# 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 |

### 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-naive 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 |

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 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 |

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

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Treatment-naive |
| 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-naive |
| 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-naive Cohort With Sustained Virologic Response at Follow-up Week 12 (SVR12)

| | |
|---|---|
| End point title | Percentage of Treated Subjects in the Treatment-naive 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-naive | | | |
|---|---|---|---|---|
| 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] |
|---|---|

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 |
|---|---|

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) |
|---|---|

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-naive | 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) |
|---|---|

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-naive | 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 |
|---|---|

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 |
|---|---|

End point timeframe:

Baseline through the last dose of study therapy plus 7 days

| End point values | Treatment-naive | 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 |
|---|---|

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 |
|---|---|

End point timeframe:

Baseline through the last dose of study therapy plus 7 days

| End point values | Treatment-naive | 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 |
|---|---|

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 |
|---|---|

End point timeframe:

Baseline through the last dose of study therapy plus 7 days

| End point values | Treatment-naive | 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

No statistical analyses for this end point

## 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 |
|---|---|

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 |
|---|---|

End point timeframe:

Follow-up week 12

| End point values | Treatment-naive | 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) |
|---|---|

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 |
|---|---|

End point timeframe:

Follow-up week 12

| End point values | Treatment-naive | 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 |
|---|---|

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 |
|---|---|

End point timeframe:

Follow-up week 12

| End point values | Treatment-naive | 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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 17.0 |

### Reporting groups

| | |
|---|---|
| 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-naive |

Reporting group description:

Previously untreated subjects received an oral fixed dose 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