



## Clinical trial results:

### A Phase 3 Evaluation of Daclatasvir in Combination with Peginterferon Lambda-1a and Ribavirin (RBV) or Telaprevir in Combination with Peginterferon Alfa-2a and RBV in Patients with Chronic Hepatitis C Genotype 1b who are Treatment Naïve or Prior Relapsers to Alfa/RBV Therapy.

#### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2011-005409-65  |
| Trial protocol           | ES IT DE PL GB  |
| Global end of trial date | 09 October 2014 |

#### Results information

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

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | AI452-021 |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01718158 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Bristol-Myers Squibb  |
| Sponsor organisation address | Bristol-Myers Squibb International Corporation, Chaussée 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                       | 09 October 2014 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 09 October 2014 |
| Was the trial ended prematurely?                     | Yes             |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the study was to compare the efficacy of pegylated interferon lambda-1a/ ribavirin/ daclatasvir (Lambda/RBV/DCV) to pegylated interferon alfa-2a/ ribavirin/ telaprevir (alfa-2a/RBV/TVR) in subjects with chronic hepatitis C virus (HCV) genotype-1b (GT-1b) infection, measured as the proportion of subjects in each treatment group.

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:

Telaprevir (TVR), a directly acting antiviral (DAA) along with a backbone of alfa/RBV, is approved for treatment of chronic HCV GT-1 infection. The safety profile of TVR in subjects with chronic HCV GT-1 infection has been well characterized in both treatment-naïve subjects and those with prior treatment failure to alfa-2a/RBV.

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 29 January 2013 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Poland: 65             |
| Country: Number of subjects enrolled | Spain: 38              |
| Country: Number of subjects enrolled | United Kingdom: 4      |
| Country: Number of subjects enrolled | Germany: 39            |
| Country: Number of subjects enrolled | Italy: 35              |
| Country: Number of subjects enrolled | Argentina: 70          |
| Country: Number of subjects enrolled | France: 11             |
| Country: Number of subjects enrolled | Israel: 54             |
| Country: Number of subjects enrolled | Japan: 120             |
| Country: Number of subjects enrolled | Korea, Republic of: 45 |
| Country: Number of subjects enrolled | Russian Federation: 72 |
| Country: Number of subjects enrolled | Taiwan: 70             |
| Country: Number of subjects enrolled | United States: 18      |
| Worldwide total number of subjects   | 641                    |
| EEA total number of subjects         | 192                    |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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)                      | 568 |
| From 65 to 84 years                       | 73  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 85 sites in 13 countries.

### Pre-assignment

Screening details:

A total of 641 subjects were enrolled, out of which 444 subjects were randomized and 440 were treated; Reasons for not being randomized: subject withdrew consent (17), poor/non-compliance (1), subject no longer met study criteria (167) and other reasons (12).

### 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>             | Lambda/RBV/DCV |

Arm description:

Subjects (treatment-naïve or prior relapsers to alfa-2a/RBV) received daclatasvir (DCV) tablets 60 mg orally, once daily for 12 weeks, pegIFNlambda-1a injection 180 µg subcutaneously, once weekly and RBV tablets for a total daily dose of 1000-1200 mg orally twice daily for 24 weeks. Subjects were originally required to be followed-up for a minimum total period of 24 weeks post-treatment and subjects with any futility criteria or lack of efficacy [HCV RNA  $\geq$  lower limit of quantitation (LLOQ) at Week 48] were required to be followed-up for a period of 48 weeks post-treatment. Following the Sponsor's decision to terminate the Lambda development program, the follow-up requirements for all study subjects irrespective of treatment response were modified to a total period of 12 weeks post-treatment.

|  |   |
|--|---|
| Arm type                               | Experimental                                |
| Investigational medicinal product name | Pegylated interferon lambda-1a              |
| Investigational medicinal product code | BMS-914143                                  |
| Other name                             | Lambda                                      |
| Pharmaceutical forms                   | Solution for infusion in pre-filled syringe |
| Routes of administration               | Subcutaneous use                            |

Dosage and administration details:

Subjects received pegIFNlambda-1a solution for injection 180 µg subcutaneously, once weekly for 24 weeks.

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

Dosage and administration details:

Subjects received ribavirin tablets for a total daily dose of 1000-1200 mg orally, twice daily for up to 24 weeks.

|  |                    |
|--|--------------------|
| 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 60 mg tablet was administered orally once daily for 12 weeks.

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | Alfa-2a/RBV/TVR |
|------------------|-----------------|

**Arm description:**

Subjects (treatment-naïve or prior relapsers to alfa-2a/RBV) received telaprevir tablets 375 mg orally, thrice daily for 12 weeks, pegIFNalpha-2a injection 180 µg subcutaneously, once weekly and ribavirin tablets for a total daily dose of 1000-1200 mg orally twice daily for up to 48 weeks [duration of treatment based on eRVR response (HCV RNA < LLOQ at Weeks 4 and 12)]. At Week 24, subjects who achieved eRVR were discontinued from therapy versus subjects who failed to achieve eRVR yet continued to demonstrate benefit from therapy received an additional 24 weeks of pegIFNalpha-2a/RBV for a total treatment course of 48 weeks. Following discontinuation of study therapy, all subjects were originally planned to complete 24 weeks of post-treatment follow-up. Following the Sponsor's decision to terminate the Lambda development program, the follow-up requirements for all study subjects irrespective of treatment response were modified to a total period of 12 weeks post-treatment.

|  |   |
|--|---|
| Arm type                               | Experimental                                |
| Investigational medicinal product name | Pegylated interferon alfa-2a                |
| Investigational medicinal product code |   |
| Other name                             | Pegasys                                     |
| Pharmaceutical forms                   | Solution for infusion in pre-filled syringe |
| Routes of administration               | Subcutaneous use                            |

**Dosage and administration details:**

Subjects received pegIFNalpha-2a solution for injection 180 µg subcutaneously, once weekly for 48 weeks.

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

**Dosage and administration details:**

Subjects received ribavirin tablets for a total daily dose of 1000-1200 mg orally, twice daily for up to 48 weeks.

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

**Dosage and administration details:**

Subjects received 2 telaprevir 375-mg tablets orally, three times daily for 12 weeks.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Lambda/RBV/DCV | Alfa-2a/RBV/TVR |
|---|----------------|-----------------|
| Started   | 294            | 146             |
| Completed   | 271            | 99              |
| Not completed                                       | 23             | 47              |
| Consent withdrawn by subject                        | 1              | 3               |
| Adverse event, non-fatal                            | 16             | 28              |
| Other reason  | -              | 1               |
| subject no longer meets study criteria              | -              | 3               |
| Lost to follow-up                                   | -              | 2               |
| Lack of efficacy                                    | 4              | 3               |

|  |   |   |
|--|---|---|
| Subject request to discontinue study therapy | 2 | 7 |
|--|---|---|

Notes:

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

Justification: Out of 641 subjects who were enrolled in the study, 444 subjects were randomized and 440 subjects got the study treatment.

**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>             | Lambda/RBV/DCV |

Arm description:

Subjects (treatment-naïve or prior relapsers to alfa-2a/RBV) received daclatasvir (DCV) tablets 60 mg orally, once daily for 12 weeks, pegIFNlambda-1a injection 180 µg subcutaneously, once weekly and RBV tablets for a total daily dose of 1000-1200 mg orally twice daily for 24 weeks. Subjects were originally required to be followed-up for a minimum total period of 24 weeks post-treatment and subjects with any futility criteria or lack of efficacy [HCV RNA  $\geq$  lower limit of quantitation (LLOQ) at Week 48] were required to be followed-up for a period of 48 weeks post-treatment. Following the Sponsor's decision to terminate the Lambda development program, the follow-up requirements for all study subjects irrespective of treatment response were modified to a total period of 12 weeks post-treatment.

|  |   |
|--|---|
| Arm type                               | Experimental                                |
| Investigational medicinal product name | Pegylated interferon lambda-1a              |
| Investigational medicinal product code | BMS-914143                                  |
| Other name                             | Lambda                                      |
| Pharmaceutical forms                   | Solution for infusion in pre-filled syringe |
| Routes of administration               | Subcutaneous use                            |

Dosage and administration details:

Subjects received pegIFNlambda-1a solution for injection 180 µg subcutaneously, once weekly for 24 weeks.

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

Dosage and administration details:

Subjects received ribavirin tablets for a total daily dose of 1000-1200 mg orally, twice daily for up to 24 weeks.

|  |                    |
|--|--------------------|
| 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 60 mg tablet was administered orally once daily for 12 weeks.

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | Alfa-2a/RBV/TVR |
|------------------|-----------------|

**Arm description:**

Subjects (treatment-naïve or prior relapsers to alfa-2a/RBV) received telaprevir tablets 375 mg orally, thrice daily for 12 weeks, pegIFNalpha-2a injection 180 µg subcutaneously, once weekly and ribavirin tablets for a total daily dose of 1000-1200 mg orally twice daily for up to 48 weeks [duration of treatment based on eRVR response (HCV RNA < LLOQ at Weeks 4 and 12)]. At Week 24, subjects who achieved eRVR were discontinued from therapy versus subjects who failed to achieve eRVR yet continued to demonstrate benefit from therapy received an additional 24 weeks of pegIFNalpha-2a/RBV for a total treatment course of 48 weeks. Following discontinuation of study therapy, all subjects were originally planned to complete 24 weeks of post-treatment follow-up. Following the Sponsor's decision to terminate the Lambda development program, the follow-up requirements for all study subjects irrespective of treatment response were modified to a total period of 12 weeks post-treatment.

|  |   |
|--|---|
| Arm type                               | Experimental                                |
| Investigational medicinal product name | Pegylated interferon alfa-2a                |
| Investigational medicinal product code |   |
| Other name                             | Pegasys                                     |
| Pharmaceutical forms                   | Solution for infusion in pre-filled syringe |
| Routes of administration               | Subcutaneous use                            |

**Dosage and administration details:**

Subjects received pegIFNalpha-2a solution for injection 180 µg subcutaneously, once weekly for 48 weeks.

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

**Dosage and administration details:**

Subjects received ribavirin tablets for a total daily dose of 1000-1200 mg orally, twice daily for up to 48 weeks.

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

**Dosage and administration details:**

Subjects received 2 telaprevir 375-mg tablets orally, three times daily for 12 weeks.

| <b>Number of subjects in period 2</b>     | Lambda/RBV/DCV | Alfa-2a/RBV/TVR |
|---|----------------|-----------------|
| Started                                   | 271            | 99              |
| Completed                                 | 284            | 130             |
| Not completed                             | 7              | 8               |
| Consent withdrawn by subject              | -              | 3               |
| Death                                     | -              | 1               |
| Follow up no longer required per protocol | 3              | 1               |
| Other reason                              | 1              | 2               |
| Lost to follow-up                         | 3              | 1               |
| Joined                                    | 20             | 39              |
| Rejoined for follow-up                    | 20             | 39              |





## Baseline characteristics

### Reporting groups

|                       |                |
|-----------------------|----------------|
| Reporting group title | Lambda/RBV/DCV |
|-----------------------|----------------|

#### Reporting group description:

Subjects (treatment-naïve or prior relapsers to alfa-2a/RBV) received daclatasvir (DCV) tablets 60 mg orally, once daily for 12 weeks, pegIFNlambda-1a injection 180 µg subcutaneously, once weekly and RBV tablets for a total daily dose of 1000-1200 mg orally twice daily for 24 weeks. Subjects were originally required to be followed-up for a minimum total period of 24 weeks post-treatment and subjects with any futility criteria or lack of efficacy [HCV RNA  $\geq$  lower limit of quantitation (LLOQ) at Week 48] were required to be followed-up for a period of 48 weeks post-treatment. Following the Sponsor's decision to terminate the Lambda development program, the follow-up requirements for all study subjects irrespective of treatment response were modified to a total period of 12 weeks post-treatment.

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Alfa-2a/RBV/TVR |
|-----------------------|-----------------|

#### Reporting group description:

Subjects (treatment-naïve or prior relapsers to alfa-2a/RBV) received telaprevir tablets 375 mg orally, thrice daily for 12 weeks, pegIFNalpha-2a injection 180 µg subcutaneously, once weekly and ribavirin tablets for a total daily dose of 1000-1200 mg orally twice daily for up to 48 weeks [duration of treatment based on eRVR response (HCV RNA < LLOQ at Weeks 4 and 12)]. At Week 24, subjects who achieved eRVR were discontinued from therapy versus subjects who failed to achieve eRVR yet continued to demonstrate benefit from therapy received an additional 24 weeks of pegIFNalpha-2a/RBV for a total treatment course of 48 weeks. Following discontinuation of study therapy, all subjects were originally planned to complete 24 weeks of post-treatment follow-up. Following the Sponsor's decision to terminate the Lambda development program, the follow-up requirements for all study subjects irrespective of treatment response were modified to a total period of 12 weeks post-treatment.

| Reporting group values                | Lambda/RBV/DCV | Alfa-2a/RBV/TVR | Total |
|---------------------------------------|----------------|-----------------|-------|
| Number of subjects                    | 294            | 146             | 440   |
| Age categorical<br>Units: Subjects    |                |                 |       |
| < 65 years                            | 256            | 131             | 387   |
| $\geq$ 65 years                       | 38             | 15              | 53    |
| Age continuous<br>Units: years        |                |                 |       |
| arithmetic mean                       | 50             | 48              |       |
| standard deviation                    | $\pm$ 12.1     | $\pm$ 13.2      | -     |
| Gender categorical<br>Units: Subjects |                |                 |       |
| Female                                | 137            | 76              | 213   |
| Male                                  | 157            | 70              | 227   |

## End points

### End points reporting groups

|                       |                |
|-----------------------|----------------|
| Reporting group title | Lambda/RBV/DCV |
|-----------------------|----------------|

#### Reporting group description:

Subjects (treatment-naïve or prior relapsers to alfa-2a/RBV) received daclatasvir (DCV) tablets 60 mg orally, once daily for 12 weeks, pegIFNlambda-1a injection 180 µg subcutaneously, once weekly and RBV tablets for a total daily dose of 1000-1200 mg orally twice daily for 24 weeks. Subjects were originally required to be followed-up for a minimum total period of 24 weeks post-treatment and subjects with any futility criteria or lack of efficacy [HCV RNA  $\geq$  lower limit of quantitation (LLOQ) at Week 48] were required to be followed-up for a period of 48 weeks post-treatment. Following the Sponsor's decision to terminate the Lambda development program, the follow-up requirements for all study subjects irrespective of treatment response were modified to a total period of 12 weeks post-treatment.

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Alfa-2a/RBV/TVR |
|-----------------------|-----------------|

#### Reporting group description:

Subjects (treatment-naïve or prior relapsers to alfa-2a/RBV) received telaprevir tablets 375 mg orally, thrice daily for 12 weeks, pegIFNalpha-2a injection 180 µg subcutaneously, once weekly and ribavirin tablets for a total daily dose of 1000-1200 mg orally twice daily for up to 48 weeks [duration of treatment based on eRVR response (HCV RNA  $<$  LLOQ at Weeks 4 and 12)]. At Week 24, subjects who achieved eRVR were discontinued from therapy versus subjects who failed to achieve eRVR yet continued to demonstrate benefit from therapy received an additional 24 weeks of pegIFNalpha-2a/RBV for a total treatment course of 48 weeks. Following discontinuation of study therapy, all subjects were originally planned to complete 24 weeks of post-treatment follow-up. Following the Sponsor's decision to terminate the Lambda development program, the follow-up requirements for all study subjects irrespective of treatment response were modified to a total period of 12 weeks post-treatment.

|                       |                |
|-----------------------|----------------|
| Reporting group title | Lambda/RBV/DCV |
|-----------------------|----------------|

#### Reporting group description:

Subjects (treatment-naïve or prior relapsers to alfa-2a/RBV) received daclatasvir (DCV) tablets 60 mg orally, once daily for 12 weeks, pegIFNlambda-1a injection 180 µg subcutaneously, once weekly and RBV tablets for a total daily dose of 1000-1200 mg orally twice daily for 24 weeks. Subjects were originally required to be followed-up for a minimum total period of 24 weeks post-treatment and subjects with any futility criteria or lack of efficacy [HCV RNA  $\geq$  lower limit of quantitation (LLOQ) at Week 48] were required to be followed-up for a period of 48 weeks post-treatment. Following the Sponsor's decision to terminate the Lambda development program, the follow-up requirements for all study subjects irrespective of treatment response were modified to a total period of 12 weeks post-treatment.

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Alfa-2a/RBV/TVR |
|-----------------------|-----------------|

#### Reporting group description:

Subjects (treatment-naïve or prior relapsers to alfa-2a/RBV) received telaprevir tablets 375 mg orally, thrice daily for 12 weeks, pegIFNalpha-2a injection 180 µg subcutaneously, once weekly and ribavirin tablets for a total daily dose of 1000-1200 mg orally twice daily for up to 48 weeks [duration of treatment based on eRVR response (HCV RNA  $<$  LLOQ at Weeks 4 and 12)]. At Week 24, subjects who achieved eRVR were discontinued from therapy versus subjects who failed to achieve eRVR yet continued to demonstrate benefit from therapy received an additional 24 weeks of pegIFNalpha-2a/RBV for a total treatment course of 48 weeks. Following discontinuation of study therapy, all subjects were originally planned to complete 24 weeks of post-treatment follow-up. Following the Sponsor's decision to terminate the Lambda development program, the follow-up requirements for all study subjects irrespective of treatment response were modified to a total period of 12 weeks post-treatment.

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

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects With Sustained Virologic Response at Follow-up Week 12 (SVR12) |
|-----------------|---|

#### End point description:

SVR12 was defined as Hepatitis C virus (HCV) RNA  $<$  LLOQ, target detected (TD) or target not detected (TND) at post-treatment follow-up Week 12. The LLOQ was 25 IU/mL. 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 (modified ITT) population, the numerator was based on subjects

meeting the response criteria and denominator based on all treated subjects.

|                      |         |
|----------------------|---------|
| End point type       | Primary |
| End point timeframe: |         |
| Follow-up Week 12    |         |

| End point values                 | Lambda/RBV/D<br>CV     | Alfa-<br>2a/RBV/TVR    |  |  |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type               | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed      | 294                    | 146                    |  |  |
| Units: Percentage of subjects    |                        |                        |  |  |
| number (confidence interval 95%) | 88.8 (85.2 to<br>92.4) | 70.5 (63.2 to<br>77.9) |  |  |

## Statistical analyses

|   |                                  |
|---|----------------------------------|
| Statistical analysis title  | Treatment difference in SVR12    |
| Statistical analysis description:   |                                  |
| The treatment difference and its two-sided 95% confidence interval (CI) were estimated using stratum-adjusted Mantel-Haenszel approach stratified by IL28B rs12979860 host genotype (CC, non-CC), treatment naive or relapse status, and region (Japan vs rest of world), using modified ITT. |                                  |
| Comparison groups   | Lambda/RBV/DCV v Alfa-2a/RBV/TVR |
| Number of subjects included in analysis   | 440                              |
| Analysis specification  | Pre-specified                    |
| Analysis type   | other <sup>[1]</sup>             |
| P-value   | < 0.0001                         |
| Method  | Stratum-adjusted Mantel-Haenszel |
| Parameter estimate  | Percentage difference            |
| Confidence interval   |                                  |
| level   | 95 %                             |
| sides   | 2-sided                          |
| lower limit   | 9.9                              |
| upper limit   | 25.7                             |

Notes:

[1] - Non-inferiority and superiority of Lambda/RBV/DCV to Alfa-2a/RBV/TVR were established because the P-value was < 0.05.

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

|   |   |
|---|---|
| End point title   | Percentage of Treatment-Naive Subjects With Sustained Virologic Response at Follow-up Week 12 (SVR12) |
| End point description:  |   |
| SVR12 was defined as HCV RNA <LLOQ, TD or TND at follow-up Week 12. The LLOQ was 25 IU/mL. 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 ITT population, the numerator was based on subjects meeting the response criteria and denominator based on all treated subjects. Here, number of subjects analysed signifies number of treatment-naïve subjects in each reporting arm. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Follow-up week 12   |   |

| <b>End point values</b>          | Lambda/RBV/D<br>CV     | Alfa-<br>2a/RBV/TVR  |  |  |
|----------------------------------|------------------------|----------------------|--|--|
| Subject group type               | Reporting group        | Reporting group      |  |  |
| Number of subjects analysed      | 235                    | 115                  |  |  |
| Units: Percentage of subjects    |                        |                      |  |  |
| number (confidence interval 95%) | 89.8 (85.9 to<br>93.7) | 72.2 (64 to<br>80.4) |  |  |

## Statistical analyses

| <b>Statistical analysis title</b>   | Treatment difference in SVR12    |
|---|----------------------------------|
| Statistical analysis description:<br>The treatment difference and its two-sided 95% CI were estimated using stratum-adjusted Mantel-Haenszel approach stratified by IL28B rs12979860 host genotype (CC, non-CC), treatment naive or relapse status, and region (Japan vs rest of world) using modified ITT. |                                  |
| Comparison groups   | Lambda/RBV/DCV v Alfa-2a/RBV/TVR |
| Number of subjects included in analysis   | 350                              |
| Analysis specification  | Pre-specified                    |
| Analysis type   | other <sup>[2]</sup>             |
| P-value   | < 0.0001                         |
| Method  | Stratum-adjusted Mantel-Haenszel |
| Parameter estimate  | Percentage difference            |
| Confidence interval   |                                  |
| level   | 95 %                             |
| sides   | 2-sided                          |
| lower limit   | 8.8                              |
| upper limit   | 26.3                             |

Notes:

[2] - Non-inferiority and superiority of Lambda/RBV/DCV to Alfa-2a/RBV/TVR were established because the P-value was < 0.05.

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

| <b>End point title</b>   | Percentage of subjects With Sustained Virologic Response at Follow-up Week 24 (SVR24) |
|--|---|
| End point description:<br>SVR24 was defined as HCV RNA levels <LLOQ, TD or TND at follow-up Week 24. The LLOQ was 25 IU/mL. HCV RNA levels were measured by the Roche COBAS® TaqMan® HCV Test version 2.0 from the central laboratory. The analysis was performed in observed population, the numerator was based on subjects meeting the response criteria and denominator based on treated subjects with HCV RNA at follow-up Week 24. Here, number of subjects analysed signifies number of treated subjects with HCV RNA at follow-up Week 24 in each reporting arm. The modified ITT analysis was not performed because not all subjects had the opportunity to reach follow-up Week 24 due to early study termination. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Follow-up Week 24  |   |

| End point values                 | Lambda/RBV/D<br>CV | Alfa-<br>2a/RBV/TVR |  |  |
|----------------------------------|--------------------|---------------------|--|--|
| Subject group type               | Reporting group    | Reporting group     |  |  |
| Number of subjects analysed      | 268                | 112                 |  |  |
| Units: Percentage of subjects    |                    |                     |  |  |
| number (confidence interval 95%) | 82.7 (78.3 to 87)  | 60.3 (52.3 to 68.2) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With Rash Related Dermatologic Events

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects With Rash Related Dermatologic Events |
|-----------------|--|

End point description:

Rash related dermatological events were graded as grade 1- mild, grade 2-moderate and grade 3-severe. The analysis was performed in modified ITT 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:

From Day 1 of study treatment up to Week 12

| End point values                 | Lambda/RBV/D<br>CV  | Alfa-<br>2a/RBV/TVR |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 294                 | 146                 |  |  |
| Units: Percentage of Subjects    |                     |                     |  |  |
| number (confidence interval 95%) | 26.5 (21.5 to 31.6) | 37 (29.2 to 44.8)   |  |  |

## Statistical analyses

|                            |                                      |
|----------------------------|--------------------------------------|
| Statistical analysis title | Treatment difference for rash events |
|----------------------------|--------------------------------------|

Statistical analysis description:

The treatment difference and its two-sided 95% CI were estimated using stratum-adjusted Mantel-Haenszel approach stratified by IL28B rs12979860 host genotype (CC, non-CC), treatment naive or relapse status, and region (Japan vs rest of world).

|                   |                                  |
|-------------------|----------------------------------|
| Comparison groups | Lambda/RBV/DCV v Alfa-2a/RBV/TVR |
|-------------------|----------------------------------|

|   |                                  |
|---|----------------------------------|
| Number of subjects included in analysis | 440                              |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority <sup>[3]</sup>       |
| P-value                                 | = 0.0177                         |
| Method                                  | Stratum-adjusted Mantel-Haenszel |
| Parameter estimate                      | Percentage difference            |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | -20.1                            |
| upper limit                             | -1.9                             |

Notes:

[3] - Superiority of Lambda/RBV/DCV to Alfa-2a/RBV/TVR was established because the P-value was < 0.05.

## Secondary: Percentage of Subjects With Treatment Emergent Cytopenic Abnormalities

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects With Treatment Emergent Cytopenic Abnormalities |
|-----------------|--|

End point description:

Treatment emergent cytopenic abnormalities included anemia, defined as hemoglobin <10 grams/deciliters, neutropenia, defined as absolute neutrophil count <750/mm<sup>3</sup> and thrombocytopenia, defined as platelets <50,000/mm<sup>3</sup>. The analysis was performed in modified ITT 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:

From Day 1 of study treatment up to Week 48

| End point values                 | Lambda/RBV/DCV     | Alfa-2a/RBV/TVR     |  |  |
|----------------------------------|--------------------|---------------------|--|--|
| Subject group type               | Reporting group    | Reporting group     |  |  |
| Number of subjects analysed      | 294                | 146                 |  |  |
| Units: Percentage of Subjects    |                    |                     |  |  |
| number (confidence interval 95%) | 10.2 (6.7 to 13.7) | 56.2 (48.1 to 64.2) |  |  |

## Statistical analyses

|                            |   |
|----------------------------|---|
| Statistical analysis title | Treatment difference in cytopenic abnormalities |
|----------------------------|---|

Statistical analysis description:

The treatment difference and its two-sided 95% CI were estimated using stratum-adjusted Mantel-Haenszel approach stratified by IL28B rs12979860 host genotype (CC, non-CC), treatment naive or relapse status, and region (Japan vs rest of world).

|                   |                                  |
|-------------------|----------------------------------|
| Comparison groups | Lambda/RBV/DCV v Alfa-2a/RBV/TVR |
|-------------------|----------------------------------|

|   |                                  |
|---|----------------------------------|
| Number of subjects included in analysis | 440                              |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority <sup>[4]</sup>       |
| P-value                                 | < 0.0001                         |
| Method                                  | Stratum-adjusted Mantel-Haenszel |
| Parameter estimate                      | Percentage difference            |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | -54.4                            |
| upper limit                             | -37.5                            |

Notes:

[4] - Superiority of Lambda/RBV/DCV to Alfa-2a/RBV/TVR was established because the P-value was <0.05.

## Secondary: Percentage of Subjects With On-treatment Interferon (IFN)-Associated flu Like Symptoms

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects With On-treatment Interferon (IFN)-Associated flu Like Symptoms |
|-----------------|--|

End point description:

Subjects were assessed for flu-like symptoms like pyrexia, chills or pain. The analysis was performed in modified ITT 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:

From Day 1 of study treatment up to Week 48

| End point values                 | Lambda/RBV/DCV    | Alfa-2a/RBV/TVR     |  |  |
|----------------------------------|-------------------|---------------------|--|--|
| Subject group type               | Reporting group   | Reporting group     |  |  |
| Number of subjects analysed      | 294               | 146                 |  |  |
| Units: Percentage of subjects    |                   |                     |  |  |
| number (confidence interval 95%) | 9.9 (6.5 to 13.3) | 27.4 (20.2 to 34.6) |  |  |

## Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Treatment difference for flu like symptoms |
|----------------------------|--|

Statistical analysis description:

The treatment difference and its two-sided 95% CI were estimated using stratum-adjusted Mantel-Haenszel approach stratified by IL28B rs12979860 host genotype (CC, non-CC), treatment-naive or prior relapse to alfa-2a/RBV, and region (Japan vs rest of world).

|                   |                                  |
|-------------------|----------------------------------|
| Comparison groups | Lambda/RBV/DCV v Alfa-2a/RBV/TVR |
|-------------------|----------------------------------|

|   |                                  |
|---|----------------------------------|
| Number of subjects included in analysis | 440                              |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority <sup>[5]</sup>       |
| P-value                                 | < 0.0001                         |
| Method                                  | Stratum-adjusted Mantel-Haenszel |
| Parameter estimate                      | Percentage difference            |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | -24.9                            |
| upper limit                             | -9.2                             |

Notes:

[5] - Superiority of Lambda/RBV/DCV to Alfa-2a/RBV/TVR was established because the P-value was <0.05.

## Secondary: Percentage of Subjects With On-treatment Interferon (IFN) Associated Musculoskeletal Symptoms

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects With On-treatment Interferon (IFN) Associated Musculoskeletal Symptoms |
|-----------------|---|

End point description:

Subjects were assessed for musculoskeletal symptoms which includes arthralgia, myalgia or back pain. The analysis was performed in modified ITT 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:

From Day 1 of study treatment up to Week 48

| End point values                 | Lambda/RBV/D<br>CV | Alfa-<br>2a/RBV/TVR |  |  |
|----------------------------------|--------------------|---------------------|--|--|
| Subject group type               | Reporting group    | Reporting group     |  |  |
| Number of subjects analysed      | 294                | 146                 |  |  |
| Units: Percentage of subjects    |                    |                     |  |  |
| number (confidence interval 95%) | 17.7 (13.3 to 22)  | 19.9 (13.4 to 26.3) |  |  |

## Statistical analyses

|                            |   |
|----------------------------|---|
| Statistical analysis title | Treatment difference for musculoskeletal symptoms |
|----------------------------|---|

Statistical analysis description:

The treatment difference and its two-sided 95% CI were estimated using stratum-adjusted Mantel-Haenszel approach stratified by IL28B rs12979860 host genotype (CC, non-CC), treatment naive or relapse status, and region (Japan vs rest of world).

|                   |                                  |
|-------------------|----------------------------------|
| Comparison groups | Lambda/RBV/DCV v Alfa-2a/RBV/TVR |
|-------------------|----------------------------------|



|   |                                  |
|---|----------------------------------|
| Number of subjects included in analysis | 440                              |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority <sup>[6]</sup>       |
| P-value                                 | = 0.584                          |
| Method                                  | Stratum-adjusted Mantel-Haenszel |
| Parameter estimate                      | Percentage difference            |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | -9.8                             |
| upper limit                             | 5.5                              |

Notes:

[6] - Superiority of Lambda/RBV/DCV to Alfa-2a/RBV/TVR was not established because the P-value was  $\geq 0.05$ . No further hierarchical testing of secondary endpoints (eg, SVR14) was conducted.

### Secondary: Number of Subjects With Adverse events (AEs), Serious Adverse Events (SAEs), Dose Reductions, and Discontinuations due to AEs during treatment period

|                 |   |
|-----------------|---|
| End point title | Number of Subjects With Adverse events (AEs), Serious Adverse Events (SAEs), Dose Reductions, and Discontinuations due to AEs during treatment period |
|-----------------|---|

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:

From Day 1 of study treatment up to Week 48

| End point values            | Lambda/RBV/D<br>CV | Alfa-<br>2a/RBV/TVR |  |  |
|-----------------------------|--------------------|---------------------|--|--|
| Subject group type          | Reporting group    | Reporting group     |  |  |
| Number of subjects analysed | 294                | 146                 |  |  |
| Units: Subjects             |                    |                     |  |  |
| AEs                         | 254                | 138                 |  |  |
| SAEs                        | 11                 | 16                  |  |  |
| Dose reduction              | 26                 | 33                  |  |  |
| Discontinuations due to AEs | 16                 | 41                  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With Extended Rapid Virologic Response (eRVR)

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects With Extended Rapid Virologic Response (eRVR) |
|-----------------|--|

---

**End point description:**

eRVR was defined as HCV RNA <LLOQ TND at Weeks 4 and 12 of treatment. The LLOQ was 25 IU/mL. 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 ITT population, the numerator was based on subjects meeting the response criteria and denominator based on all treated subjects. Missing values were imputed using backward imputation technique.

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

---

**End point timeframe:**

Weeks 4, 12

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| End point values                 | Lambda/RBV/D<br>CV     | Alfa-<br>2a/RBV/TVR    |  |  |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type               | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed      | 294                    | 146                    |  |  |
| Units: Percentage of subjects    |                        |                        |  |  |
| number (confidence interval 95%) | 76.9 (72.1 to<br>81.7) | 67.1 (59.5 to<br>74.7) |  |  |

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**Statistical analyses**

No statistical analyses for this end point

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

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|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects With Rapid Virologic Response (RVR) |
|-----------------|--|

---

**End point description:**

RVR was defined as HCV RNA <LLOQ TND at Week 4 of treatment. The LLOQ was 25 IU/mL. 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 ITT population, the numerator was based on subjects meeting the response criteria and denominator based on all treated subjects.

---

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

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**End point timeframe:**

Week 4

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| End point values                 | Lambda/RBV/D<br>CV     | Alfa-<br>2a/RBV/TVR    |  |  |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type               | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed      | 294                    | 146                    |  |  |
| Units: Percentage of subjects    |                        |                        |  |  |
| number (confidence interval 95%) | 79.3 (74.6 to<br>83.9) | 75.3 (68.4 to<br>82.3) |  |  |

---

**Statistical analyses**

No statistical analyses for this end point

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

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects With Complete Early Virologic Response (cEVR) |
|-----------------|--|

End point description:

cEVR was defined as HCV RNA <LLOQ TND at Week 12 of treatment. The LLOQ was 25 IU/mL. 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 ITT 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 12

| End point values                 | Lambda/RBV/D<br>CV  | Alfa-<br>2a/RBV/TVR |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 294                 | 146                 |  |  |
| Units: Percentage of subjects    |                     |                     |  |  |
| number (confidence interval 95%) | 93.5 (90.7 to 96.3) | 80.1 (73.7 to 86.6) |  |  |

**Statistical analyses**

No statistical analyses for this end point

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

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects With End of Treatment Response (EOTR) |
|-----------------|--|

End point description:

EOTR was defined as HCV RNA <LLOQ TND at end of treatment. The LLOQ was 25 IU/mL. 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 ITT 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:

End of treatment (up to Week 48)

| End point values                 | Lambda/RBV/D<br>CV  | Alfa-<br>2a/RBV/TVR |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 294                 | 146                 |  |  |
| Units: Percentage of subjects    |                     |                     |  |  |
| number (confidence interval 95%) | 95.6 (93.2 to 97.9) | 89 (84 to 94.1)     |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects with Treatment Emergent Grade 3 to 4 Laboratory Abnormalities

|                 |  |
|-----------------|--|
| End point title | Number of Subjects with Treatment Emergent Grade 3 to 4 Laboratory Abnormalities |
|-----------------|--|

End point description:

On-treatment emergent abnormalities were those with a higher toxicity grade than the baseline toxicity grade. Laboratory abnormalities were determined and graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 1.0. Hemoglobin: <7.5 g/dL; Platelet count: <50,000/mm<sup>3</sup>; International Normalized Ratio (INR) : >2.0\*Upper limit of normal (ULN); Leukocytes: <1,500/mm<sup>3</sup>; Lymphocytes (Absolute) : <500/mm<sup>3</sup>; Neutrophils + bands (absolute): <750/mm<sup>3</sup>; Alanine aminotransferase (ALT) : >5\*ULN; Aspartate aminotransferase (AST): >5\*ULN; Bilirubin (Total) : >2.5\*ULN; G-Glutamyl transferase (GGT): >5\*ULN; Amylase: >2.0\*ULN; Lipase: >3\*ULN; Creatinine: >1.8\*ULN. The analysis was performed on all subjects who received at least 1 dose of study therapy.

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

End point timeframe:

From Day 1 of study treatment up to Week 48

| End point values            | Lambda/RBV/D<br>CV | Alfa-<br>2a/RBV/TVR |  |  |
|-----------------------------|--------------------|---------------------|--|--|
| Subject group type          | Reporting group    | Reporting group     |  |  |
| Number of subjects analysed | 294                | 146                 |  |  |
| Units: Subjects             |                    |                     |  |  |
| Hemoglobin                  | 6                  | 30                  |  |  |
| INR                         | 2                  | 1                   |  |  |
| Leukocytes                  | 2                  | 19                  |  |  |
| Lymphocytes                 | 10                 | 30                  |  |  |
| Neutrophils + bands         | 3                  | 36                  |  |  |
| ALT                         | 13                 | 2                   |  |  |
| AST                         | 26                 | 4                   |  |  |
| Bilirubin (Total)           | 28                 | 3                   |  |  |
| Bilirubin (Direct)          | 18                 | 1                   |  |  |
| GGT                         | 40                 | 7                   |  |  |
| Amylase                     | 5                  | 5                   |  |  |
| Lipase                      | 1                  | 3                   |  |  |
| Creatinine                  | 0                  | 2                   |  |  |
| Platelet count              | 1                  | 5                   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Day 1 of study treatment up to Week 48

Adverse event reporting additional description:

On-treatment period (1 death reported at follow-up week 12).

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

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

### Reporting groups

|                       |                |
|-----------------------|----------------|
| Reporting group title | Lambda/RBV/DCV |
|-----------------------|----------------|

Reporting group description:

Subjects (treatment-naïve or prior relapsers to alfa-2a/RBV) received daclatasvir (DCV) tablets 60 mg orally, once daily for 12 weeks, pegIFNlambda-1a injection 180 µg subcutaneously, once weekly and RBV tablets for a total daily dose of 1000-1200 mg orally twice daily for 24 weeks. Subjects were originally required to be followed-up for a minimum total period of 24 weeks post-treatment and subjects with any futility criteria or lack of efficacy [HCV RNA  $\geq$  lower limit of quantitation (LLOQ) at Week 48] were required to be followed-up for a period of 48 weeks post-treatment. Following the Sponsor's decision to terminate the Lambda development program, the follow-up requirements for all study subjects irrespective of treatment response were modified to a total period of 12 weeks post-treatment.

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Alfa-2a/RBV/TVR |
|-----------------------|-----------------|

Reporting group description:

Subjects (treatment-naïve or prior relapsers to alfa-2a/RBV) received telaprevir tablets 375 mg orally, thrice daily for 12 weeks, pegIFNalpha-2a injection 180 µg subcutaneously, once weekly and ribavirin tablets for a total daily dose of 1000-1200 mg orally twice daily for up to 48 weeks [duration of treatment based on eRVR response (HCV RNA < LLOQ at Weeks 4 and 12)]. At Week 24, subjects who achieved eRVR were discontinued from therapy versus subjects who failed to achieve eRVR yet continued to demonstrate benefit from therapy received an additional 24 weeks of pegIFNalpha-2a/RBV for a total treatment course of 48 weeks. Following discontinuation of study therapy, all subjects were originally planned to complete 24 weeks of post-treatment follow-up. Following the Sponsor's decision to terminate the Lambda development program, the follow-up requirements for all study subjects irrespective of treatment response were modified to a total period of 12 weeks post-treatment.

| Serious adverse events  | Lambda/RBV/DCV   | Alfa-2a/RBV/TVR   |  |
|---|------------------|-------------------|--|
| Total subjects affected by serious adverse events                   |                  |                   |  |
| subjects affected / exposed   | 11 / 294 (3.74%) | 16 / 146 (10.96%) |  |
| number of deaths (all causes)                                       | 0                | 1                 |  |
| number of deaths resulting from adverse events                      | 0                | 0                 |  |
| Investigations  |                  |                   |  |
| Blood bilirubin increased   |                  |                   |  |
| subjects affected / exposed   | 1 / 294 (0.34%)  | 0 / 146 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 1 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0             |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                   |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| Hepatocellular carcinoma                             |                 |                 |  |
| subjects affected / exposed                          | 0 / 294 (0.00%) | 1 / 146 (0.68%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                             |                 |                 |  |
| Syncope  |                 |                 |  |
| subjects affected / exposed                          | 1 / 294 (0.34%) | 1 / 146 (0.68%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Malaise  |                 |                 |  |
| subjects affected / exposed                          | 0 / 294 (0.00%) | 2 / 146 (1.37%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Fatigue  |                 |                 |  |
| subjects affected / exposed                          | 0 / 294 (0.00%) | 1 / 146 (0.68%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders                 |                 |                 |  |
| Anaemia  |                 |                 |  |
| subjects affected / exposed                          | 0 / 294 (0.00%) | 1 / 146 (0.68%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                           |                 |                 |  |
| Pancreatitis acute                                   |                 |                 |  |
| subjects affected / exposed                          | 0 / 294 (0.00%) | 1 / 146 (0.68%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Vomiting   |                 |                 |  |
| subjects affected / exposed                          | 0 / 294 (0.00%) | 1 / 146 (0.68%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                              |                 |                 |  |
| Jaundice   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 3 / 294 (1.02%) | 0 / 146 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholelithiasis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 294 (0.34%) | 0 / 146 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic function abnormal                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 294 (0.34%) | 0 / 146 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperbilirubinaemia                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 294 (0.34%) | 0 / 146 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Liver disorder                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 294 (0.34%) | 0 / 146 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Autoimmune hepatitis                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 294 (0.00%) | 1 / 146 (0.68%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Interstitial lung disease                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 294 (0.00%) | 1 / 146 (0.68%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Rash  |                 |                 |  |
| subjects affected / exposed                     | 0 / 294 (0.00%) | 5 / 146 (3.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 5 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Drug reaction with eosinophilia and systemic symptoms |                 |                 |  |
| subjects affected / exposed                           | 0 / 294 (0.00%) | 1 / 146 (0.68%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Rash generalised                                      |                 |                 |  |
| subjects affected / exposed                           | 0 / 294 (0.00%) | 1 / 146 (0.68%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Urticaria   |                 |                 |  |
| subjects affected / exposed                           | 0 / 294 (0.00%) | 1 / 146 (0.68%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                           |                 |                 |  |
| Renal failure acute                                   |                 |                 |  |
| subjects affected / exposed                           | 0 / 294 (0.00%) | 2 / 146 (1.37%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Infections and infestations                           |                 |                 |  |
| Acinetobacter bacteraemia                             |                 |                 |  |
| subjects affected / exposed                           | 1 / 294 (0.34%) | 0 / 146 (0.00%) |  |
| occurrences causally related to treatment / all       | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Escherichia sepsis                                    |                 |                 |  |
| subjects affected / exposed                           | 1 / 294 (0.34%) | 0 / 146 (0.00%) |  |
| occurrences causally related to treatment / all       | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Streptococcal bacteraemia                             |                 |                 |  |
| subjects affected / exposed                           | 1 / 294 (0.34%) | 0 / 146 (0.00%) |  |
| occurrences causally related to treatment / all       | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |
| Pneumonia   |                 |                 |  |
| subjects affected / exposed                           | 0 / 294 (0.00%) | 1 / 146 (0.68%) |  |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Sepsis  |                 |                 |  |
| subjects affected / exposed                     | 0 / 294 (0.00%) | 1 / 146 (0.68%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 294 (0.00%) | 1 / 146 (0.68%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 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>                     | Lambda/RBV/DCV     | Alfa-2a/RBV/TVR    |  |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                    |                    |  |
| subjects affected / exposed                           | 235 / 294 (79.93%) | 136 / 146 (93.15%) |  |
| Investigations  |                    |                    |  |
| Blood uric acid increased                             |                    |                    |  |
| subjects affected / exposed                           | 8 / 294 (2.72%)    | 11 / 146 (7.53%)   |  |
| occurrences (all)                                     | 8                  | 11                 |  |
| Creatinine renal clearance decreased                  |                    |                    |  |
| subjects affected / exposed                           | 1 / 294 (0.34%)    | 9 / 146 (6.16%)    |  |
| occurrences (all)                                     | 1                  | 9                  |  |
| Alanine aminotransferase increased                    |                    |                    |  |
| subjects affected / exposed                           | 20 / 294 (6.80%)   | 4 / 146 (2.74%)    |  |
| occurrences (all)                                     | 21                 | 4                  |  |
| Aspartate aminotransferase increased                  |                    |                    |  |
| subjects affected / exposed                           | 24 / 294 (8.16%)   | 3 / 146 (2.05%)    |  |
| occurrences (all)                                     | 26                 | 3                  |  |
| Blood bilirubin increased                             |                    |                    |  |
| subjects affected / exposed                           | 20 / 294 (6.80%)   | 3 / 146 (2.05%)    |  |
| occurrences (all)                                     | 22                 | 3                  |  |
| Nervous system disorders                              |                    |                    |  |
| Headache  |                    |                    |  |
| subjects affected / exposed                           | 38 / 294 (12.93%)  | 27 / 146 (18.49%)  |  |
| occurrences (all)                                     | 69                 | 41                 |  |
| Dizziness   |                    |                    |  |

|   |                        |                         |  |
|---|------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)        | 23 / 294 (7.82%)<br>39 | 22 / 146 (15.07%)<br>24 |  |
| General disorders and administration<br>site conditions |                        |                         |  |
| Fatigue   |                        |                         |  |
| subjects affected / exposed                             | 55 / 294 (18.71%)      | 44 / 146 (30.14%)       |  |
| occurrences (all)                                       | 65                     | 48                      |  |
| Pyrexia   |                        |                         |  |
| subjects affected / exposed                             | 23 / 294 (7.82%)       | 31 / 146 (21.23%)       |  |
| occurrences (all)                                       | 29                     | 50                      |  |
| Asthenia  |                        |                         |  |
| subjects affected / exposed                             | 58 / 294 (19.73%)      | 27 / 146 (18.49%)       |  |
| occurrences (all)                                       | 66                     | 34                      |  |
| Malaise   |                        |                         |  |
| subjects affected / exposed                             | 13 / 294 (4.42%)       | 17 / 146 (11.64%)       |  |
| occurrences (all)                                       | 13                     | 17                      |  |
| Chills  |                        |                         |  |
| subjects affected / exposed                             | 9 / 294 (3.06%)        | 14 / 146 (9.59%)        |  |
| occurrences (all)                                       | 18                     | 27                      |  |
| Blood and lymphatic system disorders                    |                        |                         |  |
| Anaemia   |                        |                         |  |
| subjects affected / exposed                             | 31 / 294 (10.54%)      | 75 / 146 (51.37%)       |  |
| occurrences (all)                                       | 35                     | 79                      |  |
| Neutropenia   |                        |                         |  |
| subjects affected / exposed                             | 3 / 294 (1.02%)        | 35 / 146 (23.97%)       |  |
| occurrences (all)                                       | 3                      | 40                      |  |
| Leukopenia  |                        |                         |  |
| subjects affected / exposed                             | 0 / 294 (0.00%)        | 13 / 146 (8.90%)        |  |
| occurrences (all)                                       | 0                      | 19                      |  |
| Thrombocytopenia  |                        |                         |  |
| subjects affected / exposed                             | 1 / 294 (0.34%)        | 9 / 146 (6.16%)         |  |
| occurrences (all)                                       | 1                      | 10                      |  |
| Gastrointestinal disorders                              |                        |                         |  |
| Nausea  |                        |                         |  |
| subjects affected / exposed                             | 43 / 294 (14.63%)      | 41 / 146 (28.08%)       |  |
| occurrences (all)                                       | 56                     | 50                      |  |
| Anal pruritus   |                        |                         |  |

|   |                           |                         |  |
|---|---------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 2 / 294 (0.68%)<br>2      | 14 / 146 (9.59%)<br>16  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)   | 32 / 294 (10.88%)<br>35   | 14 / 146 (9.59%)<br>14  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)  | 14 / 294 (4.76%)<br>17    | 11 / 146 (7.53%)<br>16  |  |
| Epigastric discomfort<br>subjects affected / exposed<br>occurrences (all)                                       | 1 / 294 (0.34%)<br>1      | 9 / 146 (6.16%)<br>9    |  |
| Dry mouth<br>subjects affected / exposed<br>occurrences (all)   | 2 / 294 (0.68%)<br>2      | 8 / 146 (5.48%)<br>10   |  |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)   | 16 / 294 (5.44%)<br>16    | 8 / 146 (5.48%)<br>8    |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)  | 16 / 294 (5.44%)<br>19    | 5 / 146 (3.42%)<br>6    |  |
| Respiratory, thoracic and mediastinal disorders<br>Dyspnoea<br>subjects affected / exposed<br>occurrences (all) | 19 / 294 (6.46%)<br>22    | 25 / 146 (17.12%)<br>31 |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)   | 18 / 294 (6.12%)<br>19    | 19 / 146 (13.01%)<br>20 |  |
| Skin and subcutaneous tissue disorders<br>Pruritus<br>subjects affected / exposed<br>occurrences (all)          | 106 / 294 (36.05%)<br>120 | 59 / 146 (40.41%)<br>69 |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)  | 49 / 294 (16.67%)<br>54   | 58 / 146 (39.73%)<br>64 |  |
| Alopecia  |                           |                         |  |

|  |                         |                         |  |
|--|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 13 / 294 (4.42%)<br>13  | 17 / 146 (11.64%)<br>18 |  |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)   | 22 / 294 (7.48%)<br>22  | 17 / 146 (11.64%)<br>17 |  |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)                          | 60 / 294 (20.41%)<br>64 | 33 / 146 (22.60%)<br>36 |  |
| Musculoskeletal and connective tissue disorders<br>Myalgia<br>subjects affected / exposed<br>occurrences (all) | 37 / 294 (12.59%)<br>47 | 23 / 146 (15.75%)<br>35 |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)   | 34 / 294 (11.56%)<br>43 | 15 / 146 (10.27%)<br>22 |  |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)             | 16 / 294 (5.44%)<br>23  | 3 / 146 (2.05%)<br>3    |  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all)   | 32 / 294 (10.88%)<br>34 | 37 / 146 (25.34%)<br>41 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 25 October 2012  | The recommendations from the Food and Drug Administration following their review of the protocol at the end of phase-2 meeting on 15-Oct-2012, to clarify some inclusion/exclusion criteria and study procedures and to incorporate some administrative changes.   |
| 20 February 2013 | New safety information on telaprevir was added in to the protocol along with the clarifications on the list of prohibited medications during dosing with daclatasvir, new cardiac safety monitoring procedures and guidelines for subjects who develop clinically significant symptoms suggestive of cardiac pathology and clarify some study. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated after all subjects completed the post-dosing Week 12 follow-up visit.

Notes: