Clinical trial results:
A Phase 3, Open-Label Study with Asunaprevir and Daclatasvir Plus Peginterferon Alfa-2a (Pegasys) and Ribavirin (Copegus) (P/R) (QUAD) for Subjects Who Are Null or Partial Responders to Peginterferon Alfa-2a or -2b Plus Ribavirin with Chronic Hepatitis C Genotypes 1 or 4 Infection

Summary

EudraCT number	2011-005422-21
Trial protocol	SE DE NL ES DK IT
Global end of trial date	09 December 2013

Results information

Result version number	v1 (current)
This version publication date	30 October 2016
First version publication date	30 October 2016

Trial information

Trial identification

Sponsor protocol code	AI447-029

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01573351
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb International Corporation
Sponsor organisation address	Chaussee 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	09 December 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess efficacy, as determined by the proportion of subjects with sustained virologic response at follow-up Week 12 (SVR12), defined as hepatitis C virus (HCV) ribonucleic acid (RNA) < limit of quantitation (LOQ) 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	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	Netherlands: 8
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	Sweden: 11
Country: Number of subjects enrolled	Denmark: 8
Country: Number of subjects enrolled	France: 87
Country: Number of subjects enrolled	Germany: 47
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Argentina: 12
Country: Number of subjects enrolled	Canada: 27
Country: Number of subjects enrolled	Korea, Republic of: 37
Country: Number of subjects enrolled	Mexico: 7
Country: Number of subjects enrolled	Russian Federation: 23
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	Taiwan: 24
Country: Number of subjects enrolled	United States: 156
Worldwide total number of subjects	496
EEA total number of subjects	205

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)	451
From 65 to 84 years	45
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 79 sites in 15 countries.

Pre-assignment

Screening details:

496 enrolled; 398 treated. 98 did not enter treatment because 81 did not meet the study criteria during the screening period, 13 withdrew consent, 4 other.

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	GT-1: Asunaprevir/Daclatasvir/Peginterferon Alfa-2a/Ribavirin

Arm description:

Subjects with chronic HCV infection (genotype 1 [GT-1]) who were null or partial responders to peginterferon alfa-2a (pegINFα-2a) or peginterferon alfa-2b (pegINFα-2b) plus ribavirin were treated for 24 weeks with daclatasvir (DCV) Quad regimen followed by 24 weeks of follow-up after completion or early discontinuation of treatment. The DCV Quad regimen included daclatasvir 60 mg tablet once daily by mouth, asunaprevir 100-mg soft gel capsule twice daily by mouth, pegIFNα-2a 180 µg subcutaneous once weekly, and RBV (for subjects weighing < 75 kg the total dose was 1000 mg per day and for those weighing ≥ 75 kg the dose was 1200 mg per day; therefore, subjects were to take either 400 mg [2 tablets for subjects < 75 kg] or 600 mg [3 tablets for subjects ≥ 75 kg] in the morning with food and 600 mg [3 tablets] in the evening with food) for 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 100mg 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 60mg film coated tablet was administered orally once daily.

Investigational medicinal product name	Peginterferon Alfa-2a
Investigational medicinal product code	
Other name	PEGASYS
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Peginterferon Alfa-2a 180 micrograms/0.5 mL was administered once per week.

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

Dosage and administration details:

Ribavirin administered at a daily dose of 1000 to 1200 mg orally in two divided doses.

Arm title	GT-4: Asunaprevir/Daclatasvir/Peginterferon Alfa-2a/Ribavirin

Arm description:

Subjects with chronic HCV infection (genotype 4 [GT-4]) who were null or partial responders to peginterferon alfa-2a (pegINFα-2a) or peginterferon alfa-2b (pegINFα-2b) plus ribavirin were treated for 24 weeks with daclatasvir (DCV) Quad regimen followed by 24 weeks of follow-up after completion or early discontinuation of treatment. The DCV Quad regimen included daclatasvir 60 mg tablet once daily by mouth, asunaprevir 100-mg soft gel capsule twice daily by mouth, pegIFNα-2a 180 µg subcutaneous once weekly, and RBV (for subjects weighing < 75 kg the total dose was 1000 mg per day and for those weighing ≥ 75 kg the dose was 1200 mg per day; therefore, subjects were to take either 400 mg [2 tablets for subjects < 75 kg] or 600 mg [3 tablets for subjects ≥ 75 kg] in the morning with food and 600 mg [3 tablets] in the evening with food) for 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 100mg 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 60mg film coated tablet was administered orally once daily.

Investigational medicinal product name	Peginterferon Alfa-2a
Investigational medicinal product code	
Other name	PEGASYS
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Peginterferon Alfa-2a 180 micrograms/0.5 mL was administered once per week.

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

Dosage and administration details:

Ribavirin was administered at a daily dose of 1000 to 1200 mg orally in two divided doses.

Number of subjects in period 1[1]	GT-1: Asunaprevir/Daclatasvir/Peginterferon Alfa-2a/Ribavirin	GT-4: Asunaprevir/Daclatasvir/Peginterferon Alfa-2a/Ribavirin
Started	354	44
Completed	335	44
Not completed	19	0
Adverse event, non-fatal	7	-
Lost to follow-up	1	-
Lack of efficacy	11	-

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 496 subjects who were enrolled, only 398 were treated. Remaining 98 subjects did not receive any treatment. 81 subjects no longer met the study criteria, 13 subjects withdrew consent to participate, and 4 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	GT-1: Asunaprevir/Daclatasvir/Peginterferon Alfa-2a/Ribavirin

Arm description:

Subjects received no treatment during 24 weeks of follow-up after completion of treatment or upon early discontinuation of treatment.
Treatment included 24 weeks with DCV Quad regimen followed by 24 weeks of follow-up after completion or early discontinuation of treatment. The DCV Quad regimen included daclatasvir 60 mg tablet once daily by mouth, asunaprevir 100-mg soft gel capsule twice daily by mouth, pegIFNα-2a 180 µg subcutaneous once weekly, and ribavirin (for subjects weighing < 75 kg the total dose was 1000 mg per day and for those weighing ≥ 75 kg the dose was 1200 mg per day; therefore, subjects were to take either 400 mg [2 tablets for subjects < 75 kg] or 600 mg [3 tablets for subjects ≥ 75 kg] in the morning with food and 600 mg [3 tablets] in the evening with food) for 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 100mg 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 60mg film coated tablet was administered orally once daily.

Investigational medicinal product name	Peginterferon Alfa-2a
Investigational medicinal product code	
Other name	PEGASYS

Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Peginterferon Alfa-2a 180 micrograms/0.5 mL was administered once per week.

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

Dosage and administration details:

Ribavirin administered at a daily dose of 1000 to 1200 mg orally in two divided doses.

Arm title	GT-4: Asunaprevir/Daclatasvir/Peginterferon Alfa-2a/Ribavirin

Arm description:

Subjects received no treatment during 24 weeks of follow-up after completion of treatment or upon early discontinuation of treatment.
Treatment included 24 weeks with DCV Quad regimen followed by 24 weeks of follow-up after completion or early discontinuation of treatment. The DCV Quad regimen included daclatasvir 60 mg tablet once daily by mouth, asunaprevir 100-mg soft gel capsule twice daily by mouth, pegIFNα-2a 180 µg subcutaneous once weekly, and ribavirin (for subjects weighing < 75 kg the total dose was 1000 mg per day and for those weighing ≥ 75 kg the dose was 1200 mg per day; therefore, subjects were to take either 400 mg [2 tablets for subjects < 75 kg] or 600 mg [3 tablets for subjects ≥ 75 kg] in the morning with food and 600 mg [3 tablets] in the evening with food) for 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 100mg 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 60mg film coated tablet was administered orally once daily.

Investigational medicinal product name	Peginterferon Alfa-2a
Investigational medicinal product code	
Other name	PEGASYS
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Peginterferon Alfa 180 micrograms/0.5 mL was administered once per week.

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

Dosage and administration details:

Ribavirin administered at a daily dose of 1000 to 1200 mg orally in two divided doses.

Number of subjects in period 2	GT-1: Asunaprevir/Daclatasvir/Peginterferon Alfa-2a/Ribavirin	GT-4: Asunaprevir/Daclatasvir/Peginterferon Alfa-2a/Ribavirin
Started	335	44
Completed	344	44
Not completed	8	0
Consent withdrawn by subject	3	-
Death	1	-
Other	2	-
Lost to follow-up	2	-
Joined	17	0
Re-entering for follow-up	17	-

Baseline characteristics

Reporting groups

Reporting group title	GT-1: Asunaprevir/Daclatasvir/Peginterferon Alfa-2a/Ribavirin

Reporting group description:

Subjects with chronic HCV infection (genotype 1 [GT-1]) who were null or partial responders to peginterferon alfa-2a (pegINFα-2a) or peginterferon alfa-2b (pegINFα-2b) plus ribavirin were treated for 24 weeks with daclatasvir (DCV) Quad regimen followed by 24 weeks of follow-up after completion or early discontinuation of treatment. The DCV Quad regimen included daclatasvir 60 mg tablet once daily by mouth, asunaprevir 100-mg soft gel capsule twice daily by mouth, pegIFNα-2a 180 µg subcutaneous once weekly, and RBV (for subjects weighing < 75 kg the total dose was 1000 mg per day and for those weighing ≥ 75 kg the dose was 1200 mg per day; therefore, subjects were to take either 400 mg [2 tablets for subjects < 75 kg] or 600 mg [3 tablets for subjects ≥ 75 kg] in the morning with food and 600 mg [3 tablets] in the evening with food) for 24 weeks.

Reporting group title	GT-4: Asunaprevir/Daclatasvir/Peginterferon Alfa-2a/Ribavirin

Reporting group description:

Subjects with chronic HCV infection (genotype 4 [GT-4]) who were null or partial responders to peginterferon alfa-2a (pegINFα-2a) or peginterferon alfa-2b (pegINFα-2b) plus ribavirin were treated for 24 weeks with daclatasvir (DCV) Quad regimen followed by 24 weeks of follow-up after completion or early discontinuation of treatment. The DCV Quad regimen included daclatasvir 60 mg tablet once daily by mouth, asunaprevir 100-mg soft gel capsule twice daily by mouth, pegIFNα-2a 180 µg subcutaneous once weekly, and RBV (for subjects weighing < 75 kg the total dose was 1000 mg per day and for those weighing ≥ 75 kg the dose was 1200 mg per day; therefore, subjects were to take either 400 mg [2 tablets for subjects < 75 kg] or 600 mg [3 tablets for subjects ≥ 75 kg] in the morning with food and 600 mg [3 tablets] in the evening with food) for 24 weeks.

Reporting group values	GT-1: Asunaprevir/Daclatasvir/Peginterferon Alfa-2a/Ribavirin	GT-4: Asunaprevir/Daclatasvir/Peginterferon Alfa-2a/Ribavirin	Total
Number of subjects	354	44	398
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	320	41	361
From 65-84 years	34	3	37
Age continuous Units: years			
arithmetic mean	52.9	50.8	
full range (min-max)	19 to 76	20 to 71	-
Gender categorical Units: Subjects			
Female	114	11	125
Male	240	33	273

End points

End points reporting groups

Reporting group title	GT-1: Asunaprevir/Daclatasvir/Peginterferon Alfa-2a/Ribavirin

Reporting group description:

Subjects with chronic HCV infection (genotype 1 [GT-1]) who were null or partial responders to peginterferon alfa-2a (pegINFα-2a) or peginterferon alfa-2b (pegINFα-2b) plus ribavirin were treated for 24 weeks with daclatasvir (DCV) Quad regimen followed by 24 weeks of follow-up after completion or early discontinuation of treatment. The DCV Quad regimen included daclatasvir 60 mg tablet once daily by mouth, asunaprevir 100-mg soft gel capsule twice daily by mouth, pegIFNα-2a 180 µg subcutaneous once weekly, and RBV (for subjects weighing < 75 kg the total dose was 1000 mg per day and for those weighing ≥ 75 kg the dose was 1200 mg per day; therefore, subjects were to take either 400 mg [2 tablets for subjects < 75 kg] or 600 mg [3 tablets for subjects ≥ 75 kg] in the morning with food and 600 mg [3 tablets] in the evening with food) for 24 weeks.

Reporting group title	GT-4: Asunaprevir/Daclatasvir/Peginterferon Alfa-2a/Ribavirin

Reporting group description:

Subjects with chronic HCV infection (genotype 4 [GT-4]) who were null or partial responders to peginterferon alfa-2a (pegINFα-2a) or peginterferon alfa-2b (pegINFα-2b) plus ribavirin were treated for 24 weeks with daclatasvir (DCV) Quad regimen followed by 24 weeks of follow-up after completion or early discontinuation of treatment. The DCV Quad regimen included daclatasvir 60 mg tablet once daily by mouth, asunaprevir 100-mg soft gel capsule twice daily by mouth, pegIFNα-2a 180 µg subcutaneous once weekly, and RBV (for subjects weighing < 75 kg the total dose was 1000 mg per day and for those weighing ≥ 75 kg the dose was 1200 mg per day; therefore, subjects were to take either 400 mg [2 tablets for subjects < 75 kg] or 600 mg [3 tablets for subjects ≥ 75 kg] in the morning with food and 600 mg [3 tablets] in the evening with food) for 24 weeks.

Reporting group title	GT-1: Asunaprevir/Daclatasvir/Peginterferon Alfa-2a/Ribavirin

Reporting group description:

Subjects received no treatment during 24 weeks of follow-up after completion of treatment or upon early discontinuation of treatment.
Treatment included 24 weeks with DCV Quad regimen followed by 24 weeks of follow-up after completion or early discontinuation of treatment. The DCV Quad regimen included daclatasvir 60 mg tablet once daily by mouth, asunaprevir 100-mg soft gel capsule twice daily by mouth, pegIFNα-2a 180 µg subcutaneous once weekly, and ribavirin (for subjects weighing < 75 kg the total dose was 1000 mg per day and for those weighing ≥ 75 kg the dose was 1200 mg per day; therefore, subjects were to take either 400 mg [2 tablets for subjects < 75 kg] or 600 mg [3 tablets for subjects ≥ 75 kg] in the morning with food and 600 mg [3 tablets] in the evening with food) for 24 weeks.

Reporting group title	GT-4: Asunaprevir/Daclatasvir/Peginterferon Alfa-2a/Ribavirin

Reporting group description:

Subjects received no treatment during 24 weeks of follow-up after completion of treatment or upon early discontinuation of treatment.
Treatment included 24 weeks with DCV Quad regimen followed by 24 weeks of follow-up after completion or early discontinuation of treatment. The DCV Quad regimen included daclatasvir 60 mg tablet once daily by mouth, asunaprevir 100-mg soft gel capsule twice daily by mouth, pegIFNα-2a 180 µg subcutaneous once weekly, and ribavirin (for subjects weighing < 75 kg the total dose was 1000 mg per day and for those weighing ≥ 75 kg the dose was 1200 mg per day; therefore, subjects were to take either 400 mg [2 tablets for subjects < 75 kg] or 600 mg [3 tablets for subjects ≥ 75 kg] in the morning with food and 600 mg [3 tablets] in the evening with food) for 24 weeks.

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

End point title	Percentage of Genotype 1 Chronic Hepatitis C Infected Subjects Who Were Prior Null or Partial Responders to Peginterferon Alfa/Ribavirin Achieving a Sustained Virologic Response at Follow-Up Week 12[1]

End point description:

Sustained Virologic Response at follow-up (post treatment) Week 12 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 with genotype 1 who were prior null or partial

responders to Peginterferon Alfa/Ribavirin. HCV RNA levels were measured by the Roche COBAS® TaqMan® HCV Test version 2.0 from the central laboratory. The analysis was based on all treated subjects. Subjects missing follow-up Week 12 measurements and subjects who received non-study anti-HCV medication prior to follow-up Week 12 were counted as non-responders.

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	GT-1: Asunaprevir/Daclatasvir/Peginterferon Alfa-2a/Ribavirin	GT-4: Asunaprevir/Daclatasvir/Peginterferon Alfa-2a/Ribavirin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354	44		
Units: Percentage of Subjects				
number (confidence interval 95%)	92.9 (90.3 to 95.6)	97.7 (93.3 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Genotype 1 Chronic Hepatitis C Infected Subjects Who Were Prior Null or Partial Responders to Peginterferon Alfa/Ribavirin With Hepatitis C Virus (HCV) RNA <Lower Limit of Quantitation (LLOQ), Target not Detected

End point title	Percentage of Genotype 1 Chronic Hepatitis C Infected Subjects Who Were Prior Null or Partial Responders to Peginterferon Alfa/Ribavirin With Hepatitis C Virus (HCV) RNA <Lower Limit of Quantitation (LLOQ), Target not Detected

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.

End point type	Secondary

End point timeframe:

Week 2, 4, 6, 8, 12, 24, follow-up week 12, and follow-up week 24

End point values	GT-1: Asunaprevir/Daclatasvir/Peginterferon Alfa-2a/Ribavirin	GT-4: Asunaprevir/Daclatasvir/Peginterferon Alfa-2a/Ribavirin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354	44		
Units: Percentage of Subjects				
number (confidence interval 95%)				

Week 2	28 (23.3 to 32.6)	27.3 (14.1 to 40.4)		
Week 4	82.5 (78.5 to 86.4)	81.8 (70.4 to 93.2)		
Week 6	93.2 (90.6 to 95.8)	90.9 (82.4 to 99.4)		
Week 8	95.5 (93.3 to 97.4)	97.7 (93.3 to 100)		
Week 12	95.2 (93 to 97.4)	97.7 (93.3 to 100)		
Week 24	91 (88 to 93.9)	97.7 (93.3 to 100)		
Follow-Up Week 12	91.5 (88.6 to 94.4)	97.7 (93.3 to 100)		
Follow-Up Week 24	88.1 (84.8 to 91.5)	93.2 (85.7 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Genotype 1 Chronic Hepatitis C Infected Subjects Who Were Prior Null or Partial Responders to Peginterferon Alfa/Ribavirin with Hepatitis C Virus (HCV) RNA <Lower Limit of Quantitation (LLOQ), Target Detected or Target not Detected

End point title	Percentage of Genotype 1 Chronic Hepatitis C Infected Subjects Who Were Prior Null or Partial Responders to Peginterferon Alfa/Ribavirin with Hepatitis C Virus (HCV) RNA <Lower Limit of Quantitation (LLOQ), Target Detected or Target not Detected

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.

End point type	Secondary

End point timeframe:

Week 2, 4, 6, 8, 12, 24, and follow-up Week 24

End point values	GT-1: Asunaprevir/Daclatasvir/Peginterferon Alfa-2a/Ribavirin	GT-4: Asunaprevir/Daclatasvir/Peginterferon Alfa-2a/Ribavirin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354	44		
Units: Percentage of Subjects				
number (confidence interval 95%)				
Week 2	81.4 (77.3 to 85.4)	86.4 (76.2 to 96.5)		
Week 4	97.7 (96.2 to 99.3)	100 (100 to 100)		
Weel 6	94.4 (91.9 to 96.8)	95.5 (89.3 to 100)		

Week 8	97.5 (95.8 to 99.1)	97.7 (93.3 to 100)		
Week 12	97.2 (95.4 to 98.9)	100 (100 to 100)		
Week 24	92.4 (89.6 to 95.1)	100 (100 to 100)		
Follow-Up Week 24	88.4 (85.1 to 91.8)	95.5 (89.3 to 100)		

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

End point description:

AE was defined as any new unfavorable symptom, sign, or disease or worsening of a preexisting 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

End point values	GT-1: Asunaprevir/Daclatasvir/Peginterferon Alfa-2a/Ribavirin	GT-4: Asunaprevir/Daclatasvir/Peginterferon Alfa-2a/Ribavirin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354	44		
Units: Subjects				
SAEs	19	3		
AEs Leading to Discontinuation	15	3		
Grade 3/4 AEs	86	11		
Deaths	0	0		

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	16.1

Reporting groups

Reporting group title	GT-1:Asunaprevir/Daclatasvir/ Peginterferon Alfa-2a/Ribaviri

Reporting group description:

Subjects with chronic HCV infection (genotype 1 [GT-1]) who were null or partial responders to peginterferon alfa-2a (pegINFα-2a) or peginterferon alfa-2b (pegINFα-2b) plus ribavirin were treated for 24 weeks with daclatasvir (DCV) Quad regimen followed by 24 weeks of follow-up after completion or early discontinuation of treatment. The DCV Quad regimen included daclatasvir 60 mg tablet once daily by mouth, asunaprevir 100-mg soft gel capsule twice daily by mouth, pegIFNα-2a 180 µg subcutaneous once weekly, and RBV (for subjects weighing < 75 kg the total dose was 1000 mg per day and for those weighing ≥ 75 kg the dose was 1200 mg per day; therefore, subjects were to take either 400 mg [2 tablets for subjects < 75 kg] or 600 mg [3 tablets for subjects ≥ 75 kg] in the morning with food and 600 mg [3 tablets] in the evening with food) for 24 weeks.

Reporting group title	GT-4:Asunaprevir/Daclatasvir/ Peginterferon Alfa-2a/Ribaviri

Reporting group description:

Subjects with chronic HCV infection (genotype 4 [GT-4]) who were null or partial responders to peginterferon alfa-2a (pegINFα-2a) or peginterferon alfa-2b (pegINFα-2b) plus ribavirin were treated for 24 weeks with daclatasvir (DCV) Quad regimen followed by 24 weeks of follow-up after completion or early discontinuation of treatment. The DCV Quad regimen included daclatasvir 60 mg tablet once daily by mouth, asunaprevir 100-mg soft gel capsule twice daily by mouth, pegIFNα-2a 180 µg subcutaneous once weekly, and RBV (for subjects weighing < 75 kg the total dose was 1000 mg per day and for those weighing ≥ 75 kg the dose was 1200 mg per day; therefore, subjects were to take either 400 mg [2 tablets for subjects < 75 kg] or 600 mg [3 tablets for subjects ≥ 75 kg] in the morning with food and 600 mg [3 tablets] in the evening with food) for 24 weeks.

Serious adverse events	GT-1:Asunaprevir/Daclatasvir/ Peginterferon Alfa-2a/Ribaviri	GT-4:Asunaprevir/Daclatasvir/ Peginterferon Alfa-2a/Ribaviri	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 354 (5.37%)	3 / 44 (6.82%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 354 (0.28%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			

subjects affected / exposed	1 / 354 (0.28%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Major depression			
subjects affected / exposed	1 / 354 (0.28%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 354 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Spinal column injury			
subjects affected / exposed	1 / 354 (0.28%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic ulcer			
subjects affected / exposed	1 / 354 (0.28%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	1 / 354 (0.28%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	1 / 354 (0.28%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	1 / 354 (0.28%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 354 (0.56%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	1 / 354 (0.28%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 354 (0.28%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 354 (0.28%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 354 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			

subjects affected / exposed	1 / 354 (0.28%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus ureteric			
subjects affected / exposed	1 / 354 (0.28%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 354 (0.28%)	0 / 44 (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	3 / 354 (0.85%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 354 (0.56%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 354 (0.28%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 354 (0.28%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			

Dehydration			
subjects affected / exposed	1 / 354 (0.28%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	GT-1:Asunaprevir/Daclatasvir/ Peginterferon Alfa-2a/Ribaviri	GT-4:Asunaprevir/Daclatasvir/ Peginterferon Alfa-2a/Ribaviri	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	350 / 354 (98.87%)	43 / 44 (97.73%)	
Investigations			
Weight decreased			
subjects affected / exposed	19 / 354 (5.37%)	7 / 44 (15.91%)	
occurrences (all)	19	7	
Nervous system disorders			
Headache			
subjects affected / exposed	111 / 354 (31.36%)	13 / 44 (29.55%)	
occurrences (all)	122	17	
Dizziness			
subjects affected / exposed	30 / 354 (8.47%)	2 / 44 (4.55%)	
occurrences (all)	31	2	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	146 / 354 (41.24%)	19 / 44 (43.18%)	
occurrences (all)	155	21	
Asthenia			
subjects affected / exposed	79 / 354 (22.32%)	17 / 44 (38.64%)	
occurrences (all)	85	18	
Influenza like illness			
subjects affected / exposed	79 / 354 (22.32%)	10 / 44 (22.73%)	
occurrences (all)	90	10	
Irritability			
subjects affected / exposed	57 / 354 (16.10%)	7 / 44 (15.91%)	
occurrences (all)	58	7	
Pyrexia			

subjects affected / exposed	57 / 354 (16.10%)	7 / 44 (15.91%)	
occurrences (all)	62	7	
Injection site erythema			
subjects affected / exposed	22 / 354 (6.21%)	1 / 44 (2.27%)	
occurrences (all)	22	1	
Pain			
subjects affected / exposed	14 / 354 (3.95%)	7 / 44 (15.91%)	
occurrences (all)	14	7	
Chills			
subjects affected / exposed	16 / 354 (4.52%)	3 / 44 (6.82%)	
occurrences (all)	18	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	67 / 354 (18.93%)	10 / 44 (22.73%)	
occurrences (all)	78	12	
Neutropenia			
subjects affected / exposed	56 / 354 (15.82%)	3 / 44 (6.82%)	
occurrences (all)	77	6	
Thrombocytopenia			
subjects affected / exposed	21 / 354 (5.93%)	3 / 44 (6.82%)	
occurrences (all)	26	3	
Eye disorders			
Dry eye			
subjects affected / exposed	17 / 354 (4.80%)	4 / 44 (9.09%)	
occurrences (all)	17	4	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	63 / 354 (17.80%)	7 / 44 (15.91%)	
occurrences (all)	68	13	
Nausea			
subjects affected / exposed	61 / 354 (17.23%)	5 / 44 (11.36%)	
occurrences (all)	69	7	
Abdominal pain upper			
subjects affected / exposed	18 / 354 (5.08%)	3 / 44 (6.82%)	
occurrences (all)	18	5	
Vomiting			

subjects affected / exposed	14 / 354 (3.95%)	4 / 44 (9.09%)	
occurrences (all)	14	4	
Dry mouth			
subjects affected / exposed	11 / 354 (3.11%)	3 / 44 (6.82%)	
occurrences (all)	11	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	67 / 354 (18.93%)	6 / 44 (13.64%)	
occurrences (all)	69	6	
Dyspnoea			
subjects affected / exposed	41 / 354 (11.58%)	8 / 44 (18.18%)	
occurrences (all)	42	8	
Dyspnoea exertional			
subjects affected / exposed	18 / 354 (5.08%)	3 / 44 (6.82%)	
occurrences (all)	19	3	
Epistaxis			
subjects affected / exposed	10 / 354 (2.82%)	4 / 44 (9.09%)	
occurrences (all)	10	5	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	88 / 354 (24.86%)	16 / 44 (36.36%)	
occurrences (all)	93	17	
Rash			
subjects affected / exposed	75 / 354 (21.19%)	7 / 44 (15.91%)	
occurrences (all)	78	8	
Dry skin			
subjects affected / exposed	65 / 354 (18.36%)	6 / 44 (13.64%)	
occurrences (all)	68	7	
Alopecia			
subjects affected / exposed	60 / 354 (16.95%)	4 / 44 (9.09%)	
occurrences (all)	60	4	
Eczema			
subjects affected / exposed	10 / 354 (2.82%)	3 / 44 (6.82%)	
occurrences (all)	11	3	
Erythema			

subjects affected / exposed	10 / 354 (2.82%)	3 / 44 (6.82%)	
occurrences (all)	11	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	77 / 354 (21.75%)	12 / 44 (27.27%)	
occurrences (all)	81	14	
Depression			
subjects affected / exposed	30 / 354 (8.47%)	4 / 44 (9.09%)	
occurrences (all)	30	5	
Sleep disorder			
subjects affected / exposed	11 / 354 (3.11%)	4 / 44 (9.09%)	
occurrences (all)	12	4	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	55 / 354 (15.54%)	6 / 44 (13.64%)	
occurrences (all)	65	7	
Arthralgia			
subjects affected / exposed	35 / 354 (9.89%)	5 / 44 (11.36%)	
occurrences (all)	37	5	
Back pain			
subjects affected / exposed	29 / 354 (8.19%)	0 / 44 (0.00%)	
occurrences (all)	31	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	41 / 354 (11.58%)	6 / 44 (13.64%)	
occurrences (all)	45	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 March 2012	Permitted collection and storage of blood samples for use in future exploratory pharmacogenetic research.
31 May 2012	Added a safety update and guidance regarding the management of patients exposed to DCV/ASV (Dual therapy), who presented with unexplained pyrexia. In addition, subjects with hemophilia were excluded following Health Authorities commitments as this population is at high risk.
30 March 2013	Corrected grammatical and typographical errors as well as protocol inconsistencies with program standards. Additionally, table numbers were slightly modified to reflect a new template.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported