



## Clinical trial results:

### Open-Label, Randomized Study of Daclatasvir, Sofosbuvir, and Ribavirin for 12 vs. 16 weeks in Treatment-Naïve and Treatment-Experienced Patients with Genotype 3 Chronic Hepatitis C Infection with Compensated Advanced Fibrosis/Cirrhosis (F3/F4)

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2014-005310-28   |
| Trial protocol           | FR               |
| Global end of trial date | 18 December 2015 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 22 December 2016 |
| First version publication date | 22 December 2016 |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | AI444-326 |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02319031 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Bristol-Myers Squibb   |
| Sponsor organisation address | Chaussée de la Hulpe 185, Brussels, Belgium, 1170  |
| Public contact               | Bristol-Myers Squibb Study Director, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com |
| Scientific contact           | Bristol-Myers Squibb Study Director, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com |

Notes:

#### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 18 December 2015 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 18 December 2015 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study is to determine if the use of Daclatasvir, Sofosbuvir, and Ribavirin in combination for 12 or 16 weeks is safe and effective in the treatment of Genotype 3 Chronic Hepatitis C (HCV) in patients with HCV Genotype 3 infection and advanced fibrosis or compensated cirrhosis. Patients in this study may have already been treated prior for HCV or may have never received treatment for their HCV.

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 February 2015 |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety, 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 | France: 22    |
| Country: Number of subjects enrolled | Australia: 31 |
| Worldwide total number of subjects   | 53            |
| EEA total number of subjects         | 22            |

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) | 52 |
| From 65 to 84 years  | 1  |
| 85 years and over    | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 10 sites in 2 countries.

### Pre-assignment

Screening details:

A total of 53 subjects were enrolled and 50 were randomized and treated (24 to the 12 week arm, 26 to the 16 week arm). Reasons for non-randomized were 3 subjects no longer met study criteria.

### 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   |
| <b>Arm title</b>             | Daclatasvir + Sofosbuvir + Ribavirin (12 Weeks) |

Arm description:

Treatment-naïve and treatment-experienced participants with HCV Genotype 3 infection and advanced fibrosis or compensated cirrhosis (F3 or F4) were treated for 12 weeks with oral dosing of Daclatasvir (DCV) 60 mg once daily (QD), Sofosbuvir (SOF) 400 mg QD, and Ribavirin (RBV) 1000-1200 mg (weight based dosing) split into AM and PM dosing. Participants received either 400 mg (2 tablets for participants < 75 kg) or 600 mg (3 tablets for participants ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food. After the completion of the 12 week treatment period, participants were followed off treatment for 24 weeks. mg=milligram; kg=kilogram

|  |                    |
|--|--------------------|
| 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 received Daclatasvir orally (60 mg) QD. Daclatasvir was administered as 1 tablet in the AM.

|  |            |
|--|------------|
| Investigational medicinal product name | Sofosbuvir |
| Investigational medicinal product code |            |
| Other name                             |            |
| Pharmaceutical forms                   | Tablet     |
| Routes of administration               | Oral use   |

Dosage and administration details:

Subjects received Sofosbuvir orally (400 mg) QD. Sofosbuvir was administered as 1 tablet in the AM.

|  |                    |
|--|--------------------|
| 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 received Ribavirin administered at a daily dose of 1,000 to 1,200 mg orally in 2 divided doses. Subjects received either 400 mg (2 tablets for subjects < 75 kg) or 600 mg (3 tablets for subjects ≥ 75 kg) of Ribavirin in the morning with food and 600 mg (3 tablets) of RBV in the evening with food.

|                  |   |
|------------------|---|
| <b>Arm title</b> | Daclatasvir + Sofosbuvir + Ribavirin (16 Weeks) |
|------------------|---|

Arm description:

Treatment-naïve and treatment-experienced participants with HCV Genotype 3 infection and advanced fibrosis or compensated cirrhosis (F3 or F4) were treated for 16 weeks with oral dosing of Daclatasvir (DCV) 60 mg once daily (QD), Sofosbuvir (SOF) 400 mg QD, and Ribavirin (RBV) 1000-1200 mg (weight based dosing) split into AM and PM dosing. Participants received either 400 mg (2 tablets for participants < 75 kg) or 600 mg (3 tablets for participants ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food. After the completion of the 16 week treatment period, participants were followed off treatment for 24 weeks. mg=milligram; kg=kilogram

|  |                    |
|--|--------------------|
| 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 received Daclatasvir orally (60 mg) QD. Daclatasvir was administered as 1 tablet in the AM.

|  |            |
|--|------------|
| Investigational medicinal product name | Sofosbuvir |
| Investigational medicinal product code |            |
| Other name                             |            |
| Pharmaceutical forms                   | Tablet     |
| Routes of administration               | Oral use   |

Dosage and administration details:

Subjects received Sofosbuvir orally (400 mg) QD. Sofosbuvir was administered as 1 tablet in the AM.

|  |                    |
|--|--------------------|
| 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 received Ribavirin administered at a daily dose of 1,000 to 1,200 mg orally in 2 divided doses. Subjects received either 400 mg (2 tablets for subjects < 75 kg) or 600 mg (3 tablets for subjects ≥ 75 kg) of Ribavirin in the morning with food and 600 mg (3 tablets) of RBV in the evening with food.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | <b>Daclatasvir + Sofosbuvir + Ribavirin (12 Weeks)</b> | <b>Daclatasvir + Sofosbuvir + Ribavirin (16 Weeks)</b> |
|---|--|--|
| Started   | 24   | 26   |
| Completed   | 23   | 26   |
| Not completed                                       | 1  | 0  |
| Death   | 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 to be in the baseline period are not the same as the worldwide number enrolled in the trial as out of 53 subjects who were enrolled, 50 subjects were treated in the study.

**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   |
| <b>Arm title</b>             | Daclatasvir + Sofosbuvir + Ribavirin (12 Weeks) |

## Arm description:

No treatment was received in the follow-up period. After the completion of the 12 week treatment period, participants were followed off treatment for 24 weeks. In the treatment period, treatment-naïve and treatment-experienced participants with HCV Genotype 3 infection and advanced fibrosis or compensated cirrhosis (F3 or F4) were treated for 12 weeks with oral dosing of Daclatasvir (DCV) 60 mg once daily (QD), Sofosbuvir (SOF) 400 mg QD, and Ribavirin (RBV) 1000-1200 mg (weight based dosing) split into AM and PM dosing. Participants received either 400 mg (2 tablets for participants < 75 kg) or 600 mg (3 tablets for participants ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food.

|  |                    |
|--|--------------------|
| 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:

No treatment was received in the follow-up, however, subjects received a 60 mg Daclatasvir tablet orally QD in the treatment period.

|  |            |
|--|------------|
| Investigational medicinal product name | Sofosbuvir |
| Investigational medicinal product code |            |
| Other name                             |            |
| Pharmaceutical forms                   | Tablet     |
| Routes of administration               | Oral use   |

## Dosage and administration details:

No treatment was received in the follow-up, however, subjects received a 400 mg Sofosbuvir tablet orally QD in the treatment period.

|  |                    |
|--|--------------------|
| 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:

No treatment was received in the follow-up, however, subjects received a daily dose of 1,000 to 1,200 mg Ribavirin orally in the treatment period, which was administered as either 400 mg (2 tablets for subjects < 75 kg) or 600 mg (3 tablets for subjects ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food.

|                  |   |
|------------------|---|
| <b>Arm title</b> | Daclatasvir + Sofosbuvir + Ribavirin (16 Weeks) |
|------------------|---|

## Arm description:

No treatment was received in the follow-up period. After the completion of the 16 week treatment period, participants were followed off treatment for 24 weeks. Treatment-naïve and treatment-experienced participants with HCV Genotype 3 infection and advanced fibrosis or compensated cirrhosis (F3 or F4) were treated for 16 weeks with oral dosing of Daclatasvir (DCV) 60 mg once daily (QD), Sofosbuvir (SOF) 400 mg QD, and Ribavirin (RBV) 1000-1200 mg (weight based dosing) split into AM and PM dosing. Participants received either 400 mg (2 tablets for participants < 75 kg) or 600 mg (3 tablets for participants ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food.

|          |              |
|----------|--------------|
| 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:

No treatment was received in the follow-up, however, subjects received a 60 mg Daclatasvir tablet orally QD in the treatment period.

|  |            |
|--|------------|
| Investigational medicinal product name | Sofosbuvir |
| Investigational medicinal product code |            |
| Other name                             |            |
| Pharmaceutical forms                   | Tablet     |
| Routes of administration               | Oral use   |

Dosage and administration details:

No treatment was received in the follow-up, however, subjects received a 400 mg Sofosbuvir tablet orally QD in the treatment period.

|  |                    |
|--|--------------------|
| 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:

No treatment was received in the follow-up, however, subjects received a daily dose of 1,000 to 1,200 mg Ribavirin orally in the treatment period, which was administered as either 400 mg (2 tablets for subjects < 75 kg) or 600 mg (3 tablets for subjects ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food.

| <b>Number of subjects in period 2</b> | <b>Daclatasvir +<br/>Sofosbuvir +<br/>Ribavirin (12<br/>Weeks)</b> | <b>Daclatasvir +<br/>Sofosbuvir +<br/>Ribavirin (16 Weeks)</b> |
|---------------------------------------|--|--|
| Started                               | 23   | 26   |
| Completed                             | 23   | 26   |

## Baseline characteristics

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | Daclatasvir + Sofosbuvir + Ribavirin (12 Weeks) |
|-----------------------|---|

#### Reporting group description:

Treatment-naïve and treatment-experienced participants with HCV Genotype 3 infection and advanced fibrosis or compensated cirrhosis (F3 or F4) were treated for 12 weeks with oral dosing of Daclatasvir (DCV) 60 mg once daily (QD), Sofosbuvir (SOF) 400 mg QD, and Ribavirin (RBV) 1000-1200 mg (weight based dosing) split into AM and PM dosing. Participants received either 400 mg (2 tablets for participants < 75 kg) or 600 mg (3 tablets for participants ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food. After the completion of the 12 week treatment period, participants were followed off treatment for 24 weeks. mg=milligram; kg=kilogram

|                       |   |
|-----------------------|---|
| Reporting group title | Daclatasvir + Sofosbuvir + Ribavirin (16 Weeks) |
|-----------------------|---|

#### Reporting group description:

Treatment-naïve and treatment-experienced participants with HCV Genotype 3 infection and advanced fibrosis or compensated cirrhosis (F3 or F4) were treated for 16 weeks with oral dosing of Daclatasvir (DCV) 60 mg once daily (QD), Sofosbuvir (SOF) 400 mg QD, and Ribavirin (RBV) 1000-1200 mg (weight based dosing) split into AM and PM dosing. Participants received either 400 mg (2 tablets for participants < 75 kg) or 600 mg (3 tablets for participants ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food. After the completion of the 16 week treatment period, participants were followed off treatment for 24 weeks. mg=milligram; kg=kilogram

| Reporting group values | Daclatasvir + Sofosbuvir + Ribavirin (12 Weeks) | Daclatasvir + Sofosbuvir + Ribavirin (16 Weeks) | Total |
|------------------------|---|---|-------|
| Number of subjects     | 24  | 26  | 50    |
| Age categorical        |   |   |       |
| Units: Subjects        |   |   |       |
| < 65 years             | 23  | 26  | 49    |
| ≥ 65 years             | 1   | 0   | 1     |
| Age continuous         |   |   |       |
| Units: years           |   |   |       |
| arithmetic mean        | 53  | 55  |       |
| standard deviation     | ± 7.77  | ± 5.75  | -     |
| Gender categorical     |   |   |       |
| Units: Subjects        |   |   |       |
| Female                 | 6   | 4   | 10    |
| Male                   | 18  | 22  | 40    |

## End points

### End points reporting groups

|  |   |
|--|---|
| Reporting group title  | Daclatasvir + Sofosbuvir + Ribavirin (12 Weeks) |
| Reporting group description:   |   |
| Treatment-naïve and treatment-experienced participants with HCV Genotype 3 infection and advanced fibrosis or compensated cirrhosis (F3 or F4) were treated for 12 weeks with oral dosing of Daclatasvir (DCV) 60 mg once daily (QD), Sofosbuvir (SOF) 400 mg QD, and Ribavirin (RBV) 1000-1200 mg (weight based dosing) split into AM and PM dosing. Participants received either 400 mg (2 tablets for participants < 75 kg) or 600 mg (3 tablets for participants ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food. After the completion of the 12 week treatment period, participants were followed off treatment for 24 weeks. mg=milligram; kg=kilogram   |   |
| Reporting group title  | Daclatasvir + Sofosbuvir + Ribavirin (16 Weeks) |
| Reporting group description:   |   |
| Treatment-naïve and treatment-experienced participants with HCV Genotype 3 infection and advanced fibrosis or compensated cirrhosis (F3 or F4) were treated for 16 weeks with oral dosing of Daclatasvir (DCV) 60 mg once daily (QD), Sofosbuvir (SOF) 400 mg QD, and Ribavirin (RBV) 1000-1200 mg (weight based dosing) split into AM and PM dosing. Participants received either 400 mg (2 tablets for participants < 75 kg) or 600 mg (3 tablets for participants ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food. After the completion of the 16 week treatment period, participants were followed off treatment for 24 weeks. mg=milligram; kg=kilogram   |   |
| Reporting group title  | Daclatasvir + Sofosbuvir + Ribavirin (12 Weeks) |
| Reporting group description:   |   |
| No treatment was received in the follow-up period. After the completion of the 12 week treatment period, participants were followed off treatment for 24 weeks. In the treatment period, treatment-naïve and treatment-experienced participants with HCV Genotype 3 infection and advanced fibrosis or compensated cirrhosis (F3 or F4) were treated for 12 weeks with oral dosing of Daclatasvir (DCV) 60 mg once daily (QD), Sofosbuvir (SOF) 400 mg QD, and Ribavirin (RBV) 1000-1200 mg (weight based dosing) split into AM and PM dosing. Participants received either 400 mg (2 tablets for participants < 75 kg) or 600 mg (3 tablets for participants ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food. |   |
| Reporting group title  | Daclatasvir + Sofosbuvir + Ribavirin (16 Weeks) |
| Reporting group description:   |   |
| No treatment was received in the follow-up period. After the completion of the 16 week treatment period, participants were followed off treatment for 24 weeks. Treatment-naïve and treatment-experienced participants with HCV Genotype 3 infection and advanced fibrosis or compensated cirrhosis (F3 or F4) were treated for 16 weeks with oral dosing of Daclatasvir (DCV) 60 mg once daily (QD), Sofosbuvir (SOF) 400 mg QD, and Ribavirin (RBV) 1000-1200 mg (weight based dosing) split into AM and PM dosing. Participants received either 400 mg (2 tablets for participants < 75 kg) or 600 mg (3 tablets for participants ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food.                          |   |

### Primary: Percent of Subjects With a Sustained Virologic Response (SVR) at Follow-up Week 12 (SVR12)

|  |   |
|--|---|
| End point title  | Percent of Subjects With a Sustained Virologic Response (SVR) at Follow-up Week 12 (SVR12) <sup>[1]</sup> |
| End point description:   |   |
| SVR12, defined as percentage of subjects with hepatitis C virus (HCV) ribonucleic acid (RNA) < lower limit of quantitation (LLOQ), target detected (TD) or target not detected (TND) at follow-up Week 12. SVR12 imputation was based on Next Value Carried Backwards (NVCB) approach. HCV RNA measurements were excluded after the start of non-study anti-HCV medication on treatment or during follow-up. The analysis was performed with all treated subjects; enrolled subjects who received at least 1 dose of study drug. |   |
| End point type   | Primary   |
| End point timeframe:   |   |
| Follow-up Week 12  |   |

Notes:

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

Justification: Only descriptive summary statistics were planned for this outcome measure.

| End point values                 | Daclatasvir + Sofosbuvir + Ribavirin (12 Weeks) | Daclatasvir + Sofosbuvir + Ribavirin (16 Weeks) |  |  |
|----------------------------------|---|---|--|--|
| Subject group type               | Reporting group                                 | Reporting group                                 |  |  |
| Number of subjects analysed      | 24  | 26  |  |  |
| Units: percentage of subjects    |   |   |  |  |
| number (confidence interval 95%) | 87.5 (67.6 to 97.3)                             | 92.3 (74.9 to 99.1)                             |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percent of Participants With a Sustained Virologic Response (SVR) at Follow-up Week 4 (SVR4) and Follow-up Week 24 (SVR24)

|                 |  |
|-----------------|--|
| End point title | Percent of Participants With a Sustained Virologic Response (SVR) at Follow-up Week 4 (SVR4) and Follow-up Week 24 (SVR24) |
|-----------------|--|

End point description:

SVR4, defined as percentage of subjects with hepatitis C virus (HCV) ribonucleic acid (RNA) < lower limit of quantitation (LLOQ), target detected (TD) or target not detected (TND) at follow-up Week 4. SVR24, defined as percentage of subjects with hepatitis C virus (HCV) ribonucleic acid (RNA) < lower limit of quantitation (LLOQ), target detected (TD) or target not detected (TND) at follow-up Week 24. SVR4 imputation was based on Next Value Carried Backwards (NVCB) approach. SVR24 imputation was based on missing being treated as non-responder. HCV RNA measurements were excluded after the start of non-study anti-HCV medication on treatment or during follow-up. The analysis was performed with all treated subjects; enrolled subjects who received at least 1 dose of study drug.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Follow-up Weeks 4 and 24

| End point values                 | Daclatasvir + Sofosbuvir + Ribavirin (12 Weeks) | Daclatasvir + Sofosbuvir + Ribavirin (16 Weeks) |  |  |
|----------------------------------|---|---|--|--|
| Subject group type               | Reporting group                                 | Reporting group                                 |  |  |
| Number of subjects analysed      | 24  | 26  |  |  |
| Units: percentage of subjects    |   |   |  |  |
| number (confidence interval 95%) |   |   |  |  |
| Follow-up Week 4 (SVR4)          | 87.5 (67.6 to 97.3)                             | 96.2 (80.4 to 99.9)                             |  |  |
| Follow-up Week 24 (SVR 24)       | 87.5 (67.6 to 97.3)                             | 92.3 (74.9 to 99.1)                             |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With Death, Serious Adverse Events (SAEs), Discontinuation Due to Adverse Events (AEs), Grade 3 or Grade 4 (Grade3/4) AEs, and Grade3/4 Laboratory Abnormalities

|                 |   |
|-----------------|---|
| End point title | Number of Subjects With Death, Serious Adverse Events (SAEs), Discontinuation Due to Adverse Events (AEs), Grade 3 or Grade 4 (Grade3/4) AEs, and Grade3/4 Laboratory Abnormalities |
|-----------------|---|

End point description:

Serious adverse event (SAE) defined: a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization. Adverse event (AE) defined: any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. The degree of the adverse event or laboratory abnormality are evaluated by grades: Grade (Gr) 1=Mild, Gr 2=Moderate, Gr 3=Severe, Gr 4=Life-threatening or disabling, Gr 5=Death. Grading as per using National Cancer Institute Common Terminology Criteria (NCI CTC) Version 3.0 criteria. The analysis was performed with all treated subjects; enrolled subjects who received at least 1 dose of study drug.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Date of First Dose of Study Drug to 7 Days post last dose of study drug (up to 13 weeks or 17 weeks depending on the randomized treatment group)

| End point values                   | Daclatasvir + Sofosbuvir + Ribavirin (12 Weeks) | Daclatasvir + Sofosbuvir + Ribavirin (16 Weeks) |  |  |
|------------------------------------|---|---|--|--|
| Subject group type                 | Reporting group                                 | Reporting group                                 |  |  |
| Number of subjects analysed        | 24  | 26  |  |  |
| Units: subjects                    |   |   |  |  |
| Death                              | 1   | 0   |  |  |
| SAEs                               | 2   | 3   |  |  |
| Discontinuation due to AEs         | 0   | 0   |  |  |
| Grade 3/4 AEs                      | 2   | 2   |  |  |
| Grade 3/4 Laboratory Abnormalities | 1   | 2   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

SAEs were reported from date of first dose of study drug to 30 days post discontinuation of the last dose. Non-serious AEs were reported from date of first dose of study drug to 7 days post discontinuation of the last dose.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 18.1   |

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | Daclatasvir + Sofosbuvir + Ribavirin (12 Weeks) |
|-----------------------|---|

Reporting group description:

Treatment-naïve and treatment-experienced participants with HCV Genotype 3 infection and advanced fibrosis or compensated cirrhosis (F3 or F4) were treated for 12 weeks with oral dosing of Daclatasvir (DCV) 60 mg once daily (QD), Sofosbuvir (SOF) 400 mg QD, and Ribavirin (RBV) 1000-1200 mg (weight based dosing) split into AM and PM dosing. Participants received either 400 mg (2 tablets for participants < 75 kg) or 600 mg (3 tablets for participants ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food. After the completion of the 12 week treatment period, participants were followed off treatment for 24 weeks. mg=milligram; kg=kilogram

|                       |   |
|-----------------------|---|
| Reporting group title | Daclatasvir + Sofosbuvir + Ribavirin (16 Weeks) |
|-----------------------|---|

Reporting group description:

Treatment-naïve and treatment-experienced participants with HCV Genotype 3 infection and advanced fibrosis or compensated cirrhosis (F3 or F4) were treated for 16 weeks with oral dosing of Daclatasvir (DCV) 60 mg once daily (QD), Sofosbuvir (SOF) 400 mg QD, and Ribavirin (RBV) 1000-1200 mg (weight based dosing) split into AM and PM dosing. Participants received either 400 mg (2 tablets for participants < 75 kg) or 600 mg (3 tablets for participants ≥ 75 kg) of RBV in the morning with food and 600 mg (3 tablets) of RBV in the evening with food. After the completion of the 16 week treatment period, participants were followed off treatment for 24 weeks. mg=milligram; kg=kilogram

| Serious adverse events  | Daclatasvir + Sofosbuvir + Ribavirin (12 Weeks) | Daclatasvir + Sofosbuvir + Ribavirin (16 Weeks) |  |
|---|---|---|--|
| Total subjects affected by serious adverse events                   |   |   |  |
| subjects affected / exposed   | 2 / 24 (8.33%)                                  | 3 / 26 (11.54%)                                 |  |
| number of deaths (all causes)                                       | 1   | 0   |  |
| number of deaths resulting from adverse events                      | 0   | 0   |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |   |  |
| Basal cell carcinoma  |   |   |  |
| subjects affected / exposed   | 0 / 24 (0.00%)                                  | 1 / 26 (3.85%)                                  |  |
| occurrences causally related to treatment / all                     | 0 / 0   | 0 / 1   |  |
| deaths causally related to treatment / all                          | 0 / 0   | 0 / 0   |  |
| Vascular disorders  |   |   |  |
| Arteriosclerosis  |   |   |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 26 (3.85%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac disorders                               |                |                |  |
| Congestive cardiomyopathy                       |                |                |  |
| subjects affected / exposed                     | 1 / 24 (4.17%) | 0 / 26 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| Nervous system disorders                        |                |                |  |
| Somnolence                                      |                |                |  |
| subjects affected / exposed                     | 1 / 24 (4.17%) | 0 / 26 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| Pneumonia                                       |                |                |  |
| subjects affected / exposed                     | 0 / 24 (0.00%) | 1 / 26 (3.85%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                     | Daclatasvir +<br>Sofosbuvir +<br>Ribavirin (12<br>Weeks) | Daclatasvir +<br>Sofosbuvir +<br>Ribavirin (16 Weeks) |  |
|---|--|---|--|
| Total subjects affected by non-serious adverse events |  |   |  |
| subjects affected / exposed                           | 21 / 24 (87.50%)   | 22 / 26 (84.62%)                                      |  |
| Vascular disorders                                    |  |   |  |
| Hypertension  |  |   |  |
| subjects affected / exposed                           | 0 / 24 (0.00%)   | 3 / 26 (11.54%)                                       |  |
| occurrences (all)                                     | 0  | 3   |  |
| Nervous system disorders                              |  |   |  |
| Headache  |  |   |  |
| subjects affected / exposed                           | 7 / 24 (29.17%)  | 5 / 26 (19.23%)                                       |  |
| occurrences (all)                                     | 7  | 6   |  |
| Lethargy  |  |   |  |

|   |   |   |  |
|---|---|---|--|
| subjects affected / exposed<br>occurrences (all)  | 2 / 24 (8.33%)<br>2   | 2 / 26 (7.69%)<br>2   |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 24 (0.00%)<br>0   | 2 / 26 (7.69%)<br>5   |  |
| General disorders and administration<br>site conditions<br>Asthenia<br>subjects affected / exposed<br>occurrences (all)<br><br>Fatigue<br>subjects affected / exposed<br>occurrences (all)  | 2 / 24 (8.33%)<br>2<br><br>6 / 24 (25.00%)<br>7   | 5 / 26 (19.23%)<br>9<br><br>7 / 26 (26.92%)<br>7  |  |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Abdominal discomfort<br>subjects affected / exposed<br>occurrences (all)<br><br>Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Mouth ulceration<br>subjects affected / exposed<br>occurrences (all)<br><br>Nausea<br>subjects affected / exposed<br>occurrences (all) | 0 / 24 (0.00%)<br>0<br><br>0 / 24 (0.00%)<br>0<br><br>2 / 24 (8.33%)<br>3<br><br>1 / 24 (4.17%)<br>1<br><br>0 / 24 (0.00%)<br>0<br><br>3 / 24 (12.50%)<br>3 | 2 / 26 (7.69%)<br>2<br><br>2 / 26 (7.69%)<br>2<br><br>0 / 26 (0.00%)<br>0<br><br>4 / 26 (15.38%)<br>4<br><br>2 / 26 (7.69%)<br>2<br><br>1 / 26 (3.85%)<br>1 |  |
| Respiratory, thoracic and mediastinal<br>disorders<br>Dyspnoea<br>subjects affected / exposed<br>occurrences (all)  | 2 / 24 (8.33%)<br>2   | 3 / 26 (11.54%)<br>5  |  |

|   |                                 |                                 |  |
|---|---------------------------------|---------------------------------|--|
| <p>Skin and subcutaneous tissue disorders</p> <p>Pruritus</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>           | <p>1 / 24 (4.17%)</p> <p>1</p>  | <p>2 / 26 (7.69%)</p> <p>2</p>  |  |
| <p>Photosensitivity reaction</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>2 / 24 (8.33%)</p> <p>2</p>  | <p>0 / 26 (0.00%)</p> <p>0</p>  |  |
| <p>Hyperhidrosis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>2 / 24 (8.33%)</p> <p>2</p>  | <p>0 / 26 (0.00%)</p> <p>0</p>  |  |
| <p>Dry skin</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>2 / 24 (8.33%)</p> <p>2</p>  | <p>0 / 26 (0.00%)</p> <p>0</p>  |  |
| <p>Psychiatric disorders</p> <p>Insomnia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                            | <p>8 / 24 (33.33%)</p> <p>8</p> | <p>7 / 26 (26.92%)</p> <p>7</p> |  |
| <p>Depression</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>1 / 24 (4.17%)</p> <p>1</p>  | <p>2 / 26 (7.69%)</p> <p>2</p>  |  |
| <p>Depressed mood</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>1 / 24 (4.17%)</p> <p>2</p>  | <p>2 / 26 (7.69%)</p> <p>2</p>  |  |
| <p>Irritability</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>5 / 24 (20.83%)</p> <p>5</p> | <p>2 / 26 (7.69%)</p> <p>3</p>  |  |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 24 (0.00%)</p> <p>0</p>  | <p>3 / 26 (11.54%)</p> <p>3</p> |  |
| <p>Metabolism and nutrition disorders</p> <p>Decreased appetite</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>     | <p>0 / 24 (0.00%)</p> <p>0</p>  | <p>2 / 26 (7.69%)</p> <p>4</p>  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 27 February 2015 | This amendment addressed the following items: <ul style="list-style-type: none"><li>• Clarify the inclusion requirements for liver biopsies for those patients who are considered F3</li><li>• Provide information included in EU approved Daklinza® (daclatasvir) Product Information related to treatment indication for patients with Genotype 3 and advanced liver disease (cirrhosis)</li><li>• Contraception requirements and pregnancy testing for ribavirin (RBV) added</li><li>• Updated safety information regarding patients receiving DCV+SOF when also administered with amiodarone</li><li>• Amiodarone added to prohibited medications</li><li>• Minor editorial and format changes.</li></ul> |
| 07 May 2015      | This amendment addressed the following item: <ul style="list-style-type: none"><li>• Revision to safety information regarding patients receiving DCV+SOF when also administered with amiodarone.</li></ul>  |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26822022>