



Clinical trial results:

A Phase 3 Evaluation of a daclatasvir/asunaprevir/BMS-791325 Fixed Dose Combination in Non-cirrhotic Subjects with Genotype 1 Chronic Hepatitis C

Summary

EudraCT number	2013-002468-20
Trial protocol	FR
Global end of trial date	18 November 2014

Results information

Result version number	v1 (current)
This version publication date	28 April 2016
First version publication date	28 April 2016

Trial information

Trial identification

Sponsor protocol code	AI443-102
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01979939
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	18 November 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	18 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the proportion of treatment-naïve noncirrhotic subjects who achieved sustained virologic response at follow-up week 12, defined as hepatitis C virus RNA below lower limit of quantitation, target detected or target not detected at follow-up week 12, was significantly greater than the historical threshold of 79%.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 December 2013
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	Australia: 64
Country: Number of subjects enrolled	Canada: 68
Country: Number of subjects enrolled	France: 41
Country: Number of subjects enrolled	United States: 291
Country: Number of subjects enrolled	Puerto Rico: 8
Worldwide total number of subjects	472
EEA total number of subjects	41

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	438
From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 66 sites in the United States, Puerto Rico, Canada, France and Australia.

Pre-assignment

Screening details:

A total of 472 subjects were enrolled and 415 were treated. Remaining 57 subjects did not receive any treatment.

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	Treatment-naive

Arm description:

Previously untreated subjects received an oral fixed dose combination of daclatasvir 30 mg, asunaprevir 200 mg and beclabuvir 75 mg tablets twice daily with food for 12 weeks and followed-up for 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 30 mg was administered orally twice daily with food for 12 weeks by treatment naive subjects.

Investigational medicinal product name	Asunaprevir
Investigational medicinal product code	BMS-650032
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Asunaprevir 200 mg was administered orally twice daily with food for 12 weeks by treatment naive subjects.

Investigational medicinal product name	Beclabuvir
Investigational medicinal product code	BMS-791325
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Beclabuvir 75 mg was administered orally twice daily with food for 12 weeks by treatment naive subjects.

Arm title	Treatment-experienced
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Arm description:

Subjects previously treated with an interferon-containing regimen received an oral fixed dose combination of daclatasvir 30 mg, asunaprevir 200 mg and beclabuvir 75 mg tablets twice daily with food for 12 weeks and followed-up for 24 weeks.

Arm type	Experimental
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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 30 mg was administered orally twice daily with food for 12 weeks by treatment naive subjects.

Investigational medicinal product name	Asunaprevir
Investigational medicinal product code	BMS-650032
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Asunaprevir 200 mg was administered orally twice daily with food for 12 weeks by treatment naive subjects.

Investigational medicinal product name	Beclabuvir
Investigational medicinal product code	BMS-791325
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Beclabuvir 75 mg was administered orally twice daily with food for 12 weeks by treatment naive subjects.

Number of subjects in period 1^[1]	Treatment-naive	Treatment-experienced
Started	312	103
Completed	305	99
Not completed	7	4
Adverse event, non-fatal	-	3
Pregnancy	1	-
Lack of efficacy	6	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: Of the 472 subjects enrolled, 415 subjects were treated with at least 1 dose of study therapy.

Period 2

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

Arms

Are arms mutually exclusive?	Yes
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Arm title	Treatment-naive
Arm description: Previously untreated subjects received an oral fixed dose combination of daclatasvir 30 mg, asunaprevir 200 mg and beclabuvir 75 mg tablets twice daily with food for 12 weeks and followed-up for 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 30 mg was administered orally twice daily with food for 12 weeks by treatment naive subjects.	
Investigational medicinal product name	Asunaprevir
Investigational medicinal product code	BMS-650032
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details: Asunaprevir 200 mg was administered orally twice daily with food for 12 weeks by treatment naive subjects.	
Investigational medicinal product name	Beclabuvir
Investigational medicinal product code	BMS-791325
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details: Beclabuvir 75 mg was administered orally twice daily with food for 12 weeks by treatment naive subjects.	
Arm title	Treatment-experienced
Arm description: Subjects previously treated with an interferon-containing regimen received an oral fixed dose combination of daclatasvir 30 mg, asunaprevir 200 mg and beclabuvir 75 mg tablets twice daily with food for 12 weeks and followed-up for 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 30 mg was administered orally twice daily with food for 12 weeks by treatment naive subjects.	
Investigational medicinal product name	Asunaprevir
Investigational medicinal product code	BMS-650032
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details: Asunaprevir 200 mg was administered orally twice daily with food for 12 weeks by treatment naive subjects.	
Investigational medicinal product name	Beclabuvir
Investigational medicinal product code	BMS-791325
Other name	

Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Beclabuvir 75 mg was administered orally twice daily with food for 12 weeks by treatment naive subjects.

Number of subjects in period 2	Treatment-naive	Treatment-experienced
Started	305	99
Completed	308	98
Not completed	4	5
Consent withdrawn by subject	1	2
Death	-	1
Follow up no longer required per protocol	1	1
Lost to follow-up	2	1
Joined	7	4
Rejoined for follow-up	7	4

Baseline characteristics

Reporting groups

Reporting group title	Treatment-naive
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Reporting group description:

Previously untreated subjects received an oral fixed dose combination of daclatasvir 30 mg, asunaprevir 200 mg and beclabuvir 75 mg tablets twice daily with food for 12 weeks and followed-up for 24 weeks.

Reporting group title	Treatment-experienced
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Reporting group description:

Subjects previously treated with an interferon-containing regimen received an oral fixed dose combination of daclatasvir 30 mg, asunaprevir 200 mg and beclabuvir 75 mg tablets twice daily with food for 12 weeks and followed-up for 24 weeks.

Reporting group values	Treatment-naive	Treatment-experienced	Total
Number of subjects	312	103	415
Age categorical			
Units: Subjects			
< 65 years	293	97	390
>= 65 years	19	6	25
Age continuous			
Units: years			
arithmetic mean	50.8	55.1	
standard deviation	± 11.57	± 8.09	-
Gender categorical			
Units: Subjects			
Female	137	39	176
Male	175	64	239

End points

End points reporting groups

Reporting group title	Treatment-naïve
Reporting group description: Previously untreated subjects received an oral fixed dose combination of daclatasvir 30 mg, asunaprevir 200 mg and beclabuvir 75 mg tablets twice daily with food for 12 weeks and followed-up for 24 weeks.	
Reporting group title	Treatment-experienced
Reporting group description: Subjects previously treated with an interferon-containing regimen received an oral fixed dose combination of daclatasvir 30 mg, asunaprevir 200 mg and beclabuvir 75 mg tablets twice daily with food for 12 weeks and followed-up for 24 weeks.	
Reporting group title	Treatment-naïve
Reporting group description: Previously untreated subjects received an oral fixed dose combination of daclatasvir 30 mg, asunaprevir 200 mg and beclabuvir 75 mg tablets twice daily with food for 12 weeks and followed-up for 24 weeks.	
Reporting group title	Treatment-experienced
Reporting group description: Subjects previously treated with an interferon-containing regimen received an oral fixed dose combination of daclatasvir 30 mg, asunaprevir 200 mg and beclabuvir 75 mg tablets twice daily with food for 12 weeks and followed-up for 24 weeks.	

Primary: Percentage of Treated Subjects in the Treatment-naïve Cohort With Sustained Virologic Response at Follow-up Week 12 (SVR12)

End point title	Percentage of Treated Subjects in the Treatment-naïve Cohort With Sustained Virologic Response at Follow-up Week 12 (SVR12) ^{[1][2]}
End point description: SVR12 was defined as hepatitis C virus (HCV) RNA levels <lower limit of quantitation (LLOQ), target detected or target not detected at follow-up week 12. The LLOQ was 25 international unit per milliliter. 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, the numerator was based on subjects meeting the response criteria and denominator based on all treated subjects. Missing values were imputed using Next Value Carried Backwards approach, i.e., missing HCV RNA in the follow-up Week 12 window was imputed using the next and closest available HCV RNA measurement after the follow-up Week 12 HCV RNA 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 analysis was planned for this primary endpoint.

[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	Treatment-naïve			
Subject group type	Reporting group			
Number of subjects analysed	312			
Units: Percentage of subjects				
number (confidence interval 95%)	92.3 (89.4 to 95.3)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Subjects in the Experienced Cohort With Sustained Virologic Response at Follow-up Week 12 (SVR12) ^[3]
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End point description:

SVR12 was defined as hepatitis C virus (HCV) RNA levels <lower limit of quantitation (LLOQ), target detected or target not detected at follow-up week 12. The LLOQ was 25 international unit per milliliter, 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, the numerator was based on subjects meeting the response criteria and denominator based on all treated subjects. Missing values were imputed using Next Value Carried Backwards approach, i.e., missing HCV RNA in the follow-up Week 12 window was imputed using the next and closest available HCV RNA measurement after the follow-up Week 12 HCV RNA window.

End point type	Secondary
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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	Treatment-experienced			
Subject group type	Reporting group			
Number of subjects analysed	103			
Units: Percentage of subjects				
number (confidence interval 95%)	89.3 (83.4 to 95.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Hepatitis C Virus (HCV) RNA Levels Below Than Lower Limit of Quantitation (LLOQ) Target Detected (TD) or Target Not Detected (TND)

End point title	Percentage of Subjects With Hepatitis C Virus (HCV) RNA Levels Below Than Lower Limit of Quantitation (LLOQ) Target Detected (TD) or Target Not Detected (TND)
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End point description:

Subjects who achieved HCV RNA levels <LLOQ, TD or TND. The LLOQ was 25 international unit per milliliter. HCV RNA levels were measured by the Roche COBAS® TaqMan® HCV Test version 2.0 from the central laboratory. The analysis was performed in modified intent-to-treat population, the numerator was based on subjects meeting the response criteria and denominator based on all treated subjects.

End point type	Secondary
End point timeframe:	
Week 1, 2, 4, 6, 8, 12; follow-up Week 4, 8 and 24.	

End point values	Treatment-naïve	Treatment-experienced		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	312	103		
Units: Percentage of Subjects				
number (not applicable)				
Week 1	34.9	28.2		
Week 2	78.2	74.8		
Week 4	97.4	97.1		
Week 6	97.4	97.1		
Week 8	97.1	96.1		
Week 12	96.2	95.1		
Follow-up week 4	93.6	89.3		
Follow-up week 8	91	88.3		
Follow-up week 24	90.7	88.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects in With Hepatitis C Virus (HCV) RNA Levels Below Than Lower Limit of Quantitation (LLOQ) Target Not Detected (TND)

End point title	Percentage of Subjects in With Hepatitis C Virus (HCV) RNA Levels Below Than Lower Limit of Quantitation (LLOQ) Target Not Detected (TND)
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End point description:

Subjects who achieved HCV RNA levels <LLOQ, TND. The LLOQ was 25 international unit per milliliter, TND. HCV RNA levels were measured by the Roche COBAS® TaqMan® HCV Test version 2.0 from the central laboratory. The analysis was performed in modified intent-to-treat population, the numerator was based on subjects meeting the response criteria and denominator based on all treated subjects.

End point type	Secondary
End point timeframe:	
Week 1, 2, 4, 6, 8, 12; follow-up Week 4, 8, 12 and 24.	

End point values	Treatment-naïve	Treatment-experienced		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	312	103		
Units: Percentage of Subjects				
number (not applicable)				
Week 1	6.1	0		
Week 2	32.4	20.4		

Week 4	79.5	68.9		
Week 6	92	94.2		
Week 8	93.6	93.2		
Week 12	95.5	93.2		
Follow-up week 4	92.9	89.3		
Follow-up week 8	91	88.3		
Follow-up week 12	92	89.3		
Follow-up week 24	90.7	88.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With On-treatment Serious Adverse Events (SAEs) and Discontinuations due to Adverse Events (AEs) in Each Cohort

End point title	Number of Subjects With On-treatment Serious Adverse Events (SAEs) and Discontinuations due to Adverse Events (AEs) in Each Cohort
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End point description:

An AE was defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject or clinical investigation subject administered an investigational (medicinal) product. An SAE was defined as any untoward medical occurrence that at any dose resulted in death, was life-threatening, required inpatient hospitalization or caused prolongation of existing hospitalization. The analysis was performed on all subjects who received at least 1 dose of study therapy.

End point type	Secondary
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End point timeframe:

Baseline through the last dose of study therapy plus 7 days

End point values	Treatment-naïve	Treatment-experienced		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	312	103		
Units: Subjects				
SAEs	4	3		
Discontinuation due to AEs	0	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Anaemia on Treatment

End point title	Percentage of Subjects With Anaemia on Treatment
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End point description:

Anaemia was defined as hemoglobin level less than 10 gram per deciliter (g/dL) on treatment for subjects who had hemoglobin level equal to or above 10 g/dL at baseline. The analysis was performed on all subjects who received at least 1 dose of study therapy.

End point type	Secondary
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End point timeframe:

Baseline through the last dose of study therapy plus 7 days

End point values	Treatment-naïve	Treatment-experienced		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	312	103		
Units: Percentage of Subjects				
number (not applicable)	0.3	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Selected Treatment Emergent Grade 3 to 4 Laboratory Test Abnormalities

End point title	Number of Subjects With Selected Treatment Emergent Grade 3 to 4 Laboratory Test Abnormalities
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End point description:

Laboratory tests with Division of AIDS Version 1.0 toxicity criteria were performed and assessed. Assessment were done for following: Hemoglobin, Platelet count, International Normalized Ratio, Leukocytes, Lymphocytes, Neutrophils + bands, Total bilirubin, Alanine aminotransferase, Aspartate aminotransferase, Alkaline phosphatase, Albumin, Lipase Creatinine. Laboratory tests for which subjects had treatment emergent grade 3 to 4 abnormalities are reported below. The analysis was performed on all subjects who received at least 1 dose of study therapy.

End point type	Secondary
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End point timeframe:

Baseline through the last dose of study therapy plus 7 days

End point values	Treatment-naïve	Treatment-experienced		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	312	103		
Units: Subjects				
International Normalized Ratio	1	0		
Lymphocytes	0	1		
Neutrophils + bands	1	1		
Alanine aminotransferase	11	8		
Aspartate aminotransferase	4	5		
Lipase	11	5		

Statistical analyses

Secondary: Percentage of Subjects With Sustained Virologic Response at Follow-up Week 12 (SVR12) Associated With Hepatitis C Virus (HCV) Genotype Subtype 1a vs 1b

End point title	Percentage of Subjects With Sustained Virologic Response at Follow-up Week 12 (SVR12) Associated With Hepatitis C Virus (HCV) Genotype Subtype 1a vs 1b
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End point description:

Subjects categorized into two genotype subtypes that were assessed for SVR12 defined as HCV RNA levels <lower limit of quantitation (LLOQ), target detected or target not detected at follow-up week 12. The LLOQ was 25 international unit per milliliter. HCV RNA levels were measured by the Roche COBAS® TaqMan® HCV Test version 2.0 from the central laboratory. The analysis was performed on treated subjects, the numerator was based on subjects meeting the response criteria and denominator based on all treated subjects. Here, 'n' signifies number of subjects evaluable at the specified subgroup. Missing values were imputed using Next Value Carried Backwards approach.

End point type	Secondary
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End point timeframe:

Follow-up week 12

End point values	Treatment-naïve	Treatment-experienced		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	312	103		
Units: Percentage of Subjects				
number (confidence interval 95%)				
Genotype-1A (n= 229, 75)	90.4 (86.6 to 94.2)	85.3 (77.3 to 93.3)		
Genotype-1B (n= 83, 28)	97.6 (91.6 to 99.7)	100 (87.7 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With SVR12 Associated With IL28B rs12979860 Single Nucleotide Polymorphism (SNP) status (CC Genotype or Non-CC Genotype)

End point title	Percentage of Subjects With SVR12 Associated With IL28B rs12979860 Single Nucleotide Polymorphism (SNP) status (CC Genotype or Non-CC Genotype)
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End point description:

Subjects categorized into two genotypes based on SNP in the IL28B gene were assessed for SVR12 defined as hepatitis c virus RNA levels <lower limit of quantitation, target detected or target not detected at follow-up week 12. The LLOQ was 25 international unit per milliliter. Here '99999' signifies not available as data for the specified time point for this endpoint was not analyzed. The analysis was performed on treated subjects, the numerator was based on subjects meeting the response criteria and denominator based on all treated subjects. Missing values were imputed using Next Value Carried Backwards approach. Here, 'n' signifies number of subjects evaluable for the specified category and '99999' signifies not applicable (NA) as no subject was analysed for that specified category.

End point type	Secondary
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End point timeframe:

Follow-up week 12

End point values	Treatment-naïve	Treatment-experienced		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	312	103		
Units: Percentage of Subjects				
number (confidence interval 95%)				
CC Genotype (n= 90, 16)	94.4 (89.7 to 99.2)	93.8 (69.8 to 99.8)		
Non-CC Genotype (n=221, 87)	91.4 (87.7 to 95.1)	88.5 (81.8 to 95.2)		
Not Reported (n=1, 0)	100 (2.5 to 100)	99999 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Subjects With Sustained Virologic Response at Follow-up Week 12 (SVR12) Associated With Stage of Liver Fibrosis
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End point description:

Liver Fibrosis was determined by the Fibro test. This test was helpful in determining the presence of cirrhosis by the fibro test scores which are as follows: F0: 0-0.27; F1: >0.27-0.48; F2: 0.48-0.58; F3: >0.58-0.74; F4: >0.74-1.00. Subjects were assessed for SVR12 defined as hepatitis c virus RNA levels <lower limit of quantitation, target detected or target not detected at follow-up week 12. The LLOQ was 25 international unit per milliliter. The analysis was performed on treated subjects, the numerator was based on subjects meeting the response criteria and denominator based on all treated subjects. Missing values were imputed using Next Value Carried Backwards approach. Here, 'n' signifies number of subjects evaluable for the specified category.

End point type	Secondary
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End point timeframe:

Follow-up week 12

End point values	Treatment-naïve	Treatment-experienced		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	312	103		
Units: Percentage of Subjects				
number (confidence interval 95%)				
Fibrosis stage: F0 (n=150, 37)	90.7 (86 to 95.3)	94.6 (87.3 to 100)		
Fibrosis stage: F1 (n=73, 26)	94.5 (89.3 to 99.7)	100 (86.8 to 100)		
Fibrosis stage: F2 (n=31, 12)	100 (88.8 to 100)	66.7 (34.9 to 90.1)		

Fibrosis stage: F3 (n=41, 20)	90.2 (81.2 to 99.3)	80 (56.3 to 94.3)		
Fibrosis stage: F4 (n=17, 8)	88.2 (63.6 to 98.5)	87.5 (47.3 to 99.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline through the last dose of study therapy plus 7 days

Adverse event reporting additional description:

On-treatment period

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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Reporting groups

Reporting group title	Treatment-experienced
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Reporting group description:

Subjects previously treated with an interferon-containing regimen received an oral fixed dose combination of daclatasvir 30 mg, asunaprevir 200 mg and beclabuvir 75 mg tablets twice daily with food for 12 weeks and followed-up for 24 weeks.

Reporting group title	Treatment-naive
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Reporting group description:

Previously untreated subjects received an oral fixed dose combination of daclatasvir 30 mg, asunaprevir 200 mg and beclabuvir 75 mg tablets twice daily with food for 12 weeks and followed-up for 24 weeks.

Serious adverse events	Treatment-experienced	Treatment-naive	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 103 (2.91%)	4 / 312 (1.28%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 103 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	0 / 103 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Enterovesical fistula			

subjects affected / exposed	1 / 103 (0.97%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic pseudocyst			
subjects affected / exposed	0 / 103 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 103 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 103 (0.97%)	0 / 312 (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	0 / 103 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 103 (0.00%)	1 / 312 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	1 / 103 (0.97%)	0 / 312 (0.00%)	
occurrences causally related to treatment / all	0 / 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	Treatment-experienced	Treatment-naive	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	83 / 103 (80.58%)	246 / 312 (78.85%)	
Nervous system disorders			
Headache			
subjects affected / exposed	29 / 103 (28.16%)	77 / 312 (24.68%)	
occurrences (all)	36	89	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	14 / 103 (13.59%)	54 / 312 (17.31%)	
occurrences (all)	14	57	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	14 / 103 (13.59%)	44 / 312 (14.10%)	
occurrences (all)	14	50	
Nausea			
subjects affected / exposed	15 / 103 (14.56%)	41 / 312 (13.14%)	
occurrences (all)	17	44	
Abdominal pain			
subjects affected / exposed	1 / 103 (0.97%)	18 / 312 (5.77%)	
occurrences (all)	1	18	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	7 / 103 (6.80%)	26 / 312 (8.33%)	
occurrences (all)	7	26	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 103 (2.91%)	20 / 312 (6.41%)	
occurrences (all)	3	21	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 103 (8.74%)	15 / 312 (4.81%)	
occurrences (all)	9	15	
Upper respiratory tract infection			
subjects affected / exposed	8 / 103 (7.77%)	10 / 312 (3.21%)	
occurrences (all)	8	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 April 2014	An interim analysis was added after all subjects complete post-treatment Week 4. This interim database lock was to support pharmacokinetic modeling and simulations for exposure-response analysis.
24 July 2014	Historical threshold of sustained virologic response for treatment of chronic hepatitis c virus infection was updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported