Clinical trial results:
Open-Label, Randomized Study of Daclatasvir, Sofosbuvir, and Ribavirin for 12 vs. 16 weeks in Treatment-Naïve and Treatment-Experienced Patients with Genotype 3 Chronic Hepatitis C Infection with Compensated Advanced Fibrosis/Cirrhosis (F3/F4)

Summary

EudraCT number	2014-005310-28
Trial protocol	FR
Global end of trial date	18 December 2015

Results information

Result version number	v1 (current)
This version publication date	22 December 2016
First version publication date	22 December 2016

Trial information

Trial identification

Sponsor protocol code	AI444-326

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02319031
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	18 December 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to determine if the use of Daclatasvir, Sofosbuvir, and Ribavarin in combination for 12 or 16 weeks is safe and effective in the treatment of Genotype 3 Chronic Hepatitis C (HCV) in patients with HCV Genotype 3 infection and advanced fibrosis or compensated cirrhosis. Patients in this study may have already been treated prior for HCV or may have never received treatment for their HCV.

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	16 February 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Australia: 31
Worldwide total number of subjects	53
EEA total number of subjects	22

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)	52
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 10 sites in 2 countries.

Pre-assignment

Screening details:

A total of 53 subjects were enrolled and 50 were randomized and treated (24 to the 12 week arm, 26 to the 16 week arm). Reasons for non-randomized were 3 subjects no longer met study criteria.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Daclatasvir + Sofosbuvir + Ribavirin (12 Weeks)

Arm description:

Treatment-naïve and treatment-experienced participants with HCV Genotype 3 infection and advanced fibrosis or compensated cirrhosis (F3 or F4) were treated for 12 weeks with oral dosing of Daclatasvir (DCV) 60 mg once daily (QD), Sofosbuvir (SOF) 400 mg QD, and Ribavirin (RBV) 1000-1200 mg (weight based dosing) split into AM and PM dosing. Participants received either 400 mg (2 tablets for participants < 75 kg) or 600 mg (3 tablets for participants ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food. After the completion of the 12 week treatment period, participants were followed off treatment for 24 weeks. mg=milligram; kg=kilogram

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 (60 mg) QD. Daclatasvir was administered as 1 tablet in the AM.

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

Dosage and administration details:

Subjects received Sofosbuvir orally (400 mg) QD. Sofosbuvir was administered as 1 tablet in the AM.

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 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.

Arm title	Daclatasvir + Sofosbuvir + Ribavirin (16 Weeks)

Arm description:

Treatment-naïve and treatment-experienced participants with HCV Genotype 3 infection and advanced fibrosis or compensated cirrhosis (F3 or F4) were treated for 16 weeks with oral dosing of Daclatasvir (DCV) 60 mg once daily (QD), Sofosbuvir (SOF) 400 mg QD, and Ribavirin (RBV) 1000-1200 mg (weight based dosing) split into AM and PM dosing. Participants received either 400 mg (2 tablets for participants < 75 kg) or 600 mg (3 tablets for participants ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food. After the completion of the 16 week treatment period, participants were followed off treatment for 24 weeks. mg=milligram; kg=kilogram

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 (60 mg) QD. Daclatasvir was administered as 1 tablet in the AM.

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

Dosage and administration details:

Subjects received Sofosbuvir orally (400 mg) QD. Sofosbuvir was administered as 1 tablet in the AM.

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 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.

Number of subjects in period 1[1]	Daclatasvir + Sofosbuvir + Ribavirin (12 Weeks)	Daclatasvir + Sofosbuvir + Ribavirin (16 Weeks)
Started	24	26
Completed	23	26
Not completed	1	0
Death	1	-

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: The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial as out of 53 subjects who were enrolled, 50 subjects were treated in the study.

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?	Yes
Arm title	Daclatasvir + Sofosbuvir + Ribavirin (12 Weeks)

Arm description:

No treatment was received in the follow-up period. After the completion of the 12 week treatment period, participants were followed off treatment for 24 weeks. In the treatment period, treatment-naïve and treatment-experienced participants with HCV Genotype 3 infection and advanced fibrosis or compensated cirrhosis (F3 or F4) were treated for 12 weeks with oral dosing of Daclatasvir (DCV) 60 mg once daily (QD), Sofosbuvir (SOF) 400 mg QD, and Ribavirin (RBV) 1000-1200 mg (weight based dosing) split into AM and PM dosing. Participants received either 400 mg (2 tablets for participants < 75 kg) or 600 mg (3 tablets for participants ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food.

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:

No treatment was received in the follow-up, however, subjects received a 60 mg Daclatasvir tablet orally QD in the treatment period.

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

Dosage and administration details:

No treatment was received in the follow-up, however, subjects received a 400 mg Sofosbuvir tablet orally QD in the treatment period.

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:

No treatment was received in the follow-up, however, subjects received a daily dose of 1,000 to 1,200 mg Ribavirin orally in the treatment period, which was administered as either 400 mg (2 tablets for subjects < 75 kg) or 600 mg (3 tablets for subjects ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food.

Arm title	Daclatasvir + Sofosbuvir + Ribavirin (16 Weeks)

Arm description:

No treatment was received in the follow-up period. After the completion of the 16 week treatment period, participants were followed off treatment for 24 weeks. Treatment-naïve and treatment-experienced participants with HCV Genotype 3 infection and advanced fibrosis or compensated cirrhosis (F3 or F4) were treated for 16 weeks with oral dosing of Daclatasvir (DCV) 60 mg once daily (QD), Sofosbuvir (SOF) 400 mg QD, and Ribavirin (RBV) 1000-1200 mg (weight based dosing) split into AM and PM dosing. Participants received either 400 mg (2 tablets for participants < 75 kg) or 600 mg (3 tablets for participants ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food.

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:

No treatment was received in the follow-up, however, subjects received a 60 mg Daclatasvir tablet orally QD in the treatment period.

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

Dosage and administration details:

No treatment was received in the follow-up, however, subjects received a 400 mg Sofosbuvir tablet orally QD in the treatment period.

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:

No treatment was received in the follow-up, however, subjects received a daily dose of 1,000 to 1,200 mg Ribavirin orally in the treatment period, which was administered as either 400 mg (2 tablets for subjects < 75 kg) or 600 mg (3 tablets for subjects ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food.

Number of subjects in period 2	Daclatasvir + Sofosbuvir + Ribavirin (12 Weeks)	Daclatasvir + Sofosbuvir + Ribavirin (16 Weeks)
Started	23	26
Completed	23	26

Baseline characteristics

Reporting groups

Reporting group title	Daclatasvir + Sofosbuvir + Ribavirin (12 Weeks)

Reporting group description:

Treatment-naïve and treatment-experienced participants with HCV Genotype 3 infection and advanced fibrosis or compensated cirrhosis (F3 or F4) were treated for 12 weeks with oral dosing of Daclatasvir (DCV) 60 mg once daily (QD), Sofosbuvir (SOF) 400 mg QD, and Ribavirin (RBV) 1000-1200 mg (weight based dosing) split into AM and PM dosing. Participants received either 400 mg (2 tablets for participants < 75 kg) or 600 mg (3 tablets for participants ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food. After the completion of the 12 week treatment period, participants were followed off treatment for 24 weeks. mg=milligram; kg=kilogram

Reporting group title	Daclatasvir + Sofosbuvir + Ribavirin (16 Weeks)

Reporting group description:

Treatment-naïve and treatment-experienced participants with HCV Genotype 3 infection and advanced fibrosis or compensated cirrhosis (F3 or F4) were treated for 16 weeks with oral dosing of Daclatasvir (DCV) 60 mg once daily (QD), Sofosbuvir (SOF) 400 mg QD, and Ribavirin (RBV) 1000-1200 mg (weight based dosing) split into AM and PM dosing. Participants received either 400 mg (2 tablets for participants < 75 kg) or 600 mg (3 tablets for participants ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food. After the completion of the 16 week treatment period, participants were followed off treatment for 24 weeks. mg=milligram; kg=kilogram

Reporting group values	Daclatasvir + Sofosbuvir + Ribavirin (12 Weeks)	Daclatasvir + Sofosbuvir + Ribavirin (16 Weeks)	Total
Number of subjects	24	26	50
Age categorical			
Units: Subjects			
< 65 years	23	26	49
>= 65 years	1	0	1
Age continuous			
Units: years			
arithmetic mean	53	55	
standard deviation	± 7.77	± 5.75	-
Gender categorical			
Units: Subjects			
Female	6	4	10
Male	18	22	40

End points

End points reporting groups

Reporting group title	Daclatasvir + Sofosbuvir + Ribavirin (12 Weeks)

Reporting group description:

Treatment-naïve and treatment-experienced participants with HCV Genotype 3 infection and advanced fibrosis or compensated cirrhosis (F3 or F4) were treated for 12 weeks with oral dosing of Daclatasvir (DCV) 60 mg once daily (QD), Sofosbuvir (SOF) 400 mg QD, and Ribavirin (RBV) 1000-1200 mg (weight based dosing) split into AM and PM dosing. Participants received either 400 mg (2 tablets for participants < 75 kg) or 600 mg (3 tablets for participants ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food. After the completion of the 12 week treatment period, participants were followed off treatment for 24 weeks. mg=milligram; kg=kilogram

Reporting group title	Daclatasvir + Sofosbuvir + Ribavirin (16 Weeks)

Reporting group description:

Treatment-naïve and treatment-experienced participants with HCV Genotype 3 infection and advanced fibrosis or compensated cirrhosis (F3 or F4) were treated for 16 weeks with oral dosing of Daclatasvir (DCV) 60 mg once daily (QD), Sofosbuvir (SOF) 400 mg QD, and Ribavirin (RBV) 1000-1200 mg (weight based dosing) split into AM and PM dosing. Participants received either 400 mg (2 tablets for participants < 75 kg) or 600 mg (3 tablets for participants ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food. After the completion of the 16 week treatment period, participants were followed off treatment for 24 weeks. mg=milligram; kg=kilogram

Reporting group title	Daclatasvir + Sofosbuvir + Ribavirin (12 Weeks)

Reporting group description:

No treatment was received in the follow-up period. After the completion of the 12 week treatment period, participants were followed off treatment for 24 weeks. In the treatment period, treatment-naïve and treatment-experienced participants with HCV Genotype 3 infection and advanced fibrosis or compensated cirrhosis (F3 or F4) were treated for 12 weeks with oral dosing of Daclatasvir (DCV) 60 mg once daily (QD), Sofosbuvir (SOF) 400 mg QD, and Ribavirin (RBV) 1000-1200 mg (weight based dosing) split into AM and PM dosing. Participants received either 400 mg (2 tablets for participants < 75 kg) or 600 mg (3 tablets for participants ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food.

Reporting group title	Daclatasvir + Sofosbuvir + Ribavirin (16 Weeks)

Reporting group description:

No treatment was received in the follow-up period. After the completion of the 16 week treatment period, participants were followed off treatment for 24 weeks. Treatment-naïve and treatment-experienced participants with HCV Genotype 3 infection and advanced fibrosis or compensated cirrhosis (F3 or F4) were treated for 16 weeks with oral dosing of Daclatasvir (DCV) 60 mg once daily (QD), Sofosbuvir (SOF) 400 mg QD, and Ribavirin (RBV) 1000-1200 mg (weight based dosing) split into AM and PM dosing. Participants received either 400 mg (2 tablets for participants < 75 kg) or 600 mg (3 tablets for participants ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food.

Primary: Percent of Subjects With a Sustained Virologic Response (SVR) at Follow-up Week 12 (SVR12)

End point title	Percent of Subjects With a Sustained Virologic Response (SVR) at Follow-up Week 12 (SVR12)[1]

End point description:

SVR12, defined as percentage of subjects with hepatitis C virus (HCV) ribonucleic acid (RNA) < lower limit of quantitation (LLOQ), target detected (TD) or target not detected (TND) at follow-up Week 12. SVR12 imputation was based on Next Value Carried Backwards (NVCB) approach. HCV RNA measurements were excluded after the start of non-study anti-HCV medication on treatment or during follow-up. The analysis was performed with all treated subjects; enrolled subjects who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

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

End point values	Daclatasvir + Sofosbuvir + Ribavirin (12 Weeks)	Daclatasvir + Sofosbuvir + Ribavirin (16 Weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	26		
Units: percentage of subjects				
number (confidence interval 95%)	87.5 (67.6 to 97.3)	92.3 (74.9 to 99.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Participants With a Sustained Virologic Response (SVR) at Follow-up Week 4 (SVR4) and Follow-up Week 24 (SVR24)

End point title	Percent of Participants With a Sustained Virologic Response (SVR) at Follow-up Week 4 (SVR4) and Follow-up Week 24 (SVR24)

End point description:

SVR4, defined as percentage of subjects with hepatitis C virus (HCV) ribonucleic acid (RNA) < lower limit of quantitation (LLOQ), target detected (TD) or target not detected (TND) at follow-up Week 4. SVR24, defined as percentage of subjects with hepatitis C virus (HCV) ribonucleic acid (RNA) < lower limit of quantitation (LLOQ), target detected (TD) or target not detected (TND) at follow-up Week 24. SVR4 imputation was based on Next Value Carried Backwards (NVCB) approach. SVR24 imputation was based on missing being treated as non-responder. HCV RNA measurements were excluded after the start of non-study anti-HCV medication on treatment or during follow-up. The analysis was performed with all treated subjects; enrolled subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Follow-up Weeks 4 and 24

End point values	Daclatasvir + Sofosbuvir + Ribavirin (12 Weeks)	Daclatasvir + Sofosbuvir + Ribavirin (16 Weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	26		
Units: percentage of subjects				
number (confidence interval 95%)				
Follow-up Week 4 (SVR4)	87.5 (67.6 to 97.3)	96.2 (80.4 to 99.9)		
Follow-up Week 24 (SVR 24)	87.5 (67.6 to 97.3)	92.3 (74.9 to 99.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Death, Serious Adverse Events (SAEs), Discontinuation Due to Adverse Events (AEs), Grade 3 or Grade 4 (Grade3/4) AEs, and Grade3/4 Laboratory Abnormalities

End point title	Number of Subjects With Death, Serious Adverse Events (SAEs), Discontinuation Due to Adverse Events (AEs), Grade 3 or Grade 4 (Grade3/4) AEs, and Grade3/4 Laboratory Abnormalities

End point description:

Serious adverse event (SAE) defined: a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization. Adverse event (AE) defined: any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. The degree of the adverse event or laboratory abnormality are evaluated by grades: Grade (Gr) 1=Mild, Gr 2=Moderate, Gr 3=Severe, Gr 4=Life-threatening or disabling, Gr 5=Death. Grading as per using National Cancer Institute Common Terminology Criteria (NCI CTC) Version 3.0 criteria. The analysis was performed with all treated subjects; enrolled subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Date of First Dose of Study Drug to 7 Days post last dose of study drug (up to 13 weeks or 17 weeks depending on the randomized treatment group)

End point values	Daclatasvir + Sofosbuvir + Ribavirin (12 Weeks)	Daclatasvir + Sofosbuvir + Ribavirin (16 Weeks)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	26		
Units: subjects				
Death	1	0		
SAEs	2	3		
Discontinuation due to AEs	0	0		
Grade 3/4 AEs	2	2		
Grade 3/4 Laboratory Abnormalities	1	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs were reported from date of first dose of study drug to 30 days post discontinuation of the last dose. Non-serious AEs were reported from date of first dose of study drug to 7 days post discontinuation of the last dose.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Daclatasvir + Sofosbuvir + Ribavirin (12 Weeks)

Reporting group description:

Treatment-naïve and treatment-experienced participants with HCV Genotype 3 infection and advanced fibrosis or compensated cirrhosis (F3 or F4) were treated for 12 weeks with oral dosing of Daclatasvir (DCV) 60 mg once daily (QD), Sofosbuvir (SOF) 400 mg QD, and Ribavirin (RBV) 1000-1200 mg (weight based dosing) split into AM and PM dosing. Participants received either 400 mg (2 tablets for participants < 75 kg) or 600 mg (3 tablets for participants ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food. After the completion of the 12 week treatment period, participants were followed off treatment for 24 weeks. mg=milligram; kg=kilogram

Reporting group title	Daclatasvir + Sofosbuvir + Ribavirin (16 Weeks)

Reporting group description:

Treatment-naïve and treatment-experienced participants with HCV Genotype 3 infection and advanced fibrosis or compensated cirrhosis (F3 or F4) were treated for 16 weeks with oral dosing of Daclatasvir (DCV) 60 mg once daily (QD), Sofosbuvir (SOF) 400 mg QD, and Ribavirin (RBV) 1000-1200 mg (weight based dosing) split into AM and PM dosing. Participants received either 400 mg (2 tablets for participants < 75 kg) or 600 mg (3 tablets for participants ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food. After the completion of the 16 week treatment period, participants were followed off treatment for 24 weeks. mg=milligram; kg=kilogram

Serious adverse events	Daclatasvir + Sofosbuvir + Ribavirin (12 Weeks)	Daclatasvir + Sofosbuvir + Ribavirin (16 Weeks)	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 24 (8.33%)	3 / 26 (11.54%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arteriosclerosis			

subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Congestive cardiomyopathy			
subjects affected / exposed	1 / 24 (4.17%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Somnolence			
subjects affected / exposed	1 / 24 (4.17%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Daclatasvir + Sofosbuvir + Ribavirin (12 Weeks)	Daclatasvir + Sofosbuvir + Ribavirin (16 Weeks)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 24 (87.50%)	22 / 26 (84.62%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 24 (0.00%)	3 / 26 (11.54%)	
occurrences (all)	0	3	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 24 (29.17%)	5 / 26 (19.23%)	
occurrences (all)	7	6	
Lethargy			

subjects affected / exposed	2 / 24 (8.33%)	2 / 26 (7.69%)	
occurrences (all)	2	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 24 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	5	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 24 (8.33%)	5 / 26 (19.23%)	
occurrences (all)	2	9	
Fatigue			
subjects affected / exposed	6 / 24 (25.00%)	7 / 26 (26.92%)	
occurrences (all)	7	7	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 24 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Abdominal discomfort			
subjects affected / exposed	0 / 24 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Abdominal pain upper			
subjects affected / exposed	2 / 24 (8.33%)	0 / 26 (0.00%)	
occurrences (all)	3	0	
Diarrhoea			
subjects affected / exposed	1 / 24 (4.17%)	4 / 26 (15.38%)	
occurrences (all)	1	4	
Mouth ulceration			
subjects affected / exposed	0 / 24 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Nausea			
subjects affected / exposed	3 / 24 (12.50%)	1 / 26 (3.85%)	
occurrences (all)	3	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 24 (8.33%)	3 / 26 (11.54%)	
occurrences (all)	2	5	

Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 24 (4.17%)	2 / 26 (7.69%)	
occurrences (all)	1	2	
Photosensitivity reaction			
subjects affected / exposed	2 / 24 (8.33%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Hyperhidrosis			
subjects affected / exposed	2 / 24 (8.33%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Dry skin			
subjects affected / exposed	2 / 24 (8.33%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	8 / 24 (33.33%)	7 / 26 (26.92%)	
occurrences (all)	8	7	
Depression			
subjects affected / exposed	1 / 24 (4.17%)	2 / 26 (7.69%)	
occurrences (all)	1	2	
Depressed mood			
subjects affected / exposed	1 / 24 (4.17%)	2 / 26 (7.69%)	
occurrences (all)	2	2	
Irritability			
subjects affected / exposed	5 / 24 (20.83%)	2 / 26 (7.69%)	
occurrences (all)	5	3	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 24 (0.00%)	3 / 26 (11.54%)	
occurrences (all)	0	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 24 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 February 2015	This amendment addressed the following items: • Clarify the inclusion requirements for liver biopsies for those patients who are considered F3 • Provide information included in EU approved Daklinza® (daclatasvir) Product Information related to treatment indication for patients with Genotype 3 and advanced liver disease (cirrhosis) • Contraception requirements and pregnancy testing for ribavirin (RBV) added • Updated safety information regarding patients receiving DCV+SOF when also administered with amiodarone • Amiodarone added to prohibited medications • Minor editorial and format changes.
07 May 2015	This amendment addressed the following item: • Revision to safety information regarding patients receiving DCV+SOF when also administered with amiodarone.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26822022