



Clinical trial results:

An Open-Label Re-treatment Study with Peg-Interferon Alfa-2a, Ribavirin and BMS-790052 With or Without BMS-650032 for Subjects With Chronic Hepatitis C.

Summary

EudraCT number	2011-000836-27
Trial protocol	IE GB ES SE DK IT AT NL GR
Global end of trial date	23 September 2014

Results information

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

Trial information

Trial identification

Sponsor protocol code	AI444-026
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01428063
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol Myers Squibb
Sponsor organisation address	Chaussee de la Hulpe 185, Brussels, Belgium,
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	23 September 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	23 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to assess the efficacy based on the percentage of subjects with sustained virologic response for 12 weeks (SVR12), in both the global and site-specific cohorts.

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	06 October 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 12
Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Canada: 20
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	France: 30
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Korea, Republic of: 13
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	Taiwan: 14
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	United States: 137

Worldwide total number of subjects	276
EEA total number of subjects	65

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)	248
From 65 to 84 years	28
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 92 centers in 20 countries.

Pre-assignment

Screening details:

A total of 228 subjects enrolled, of which 227 received treatment; 206 completed the study. The majority of subjects discontinued due to lack of efficacy and adverse events.

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Daclatasvir + Asunaprevir

Arm description:

Subjects received daclatasvir (DCV), 60 mg tablet, by mouth once daily + asunaprevir (ASV), 100 mg capsule, by mouth twice daily for 24 weeks.

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

Dosage and administration details:

Subjects were administered with DCV 60 mg orally twice daily.

Investigational medicinal product name	Asunaprevir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects were administered with ASV 100 mg orally twice daily.

Arm title	DCV + ASV + pegIFN-2a+ Ribavirin
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Arm description:

Subjects received DCV, 60 mg tablet, by mouth once daily + ASV, 100 mg capsule or 200 mg tablet, by mouth twice daily + pegylated interferon alfa-2a (pegIFNα2a), 80 µg solution, subcutaneously weekly + ribavirin (RBV), weight based dosing (<75 kg = 1000 mg once daily; ≥75 kg = 1200 mg once daily) for 24 weeks.

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

Dosage and administration details:

Subjects were administered with DCV 60 mg orally twice daily.

Investigational medicinal product name	Asunaprevir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects were administered with ASV 100 mg orally twice daily.

Investigational medicinal product name	Pegylated interferon alfa-2a (pegIFN α -2a)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects were administered with 80 μ g pegIFN α -2a subcutaneously.

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

Dosage and administration details:

Subjects were administered with ribavirin orally, based on weight <75 kg = 1000 mg once daily or $\geq$ 75 kg = 1200 mg once daily.

Arm title	DCV + pegIFN-2a+ RBV
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Arm description:

Subjects received DCV, 60 mg tablet, by mouth once daily + pegIFN α 2a, 80 μ g solution, subcutaneously weekly + RBV, weight based dosing (<75 kg = 1000 mg once daily; $\geq$ 75 kg = 1200 mg once daily) for 24 weeks.

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

Dosage and administration details:

Subjects were administered with DCV 60 mg orally twice daily.

Investigational medicinal product name	Pegylated interferon alfa-2a (pegIFN α -2a)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects were administered with 80 μ g pegIFN α -2a subcutaneously.

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

Dosage and administration details:

Subjects were administered with ribavirin orally, based on weight <75 kg = 1000 mg once daily or $\geq$ 75 kg = 1200 mg once daily.

Number of subjects in period 1 ^[1]	Daclatasvir + Asunaprevir	DCV + ASV + pegIFN-2a+ Ribavirin	DCV + pegIFN-2a+ RBV
Started	99	122	6
Completed	89	112	5
Not completed	10	10	1
Adverse event, non-fatal	2	3	-
No longer meets study criteria	-	1	-
Lost to follow-up	-	2	-
Lack of efficacy	8	4	1

Notes:

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

Justification: The number of subjects reported in the baseline period are different from the worldwide number enrolled in the trial as 49 subjects discontinued from the study due to various reasons.

Baseline characteristics

Reporting groups

Reporting group title	Daclatasvir + Asunaprevir
Reporting group description:	
Subjects received daclatasvir (DCV), 60 mg tablet, by mouth once daily + asunaprevir (ASV), 100 mg capsule, by mouth twice daily for 24 weeks.	
Reporting group title	DCV + ASV + pegIFN-2a+ Ribavirin
Reporting group description:	
Subjects received DCV, 60 mg tablet, by mouth once daily + ASV, 100 mg capsule or 200 mg tablet, by mouth twice daily + pegylated interferon alfa-2a (pegIFN α 2a), 80 μ g solution, subcutaneously weekly + ribavirin (RBV), weight based dosing (<75 kg = 1000 mg once daily; $\geq$ 75 kg = 1200 mg once daily) for 24 weeks.	
Reporting group title	DCV + pegIFN-2a+ RBV
Reporting group description:	
Subjects received DCV, 60 mg tablet, by mouth once daily + pegIFN α 2a, 80 μ g solution, subcutaneously weekly + RBV, weight based dosing (<75 kg = 1000 mg once daily; $\geq$ 75 kg = 1200 mg once daily) for 24 weeks.	

Reporting group values	Daclatasvir + Asunaprevir	DCV + ASV + pegIFN-2a+ Ribavirin	DCV + pegIFN-2a+ RBV
Number of subjects	99	122	6
Age categorical			
Units: Subjects			
Younger than 65 years	80	114	6
65 years and older	19	8	0
Gender categorical			
Units: Subjects			
Female	48	84	2
Male	51	38	4

Reporting group values	Total		
Number of subjects	227		
Age categorical			
Units: Subjects			
Younger than 65 years	200		
65 years and older	27		
Gender categorical			
Units: Subjects			
Female	134		
Male	93		

End points

End points reporting groups

Reporting group title	Daclatasvir + Asunaprevir
Reporting group description: Subjects received daclatasvir (DCV), 60 mg tablet, by mouth once daily + asunaprevir (ASV), 100 mg capsule, by mouth twice daily for 24 weeks.	
Reporting group title	DCV + ASV + pegIFN-2a+ Ribavirin
Reporting group description: Subjects received DCV, 60 mg tablet, by mouth once daily + ASV,100 mg capsule or 200 mg tablet, by mouth twice daily + pegylated interferon alfa-2a (pegIFN2a), 80 µg solution, subcutaneously weekly + ribavirin (RBV), weight based dosing (<75 kg = 1000 mg once daily; ≥75 kg = 1200 mg once daily) for 24 weeks.	
Reporting group title	DCV + pegIFN-2a+ RBV
Reporting group description: Subjects received DCV, 60 mg tablet, by mouth once daily + pegIFN2a, 80 µg solution, subcutaneously weekly + RBV, weight based dosing (<75 kg = 1000 mg once daily; ≥75 kg = 1200 mg once daily) for 24 weeks.	
Subject analysis set title	DCV + ASV + pegIFN-2a+ Ribavirin (Genotype 1)
Subject analysis set type	Full analysis
Subject analysis set description: Genotype 1 subjects received DCV, 60 mg tablet, by mouth once daily + ASV,100 mg capsule or 200 mg tablet, by mouth twice daily + pegIFN2a, 80 µg solution, subcutaneously weekly + ribavirin (RBV), weight based dosing (<75 kg=1000 mg once daily; ≥75 kg=1200 mg once daily) for 24 weeks.	
Subject analysis set title	DCV + ASV + pegIFN-2a+ Ribavirin (Genotype 4)
Subject analysis set type	Full analysis
Subject analysis set description: Genotype 4 subjects received DCV, 60 mg tablet, by mouth once daily + ASV,100 mg capsule or 200 mg tablet, by mouth twice daily + pegylated interferon alfa-2a(pegIFN2a), 80 µg solution, subcutaneously weekly + ribavirin (RBV), weight based dosing (<75 kg=1000 mg once daily; ≥75 kg=1200 mg once daily) for 24 weeks.	
Subject analysis set title	DCV + ASV + pegIFN-2a+ RBV (Prior DCV Failures)
Subject analysis set type	Sub-group analysis
Subject analysis set description: subjects who were nor responders to earlier DCV/pegIFN/RBV therapy were administered with DCV, 60 mg tablet, by mouth once daily + ASV,100 mg capsule or 200 mg tablet, by mouth twice daily + pegIFN2a, 80 µg solution, subcutaneously weekly + RBV, weight based dosing (<75 kg=1000 mg once daily; ≥75 kg=1200 mg once daily) for 24 weeks.	
Subject analysis set title	DCV + ASV + pegIFN-2a+ RBV (Prior ASV Failures)
Subject analysis set type	Sub-group analysis
Subject analysis set description: subjects who were nor responders to earlier ASV/pegIFN/RBV therapy were administered with DCV, 60 mg tablet, by mouth once daily + ASV,100 mg capsule or 200 mg tablet, by mouth twice daily + pegIFN2a, 80 µg solution, subcutaneously weekly + RBV, weight based dosing (<75 kg=1000 mg once daily; ≥75 kg=1200 mg once daily) for 24 weeks.	
Subject analysis set title	DCV + ASV + pegIFN-2a+ RBV (Prior BOC Failures)
Subject analysis set type	Sub-group analysis
Subject analysis set description: subjects who were nor responders to earlier boceprevir(BOC) /pegIFN/RBV therapy were administered with DCV, 60 mg tablet, by mouth once daily + ASV,100 mg capsule or 200 mg tablet, by mouth twice daily + pegIFN2a, 80 µg solution, subcutaneously weekly + RBV, weight based dosing (<75 kg=1000 mg once daily; ≥75 kg=1200 mg once daily) for 24 weeks.	
Subject analysis set title	DCV + ASV + pegIFN-2a+ RBV (Prior TVR Failures)
Subject analysis set type	Sub-group analysis
Subject analysis set description: subjects who were nor responders to earlier telaprevir (TVR) /pegIFN/RBV therapy were administered with DCV, 60 mg tablet, by mouth once daily + ASV,100 mg capsule or 200 mg tablet, by mouth twice	

daily + pegIFNα2a, 80 µg solution, subcutaneously weekly + RBV, weight based dosing (<75 kg=1000 mg once daily; ≥75 kg=1200 mg once daily) for 24 weeks.

Subject analysis set title	DCV + ASV + pegIFN-2a+ RBV (Treatment Naive)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

HCV GT-1a infection treatment-naive subjects were administered with DCV, 60 mg tablet, by mouth once daily + ASV, 100 mg capsule or 200 mg tablet, by mouth twice daily + pegIFNα2a, 80 µg solution, subcutaneously weekly + RBV, weight based dosing (<75 kg=1000 mg once daily; ≥75 kg=1200 mg once daily) for 12 weeks.

Subject analysis set title	DCV + ASV + pegIFN-2a+ RBV (pegIFNα /RBV Relapsers)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PegIFNα /RBV relapsers were administered with DCV, 60 mg tablet, by mouth once daily + ASV, 100 mg capsule or 200 mg tablet, by mouth twice daily + pegIFNα2a, 80 µg solution, subcutaneously weekly + RBV, weight based dosing (<75 kg=1000 mg once daily; ≥75 kg=1200 mg once daily) for 12 week.

Primary: Percentage of Genotype 1 Subjects who Were Prior Non-Responders to pegIFNα-2a/RBV With Sustained Virologic Response at Follow-up Week 12 (SVR12)

End point title	Percentage of Genotype 1 Subjects who Were Prior Non-Responders to pegIFNα-2a/RBV With Sustained Virologic Response at Follow-up Week 12 (SVR12) ^[1]
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End point description:

SVR12 was defined as hepatitis C virus RNA less than the lower limit of quantitation, target detected or target not detected at follow-up Week 12. Here, 'Number of Subjects Analysed' signifies subjects evaluable for SVR12 at week 12. The analysis was performed in Intent-to-Treat population defined as all treated subjects defined as subjects who received at least 1 dose of study therapy.

End point type	Primary
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End point timeframe:

Week 12 (Follow-up period)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive summary statistics was planned for this outcome measure

End point values	DCV + ASV + pegIFN-2a+ Ribavirin (Genotype 1)			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: Percentage of subjects				
number (confidence interval 95%)	94.6 (81.8 to 99.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Sustained Virologic Response at Follow-up Week 12 (SVR12)

End point title	Percentage of Subjects With Sustained Virologic Response at Follow-up Week 12 (SVR12) ^[2]
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End point description:

SVR12 was defined as hepatitis C virus (HCV) RNA less than the lower limit of quantitation, target

detected or target not detected at follow-up Week 12. Here, 'Number of subjects Analysed' signifies subjects evaluable for this outcome measure. The analysis was performed in all treated subjects defined as subjects who received at least 1 dose of study therapy.

End point type	Secondary
End point timeframe:	
Week 12 (Follow-up period)	

Notes:

[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 be assessed for pre-specified reporting group.

End point values	Daclatasvir + Asunaprevir	DCV + pegIFN-2a+ RBV	DCV + ASV + pegIFN-2a+ Ribavirin (Genotype 4)	DCV + ASV + pegIFN-2a+ RBV (Prior DCV Failures)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	99	6	10	10
Units: Percentage of subjects				
number (confidence interval 95%)	85.9 (77.4 to 92)	50 (11.8 to 88.2)	90 (55.5 to 99.7)	40 (12.2 to 73.8)

End point values	DCV + ASV + pegIFN-2a+ RBV (Prior ASV Failures)	DCV + ASV + pegIFN-2a+ RBV (Prior BOC Failures)	DCV + ASV + pegIFN-2a+ RBV (Prior TVR Failures)	DCV + ASV + pegIFN-2a+ RBV (Treatment Naive)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	11	13	25
Units: Percentage of subjects				
number (confidence interval 95%)	100 (54.1 to 100)	90.9 (58.7 to 99.8)	76.9 (46.2 to 95)	84 (63.9 to 95.5)

End point values	DCV + ASV + pegIFN-2a+ RBV (pegIFNa /RBV Relapsers)			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: Percentage of subjects				
number (confidence interval 95%)	88.9 (51.8 to 99.7)			

Statistical analyses

No statistical analyses for this end point

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

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

RVR was defined as the status at which the proportion of subjects with hepatitis C virus (HCV) RNA less than the lower limit of quantitation, target not detected at Week 4. Here, 'Number of subjects Analysed' signifies subjects evaluable for this outcome measure. The analysis was performed in all treated subjects defined as subjects who received at least 1 dose of study therapy.

End point type	Secondary
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End point timeframe:

Week 4

End point values	Daclatasvir + Asunaprevir	DCV + ASV + pegIFN-2a+ Ribavirin	DCV + pegIFN-2a+ RBV	DCV + ASV + pegIFN-2a+ RBV (Prior DCV Failures)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	99	48	6	10
Units: Percentage of subjects				
number (not applicable)	72.7	91.7	83.3	70

End point values	DCV + ASV + pegIFN-2a+ RBV (Prior ASV Failures)	DCV + ASV + pegIFN-2a+ RBV (Prior BOC Failures)	DCV + ASV + pegIFN-2a+ RBV (Prior TVR Failures)	DCV + ASV + pegIFN-2a+ RBV (Treatment Naive)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	11	13	25
Units: Percentage of subjects				
number (not applicable)	83.3	90.9	76.9	76

End point values	DCV + ASV + pegIFN-2a+ RBV (pegIFNa /RBV Relapsers)			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: Percentage of subjects				
number (not applicable)	88.9			

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)
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End point description:

eRVR was defined as the status at which the proportion of subjects with hepatitis C virus (HCV) RNA less than the lower limit of quantitation, target not detected at both weeks 4 and 12. Here, 'Number of subjects Analysed' signifies subjects evaluable for this outcome measure. The analysis was performed in all treated subjects defined as subjects who received at least 1 dose of study therapy.

End point type	Secondary
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End point timeframe:

Week 4 and 12

End point values	Daclatasvir + Asunaprevir	DCV + ASV + pegIFN-2a+ Ribavirin	DCV + pegIFN-2a+ RBV	DCV + ASV + pegIFN-2a+ RBV (Prior DCV Failures)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	99	48	6	10
Units: Percentage of subjects				
number (not applicable)	67.7	87.5	83.3	70

End point values	DCV + ASV + pegIFN-2a+ RBV (Prior ASV Failures)	DCV + ASV + pegIFN-2a+ RBV (Prior BOC Failures)	DCV + ASV + pegIFN-2a+ RBV (Prior TVR Failures)	DCV + ASV + pegIFN-2a+ RBV (Treatment Naive)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	11	13	25
Units: Percentage of subjects				
number (not applicable)	83.3	81.8	76.9	64

End point values	DCV + ASV + pegIFN-2a+ RBV (pegIFNa /RBV Relapsers)			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: Percentage of subjects				
number (not applicable)	88.9			

Statistical analyses

No statistical analyses for this end point

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

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

cEVR was defined as the status at which the proportion of subjects with hepatitis C virus (HCV) RNA less than the lower limit of quantitation, target not detected at week 12. Here, 'Number of subjects Analysed' signifies subjects evaluable for this outcome measure. The analysis was performed in all treated subjects defined as subjects who received at least 1 dose of study therapy.

End point type	Secondary
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End point timeframe:

Week 12

End point values	Daclatasvir + Asunaprevir	DCV + ASV + pegIFN-2a+ Ribavirin	DCV + pegIFN-2a+ RBV	DCV + ASV + pegIFN-2a+ RBV (Prior DCV Failures)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	99	48	6	10
Units: Percentage of subjects				
number (not applicable)	87.9	95.8	83.3	90

End point values	DCV + ASV + pegIFN-2a+ RBV (Prior ASV Failures)	DCV + ASV + pegIFN-2a+ RBV (Prior BOC Failures)	DCV + ASV + pegIFN-2a+ RBV (Prior TVR Failures)	DCV + ASV + pegIFN-2a+ RBV (Treatment Naive)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	11	13	25
Units: Percentage of subjects				
number (not applicable)	100	90.9	92.3	76

End point values	DCV + ASV + pegIFN-2a+ RBV (pegIFNa /RBV Relapsers)			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: Percentage of subjects				
number (not applicable)	88.9			

Statistical analyses

No statistical analyses for this end point

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

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

EOTR was defined as the status at which the proportion of subjects with hepatitis C virus (HCV) RNA less than the lower limit of quantitation, target not detected at end of treatment. Here, 'Number of subjects Analysed' signifies subjects evaluable for this outcome measure. The analysis was performed in all treated subjects defined as subjects who received at least 1 dose of study therapy.

End point type	Secondary
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End point timeframe:

End of the study (Week 24)

End point values	Daclatasvir + Asunaprevir	DCV + ASV + pegIFN-2a+ Ribavirin	DCV + pegIFN-2a+ RBV	DCV + ASV + pegIFN-2a+ RBV (Prior DCV Failures)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	99	48	6	10
Units: Percentage of subjects				
number (not applicable)	85.9	97.9	83.3	90

End point values	DCV + ASV + pegIFN-2a+ RBV (Prior ASV Failures)	DCV + ASV + pegIFN-2a+ RBV (Prior BOC Failures)	DCV + ASV + pegIFN-2a+ RBV (Prior TVR Failures)	DCV + ASV + pegIFN-2a+ RBV (Treatment Naive)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	11	13	25
Units: Percentage of subjects				
number (not applicable)	100	90.9	92.3	84

End point values	DCV + ASV + pegIFN-2a+ RBV (pegIFNa /RBV Relapsers)			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: Percentage of subjects				
number (not applicable)	88.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Sustained Virologic Response at Follow-up Week 24 (SVR24)

End point title	Percentage of Subjects With Sustained Virologic Response at Follow-up Week 24 (SVR24)
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End point description:

AE was defined as any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that does not necessarily have a causal relationship with treatment. SAE was defined as a medical event that at any dose resulted in death, persistent or significant disability/incapacity, or drug dependency/abuse; was life-threatening, an important medical event, or a congenital anomaly/birth defect; or required or prolonged hospitalisation. Here, 'Number of subjects Analysed' signifies subjects evaluable for this outcome measure. The analysis was performed in all treated subjects defined as subjects who received at least 1 dose of study therapy.

End point type Secondary

End point timeframe:

For AEs: From Day 1, first dose until subject's last scheduled visit. For SAEs: Date of subject's written consent until 30 days post discontinuation of dosing or participation in the study if last scheduled visit occurred at a later time (72 Week)

End point values	Daclatasvir + Asunaprevir	DCV + ASV + pegIFN-2a+ Ribavirin	DCV + pegIFN-2a+ RBV	DCV + ASV + pegIFN-2a+ RBV (Prior DCV Failures)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	99	48	6	10
Units: Subjects				
SAEs	4	0	0	0
AEs leading to discontinuation of therapy	2	2	0	0
Death	0	0	0	0

End point values	DCV + ASV + pegIFN-2a+ RBV (Prior ASV Failures)	DCV + ASV + pegIFN-2a+ RBV (Prior BOC Failures)	DCV + ASV + pegIFN-2a+ RBV (Prior TVR Failures)	DCV + ASV + pegIFN-2a+ RBV (Treatment Naive)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	11	13	25
Units: Subjects				
SAEs	0	2	0	1
AEs leading to discontinuation of therapy	1	0	0	2
Death	0	0	0	0

End point values	DCV + ASV + pegIFN-2a+ RBV (pegIFNa /RBV Relapsers)			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: Subjects				
SAEs	0			
AEs leading to discontinuation of therapy	0			

Death	0			
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Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For AEs: From Day 1, first dose until subject's last scheduled visit. For SAEs: Date of subject's written consent until 30 days post discontinuation of dosing or participation in the study if the last scheduled visit occurred later (72 weeks).

Adverse event reporting additional description:

On treatment period.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Daclatasvir + Asunaprevir
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Reporting group description:

Subjects received daclatasvir (DCV), 60 mg tablet, by mouth once daily + asunaprevir (ASV), 100 mg capsule, by mouth twice daily for 24 weeks.

Reporting group title	DCV + ASV + pegIFN-2a+ Ribavirin
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Reporting group description:

Subjects received DCV, 60 mg tablet, by mouth once daily + ASV, 100 mg capsule or 200 mg tablet, by mouth twice daily + pegylated interferon alfa-2a(pegIFN2a), 80 µg solution, subcutaneously weekly + ribavirin (RBV), weight based dosing (<75 kg = 1000 mg once daily; ≥75 kg = 1200 mg once daily) for 24 weeks.

Reporting group title	DCV + pegIFN-2a+ RBV
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Reporting group description:

Subjects received DCV, 60 mg tablet, by mouth once daily + pegIFN2a, 80 µg solution, subcutaneously weekly + RBV, weight based dosing (<75 kg = 1000 mg once daily; ≥75 kg = 1200 mg once daily) for 24 weeks.

Serious adverse events	Daclatasvir + Asunaprevir	DCV + ASV + pegIFN-2a+ Ribavirin	DCV + pegIFN-2a+ RBV
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 99 (4.04%)	3 / 122 (2.46%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 99 (1.01%)	0 / 122 (0.00%)	0 / 6 (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
Breast cancer			

subjects affected / exposed	1 / 99 (1.01%)	0 / 122 (0.00%)	0 / 6 (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
Neuroendocrine carcinoma of the skin			
subjects affected / exposed	1 / 99 (1.01%)	0 / 122 (0.00%)	0 / 6 (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
Uterine leiomyoma			
subjects affected / exposed	1 / 99 (1.01%)	0 / 122 (0.00%)	0 / 6 (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
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 99 (0.00%)	1 / 122 (0.82%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Radiculopathy			
subjects affected / exposed	0 / 99 (0.00%)	1 / 122 (0.82%)	0 / 6 (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			
Pneumonitis			
subjects affected / exposed	0 / 99 (0.00%)	1 / 122 (0.82%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 99 (1.01%)	0 / 122 (0.00%)	0 / 6 (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
Infections and infestations			
Staphylococcal bacteraemia			

subjects affected / exposed	0 / 99 (0.00%)	1 / 122 (0.82%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Daclatasvir + Asunaprevir	DCV + ASV + pegIFN-2a+ Ribavirin	DCV + pegIFN-2a+ RBV
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 99 (58.59%)	118 / 122 (96.72%)	6 / 6 (100.00%)
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 99 (2.02%)	15 / 122 (12.30%)	0 / 6 (0.00%)
occurrences (all)	2	15	0
Chills			
subjects affected / exposed	1 / 99 (1.01%)	10 / 122 (8.20%)	2 / 6 (33.33%)
occurrences (all)	1	11	2
Fatigue			
subjects affected / exposed	15 / 99 (15.15%)	65 / 122 (53.28%)	3 / 6 (50.00%)
occurrences (all)	15	65	3
Influenza like illness			
subjects affected / exposed	5 / 99 (5.05%)	45 / 122 (36.89%)	3 / 6 (50.00%)
occurrences (all)	6	47	3
Pyrexia			
subjects affected / exposed	4 / 99 (4.04%)	17 / 122 (13.93%)	2 / 6 (33.33%)
occurrences (all)	4	18	3
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	0 / 99 (0.00%)	0 / 122 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Vaginal haemorrhage			
subjects affected / exposed	0 / 99 (0.00%)	0 / 122 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	5 / 99 (5.05%) 7	14 / 122 (11.48%) 15	2 / 6 (33.33%) 2
Dyspnoea subjects affected / exposed occurrences (all)	0 / 99 (0.00%) 0	12 / 122 (9.84%) 12	2 / 6 (33.33%) 2
Nasal dryness subjects affected / exposed occurrences (all)	0 / 99 (0.00%) 0	1 / 122 (0.82%) 1	1 / 6 (16.67%) 1
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	0 / 99 (0.00%) 0	6 / 122 (4.92%) 6	1 / 6 (16.67%) 1
Insomnia subjects affected / exposed occurrences (all)	3 / 99 (3.03%) 3	25 / 122 (20.49%) 27	2 / 6 (33.33%) 2
Irritability subjects affected / exposed occurrences (all)	1 / 99 (1.01%) 1	11 / 122 (9.02%) 11	1 / 6 (16.67%) 1
Investigations Transaminases increased subjects affected / exposed occurrences (all)	1 / 99 (1.01%) 1	1 / 122 (0.82%) 1	1 / 6 (16.67%) 1
Weight decreased subjects affected / exposed occurrences (all)	1 / 99 (1.01%) 1	4 / 122 (3.28%) 4	1 / 6 (16.67%) 1
Cardiac disorders Angina pectoris subjects affected / exposed occurrences (all)	0 / 99 (0.00%) 0	0 / 122 (0.00%) 0	1 / 6 (16.67%) 1
Nervous system disorders Amnesia subjects affected / exposed occurrences (all)	0 / 99 (0.00%) 0	1 / 122 (0.82%) 1	1 / 6 (16.67%) 1
Dysgeusia subjects affected / exposed occurrences (all)	0 / 99 (0.00%) 0	8 / 122 (6.56%) 8	1 / 6 (16.67%) 1

Headache subjects affected / exposed occurrences (all)	17 / 99 (17.17%) 23	43 / 122 (35.25%) 50	3 / 6 (50.00%) 3
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	1 / 99 (1.01%) 1	23 / 122 (18.85%) 24	0 / 6 (0.00%) 0
Lymphopenia subjects affected / exposed occurrences (all)	0 / 99 (0.00%) 0	5 / 122 (4.10%) 5	1 / 6 (16.67%) 1
Neutropenia subjects affected / exposed occurrences (all)	1 / 99 (1.01%) 1	30 / 122 (24.59%) 36	0 / 6 (0.00%) 0
Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 99 (0.00%) 0	9 / 122 (7.38%) 9	1 / 6 (16.67%) 1
Eye disorders			
Dry eye subjects affected / exposed occurrences (all)	0 / 99 (0.00%) 0	3 / 122 (2.46%) 3	1 / 6 (16.67%) 1
Ocular icterus subjects affected / exposed occurrences (all)	0 / 99 (0.00%) 0	0 / 122 (0.00%) 0	1 / 6 (16.67%) 1
Visual acuity reduced subjects affected / exposed occurrences (all)	0 / 99 (0.00%) 0	1 / 122 (0.82%) 1	1 / 6 (16.67%) 1
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	5 / 99 (5.05%) 5	9 / 122 (7.38%) 9	2 / 6 (33.33%) 2
Abdominal pain upper subjects affected / exposed occurrences (all)	6 / 99 (6.06%) 7	8 / 122 (6.56%) 8	0 / 6 (0.00%) 0
Constipation subjects affected / exposed occurrences (all)	5 / 99 (5.05%) 5	4 / 122 (3.28%) 4	0 / 6 (0.00%) 0
Diarrhoea			

subjects affected / exposed	9 / 99 (9.09%)	33 / 122 (27.05%)	0 / 6 (0.00%)
occurrences (all)	12	37	0
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 99 (2.02%)	2 / 122 (1.64%)	1 / 6 (16.67%)
occurrences (all)	2	2	1
Nausea			
subjects affected / exposed	14 / 99 (14.14%)	31 / 122 (25.41%)	1 / 6 (16.67%)
occurrences (all)	15	32	1
Vomiting			
subjects affected / exposed	5 / 99 (5.05%)	5 / 122 (4.10%)	1 / 6 (16.67%)
occurrences (all)	6	6	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 99 (3.03%)	13 / 122 (10.66%)	2 / 6 (33.33%)
occurrences (all)	3	13	2
Dry skin			
subjects affected / exposed	2 / 99 (2.02%)	22 / 122 (18.03%)	2 / 6 (33.33%)
occurrences (all)	2	22	2
Erythema			
subjects affected / exposed	1 / 99 (1.01%)	3 / 122 (2.46%)	1 / 6 (16.67%)
occurrences (all)	1	3	1
Petechiae			
subjects affected / exposed	0 / 99 (0.00%)	0 / 122 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	5 / 99 (5.05%)	23 / 122 (18.85%)	3 / 6 (50.00%)
occurrences (all)	5	24	3
Rash generalised			
subjects affected / exposed	0 / 99 (0.00%)	10 / 122 (8.20%)	0 / 6 (0.00%)
occurrences (all)	0	10	0
Rash			
subjects affected / exposed	3 / 99 (3.03%)	15 / 122 (12.30%)	0 / 6 (0.00%)
occurrences (all)	3	15	0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	6 / 99 (6.06%)	16 / 122 (13.11%)	2 / 6 (33.33%)
occurrences (all)	6	17	2
Back pain			
subjects affected / exposed	4 / 99 (4.04%)	7 / 122 (5.74%)	0 / 6 (0.00%)
occurrences (all)	4	10	0
Limb discomfort			
subjects affected / exposed	0 / 99 (0.00%)	0 / 122 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	0 / 99 (0.00%)	8 / 122 (6.56%)	0 / 6 (0.00%)
occurrences (all)	0	8	0
Myalgia			
subjects affected / exposed	5 / 99 (5.05%)	14 / 122 (11.48%)	2 / 6 (33.33%)
occurrences (all)	5	14	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 99 (7.07%)	3 / 122 (2.46%)	0 / 6 (0.00%)
occurrences (all)	7	3	0
Viral rhinitis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 122 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	9 / 99 (9.09%)	0 / 122 (0.00%)	0 / 6 (0.00%)
occurrences (all)	9	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 99 (1.01%)	20 / 122 (16.39%)	2 / 6 (33.33%)
occurrences (all)	1	20	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 January 2012	The 48-week post-treatment follow-up period was reduced to 24-weeks, revised treatment population, primary endpoint to additionally specify that they include subjects that are prior non-responders to pegIFNalpha-2a/RBV, revised the on treatment futility rules from the Week 4 and Week 12 criteria to a Week 8 Futility only that includes any detectable Hepatitis C virus (HCV) RNA ($\geq$ lower limit of quantification) results after Week 8 (with no confirmation HCV RNA value required), revised the futility rule definitions, revised the definition of a relapse, revised the wording regarding the timing of the 1st interim analysis, reduced the safety endpoint measurements from the last dose of study drug therapy from 30-days to 7-days for treated subjects and wording modifications designed to clarify or correct inconsistencies in the protocol procedures.
20 March 2012	Removed Week 8 treatment futility rule of genotype-(GT)-2 and GT-3 subjects, updated futility rule to Week 8 for GT-1 and GT-4 subjects and added that confirmation of HCV RNA is required within 2 weeks of Week 8 result, updated definition of virologic breakthrough, updated study design to allow rollover of treatment naive GT-1b subjects assigned to the placebo arm in AI447028 who were treated with the combination of asunaprevir and daclatasvir therapy, these subjects met pre-defined rescue therapy criteria and could have been treated with daclatasvir/asunaprevir/pegIFNalpha/RBV therapy (daclatasvir and asunaprevir plus pegIFNalpha-2a/RBV) for 24 weeks at the discretion of the investigator, added new formulation of 60 mg tablets daclatasvir and 100 mg capsules of asunaprevir, updated reasons for discontinuation from treatment, updated rules for dose modifications and interruptions, revised timing of primary objective to SVR12, revised sample size of HCV GT-1 or -4 subjects who were prior non-responders to pegIFNalpha-2a/RBV, added sample size for HCV GT-1b treatment-naive subjects, updated interim and final analysis based on SVR12 rate instead of SVR24.
25 May 2012	Added new safety information as well as guidance regarding the management of subjects exposed to combination therapy with asunaprevir and daclatasvir who present with unexplained pyrexia.
20 November 2012	Clarified that women of child bearing potential (WOCBP) and men who were sexually active with WOCBP who rolled over from Study AI447028 and took daclatasvir/asunaprevir therapy were to use 1 method of contraception throughout the study and for a minimum of 12 weeks after discontinuation of ASV and DCV. Oral contraceptive pills were allowed but were not considered an effective form of contraception.
13 June 2013	Revised guidance for contraception for WOCBP and male subjects sexually active with WOCBP and added the option to treat subjects receiving rescue therapy for either 24 or 48 weeks.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported