continuous Units: years			
arithmetic mean	57.2	50	48.1
standard deviation	± 14.94	± 11.15	± 6.09
Gender categorical Units: Subjects			
Female	11	5	2
Male	9	7	7
Hepatitis C Virus RNA Distribution Units: Subjects			
<800,000 IU/mL	4	5	0
≥800,000 IU/mL	16	7	9
Randomization Stratum Units: Subjects			
Hepatitis C Virus Genotype 1b	20	0	0
Hepatitis C Virus Genotype 1a	0	12	9

Reporting group values	Total		
Number of subjects	168		
Age categorical Units: Subjects			
< 21 years	2		
Between 21 and 64 years	133		
>=65 years	33		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		

Gender categorical Units: Subjects			
Female	86		
Male	82		
Hepatitis C Virus RNA Distribution Units: Subjects			
<800,000 IU/mL	35		
≥800,000 IU/mL	133		
Randomization Stratum Units: Subjects			
Hepatitis C Virus Genotype 1b	147		
Hepatitis C Virus Genotype 1a	21		

End points

End points reporting groups

Reporting group title	Genotype 1b: Daclatasvir + Simeprevir (Naive)

Reporting group description:

Subjects with no prior treatment of hepatitis C virus genotype 1b. Received daclatasvir 30 mg with or without food and simeprevir 150 mg with a light to standard meal once daily (QD), for a period of 12 weeks or 24 weeks based on re-randomization and continued into a post-treatment follow-up period.

Reporting group title	Genotype 1b: Daclatasvir + Simeprevir (Null)

Reporting group description:

Subjects with hepatitis C virus genotype 1b, and who never attained ≥2 log10 decline in hepatitis C virus RNA levels after at least 12 weeks of prior therapy with peginterferon/ribavirin. Received daclatasvir 30 mg with or without food and simeprevir 150 mg with a light to standard meal QD, for a period of 12 or 24 weeks based on re-randomization and continued into post-treatment follow-up.

Reporting group title	Genotype 1b: Daclatasvir + Simeprevir + Ribavirin (Naive)

Reporting group description:

Subjects with no prior treatment of hepatitis C virus genotype 1b. Received daclatasvir 30 mg with or without food, simeprevir 150 mg with a light to standard meal QD, and weight stratified (1000/1200 mg for participants weighing <75/>= 75 kg, respectively) ribavirin twice daily (BID) for a period of 12 or 24 weeks based on re-randomization and continued into post-treatment follow-up.

Reporting group title	Genotype 1b: Daclatasvir + Simeprevir + Ribavirin (Null)

Reporting group description:

Subjects with hepatitis C virus genotype 1b, who never attained ≥2 log10 decline in hepatitis C virus RNA level after at least 12 weeks of prior therapy with peginterferon/ribavirin. Received daclatasvir 30 mg with or without food, simeprevir 150 mg with a light to standard meal QD, and weight stratified (1000/1200 mg for participants weighing <75/>=75 kg, respectively) ribavirin BID were continued to receive treatment for a period of 12 or 24 weeks based on re-randomization and continued into post-treatment follow-up period.

Reporting group title	Genotype 1a: Daclatasvir + Simeprevir + Ribavirin (Naive)

Reporting group description:

Subjects with no prior treatment of hepatitis C virus genotype 1a. Received daclatasvir 30 mg with or without food, simeprevir 150 mg with a light to standard meal QD, and weight stratified (1000/1200 mg for participants weighing <75/>=75 kg, respectively) ribavirin BID for a period of 24 weeks and continued into post-treatment follow-up period of 24 weeks.

Reporting group title	Genotype 1a: Daclatasvir + Simeprevir + Ribavirin (Null)

Reporting group description:

Subjects with hepatitis C virus genotype 1a, who never attained ≥2 log10 decline in hepatitis C virus RNA level after at least 12 weeks of prior therapy. Received daclatasvir 30 mg with or without food, simeprevir 150 mg with a light to standard meal QD, and weight stratified (1000/1200 mg for participants weighing <75/>=75 kg, respectively) ribavirin BID for a period of 24 weeks and continued into post-treatment follow-up period of 24 weeks.

Reporting group title	Genotype 1b: Daclatasvir + Simeprevir (Naive)

Reporting group description:

Post-treatment follow-up for either 24 or 36 weeks depending on the duration of treatment assigned for subjects with no prior treatment of hepatitis C virus genotype 1b. Received daclatasvir 30 mg with or without food and simeprevir 150 mg with a light to standard meal once daily (QD), for a period of 12 weeks or 24 weeks based on re-randomization and continued into a post-treatment follow-up period.

Reporting group title	Genotype 1b: Daclatasvir + Simeprevir (Null)

Reporting group description:

Post-treatment follow-up for either 24 or 36 weeks depending on the duration of treatment assigned for subjects with hepatitis C virus genotype 1b, and who never attained ≥2 log10 decline in hepatitis C virus RNA levels after at least 12 weeks of prior therapy with peginterferon/ribavirin. Received daclatasvir 30 mg with or without food and simeprevir 150 mg with a light to standard meal QD, for a period of 12 or 24 weeks based on re-randomization and continued into post-treatment follow-up.

Reporting group title	Genotype 1b: Daclatasvir + Simeprevir + Ribavirin (Naive)

Reporting group description:

Post-treatment follow-up for either 24 or 36 weeks depending on the duration of treatment assigned for subjects with no prior treatment of hepatitis C virus genotype 1b. Received daclatasvir 30 mg with or without food, simeprevir 150 mg with a light to standard meal QD, and weight stratified (1000/1200 mg

for participants weighing <75/>= 75 kg, respectively) ribavirin twice daily (BID) for a period of 12 or 24 weeks based on re-randomization and continued into post-treatment follow-up.

Reporting group title	Genotype 1b: Daclatasvir + Simeprevir + Ribavirin (Null)

Reporting group description:

Post-treatment follow-up for either 24 or 36 weeks depending on the duration of treatment assigned for subjects with hepatitis C virus genotype 1b, who never attained ≥2 log10 decline in hepatitis C virus RNA level after at least 12 weeks of prior therapy with peginterferon/ribavirin. Received daclatasvir 30 mg with or without food, simeprevir 150 mg with a light to standard meal QD, and weight stratified (1000/1200 mg for participants weighing <75/>=75 kg, respectively) ribavirin BID were continued to receive treatment for a period of 12 or 24 weeks based on re-randomization and continued into post-treatment follow-up period.

Reporting group title	Genotype 1a: Daclatasvir + Simeprevir + Ribavirin (Naive)

Reporting group description:

Post-treatment follow-up for 24 weeks for subjects with no prior treatment of hepatitis C virus genotype 1a. Received daclatasvir 30 mg with or without food, simeprevir 150 mg with a light to standard meal QD, and weight stratified (1000/1200 mg for participants weighing <75/>=75 kg, respectively) ribavirin BID for a period of 24 weeks and continued into post-treatment follow-up period of 24 weeks.

Reporting group title	Genotype 1a: Daclatasvir + Simeprevir + Ribavirin (Null)

Reporting group description:

Post-treatment follow-up for 24 weeks for subjects with hepatitis C virus genotype 1a, who never attained ≥2 log10 decline in hepatitis C virus RNA level after at least 12 weeks of prior therapy. Received daclatasvir 30 mg with or without food, simeprevir 150 mg with a light to standard meal QD, and weight stratified (1000/1200 mg for participants weighing <75/>=75 kg, respectively) ribavirin BID for a period of 24 weeks and continued into post-treatment follow-up period of 24 weeks.

Subject analysis set title	Genotype 1b: Daclatasvir + Simeprevir (Naive + Null)
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects with hepatitis C virus genotype 1b and who either had no prior treatment or had never attained ≥2 log10 decline in hepatitis C virus RNA levels after at least 12 weeks of prior therapy with peginterferon/ribavirin. Received daclatasvir 30 mg with or without food and simeprevir 150 mg with a light to standard meal once daily (QD), for a period of 12 weeks or 24 weeks based on re-randomization and continued into a post-treatment follow-up period.

Subject analysis set title	Genotype1b: Daclatasvir +Simeprevir + Ribavirin (Naive + Null)
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects with hepatitis C virus genotype 1b and who either had no prior treatment or had never attained ≥2 log10 decline in hepatitis C virus RNA levels after at least 12 weeks of prior therapy with peginterferon/ribavirin. Received daclatasvir 30 mg with or without food, simeprevir 150 mg with a light to standard meal QD, and weight stratified (1000/1200 mg for subjects weighing <75/>= 75 kg, respectively) ribavirin twice daily (BID) for a period of 12 or 24 weeks based on re-randomization and continued into post-treatment follow-up.

Subject analysis set title	Genotype1a: Daclatasvir +Simeprevir + Ribavirin(Naive + Null)
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects with hepatitis C virus genotype 1a and who either had no prior treatment or had never attained ≥2 log10 decline in hepatitis C virus RNA levels after at least 12 weeks of prior therapy with peginterferon/ribavirin. Received daclatasvir 30 mg with or without food, simeprevir 150 mg with a light to standard meal QD, and weight stratified (1000/1200 mg for subjects weighing <75/>=75 kg, respectively) ribavirin BID for a period of 24 weeks and continued into post-treatment follow-up period of 24 weeks.

Primary: Percentage of Subjects With Sustained Virologic Response Rate at Post-treatment Week 12 (SVR12)

End point title	Percentage of Subjects With Sustained Virologic Response Rate at Post-treatment Week 12 (SVR12)[1]

End point description:

SVR12 rate was defined as hepatitis C virus (HCV) RNA levels to be <lower limit of quantitation, target detected or target not detected, at post-treatment Week 12. HCV RNA levels were measured by the Roche COBAS® TaqMan® HCV Test version 2.0 from the central laboratory. All participants who were randomized and received at least 1 dose of active study therapy (daclatasvir, simeprevir, ribavirin).

End point type	Primary

End point timeframe:

Post Treatment Week 12 (Follow-up period)

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: Only descriptive summary statistics were planned for this outcome measure.

End point values	Genotype 1b: Daclatasvir + Simeprevir (Naive)	Genotype 1b: Daclatasvir + Simeprevir (Null)	Genotype 1b: Daclatasvir + Simeprevir + Ribavirin (Naive)	Genotype 1b: Daclatasvir + Simeprevir + Ribavirin (Null)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	23	51	20
Units: Percentage of subjects				
number (confidence interval 80%)	84.9 (78.6 to 91.2)	69.6 (57.3 to 81.9)	74.5 (66.7 to 82.3)	95 (88.8 to 100)

End point values	Genotype 1a: Daclatasvir + Simeprevir + Ribavirin (Naive)	Genotype 1a: Daclatasvir + Simeprevir + Ribavirin (Null)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	9[2]		
Units: Percentage of subjects				
number (confidence interval 80%)	66.7 (49.2 to 84.1)	0 (-99999 to 99999)		

Notes:

[2] - As no subjects achieved SVR12, 80% confidence interval value is not available.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Rapid Virologic Response (RVR)

End point title	Percentage of Subjects With Rapid Virologic Response (RVR)

End point description:

RVR was defined as hepatitis C virus (HCV) RNA levels to be <lower limit of quantitation, target not detected at Week 4. HCV RNA levels were measured by the Roche COBAS® TaqMan® HCV Test version 2.0 from the central laboratory. All treated subjects.

End point type	Secondary

End point timeframe:

Week 4

End point values	Genotype 1b: Daclatasvir + Simeprevir (Naive)	Genotype 1b: Daclatasvir + Simeprevir (Null)	Genotype 1b: Daclatasvir + Simeprevir + Ribavirin (Naive)	Genotype 1b: Daclatasvir + Simeprevir + Ribavirin (Null)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	23	51	20
Units: Percentage of Subjects				
number (confidence interval 80%)	79.2 (72.1 to 86.4)	69.6 (57.3 to 81.9)	68.6 (60.3 to 77)	85 (74.8 to 95.2)

End point values	Genotype 1a: Daclatasvir + Simeprevir + Ribavirin (Naive)	Genotype 1a: Daclatasvir + Simeprevir + Ribavirin (Null)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	9		
Units: Percentage of Subjects				
number (confidence interval 80%)	75 (59 to 91)	33.3 (13.2 to 53.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Complete Early Virologic Response (cEVR)

End point title	Percentage of Subjects With Complete Early Virologic Response (cEVR)

End point description:

cEVR was defined as hepatitis C virus (HCV) RNA levels to be <lower limit of quantitation, target not detected at Week 12. HCV RNA levels were measured by the Roche COBAS® TaqMan® HCV Test version 2.0 from the central laboratory. All treated subejcts.

End point type	Secondary

End point timeframe:

Week 12

End point values	Genotype 1b: Daclatasvir + Simeprevir (Naive)	Genotype 1b: Daclatasvir + Simeprevir (Null)	Genotype 1b: Daclatasvir + Simeprevir + Ribavirin (Naive)	Genotype 1b: Daclatasvir + Simeprevir + Ribavirin (Null)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	23	51	20
Units: Percentage of Subjects				
number (confidence interval 80%)	84.9 (78.6 to 91.2)	73.9 (62.2 to 85.6)	82.4 (75.5 to 89.2)	90 (81.4 to 98.6)

End point values	Genotype 1a: Daclatasvir + Simeprevir + Ribavirin (Naive)	Genotype 1a: Daclatasvir + Simeprevir + Ribavirin (Null)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	9		
Units: Percentage of Subjects				
number (confidence interval 80%)	66.7 (49.2 to 84.1)	11.1 (0 to 24.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Extended Rapid Virologic Response (eRVR)

End point title	Percentage of Subjects With Extended Rapid Virologic Response (eRVR)

End point description:

eRVR were defined as hepatitis C virus (HCV) RNA levels to be <lower limit of quantitation, target not detected at both Week 4 and Week 12. HCV RNA levels were measured by the Roche COBAS® TaqMan® HCV Test version 2.0 from the central laboratory. All treated subjects.

End point type	Secondary

End point timeframe:

Week 4 and Week 12

End point values	Genotype 1b: Daclatasvir + Simeprevir (Naive)	Genotype 1b: Daclatasvir + Simeprevir (Null)	Genotype 1b: Daclatasvir + Simeprevir + Ribavirin (Naive)	Genotype 1b: Daclatasvir + Simeprevir + Ribavirin (Null)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	23	51	20
Units: Percentage of Subject				
number (confidence interval 80%)	71.7 (63.8 to 79.6)	60.9 (47.8 to 73.9)	62.7 (54.1 to 71.4)	75 (62.6 to 87.4)

End point values	Genotype 1a: Daclatasvir + Simeprevir + Ribavirin (Naive)	Genotype 1a: Daclatasvir + Simeprevir + Ribavirin (Null)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	9		
Units: Percentage of Subject				

number (confidence interval 80%)	58.3 (40.1 to 76.6)	11.1 (0 to 24.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With End of Treatment Response (EOTR)

End point title	Percentage of Subjects With End of Treatment Response (EOTR)

End point description:

EOTR were defined as hepatitis C virus (HCV) RNA levels <lower limit of quantitation, target not detected at end of treatment. HCV RNA levels were measured by the Roche COBAS® TaqMan® HCV Test version 2.0 from the central laboratory. All treated subjects.

End point type	Secondary

End point timeframe:

End of treatment (Week 24)

End point values	Genotype 1b: Daclatasvir + Simeprevir (Naive)	Genotype 1b: Daclatasvir + Simeprevir (Null)	Genotype 1b: Daclatasvir + Simeprevir + Ribavirin (Naive)	Genotype 1b: Daclatasvir + Simeprevir + Ribavirin (Null)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	23	51	20
Units: Percentage of Subjects				
number (confidence interval 80%)	88.7 (83.1 to 94.3)	78.3 (67.2 to 89.3)	78.4 (71.1 to 85.8)	95 (88.8 to 100)

End point values	Genotype 1a: Daclatasvir + Simeprevir + Ribavirin (Naive)	Genotype 1a: Daclatasvir + Simeprevir + Ribavirin (Null)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	9		
Units: Percentage of Subjects				
number (confidence interval 80%)	66.7 (49.2 to 84.1)	0 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Sustained Virologic Response at Follow-up Week 12 (SVR12) by rs12979860 Single Nucleotide Polymorphisms in the IL-28B Gene Categories

End point title	Percentage of Subjects With Sustained Virologic Response at Follow-up Week 12 (SVR12) by rs12979860 Single Nucleotide Polymorphisms in the IL-28B Gene Categories

End point description:

Subjects were categorized into 3 genotypes based on single nucleotide polymorphisms in the IL28B gene. SVR12 was defined as hepatitis C virus (HCV) RNA levels below lower limit of quantitation, target detected or target not detected at follow-up Week 12. HCV RNA levels were measured by the Roche COBAS® TaqMan® HCV Test version 2.0 from the central laboratory. All treated subjects. Here 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Post-treatment Week 12 (Follow-up period)

End point values	Genotype 1b: Daclatasvir + Simeprevir (Naive)	Genotype 1b: Daclatasvir + Simeprevir (Null)	Genotype 1b: Daclatasvir + Simeprevir + Ribavirin (Naive)	Genotype 1b: Daclatasvir + Simeprevir + Ribavirin (Null)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	23	51	20
Units: Percentage of Subjects				
number (not applicable)				
IL28B Genotype CC type (n= 16,1,13,1,3,0)	87.5	100	84.6	100
IL28B Genotype CT type (n= 22,15, 28,10,9,8)	95.5	60	82.1	90
IL28B Genotype TT type (n= 12,6,10,7,0,1)	66.7	83.3	40	100

End point values	Genotype 1a: Daclatasvir + Simeprevir + Ribavirin (Naive)	Genotype 1a: Daclatasvir + Simeprevir + Ribavirin (Null)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	9		
Units: Percentage of Subjects				
number (not applicable)				
IL28B Genotype CC type (n= 16,1,13,1,3,0)	66.7	99999		
IL28B Genotype CT type (n= 22,15, 28,10,9,8)	66.7	0		
IL28B Genotype TT type (n= 12,6,10,7,0,1)	99999	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Serious Adverse Events (SAEs) and Discontinuations Due to Adverse Events (AEs) and Who Died

End point title	Number of Subjects With Serious Adverse Events (SAEs) and Discontinuations Due to Adverse Events (AEs) and Who Died

End point description:

AE was defined as any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that does not necessarily have a causal relationship with treatment. SAE was defined as a medical event that at any dose resulted in death, persistent or significant disability/incapacity, or drug dependency/abuse; was life-threatening, an important medical event, or a congenital anomaly/birth defect; or required or prolonged hospitalization. Based on the severity, AEs were categorized as Grade (Gr) 1=Mild, Gr 2=Moderate, Gr 3=Severe, Gr 4=Life-threatening or disabling, Gr 5=Death. All treated subjects.

End point type	Secondary

End point timeframe:

From start of treatment (Day 1) up to 7 days post last dose of study treatment (Week 24)

End point values	Genotype 1b: Daclatasvir + Simeprevir (Naive + Null)	Genotype1b: Daclatasvir +Simeprevir + Ribavirin (Naive + Null)	Genotype1a: Daclatasvir +Simeprevir + Ribavirin(Naive + Null)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	76	71	21	
Units: Subjects				
SAEs	7	3	1	
AEs Leading to Discontinuation	2	2	0	
Death	1	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of treatment (Day 1) up to 7 days post last dose of study treatment (24 Weeks)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Genotype 1b: Daclatasvir + Simeprevir (Naive + Null)

Reporting group description:

Subjects with hepatitis C virus genotype 1b and who either had no prior treatment or had never attained ≥2 log10 decline in hepatitis C virus RNA levels after at least 12 weeks of prior therapy with peginterferon/ribavirin. Received daclatasvir 30 mg with or without food and simeprevir 150 mg with a light to standard meal once daily (QD), for a period of 12 weeks or 24 weeks based on re-randomization and continued into a post-treatment follow-up period.

Reporting group title	Genotype1b: Daclatasvir +Simeprevir + Ribavirin (Naive + Null)

Reporting group description:

Subjects with hepatitis C virus genotype 1b and who either had no prior treatment or had never attained ≥2 log10 decline in hepatitis C virus RNA levels after at least 12 weeks of prior therapy with peginterferon/ribavirin. Received daclatasvir 30 mg with or without food, simeprevir 150 mg with a light to standard meal QD, and weight stratified (1000/1200 mg for subjects weighing <75/>= 75 kg, respectively) ribavirin twice daily (BID) for a period of 12 or 24 weeks based on re-randomization and continued into post-treatment follow-up.

Reporting group title	Genotype1a: Daclatasvir +Simeprevir + Ribavirin(Naive + Null)

Reporting group description:

Subjects with hepatitis C virus genotype 1a and who either had no prior treatment or had never attained ≥2 log10 decline in hepatitis C virus RNA levels after at least 12 weeks of prior therapy with peginterferon/ribavirin. Received daclatasvir 30 mg with or without food, simeprevir 150 mg with a light to standard meal QD, and weight stratified (1000/1200 mg for subjects weighing <75/>=75 kg, respectively) ribavirin BID for a period of 24 weeks and continued into post-treatment follow-up period of 24 weeks.

Serious adverse events	Genotype 1b: Daclatasvir + Simeprevir (Naive + Null)	Genotype1b: Daclatasvir +Simeprevir + Ribavirin (Naive + Null)	Genotype1a: Daclatasvir +Simeprevir + Ribavirin(Naive + Null)
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 76 (9.21%)	3 / 71 (4.23%)	1 / 21 (4.76%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic cancer			
subjects affected / exposed	0 / 76 (0.00%)	0 / 71 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
Post lumbar puncture syndrome			
subjects affected / exposed	1 / 76 (1.32%)	0 / 71 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 76 (0.00%)	1 / 71 (1.41%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis superficial			
subjects affected / exposed	0 / 76 (0.00%)	1 / 71 (1.41%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Hypoaesthesia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 71 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial haematoma			
subjects affected / exposed	1 / 76 (1.32%)	0 / 71 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 76 (1.32%)	0 / 71 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurotoxicity			
subjects affected / exposed	1 / 76 (1.32%)	0 / 71 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			

subjects affected / exposed	1 / 76 (1.32%)	0 / 71 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 71 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver disorder			
subjects affected / exposed	0 / 76 (0.00%)	1 / 71 (1.41%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 76 (1.32%)	0 / 71 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 76 (1.32%)	1 / 71 (1.41%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 76 (0.00%)	0 / 71 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 76 (0.00%)	1 / 71 (1.41%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	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	Genotype 1b: Daclatasvir + Simeprevir (Naive + Null)	Genotype1b: Daclatasvir +Simeprevir + Ribavirin (Naive + Null)	Genotype1a: Daclatasvir +Simeprevir + Ribavirin(Naive + Null)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 76 (64.47%)	63 / 71 (88.73%)	21 / 21 (100.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 76 (0.00%)	1 / 71 (1.41%)	2 / 21 (9.52%)
occurrences (all)	0	2	2
Hypertension			
subjects affected / exposed	5 / 76 (6.58%)	2 / 71 (2.82%)	1 / 21 (4.76%)
occurrences (all)	5	2	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	15 / 76 (19.74%)	16 / 71 (22.54%)	5 / 21 (23.81%)
occurrences (all)	17	19	9
Chills			
subjects affected / exposed	1 / 76 (1.32%)	2 / 71 (2.82%)	2 / 21 (9.52%)
occurrences (all)	1	2	3
Fatigue			
subjects affected / exposed	6 / 76 (7.89%)	11 / 71 (15.49%)	7 / 21 (33.33%)
occurrences (all)	6	12	10
Influenza like illness			
subjects affected / exposed	5 / 76 (6.58%)	1 / 71 (1.41%)	3 / 21 (14.29%)
occurrences (all)	5	1	7
Irritability			
subjects affected / exposed	3 / 76 (3.95%)	1 / 71 (1.41%)	2 / 21 (9.52%)
occurrences (all)	3	1	3
Pain			
subjects affected / exposed	3 / 76 (3.95%)	1 / 71 (1.41%)	2 / 21 (9.52%)
occurrences (all)	3	1	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 76 (2.63%)	7 / 71 (9.86%)	4 / 21 (19.05%)
occurrences (all)	3	9	4
Dyspnoea			

subjects affected / exposed	4 / 76 (5.26%)	11 / 71 (15.49%)	2 / 21 (9.52%)
occurrences (all)	4	11	4
Epistaxis			
subjects affected / exposed	0 / 76 (0.00%)	2 / 71 (2.82%)	2 / 21 (9.52%)
occurrences (all)	0	2	2
Rhinorrhoea			
subjects affected / exposed	1 / 76 (1.32%)	0 / 71 (0.00%)	2 / 21 (9.52%)
occurrences (all)	1	0	2
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	0 / 76 (0.00%)	0 / 71 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	5
Depression			
subjects affected / exposed	0 / 76 (0.00%)	2 / 71 (2.82%)	2 / 21 (9.52%)
occurrences (all)	0	2	2
Insomnia			
subjects affected / exposed	4 / 76 (5.26%)	7 / 71 (9.86%)	1 / 21 (4.76%)
occurrences (all)	4	7	3
Sleep disorder			
subjects affected / exposed	5 / 76 (6.58%)	5 / 71 (7.04%)	3 / 21 (14.29%)
occurrences (all)	7	6	5
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	2 / 76 (2.63%)	0 / 71 (0.00%)	2 / 21 (9.52%)
occurrences (all)	2	0	2
Headache			
subjects affected / exposed	16 / 76 (21.05%)	10 / 71 (14.08%)	6 / 21 (28.57%)
occurrences (all)	22	10	7
Paraesthesia			
subjects affected / exposed	2 / 76 (2.63%)	2 / 71 (2.82%)	3 / 21 (14.29%)
occurrences (all)	2	2	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 76 (1.32%)	12 / 71 (16.90%)	5 / 21 (23.81%)
occurrences (all)	2	13	7
Neutropenia			

subjects affected / exposed	0 / 76 (0.00%)	0 / 71 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	8
Thrombocytopenia			
subjects affected / exposed	0 / 76 (0.00%)	1 / 71 (1.41%)	2 / 21 (9.52%)
occurrences (all)	0	1	4
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 76 (1.32%)	1 / 71 (1.41%)	2 / 21 (9.52%)
occurrences (all)	1	1	2
Visual acuity reduced			
subjects affected / exposed	0 / 76 (0.00%)	0 / 71 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	3
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	4 / 76 (5.26%)	0 / 71 (0.00%)	2 / 21 (9.52%)
occurrences (all)	4	0	4
Abdominal pain			
subjects affected / exposed	4 / 76 (5.26%)	2 / 71 (2.82%)	5 / 21 (23.81%)
occurrences (all)	4	2	6
Abdominal pain upper			
subjects affected / exposed	3 / 76 (3.95%)	5 / 71 (7.04%)	1 / 21 (4.76%)
occurrences (all)	3	5	1
Constipation			
subjects affected / exposed	6 / 76 (7.89%)	5 / 71 (7.04%)	4 / 21 (19.05%)
occurrences (all)	9	5	5
Diarrhoea			
subjects affected / exposed	5 / 76 (6.58%)	2 / 71 (2.82%)	2 / 21 (9.52%)
occurrences (all)	5	2	3
Dyspepsia			
subjects affected / exposed	2 / 76 (2.63%)	5 / 71 (7.04%)	0 / 21 (0.00%)
occurrences (all)	2	5	0
Gastric disorder			
subjects affected / exposed	0 / 76 (0.00%)	0 / 71 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	3
Gastrooesophageal reflux disease			

subjects affected / exposed	3 / 76 (3.95%)	4 / 71 (5.63%)	0 / 21 (0.00%)
occurrences (all)	4	4	0
Nausea			
subjects affected / exposed	14 / 76 (18.42%)	11 / 71 (15.49%)	4 / 21 (19.05%)
occurrences (all)	18	11	5
Vomiting			
subjects affected / exposed	0 / 76 (0.00%)	3 / 71 (4.23%)	2 / 21 (9.52%)
occurrences (all)	0	3	4
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 76 (1.32%)	12 / 71 (16.90%)	3 / 21 (14.29%)
occurrences (all)	3	19	4
Jaundice			
subjects affected / exposed	1 / 76 (1.32%)	4 / 71 (5.63%)	0 / 21 (0.00%)
occurrences (all)	1	4	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 76 (3.95%)	4 / 71 (5.63%)	0 / 21 (0.00%)
occurrences (all)	3	4	0
Dry skin			
subjects affected / exposed	5 / 76 (6.58%)	5 / 71 (7.04%)	4 / 21 (19.05%)
occurrences (all)	5	5	5
Eczema			
subjects affected / exposed	0 / 76 (0.00%)	2 / 71 (2.82%)	2 / 21 (9.52%)
occurrences (all)	0	2	2
Photosensitivity reaction			
subjects affected / exposed	6 / 76 (7.89%)	3 / 71 (4.23%)	1 / 21 (4.76%)
occurrences (all)	7	5	3
Pruritus			
subjects affected / exposed	5 / 76 (6.58%)	15 / 71 (21.13%)	5 / 21 (23.81%)
occurrences (all)	5	16	8
Rash			
subjects affected / exposed	3 / 76 (3.95%)	9 / 71 (12.68%)	3 / 21 (14.29%)
occurrences (all)	3	10	6
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	4 / 76 (5.26%)	0 / 71 (0.00%)	1 / 21 (4.76%)
occurrences (all)	5	0	2
Myalgia			
subjects affected / exposed	3 / 76 (3.95%)	1 / 71 (1.41%)	2 / 21 (9.52%)
occurrences (all)	3	1	3
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 76 (2.63%)	3 / 71 (4.23%)	2 / 21 (9.52%)
occurrences (all)	3	3	2
Influenza			
subjects affected / exposed	0 / 76 (0.00%)	2 / 71 (2.82%)	2 / 21 (9.52%)
occurrences (all)	0	2	2
Nasopharyngitis			
subjects affected / exposed	10 / 76 (13.16%)	9 / 71 (12.68%)	2 / 21 (9.52%)
occurrences (all)	12	11	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 76 (3.95%)	1 / 71 (1.41%)	4 / 21 (19.05%)
occurrences (all)	3	2	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 December 2012	The primary purpose of this amendment was to clarify certain inclusion and exclusion criteria and maintain consistency with other direct-acting antiviral program Phase 2 studies. In addition there were other minor administrative changes. A summary, but not the full list of changes included in this amendment are bulleted below. • Changed the week for the interim analysis referring to treatment Week 12 to Week 16. Clarified that this would encompass subjects treated for at least 12 weeks of treatment and 4 weeks post treatment follow-up, (subtype 1b), or 16 weeks of treatment, (subtype 1a or 1b), or prematurely discontinued from the study • Changed from a minimum of 10% black/African-American to Approximately 10% black/African American • Additional information provided on how to define a Null responder • Additional criteria provided defining F3 cirrhosis. Reference to support this addition also added. • Further clarification on the types of psychiatric disorders and substance abuse that would be exclusionary in the study • Removed "confirmed" reference under the Laboratory exclusion criteria • Under prohibited and/or restricted treatments - included timeframe surrounding the stopping of such medications and starting study drug • Under prohibited and/or restricted treatments - Additional restricted medications added under CYP3A4 inducers • ECG added to Week 8 and End of Treatment study visits while in Treatment Phase and Week 8 and End of Treatment study visits if subject is in Rescue Treatment Phase • Added a timeframe for how long the post treatment follow-up period should be for 1b subjects that discontinue prior to re-randomization • Added the following sections; "Post Treatment Study Follow up", "Withdrawal of Consent", and "Lost to Follow up" • Additional language added regarding study drug disposal and return • Time window added for the Week 2 PK samples • Added a note regarding the definition of HCV RNA results

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported