Clinical trial results:
A Phase 3 Study with Asunaprevir and Daclatasvir (DUAL) for Null or Partial Responders to Peginterferon Alfa and Ribavirin (P/R), Intolerant or Ineligible to P/R Subjects and Treatment- Naive Subjects with Chronic Hepatitis C Genotype 1b Infection.

Summary

EudraCT number	2011-005446-35
Trial protocol	IE AT GB NL ES DE IT
Global end of trial date	20 September 2014

Results information

Result version number	v1 (current)
This version publication date	01 July 2016
First version publication date	01 July 2016

Trial information

Trial identification

Sponsor protocol code	AI447-028

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01581203
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussee de la Hulpe 185, Brussels, Belgium, 1170
Public contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, clinical.trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, 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	20 September 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

For the prior null or partial responders to peginterferon alfa and ribavirin (pegIFN alfa/ribavirin) cohort: To estimate efficacy, as determined by the proportion of subjects with sustained virologic response at post-treatment Week 12 (SVR12), defined as hepatitis C virus (HCV) RNA <limit of quantitation at post-treatment Week 12.
For the treatment naive cohort: To determine whether the SVR12 rate in subjects treated with daclatasvir/asunaprevir therapy is similar to the historical SVR rate for telaprevir in combination with pegIFN alfa/ribavirin in previously untreated, genotype 1b, HCV subjects.

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	11 May 2012
Long term follow-up planned	Yes
Long term follow-up rationale	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	Argentina: 25
Country: Number of subjects enrolled	Austria: 37
Country: Number of subjects enrolled	Australia: 89
Country: Number of subjects enrolled	Canada: 57
Country: Number of subjects enrolled	France: 118
Country: Number of subjects enrolled	Germany: 76
Country: Number of subjects enrolled	Ireland: 9
Country: Number of subjects enrolled	Israel: 24
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Korea, Republic of: 92
Country: Number of subjects enrolled	Netherlands: 19
Country: Number of subjects enrolled	New Zealand: 8
Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Russian Federation: 34
Country: Number of subjects enrolled	Spain: 24

Country: Number of subjects enrolled	Taiwan: 121
Country: Number of subjects enrolled	United Kingdom: 24
Country: Number of subjects enrolled	United States: 190
Worldwide total number of subjects	975
EEA total number of subjects	335

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)	784
From 65 to 84 years	191
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 116 sites in 18 countries.

Pre-assignment

Screening details:

A total of 975 subjects were enrolled, of which 747 were treated. Remaining 228 subjects did not receive any treatment; Reasons: no longer met the study criteria-192, subject withdrew consent to participate-29; other reasons-7.

Period 1

Period 1 title	Treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Randomized treatment assignment in the treatment naive cohort was placebo-controlled and investigator site, subject and sponsor were blinded until the Week 12 visit.

Arms

Are arms mutually exclusive?	Yes
Arm title	Prior Null or partial responder: Asunaprevir+ Daclatasvir

Arm description:

Subjects with Hepatitis C virus genotype 1b, null or partial responder to peginterferon alfa and ribavirin received daclatasvir 60 mg orally once daily and asunaprevir 100 mg orally twice daily for up to 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Asunaprevir
Investigational medicinal product code	BMS-650032
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Asunaprevir 100-mg softgel capsule was administered twice daily.

Investigational medicinal product name	Daclatasvir
Investigational medicinal product code	BMS-790052
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Daclatasvir 60-mg film coated tablet was administered once daily.

Arm title	Intolerant or Ineligible: Asunaprevir+ Daclatasvir

Arm description:

Subjects with Hepatitis C virus genotype 1b, intolerant to or ineligible for peginterferon alfa and ribavirin received daclatasvir 60 mg orally once daily and asunaprevir 100 mg orally twice daily for up to 24 weeks.

Arm type	Experimental

Investigational medicinal product name	Daclatasvir
Investigational medicinal product code	BMS-790052
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Daclatasvir 60-mg film coated tablet was administered once daily.

Investigational medicinal product name	Asunaprevir
Investigational medicinal product code	BMS-650032
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Asunaprevir 100-mg softgel capsule was administered twice daily.

Arm title	Treatment-naive: Asunaprevir+ Daclatasvir

Arm description:

Treatment-naive subjects with Hepatitis C virus genotype 1b received daclatasvir 60 mg orally once daily, asunaprevir 100 mg twice daily for up to 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Daclatasvir
Investigational medicinal product code	BMS-790052
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Daclatasvir 60-mg film coated tablet was administered orally once daily.

Investigational medicinal product name	Asunaprevir
Investigational medicinal product code	BMS-650032
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Asunaprevir 100-mg softgel capsule was administered orally twice daily.

Arm title	Treatment-naive: Placebo for Asunaprevir + Daclatasvir

Arm description:

Treatment-naive subjects with Hepatitis C virus genotype 1b received placebo of daclatasvir once daily and placebo of asunaprevir twice daily for 12 weeks. Subjects were then entered in study NCT01428063 where they receive daclatasvir 60 mg once daily and asunaprevir 100 mg twice daily for 24 weeks.

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

Dosage and administration details:

Placebo matched to daclatasvir was administered once daily.

Investigational medicinal product name	Placebo (for Asunaprevir)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to asunaprevir was administered twice daily.

Number of subjects in period 1[1]	Prior Null or partial responder: Asunaprevir+ Daclatasvir	Intolerant or Ineligible: Asunaprevir+ Daclatasvir	Treatment-naive: Asunaprevir+ Daclatasvir
Started	205	235	205
Completed	177	208	190
Not completed	28	27	15
Consent withdrawn by subject	-	4	-
Adverse event, non-fatal	2	2	6
Subject request to discontinue study treatment	-	1	-
Lost to follow-up	-	-	1
Lack of efficacy	26	20	8

Number of subjects in period 1[1]	Treatment-naive: Placebo for Asunaprevir + Daclatasvir
Started	102
Completed	102
Not completed	0
Consent withdrawn by subject	-
Adverse event, non-fatal	-
Subject request to discontinue study treatment	-
Lost to follow-up	-
Lack of efficacy	-

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 975 subjects who were enrolled, only 747 were treated. Remaining 228 subjects did not receive any treatment. 192 subjects no longer met the study criteria, 29 subjects withdrew consent to participate, and 7 due to other reasons.

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	Prior Null or partial responder: Asunaprevir+ Daclatasvir

Arm description:

Subjects with Hepatitis C virus genotype 1b, null or partial responder to peginterferon alfa and ribavirin received daclatasvir 60 mg once daily and asunaprevir 100 mg twice daily for 24 weeks. Subjects were followed for 24 weeks of follow-up after completion of treatment or upon early discontinuation of treatment.

Arm type	Experimental
Investigational medicinal product name	Daclatasvir
Investigational medicinal product code	BMS-790052
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Daclatasvir 60-mg film coated tablet was administered once daily.

Investigational medicinal product name	Asunaprevir
Investigational medicinal product code	BMS-650032
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Asunaprevir 100-mg softgel capsule was administered twice daily.

Arm title	Intolerant or Ineligible: Asunaprevir+ Daclatasvir

Arm description:

Subjects with Hepatitis C virus genotype 1b, intolerant to or ineligible for peginterferon alfa and ribavirin received daclatasvir 60 mg once daily and asunaprevir 100 mg twice daily for 24 weeks. Subjects were followed for 24 weeks of follow-up after completion of treatment or upon early discontinuation of treatment.

Arm type	Experimental
Investigational medicinal product name	Asunaprevir
Investigational medicinal product code	BMS-650032
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Asunaprevir 100-mg softgel capsule was administered twice daily.

Investigational medicinal product name	Daclatasvir
Investigational medicinal product code	BMS-790052
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Daclatasvir 60-mg film coated tablet was administered once daily.

Arm title	Treatment-naive: Asunaprevir+ Daclatasvir

Arm description:

Treatment-naive subjects with Hepatitis C virus genotype 1b received daclatasvir 60 mg orally once daily, asunaprevir 100 mg twice daily for up to 24 weeks. Subjects were then followed for 24 weeks of follow-up after completion of treatment or upon early discontinuation of treatment.

Arm type	Experimental
Investigational medicinal product name	Asunaprevir
Investigational medicinal product code	BMS-650032
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Asunaprevir 100-mg softgel capsule was administered orally twice daily.

Investigational medicinal product name	Daclatasvir
Investigational medicinal product code	BMS-790052
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Daclatasvir 60-mg film coated tablet was administered orally once daily.

Number of subjects in period 2[2]	Prior Null or partial responder: Asunaprevir+ Daclatasvir	Intolerant or Ineligible: Asunaprevir+ Daclatasvir	Treatment-naive: Asunaprevir+ Daclatasvir
Started	203	230	204
Completed	202	228	204
Not completed	1	2	0
Consent withdrawn by subject	1	1	-
Lost to follow-up	-	1	-

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: The number of subjects starting the follow-up period includes those completing previous period plus those that re-joined for followup.

Baseline characteristics

Reporting groups	
Reporting group title	Prior Null or partial responder: Asunaprevir+ Daclatasvir
Reporting group description:	
Subjects with Hepatitis C virus genotype 1b, null or partial responder to peginterferon alfa and ribavirin received daclatasvir 60 mg orally once daily and asunaprevir 100 mg orally twice daily for up to 24 weeks.	
Reporting group title	Intolerant or Ineligible: Asunaprevir+ Daclatasvir
Reporting group description:	
Subjects with Hepatitis C virus genotype 1b, intolerant to or ineligible for peginterferon alfa and ribavirin received daclatasvir 60 mg orally once daily and asunaprevir 100 mg orally twice daily for up to 24 weeks.	
Reporting group title	Treatment-naive: Asunaprevir+ Daclatasvir
Reporting group description:	
Treatment-naive subjects with Hepatitis C virus genotype 1b received daclatasvir 60 mg orally once daily, asunaprevir 100 mg twice daily for up to 24 weeks.	
Reporting group title	Treatment-naive: Placebo for Asunaprevir + Daclatasvir
Reporting group description:	
Treatment-naive subjects with Hepatitis C virus genotype 1b received placebo of daclatasvir once daily and placebo of asunaprevir twice daily for 12 weeks. Subjects were then entered in study NCT01428063 where they receive daclatasvir 60 mg once daily and asunaprevir 100 mg twice daily for 24 weeks.	

Reporting group values	Prior Null or partial responder: Asunaprevir+ Daclatasvir	Intolerant or Ineligible: Asunaprevir+ Daclatasvir	Treatment-naive: Asunaprevir+ Daclatasvir
Number of subjects	205	235	205
Age categorical Units: Subjects			
<65 years	161	175	176
>=65 years	44	60	29
Age continuous Units: years			
arithmetic mean	56.1	58	53.1
standard deviation	± 10.51	± 9.94	± 11.69
Gender categorical Units: Subjects			
Female	94	137	104
Male	111	98	101

Reporting group values	Treatment-naive: Placebo for Asunaprevir + Daclatasvir	Total	
Number of subjects	102	747	
Age categorical Units: Subjects			
<65 years	84	596	
>=65 years	18	151	
Age continuous Units: years			
arithmetic mean	52.5		

standard deviation	± 12.89	-	

Gender categorical Units: Subjects			
Female	48	383	
Male	54	364	

End points

End points reporting groups

Reporting group title	Prior Null or partial responder: Asunaprevir+ Daclatasvir
Reporting group description:	
Subjects with Hepatitis C virus genotype 1b, null or partial responder to peginterferon alfa and ribavirin received daclatasvir 60 mg orally once daily and asunaprevir 100 mg orally twice daily for up to 24 weeks.	
Reporting group title	Intolerant or Ineligible: Asunaprevir+ Daclatasvir
Reporting group description:	
Subjects with Hepatitis C virus genotype 1b, intolerant to or ineligible for peginterferon alfa and ribavirin received daclatasvir 60 mg orally once daily and asunaprevir 100 mg orally twice daily for up to 24 weeks.	
Reporting group title	Treatment-naive: Asunaprevir+ Daclatasvir
Reporting group description:	
Treatment-naive subjects with Hepatitis C virus genotype 1b received daclatasvir 60 mg orally once daily, asunaprevir 100 mg twice daily for up to 24 weeks.	
Reporting group title	Treatment-naive: Placebo for Asunaprevir + Daclatasvir
Reporting group description:	
Treatment-naive subjects with Hepatitis C virus genotype 1b received placebo of daclatasvir once daily and placebo of asunaprevir twice daily for 12 weeks. Subjects were then entered in study NCT01428063 where they receive daclatasvir 60 mg once daily and asunaprevir 100 mg twice daily for 24 weeks.	
Reporting group title	Prior Null or partial responder: Asunaprevir+ Daclatasvir
Reporting group description:	
Subjects with Hepatitis C virus genotype 1b, null or partial responder to peginterferon alfa and ribavirin received daclatasvir 60 mg once daily and asunaprevir 100 mg twice daily for 24 weeks. Subjects were followed for 24 weeks of follow-up after completion of treatment or upon early discontinuation of treatment.	
Reporting group title	Intolerant or Ineligible: Asunaprevir+ Daclatasvir
Reporting group description:	
Subjects with Hepatitis C virus genotype 1b, intolerant to or ineligible for peginterferon alfa and ribavirin received daclatasvir 60 mg once daily and asunaprevir 100 mg twice daily for 24 weeks. Subjects were followed for 24 weeks of follow-up after completion of treatment or upon early discontinuation of treatment.	
Reporting group title	Treatment-naive: Asunaprevir+ Daclatasvir
Reporting group description:	
Treatment-naive subjects with Hepatitis C virus genotype 1b received daclatasvir 60 mg orally once daily, asunaprevir 100 mg twice daily for up to 24 weeks. Subjects were then followed for 24 weeks of follow-up after completion of treatment or upon early discontinuation of treatment.	

Primary: Percentage of Genotype 1b Chronic Hepatitis C Infected Subjects Who Were Prior Null or Partial Responders to Peginterferon Alfa/Ribavirin or Treatment Naive Achieving Sustained Virologic Response at Follow-Up Week 12 (SVR12)

End point title	Percentage of Genotype 1b Chronic Hepatitis C Infected Subjects Who Were Prior Null or Partial Responders to Peginterferon Alfa/Ribavirin or Treatment Naive Achieving Sustained Virologic Response at Follow-Up Week 12 (SVR12)[1][2]
End point description:	
Sustained Virologic Response at Post-Treatment Week 12 was defined as hepatitis C Virus (HCV) RNA levels to be <lower limit of quantitation i.e., 25 international unit per milliliter, target detected or target not detected, at follow-up Week 12 for subjects who were prior null or partial responders to Peginterferon Alfa/Ribavirin or were treatment-naive. HCV RNA levels were measured by the Roche COBAS® TaqMan® HCV Test version 2.0 from the central laboratory. The analysis was performed in all genotype 1b subjects who received at least 1 dose of study therapy, active or placebo. For subjects who missed the follow-up Week 12 visit, SVR12 was imputed using the first available HCV RNA measurement	

after the follow-up Week 12 window.

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.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to evaluate for the specified arm only.

End point values	Prior Null or partial responder: Asunaprevir+ Daclatasvir	Treatment-naive: Asunaprevir+ Daclatasvir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	205	203		
Units: Percentage of Subjects				
number (confidence interval 95%)	82.4 (77.2 to 87.6)	91.1 (87.2 to 95)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Genotype 1b Chronic Hepatitis C Infected Subjects Who Were Intolerant to or Ineligible For Peginterferon Alfa/Ribavirin Achieving Sustained Virologic Response at Follow-Up Week 12 (SVR12)

End point title	Percentage of Genotype 1b Chronic Hepatitis C Infected Subjects Who Were Intolerant to or Ineligible For Peginterferon Alfa/Ribavirin Achieving Sustained Virologic Response at Follow-Up Week 12 (SVR12)[3]

End point description:

SVR12 rate was defined as hepatitis C Virus (HCV) RNA levels to be <lower limit of quantitation i.e., 25 international unit per milliliter target detected or target not detected, at follow-up Week 12 for subjects who were intolerant to or ineligible for Peginterferon Alfa/Ribavirin (pegIFNalfa/RBV). HCV RNA levels were measured by the Roche COBAS® TaqMan® HCV Test version 2.0 from the central laboratory. All genotype 1b subjects who received at least 1 dose of study therapy, active or placebo. For subjects who missed the follow-up Week 12 visit, SVR12 was imputed using the first available HCV RNA measurement after the follow-up Week 12 window.

End point type	Secondary

End point timeframe:

Follow-Up Week 12

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to evaluate for the specified arm only.

End point values	Intolerant or Ineligible: Asunaprevir+ Daclatasvir			
Subject group type	Reporting group			
Number of subjects analysed	235			
Units: Percentage of subjects				
number (confidence interval 95%)	82.6 (77.7 to 87.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Anaemia

End point title	Percentage of Subjects with Anaemia[4]

End point description:

Anaemia was defined as the decline in hemoglobin levels below 10 gram/deciliter. The analysis was performed on all treated subjects who received at least 1 dose of study therapy. Number of subjects analysed refers to number of subjects that were evaluable for this outcome measure on treatment.

End point type	Secondary

End point timeframe:

From start of study treatment up to 7 days post last dose of study treatment

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to evaluate for the specified arm only.

End point values	Prior Null or partial responder: Asunaprevir+ Daclatasvir	Intolerant or Ineligible: Asunaprevir+ Daclatasvir	Treatment-naive: Asunaprevir+ Daclatasvir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	205	234	203	
Units: Percentage of Subjects				
number (not applicable)	1.5	3	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Rash Events

End point title	Percentage of Subjects With Rash Events[5]

End point description:

Rash was defined as occurrence of dermatitis allergic, vasculitic rash, eczema, purpura, petechiae, dermatitis acneiform, ecchymosis, gingival disorder, cheilitis, pemphigoid, acute generalized exanthematous pustulosis, dermatitis, dermatitis bullous/exfoliative/exfoliative generalised, drug eruption, drug rash with eosinophilia and systemic symptoms, erythema multiforme, fixed eruption, haemorrhagic urticaria, idiopathic urticaria, exfoliative/genital/mucocutaneous rash, oral mucosal eruption, urticarial, rash erythematous/follicular/generalized/macular/maculo-papular/

maculovesicular/morbilliform/popular/papulosquamous/pruritic/pustular/vesicular, septic rash, Stevens-Johnson syndrome, tongue eruption, toxic epidermal necrolysis, toxic skin eruption, and urticaria popular. The analysis was performed on all treated subjects who received at least 1 dose of study therapy. Number of subjects analysed signifies subjects evaluable for this outcome measure on treatment.

End point type	Secondary

End point timeframe:

From start of study treatment up to 7 days post last dose of study treatment

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to evaluate for the specified arm only.

End point values	Prior Null or partial responder: Asunaprevir+ Daclatasvir	Intolerant or Ineligible: Asunaprevir+ Daclatasvir	Treatment-naive: Asunaprevir+ Daclatasvir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	205	235	205	
Units: Percentage of Subjects				
number (not applicable)	5.4	8.1	7.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Serious Adverse Events (SAEs), Discontinuations Due to Adverse Events (AEs), Grade 3 to 4 AEs, and Who Died During Treatment Period

End point title	Number of Subjects With Serious Adverse Events (SAEs), Discontinuations Due to Adverse Events (AEs), Grade 3 to 4 AEs, and Who Died During Treatment Period[6]

End point description:

AE was defined as any new unfavorable symptom, sign, or disease or worsening of a pre-existing condition that does not has 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 hospitalisation. Grade 3 to 4 AE were also reported. The analysis was performed on all treated subjects who received at least 1 dose of study therapy.

End point type	Secondary

End point timeframe:

From start of study treatment up to 7 days post last dose of study treatment

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to evaluate for the specified arm only.

End point values	Prior Null or partial responder: Asunaprevir+ Daclatasvir	Intolerant or Ineligible: Asunaprevir+ Daclatasvir	Treatment-naive: Asunaprevir+ Daclatasvir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	205	235	205	
Units: Subjects				

number (not applicable)				
SAEs	11	16	12	
AEs Leading to Discontinuation	2	2	6	
Grade 3/4 AEs	15	21	14	
Death	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Genotype 1b Chronic Hepatitis C Infected Treatment-naive Subjects With Selected Grade 3-4 Laboratory Abnormalities During the First 12 Weeks of Treatment

End point title	Percentage of Genotype 1b Chronic Hepatitis C Infected Treatment-naive Subjects With Selected Grade 3-4 Laboratory Abnormalities During the First 12 Weeks of Treatment[7]

End point description:

Clinically significant changes in laboratory abnormalities were defined as Hemoglobin as 6.50–7.4 g/dL for grade 3 and/or <6.5 g/dL for grade 4, absolute neutrophil count for Grade 3 <1.0 to 0.5*10^9/L, Grade 4 <0.5*10^9/L. Alanine aminotransferase as 5.1–10.0* ULN for grade 3 and/or > 10.0* (upper limit of normal) ULN for grade 4, Aspartate aminotransferase as 5.1–10.0*ULN for grade 3 and/or > 10.0*ULN for grade 4, Bilirubin (Total) as 2.6–5.0*ULN for grade 3 and/or > 5.0*ULN for grade 4. The analysis was performed on all treated subjects who received at least 1 dose of study therapy. Here, 'Number of subjects analysed' signifies the subjects evaluable for this outcome at week 12.

End point type	Secondary

End point timeframe:

Through Week 12

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to evaluate for the specified arm only.

End point values	Treatment-naive: Asunaprevir+ Daclatasvir	Treatment-naive: Placebo for Asunaprevir + Daclatasvir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203	102		
Units: Percentage of Subjects				
number (confidence interval 95%)				
Hemoglobin	0 (0 to 0)	1 (0 to 2.9)		
Neutrophils + Bands	1 (0 to 2.3)	1 (0 to 2.9)		
Alanine Aminotransferase	2 (0.1 to 3.9)	2 (0 to 4.7)		
Aspartate Aminotransferase	1.5 (0 to 3.1)	1 (0 to 2.9)		
Bilirubin Total	0 (0 to 0)	1 (0 to 2.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Sustained Virologic Response (SVR12) by rs12979860 Single Nucleotide Polymorphisms (SNP) in the IL28B Gene

End point title	Percentage of Subjects With Sustained Virologic Response (SVR12) by rs12979860 Single Nucleotide Polymorphisms (SNP) in the IL28B Gene[8]

End point description:

SVR12 rate was defined as HCV RNA levels to be < lower limit of quantitation i.e., 25 international unit per milliliter, 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. SNP included wild type (common homozygous), mixed (heterozygous), mutant (minor homozygous). Here 'n' specify the number of subjects analysed for specified time point in each group, respectively. The analysis was performed on all treated subjects who received at least 1 dose of study therapy.

End point type	Secondary

End point timeframe:

Post-treatment Week 12

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to evaluate for the specified arm only.

End point values	Prior Null or partial responder: Asunaprevir+ Daclatasvir	Intolerant or Ineligible: Asunaprevir+ Daclatasvir	Treatment-naive: Asunaprevir+ Daclatasvir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	205	235	203	
Units: Percentage of Subjects				
number (confidence interval 80%)				
CC wild type (n= 29, 82, 76)	75.9 (65.7 to 86)	80.5 (74.9 to 86.1)	89.5 (85 to 94)	
CT heterozygous (n= 123, 102, 99)	81.3 (76.8 to 85.8)	81.4 (76.4 to 86.3)	87.9 (83.7 to 92.1)	
TT minor homozygous (n= 50, 41, 28)	86 (79.7 to 92.3)	87.8 (81.3 to 94.4)	96.4 (91.9 to 100)	
Not reported (n=3, 10, 0)	100 (100 to 100)	70 (51.4 to 88.6)	0 (0 to 0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Genotype 1b Chronic Hepatitis C Infected Subjects With Hepatitis C Virus (HCV) RNA <Lower Limit of Quantitation (LLOQ), Target not Detected

End point title	Percentage of Genotype 1b Chronic Hepatitis C Infected Subjects With Hepatitis C Virus (HCV) RNA <Lower Limit of Quantitation (LLOQ), Target not Detected[9]

End point description:

HCV RNA levels to be <LLOQ i.e. 25 international unit per milliliter, target not detected. HCV RNA levels were measured by the Roche COBAS® TaqMan® HCV Test version 2.0 from the central laboratory. The analysis was performed on all treated subjects who received at least 1 dose of study therapy. Here, '99999' represents not estimable data for specified categories in respective arms.
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End point type	Secondary

End point timeframe:

Baseline, Week 2, 4, 6, 8, 10, 12, 16, 20, 24, follow-up week 12, and follow-up week 24

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to evaluate for the specified arm only.

End point values	Prior Null or partial responder: Asunaprevir+ Daclatasvir	Intolerant or Ineligible: Asunaprevir+ Daclatasvir	Treatment-naive: Asunaprevir+ Daclatasvir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	205	235	203	
Units: Percentage of Subjects				
number (confidence interval 95%)				
Baseline	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	
Week 2	16.1 (11.1 to 21.1)	19.1 (14.1 to 24.2)	27.6 (21.4 to 33.7)	
Week 4	73.2 (67.1 to 79.2)	67.7 (61.7 to 73.6)	82.8 (77.6 to 88)	
Week 6	90.2 (86.2 to 94.3)	84.7 (80.1 to 89.3)	89.7 (85.5 to 93.8)	
Week 8	88.8 (84.5 to 93.1)	88.9 (84.9 to 92.9)	96.6 (94 to 99.1)	
Week 10	99999 (99999 to 99999)	99999 (99999 to 99999)	88.2 (83.7 to 92.6)	
Week 12	88.8 (84.5 to 93.1)	87.2 (83 to 91.5)	94.1 (90.8 to 97.3)	
Week 16	87.8 (83.3 to 92.3)	86.8 (82.5 to 91.1)	92.6 (89 to 96.2)	
Week 20	83.9 (78.9 to 88.9)	86.8 (82.5 to 91.1)	90.1 (86 to 94.2)	
Week 24	83.4 (78.3 to 88.5)	83.8 (79.1 to 88.5)	88.7 (84.3 to 93)	
Follow-up Week 12	81.5 (76.1 to 86.8)	78.7 (73.5 to 84)	88.7 (84.3 to 93)	
Follow-up Week 24	80.5 (75.1 to 85.9)	80.9 (75.8 to 85.9)	90.1 (86 to 94.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Genotype 1b Chronic Hepatitis C Infected Subjects with Hepatitis C Virus (HCV) RNA <Lower Limit of Quantitation (LLOQ), Target Detected or Target not Detected

End point title	Percentage of Genotype 1b Chronic Hepatitis C Infected Subjects with Hepatitis C Virus (HCV) RNA <Lower Limit of Quantitation (LLOQ), Target Detected or Target not Detected[10]

End point description:

HCV RNA levels to be <LLOQ i.e., 25 international unit per milliliter, target detected or target not detected. HCV RNA levels were measured by the Roche COBAS® TaqMan® HCV Test version 2.0 from the central laboratory. The analysis was performed on all treated subjects who received at least 1 dose of study therapy. Here, '99999' represents not estimable data for specified categories in respective arms.

End point type	Secondary

End point timeframe:

Baseline, Week 2, 4, 6, 8, 10, 12, 16, 20, 24 and follow-up Week 24

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to evaluate for the specified arm only.

End point values	Prior Null or partial responder: Asunaprevir+ Daclatasvir	Intolerant or Ineligible: Asunaprevir+ Daclatasvir	Treatment-naive: Asunaprevir+ Daclatasvir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	205	235	203	
Units: Percentage of Subjects				
number (confidence interval 95%)				
Baseline	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	
Week 2	64.9 (58.3 to 71.4)	68.1 (62.1 to 74)	81.3 (75.9 to 86.6)	
Week 4	96.6 (94.1 to 99.1)	91.9 (88.4 to 95.4)	97 (94.7 to 99.4)	
Week 6	94.1 (90.9 to 97.4)	92.3 (88.9 to 95.7)	94.6 (91.5 to 97.7)	
Week 8	92.7 (89.1 to 96.2)	91.9 (88.4 to 95.4)	97.5 (95.4 to 99.7)	
Week 10	99999 (99999 to 99999)	99999 (99999 to 99999)	89.2 (84.9 to 93.4)	
Week 12	91.2 (87.3 to 95.1)	91.1 (87.4 to 94.7)	96.6 (94 to 99.1)	
Week 16	90.2 (86.2 to 94.3)	89.8 (85.9 to 93.7)	94.6 (91.5 to 97.7)	
Week 20	86.3 (81.6 to 91)	88.9 (84.9 to 92.9)	92.1 (88.4 to 95.8)	
Week 24	84.9 (80 to 89.8)	84.7 (80.1 to 89.3)	90.1 (86 to 94.2)	
Follow-up Week 24	81.5 (76.1 to 86.8)	81.3 (76.3 to 86.3)	90.6 (86.6 to 94.6)	

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)[11]

End point description:

eRVR was defined as hepatitis C virus RNA levels to be <lower limit of quantitation i.e., 25 IU/mL 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. The analysis was performed on all treated subjects who received at least 1 dose of study therapy.

End point type	Secondary

End point timeframe:

Week 4 and Week 12

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint was planned to evaluate for the specified arm only.

End point values	Prior Null or partial responder: Asunaprevir+ Daclatasvir	Intolerant or Ineligible: Asunaprevir+ Daclatasvir	Treatment-naive: Asunaprevir+ Daclatasvir	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	205	235	203	
Units: Percentage of Subjects				
number (confidence interval 95%)	68.3 (61.9 to 74.7)	63.4 (57.2 to 69.6)	80.3 (74.8 to 85.8)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study treatment up to 7 days post last dose of study treatment

Adverse event reporting additional description:

On-treatment

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Prior Null or partial responder: Asunaprevir+ Daclatasvir

Reporting group description:

Subjects with Hepatitis C virus genotype 1b, null or partial responder to peginterferon alfa and ribavirin received daclatasvir 60 mg orally once daily and asunaprevir 100 mg orally twice daily for up to 24 weeks.

Reporting group title	Intolerant or Ineligible: Asunaprevir+ Daclatasvir

Reporting group description:

Subjects with Hepatitis C virus genotype 1b, intolerant to or ineligible for peginterferon alfa and ribavirin received daclatasvir 60 mg orally once daily and asunaprevir 100 mg orally twice daily for up to 24 weeks.

Reporting group title	Treatment-naive: Asunaprevir+ Daclatasvir

Reporting group description:

Treatment-naive subjects with Hepatitis C virus genotype 1b received daclatasvir 60 mg orally once daily, and asunaprevir 100 mg twice daily for up to 24 weeks.

Serious adverse events	Prior Null or partial responder: Asunaprevir+ Daclatasvir	Intolerant or Ineligible: Asunaprevir+ Daclatasvir	Treatment-naive: Asunaprevir+ Daclatasvir
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 205 (5.37%)	16 / 235 (6.81%)	12 / 205 (5.85%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	3 / 205 (1.46%)	3 / 235 (1.28%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain neoplasm			
subjects affected / exposed	1 / 205 (0.49%)	0 / 235 (0.00%)	0 / 205 (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

Hepatic neoplasm			
subjects affected / exposed	1 / 205 (0.49%)	0 / 235 (0.00%)	0 / 205 (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
Lung adenocarcinoma			
subjects affected / exposed	0 / 205 (0.00%)	0 / 235 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Liver Transplant			
subjects affected / exposed	0 / 205 (0.00%)	1 / 235 (0.43%)	0 / 205 (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
General disorders and administration site conditions			
Colitis			
subjects affected / exposed	0 / 205 (0.00%)	1 / 235 (0.43%)	0 / 205 (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
Chest pain			
subjects affected / exposed	1 / 205 (0.49%)	0 / 235 (0.00%)	0 / 205 (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
Non-cardiac Chest pain			
subjects affected / exposed	0 / 205 (0.00%)	1 / 235 (0.43%)	0 / 205 (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
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 205 (0.00%)	1 / 235 (0.43%)	0 / 205 (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
Respiratory, thoracic and mediastinal disorders			
Bronchiectasis			

subjects affected / exposed	0 / 205 (0.00%)	0 / 235 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 205 (0.49%)	0 / 235 (0.00%)	0 / 205 (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
Haemothorax			
subjects affected / exposed	1 / 205 (0.49%)	0 / 235 (0.00%)	0 / 205 (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
Pleural effusion			
subjects affected / exposed	0 / 205 (0.00%)	1 / 235 (0.43%)	0 / 205 (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
Pneumothorax			
subjects affected / exposed	0 / 205 (0.00%)	0 / 235 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 205 (0.00%)	1 / 235 (0.43%)	0 / 205 (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
Bipolar disorder			
subjects affected / exposed	1 / 205 (0.49%)	0 / 235 (0.00%)	0 / 205 (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
Depression			
subjects affected / exposed	0 / 205 (0.00%)	0 / 235 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	0 / 205 (0.00%)	0 / 235 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 205 (0.00%)	0 / 235 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	1 / 205 (0.49%)	0 / 235 (0.00%)	0 / 205 (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
Rib fracture			
subjects affected / exposed	1 / 205 (0.49%)	0 / 235 (0.00%)	0 / 205 (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
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	0 / 205 (0.00%)	2 / 235 (0.85%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 205 (0.00%)	1 / 235 (0.43%)	0 / 205 (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
Sinus bradycardia			
subjects affected / exposed	0 / 205 (0.00%)	0 / 235 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Neuropathy peripheral			

subjects affected / exposed	1 / 205 (0.49%)	0 / 235 (0.00%)	0 / 205 (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
Sciatica			
subjects affected / exposed	0 / 205 (0.00%)	1 / 235 (0.43%)	0 / 205 (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
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 205 (0.00%)	1 / 235 (0.43%)	0 / 205 (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
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 205 (0.00%)	1 / 235 (0.43%)	0 / 205 (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
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	0 / 205 (0.00%)	1 / 235 (0.43%)	0 / 205 (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
Constipation			
subjects affected / exposed	0 / 205 (0.00%)	0 / 235 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 205 (0.00%)	0 / 235 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary colic			

subjects affected / exposed	0 / 205 (0.00%)	0 / 235 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 205 (0.00%)	0 / 235 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 205 (0.00%)	1 / 235 (0.43%)	0 / 205 (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
Osteoarthritis			
subjects affected / exposed	0 / 205 (0.00%)	0 / 235 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess intestinal			
subjects affected / exposed	1 / 205 (0.49%)	0 / 235 (0.00%)	0 / 205 (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
Acute tonsillitis			
subjects affected / exposed	0 / 205 (0.00%)	0 / 235 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 205 (0.00%)	1 / 235 (0.43%)	0 / 205 (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
Otitis media			
subjects affected / exposed	0 / 205 (0.00%)	1 / 235 (0.43%)	0 / 205 (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

Pneumonia bacterial			
subjects affected / exposed	0 / 205 (0.00%)	1 / 235 (0.43%)	0 / 205 (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
Pyelonephritis			
subjects affected / exposed	0 / 205 (0.00%)	0 / 235 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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	Prior Null or partial responder: Asunaprevir+ Daclatasvir	Intolerant or Ineligible: Asunaprevir+ Daclatasvir	Treatment-naive: Asunaprevir+ Daclatasvir
Total subjects affected by non-serious adverse events			
subjects affected / exposed	167 / 205 (81.46%)	203 / 235 (86.38%)	172 / 205 (83.90%)
Vascular disorders			
Hypertension			
subjects affected / exposed	12 / 205 (5.85%)	9 / 235 (3.83%)	7 / 205 (3.41%)
occurrences (all)	14	11	7
Nervous system disorders			
Dizziness			
subjects affected / exposed	19 / 205 (9.27%)	19 / 235 (8.09%)	14 / 205 (6.83%)
occurrences (all)	21	20	15
Headache			
subjects affected / exposed	50 / 205 (24.39%)	59 / 235 (25.11%)	50 / 205 (24.39%)
occurrences (all)	76	74	62
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	12 / 205 (5.85%)	26 / 235 (11.06%)	4 / 205 (1.95%)
occurrences (all)	12	27	4
Fatigue			
subjects affected / exposed	45 / 205 (21.95%)	52 / 235 (22.13%)	43 / 205 (20.98%)
occurrences (all)	46	59	46
Influenza like illness			

subjects affected / exposed	7 / 205 (3.41%)	5 / 235 (2.13%)	11 / 205 (5.37%)
occurrences (all)	8	5	12
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	8 / 205 (3.90%)	18 / 235 (7.66%)	8 / 205 (3.90%)
occurrences (all)	8	23	8
Abdominal pain upper			
subjects affected / exposed	10 / 205 (4.88%)	18 / 235 (7.66%)	16 / 205 (7.80%)
occurrences (all)	10	20	16
Constipation			
subjects affected / exposed	20 / 205 (9.76%)	17 / 235 (7.23%)	10 / 205 (4.88%)
occurrences (all)	23	17	11
Diarrhoea			
subjects affected / exposed	27 / 205 (13.17%)	47 / 235 (20.00%)	24 / 205 (11.71%)
occurrences (all)	34	56	30
Dyspepsia			
subjects affected / exposed	8 / 205 (3.90%)	14 / 235 (5.96%)	8 / 205 (3.90%)
occurrences (all)	9	14	10
Nausea			
subjects affected / exposed	22 / 205 (10.73%)	28 / 235 (11.91%)	25 / 205 (12.20%)
occurrences (all)	27	29	30
Vomiting			
subjects affected / exposed	8 / 205 (3.90%)	7 / 235 (2.98%)	11 / 205 (5.37%)
occurrences (all)	9	7	12
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	18 / 205 (8.78%)	21 / 235 (8.94%)	14 / 205 (6.83%)
occurrences (all)	18	21	14
Oropharyngeal pain			
subjects affected / exposed	7 / 205 (3.41%)	2 / 235 (0.85%)	12 / 205 (5.85%)
occurrences (all)	8	3	12
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	8 / 205 (3.90%)	12 / 235 (5.11%)	11 / 205 (5.37%)
occurrences (all)	8	12	11
Pruritus			

subjects affected / exposed	14 / 205 (6.83%)	18 / 235 (7.66%)	8 / 205 (3.90%)
occurrences (all)	15	18	8
Psychiatric disorders			
Insomnia			
subjects affected / exposed	20 / 205 (9.76%)	9 / 235 (3.83%)	16 / 205 (7.80%)
occurrences (all)	20	10	19
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	17 / 205 (8.29%)	15 / 235 (6.38%)	10 / 205 (4.88%)
occurrences (all)	17	15	10
Myalgia			
subjects affected / exposed	7 / 205 (3.41%)	22 / 235 (9.36%)	13 / 205 (6.34%)
occurrences (all)	7	23	14
Back pain			
subjects affected / exposed	8 / 205 (3.90%)	11 / 235 (4.68%)	11 / 205 (5.37%)
occurrences (all)	8	11	11
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	16 / 205 (7.80%)	13 / 235 (5.53%)	18 / 205 (8.78%)
occurrences (all)	19	14	18
Upper respiratory tract infection			
subjects affected / exposed	13 / 205 (6.34%)	17 / 235 (7.23%)	16 / 205 (7.80%)
occurrences (all)	14	19	16

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 June 2012	Updated the protocol with new safety information and added guidance regarding the management of subjects treated with daclatasvir/asunaprevir with unexplained pyrexia. Hemophilia was added as an exclusion criteria.
21 August 2012	Added the collection of cortisol in urine at Day 1, Week 12, and Week 24. Modified the research hypothesis by adding a well-defined criterion for the success of daclatasvir/asunaprevir therapy in the treatment-naive cohort. Separated the primary objective into 1 objective for prior null or partial responders to pegylated-interferon and a second for treatment-naive subjects, in accordance with the modification to the research hypothesis.
14 June 2013	Added description of available data for subjects who have received rescue therapy with QUAD (ASV/DCV/pegIFN-alpha/RBV) rescue therapy. Added option for subjects to continue rescue therapy with QUAD for 48 weeks. Revised contraception guidance for women of childbearing potential (WOCBP) and male subjects sexually active with WOCBP.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported