



## Clinical trial results:

### A Randomized, Open-Labelled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 and ABT-333 Co-administered with Ribavirin Compared to Telaprevir Co-administered with Pegylated Interferon -2a and Ribavirin in Treatment-Experienced Adults with Chronic Hepatitis C Genotype 1 Virus Infection (MALACHITE II)

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2012-003738-18 |
| Trial protocol           | HU FI SK PL    |
| Global end of trial date | 20 July 2015   |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 29 July 2016 |
| First version publication date | 29 July 2016 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | M13-862 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01854528 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | AbbVie Deutschland GmbH & Co. KG  |
| Sponsor organisation address | Abbott House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6 4XE |
| Public contact               | Global Medical Information, AbbVie, 001 800-633-9110,   |
| Scientific contact           | Yan Luo, MD, PhD, AbbVie, yan.luo@abbvie.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                       | 20 July 2015 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 20 July 2015 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study is to assess the efficacy (the percentage of subjects achieving 12-week sustained virologic response, SVR12, [HCV RNA < LLOQ 12 weeks post-treatment]) and safety of ABT-450/r/ABT-267 and ABT-333 co-administered with RBV for 12 weeks compared to 12 weeks of treatment with telaprevir and pegIFN/RBV followed by either 12 weeks or 36 weeks of pegIFN/RBV, per local prescribing information, in treatment-experienced HCV genotype 1-infected adults.

Protection of trial subjects:

Subject read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 18 June 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: 34    |
| Country: Number of subjects enrolled | Slovakia: 15  |
| Country: Number of subjects enrolled | Finland: 1    |
| Country: Number of subjects enrolled | Hungary: 17   |
| Country: Number of subjects enrolled | Argentina: 1  |
| Country: Number of subjects enrolled | Australia: 20 |
| Country: Number of subjects enrolled | Chile: 9      |
| Country: Number of subjects enrolled | Romania: 57   |
| Worldwide total number of subjects   | 154           |
| EEA total number of subjects         | 124           |

Notes:

### Subjects enrolled per age group

|   |   |
|---|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23          | 0 |

|                           |     |
|---------------------------|-----|
| months)                   |     |
| Children (2-11 years)     | 0   |
| Adolescents (12-17 years) | 0   |
| Adults (18-64 years)      | 152 |
| From 65 to 84 years       | 2   |
| 85 years and over         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 154 subjects were randomized: 6 subjects did not receive at least 1 dose of study drug and were excluded from the analyses; 148 subjects received at least 1 dose and were included in the intent-to-treat (ITT) population.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Not blinded                    |

### Arms

|                              |           |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes       |
| <b>Arm title</b>             | 3-DAA/RBV |

Arm description:

3-DAA (ABT-450/r/ABT-267 [150 mg/ 100 mg/ 25 mg once daily] and ABT-333 [250 mg twice daily]) plus weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for 12 weeks.

|  |  |
|--|--|
| Arm type                               | Experimental   |
| Investigational medicinal product name | ABT-450/r/ABT-267  |
| Investigational medicinal product code |  |
| Other name                             | ABT-267 also known as ombitasvir, ABT-450 also known as paritaprevir, Viekirax |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use   |

Dosage and administration details:

ABT-450 (150 mg) coformulated with ritonavir (100 mg) and ABT-267 (25 mg) administered once daily

|  |                    |
|--|--------------------|
| Investigational medicinal product name | ABT-333            |
| Investigational medicinal product code |                    |
| Other name                             | dasabuvir, Exviera |
| Pharmaceutical forms                   | Tablet             |
| Routes of administration               | Oral use           |

Dosage and administration details:

ABT-333 250 mg administered twice daily

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

Dosage and administration details:

weight-based ribivarin administered twice daily

|                  |         |
|------------------|---------|
| <b>Arm title</b> | TPV/RBV |
|------------------|---------|

Arm description:

TPV (750 mg every 8 hours) coadministered with pegIFN (180 micrograms subcutaneously [SC] weekly) and weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for 12 weeks, followed by pegIFN (180 micrograms SC weekly) and weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for either 12 or 36 weeks, per local prescribing information.

|          |                   |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

|   |  |
|---|--|
| Investigational medicinal product name  | Pegylated Interferon a-2a (PegINF)           |
| Investigational medicinal product code  |  |
| Other name  |  |
| Pharmaceutical forms  | Solution for injection in pre-filled syringe |
| Routes of administration  | Subcutaneous use                             |
| Dosage and administration details:<br>PegINF 180 mcg administered weekly              |  |
| Investigational medicinal product name  | Telaprevir                                   |
| Investigational medicinal product code  |  |
| Other name  |  |
| Pharmaceutical forms  | Film-coated tablet                           |
| Routes of administration  | Oral use                                     |
| Dosage and administration details:<br>telepravir 750 mg administered every 8 hours.   |  |
| Investigational medicinal product name  | Ribivarin                                    |
| Investigational medicinal product code  |  |
| Other name  |  |
| Pharmaceutical forms  | Tablet                                       |
| Routes of administration  | Oral use                                     |
| Dosage and administration details:<br>weight-based ribivarin administered twice daily |  |

| <b>Number of subjects in period 1<sup>[1]</sup></b> | 3-DAA/RBV | TPV/RBV |
|---|-----------|---------|
| Started   | 101       | 47      |
| Completed   | 101       | 32      |
| Not completed                                       | 0         | 15      |
| Virologic failure                                   | -         | 9       |
| Adverse event                                       | -         | 4       |
| Withdrawal by subject                               | -         | 2       |

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: A total of 154 subjects were randomized: 6 subjects did not receive at least 1 dose of study drug and were excluded from the analyses; 148 subjects received at least 1 dose and were included in the intent-to-treat (ITT) population.

## Baseline characteristics

### Reporting groups

|   |           |
|---|-----------|
| Reporting group title   | 3-DAA/RBV |
| Reporting group description:<br>3-DAA (ABT-450/r/ABT-267 [150 mg/ 100 mg/ 25 mg once daily] and ABT-333 [250 mg twice daily]) plus weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for 12 weeks.   |           |
| Reporting group title   | TPV/RBV   |
| Reporting group description:<br>TPV (750 mg every 8 hours) coadministered with pegIFN (180 micrograms subcutaneously [SC] weekly) and weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for 12 weeks, followed by pegIFN (180 micrograms SC weekly) and weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for either 12 or 36 weeks, per local prescribing information. |           |

| Reporting group values   | 3-DAA/RBV | TPV/RBV | Total |
|--|-----------|---------|-------|
| Number of subjects   | 101       | 47      | 148   |
| Age categorical  |           |         |       |
| Units: Subjects  |           |         |       |
| Age continuous   |           |         |       |
| All randomized subjects who received at least 1 dose of study drug (ITT population) were included in baseline analysis population. |           |         |       |
| Units: years   |           |         |       |
| arithmetic mean  | 46.9      | 45      |       |
| standard deviation   | ± 12.15   | ± 10.35 | -     |
| Gender categorical   |           |         |       |
| All randomized subjects who received at least 1 dose of study drug (ITT population) were included in baseline analysis population. |           |         |       |
| Units: Subjects  |           |         |       |
| Female   | 46        | 19      | 65    |
| Male   | 55        | 28      | 83    |

## End points

### End points reporting groups

|   |           |
|---|-----------|
| Reporting group title   | 3-DAA/RBV |
| Reporting group description:<br>3-DAA (ABT-450/r/ABT-267 [150 mg/ 100 mg/ 25 mg once daily] and ABT-333 [250 mg twice daily]) plus weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for 12 weeks.   |           |
| Reporting group title   | TPV/RBV   |
| Reporting group description:<br>TPV (750 mg every 8 hours) coadministered with pegIFN (180 micrograms subcutaneously [SC] weekly) and weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for 12 weeks, followed by pegIFN (180 micrograms SC weekly) and weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for either 12 or 36 weeks, per local prescribing information. |           |

### Primary: Percentage of Subjects With Sustained Virologic Response 12 Weeks After Treatment

|   |   |
|---|---|
| End point title   | Percentage of Subjects With Sustained Virologic Response 12 Weeks After Treatment |
| End point description:<br>The percentage of subjects with sustained virologic response (plasma Hepatitis C virus ribonucleic acid [HCV RNA] level less than the lower limit of quantitation [ $< \text{LLOQ}$ ]) 12 weeks after the last dose of study drug. The LLOQ for the assay was 25 IU/mL. |   |
| End point type  | Primary   |
| End point timeframe:<br>12 weeks after the last dose of study drug  |   |

| End point values              | 3-DAA/RBV          | TPV/RBV           |  |  |
|-------------------------------|--------------------|-------------------|--|--|
| Subject group type            | Reporting group    | Reporting group   |  |  |
| Number of subjects analysed   | 101 <sup>[1]</sup> | 47 <sup>[2]</sup> |  |  |
| Units: percentage of subjects |                    |                   |  |  |
| number (not applicable)       | 100                | 66                |  |  |

Notes:

[1] - ITT population: All randomized subjects who received at least 1 dose of study drug.

[2] - ITT population: All randomized subjects who received at least 1 dose of study drug.

### Statistical analyses

|   |                        |
|---|------------------------|
| Statistical analysis title  | Statistical Analysis 1 |
| Statistical analysis description:<br>P-value for the difference in sustained virologic response rates 12 weeks after the last dose between treatment groups with HCV subgenotype (1a, non-1a) from stratum adjusted Mantel-Haenszel with previous type of response to pegIFN/RBV treatment (relapser, partial or null responder) as strata. |                        |
| Comparison groups   | 3-DAA/RBV v TPV/RBV    |

|   |                                  |
|---|----------------------------------|
| Number of subjects included in analysis | 148                              |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | other                            |
| P-value                                 | < 0.001                          |
| Method                                  | Stratum adjusted Mantel-Haenszel |
| Parameter estimate                      | Mean difference (final values)   |
| Point estimate                          | 34.26                            |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | 21.09                            |
| upper limit                             | 47.42                            |

### Secondary: Mean Change From Baseline to Final Treatment Visit in the Mental Component Summary (MCS) Score of the Short-Form 36 Health Survey - Version 2 (SF-36v2)

|                        |  |
|------------------------|--|
| End point title        | Mean Change From Baseline to Final Treatment Visit in the Mental Component Summary (MCS) Score of the Short-Form 36 Health Survey - Version 2 (SF-36v2)  |
| End point description: | The SF-36v2 is a general health-related quality of life (HRQoL) instrument with extensive use in multiple disease states. The SF-36v2 instrument comprises a total of 36 items (questions) targeting a subject's functional health and well-being in 8 domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health). Domain scores were aggregated into an MCS score (from 0 to 100; a higher score indicates better mental function and well-being). |
| End point type         | Secondary  |
| End point timeframe:   | Baseline and Final Treatment Visit (up to Week 12 for 3-DAA/RBV and up to Week 24 or 48 for TPV/RBV)   |

| End point values                     | 3-DAA/RBV          | TPV/RBV           |  |  |
|--------------------------------------|--------------------|-------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group   |  |  |
| Number of subjects analysed          | 101 <sup>[3]</sup> | 45 <sup>[4]</sup> |  |  |
| Units: units on a scale              |                    |                   |  |  |
| arithmetic mean (standard deviation) | -1.3 (± 8.32)      | -9.8 (± 11.05)    |  |  |

Notes:

[3] - All subjects in the ITT population with evaluable data

[4] - All subjects in the ITT population with evaluable data

### Statistical analyses

|                                   |  |
|-----------------------------------|--|
| Statistical analysis title        | Statistical Analysis 1   |
| Statistical analysis description: | P-value from ANCOVA model including baseline score and region as covariates and treatment arm as a factor. |
| Comparison groups                 | 3-DAA/RBV v TPV/RBV  |



|   |                    |
|---|--------------------|
| Number of subjects included in analysis | 146                |
| Analysis specification                  | Pre-specified      |
| Analysis type                           | other              |
| P-value                                 | < 0.001            |
| Method                                  | ANCOVA             |
| Parameter estimate                      | LS mean difference |
| Point estimate                          | 8.64               |
| Confidence interval                     |                    |
| level                                   | 95 %               |
| sides                                   | 2-sided            |
| lower limit                             | 5.43               |
| upper limit                             | 11.85              |

## Secondary: Mean Change From Baseline to Final Treatment Visit in the Physical Component Summary (PCS) Score of the Short-Form 36 Health Survey - Version 2 (SF-36v2)

|                 |   |
|-----------------|---|
| End point title | Mean Change From Baseline to Final Treatment Visit in the Physical Component Summary (PCS) Score of the Short-Form 36 Health Survey - Version 2 (SF-36v2) |
|-----------------|---|

End point description:

The SF-36v2 is a general health-related quality of life (HRQoL) instrument with extensive use in multiple disease states. The SF-36v2 instrument comprises a total of 36 items (questions) targeting a subject's functional health and well-being in 8 domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health). Domain scores were aggregated into a PCS score (range = 0 to 100; a higher score indicates better mental function and well-being).

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

End point timeframe:

Baseline and Final Treatment Visit (up to Week 12 for 3-DAA/RBV and up to Week 24 or 48 for TPV/RBV)

| End point values                     | 3-DAA/RBV          | TPV/RBV           |  |  |
|--------------------------------------|--------------------|-------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group   |  |  |
| Number of subjects analysed          | 101 <sup>[5]</sup> | 45 <sup>[6]</sup> |  |  |
| Units: units of a scale              |                    |                   |  |  |
| arithmetic mean (standard deviation) | 0.4 (± 7.16)       | -7.7 (± 7.72)     |  |  |

Notes:

[5] - All subjects in the ITT population with evaluable data

[6] - All subjects in the ITT population with evaluable data

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

P-value from ANCOVA model including baseline score and region as covariates and treatment arm as a factor.

|                   |                     |
|-------------------|---------------------|
| Comparison groups | 3-DAA/RBV v TPV/RBV |
|-------------------|---------------------|

|   |                    |
|---|--------------------|
| Number of subjects included in analysis | 146                |
| Analysis specification                  | Pre-specified      |
| Analysis type                           | other              |
| P-value                                 | < 0.001            |
| Method                                  | ANCOVA             |
| Parameter estimate                      | LS mean difference |
| Point estimate                          | 7.55               |
| Confidence interval                     |                    |
| level                                   | 95 %               |
| sides                                   | 2-sided            |
| lower limit                             | 5.11               |
| upper limit                             | 9.98               |

## Secondary: Percentage of Subjects With Sustained Virologic Response 24 Weeks After Treatment

|  |   |
|--|---|
| End point title  | Percentage of Subjects With Sustained Virologic Response 24 Weeks After Treatment |
| End point description:   |   |
| The percentage of subjects with sustained virologic response (plasma Hepatitis C virus ribonucleic acid [HCV RNA] level less than the lower limit of quantitation [< LLOQ]) 24 weeks after the last dose of study drug. The LLOQ for the assay was 25 IU/mL. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| 24 weeks after the last dose of study drug   |   |

| End point values              | 3-DAA/RBV          | TPV/RBV           |  |  |
|-------------------------------|--------------------|-------------------|--|--|
| Subject group type            | Reporting group    | Reporting group   |  |  |
| Number of subjects analysed   | 101 <sup>[7]</sup> | 47 <sup>[8]</sup> |  |  |
| Units: percentage of subjects |                    |                   |  |  |
| number (not applicable)       | 99                 | 66                |  |  |

Notes:

[7] - All subjects in the ITT population with evaluable data

[8] - All subjects in the ITT population with evaluable data

## Statistical analyses

|   |                        |
|---|------------------------|
| Statistical analysis title  | Statistical Analysis 1 |
| Statistical analysis description:   |                        |
| P-value from logistic regression model including treatment arm, baseline log <sub>10</sub> HCV RNA level, HCV subgenotype, and previous response to pegIFN/RBV treatment as predictors. |                        |
| Comparison groups   | 3-DAA/RBV v TPV/RBV    |
| Number of subjects included in analysis   | 148                    |
| Analysis specification  | Pre-specified          |
| Analysis type   | other                  |
| P-value   | < 0.001                |
| Method  | Regression, Logistic   |
| Parameter estimate  | Odds ratio (OR)        |
| Point estimate  | 54.7                   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 6.9     |
| upper limit         | 435.1   |

### Secondary: Percentage of Subjects With Virologic Failure During Treatment

|  |  |
|--|--|
| End point title  | Percentage of Subjects With Virologic Failure During Treatment |
| End point description:   |  |
| Virologic failure during treatment was defined as HCV ribonucleic acid (RNA) confirmed greater than or equal to the lower limit of quantification ( $\geq$ LLOQ) after HCV RNA < LLOQ during treatment or confirmed HCV RNA $\geq$ LLOQ at the end of treatment. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Baseline to end of treatment (12 weeks for 3-DAA/RBV and 24 or 48 weeks for TPV/RBV)   |  |

| End point values                 | 3-DAA/RBV          | TPV/RBV            |  |  |
|----------------------------------|--------------------|--------------------|--|--|
| Subject group type               | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed      | 101 <sup>[9]</sup> | 47 <sup>[10]</sup> |  |  |
| Units: percentage of subjects    |                    |                    |  |  |
| number (confidence interval 95%) | 0 (0 to 3.7)       | 19.1 (7.9 to 30.4) |  |  |

Notes:

[9] - ITT population

[10] - ITT population

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With Virologic Relapse After Treatment

|   |   |
|---|---|
| End point title   | Percentage of Subjects With Virologic Relapse After Treatment |
| End point description:  |   |
| Subjects who completed treatment with plasma HCV RNA less than the lower limit of quantification (<LLOQ) at the end of treatment were considered to have virologic relapse if they had confirmed HCV RNA $\geq$ LLOQ during the posttreatment period. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Between end of treatment (Week 12 for 3-DAA/RBV and Week 24 or 48 for TPV/RBV) and Post-treatment (up to Week 12 Post-treatment)  |   |

| <b>End point values</b>          | 3-DAA/RBV           | TPV/RBV            |  |  |
|----------------------------------|---------------------|--------------------|--|--|
| Subject group type               | Reporting group     | Reporting group    |  |  |
| Number of subjects analysed      | 101 <sup>[11]</sup> | 47 <sup>[12]</sup> |  |  |
| Units: percentage of subjects    |                     |                    |  |  |
| number (confidence interval 95%) | 0 (0 to 3.7)        | 6.3 (0 to 14.6)    |  |  |

Notes:

[11] - ITT population

[12] - ITT population

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs were collected from the time of study drug administration to 30 days after last dose of study drug (up to 52 weeks); SAEs were also collected from the time that informed consent was obtained until the end of the study (total up to 101 weeks).

Adverse event reporting additional description:

AEs were collected from first dose to 30 days after last dose (16 weeks for 12-week treatment, 28 weeks for 24-week treatment, 52 weeks for 48-week treatment); SAEs were collected from the time that informed consent was obtained to end of study (up to 65 weeks for 12-week treatment, 77 weeks for 24-week treatment, 101 weeks for 48-week treatment).

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

### Dictionary used

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

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | 3-DAA/RBV |
|-----------------------|-----------|

Reporting group description:

3-DAA (ABT-450/r/ABT-267 [150 mg/ 100 mg/ 25 mg once daily] and ABT-333 [250 mg twice daily]) plus weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for 12 weeks.

|                       |         |
|-----------------------|---------|
| Reporting group title | TPV/RBV |
|-----------------------|---------|

Reporting group description:

TPV (750 mg every 8 hours) coadministered with pegIFN (180 micrograms subcutaneously [SC] weekly) and weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for 12 weeks, followed by pegIFN (180 micrograms SC weekly) and weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for either 12 or 36 weeks, per local prescribing information.

| Serious adverse events                            | 3-DAA/RBV       | TPV/RBV         |  |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events |                 |                 |  |
| subjects affected / exposed                       | 1 / 101 (0.99%) | 5 / 47 (10.64%) |  |
| number of deaths (all causes)                     | 1               | 0               |  |
| number of deaths resulting from adverse events    |                 |                 |  |
| Nervous system disorders                          |                 |                 |  |
| Epilepsy  |                 |                 |  |
| subjects affected / exposed                       | 1 / 101 (0.99%) | 0 / 47 (0.00%)  |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders              |                 |                 |  |
| Anaemia   |                 |                 |  |
| subjects affected / exposed                       | 0 / 101 (0.00%) | 2 / 47 (4.26%)  |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| General disorders and administration              |                 |                 |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| site conditions                                 |                 |                |  |
| Injection site phlebitis                        |                 |                |  |
| subjects affected / exposed                     | 0 / 101 (0.00%) | 1 / 47 (2.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Gastrointestinal disorders                      |                 |                |  |
| Abdominal pain                                  |                 |                |  |
| subjects affected / exposed                     | 0 / 101 (0.00%) | 1 / 47 (2.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Skin and subcutaneous tissue disorders          |                 |                |  |
| Eczema  |                 |                |  |
| subjects affected / exposed                     | 0 / 101 (0.00%) | 1 / 47 (2.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Infections and infestations                     |                 |                |  |
| Appendicitis                                    |                 |                |  |
| subjects affected / exposed                     | 1 / 101 (0.99%) | 0 / 47 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Diarrhoea infectious                            |                 |                |  |
| subjects affected / exposed                     | 0 / 101 (0.00%) | 1 / 47 (2.13%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Staphylococcal sepsis                           |                 |                |  |
| subjects affected / exposed                     | 0 / 101 (0.00%) | 1 / 47 (2.13%) |  |
| 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>                     | 3-DAA/RBV         | TPV/RBV          |  |
| Total subjects affected by non-serious adverse events |                   |                  |  |
| subjects affected / exposed                           | 54 / 101 (53.47%) | 43 / 47 (91.49%) |  |
| Nervous system disorders                              |                   |                  |  |

|  |                         |                        |  |
|--|-------------------------|------------------------|--|
| Dizziness<br>subjects affected / exposed<br>occurrences (all)        | 5 / 101 (4.95%)<br>5    | 7 / 47 (14.89%)<br>8   |  |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)        | 1 / 101 (0.99%)<br>1    | 4 / 47 (8.51%)<br>4    |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)         | 29 / 101 (28.71%)<br>34 | 21 / 47 (44.68%)<br>23 |  |
| Lethargy<br>subjects affected / exposed<br>occurrences (all)         | 5 / 101 (4.95%)<br>5    | 3 / 47 (6.38%)<br>3    |  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)     | 0 / 101 (0.00%)<br>0    | 3 / 47 (6.38%)<br>3    |  |
| Blood and lymphatic system disorders                                 |                         |                        |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)          | 3 / 101 (2.97%)<br>5    | 14 / 47 (29.79%)<br>20 |  |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)       | 0 / 101 (0.00%)<br>0    | 5 / 47 (10.64%)<br>12  |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)      | 1 / 101 (0.99%)<br>1    | 12 / 47 (25.53%)<br>24 |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all) | 0 / 101 (0.00%)<br>0    | 4 / 47 (8.51%)<br>4    |  |
| General disorders and administration site conditions                 |                         |                        |  |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)         | 8 / 101 (7.92%)<br>8    | 16 / 47 (34.04%)<br>16 |  |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)       | 0 / 101 (0.00%)<br>0    | 3 / 47 (6.38%)<br>3    |  |
| Chills   |                         |                        |  |

|                                       |                   |                  |  |
|---------------------------------------|-------------------|------------------|--|
| subjects affected / exposed           | 3 / 101 (2.97%)   | 5 / 47 (10.64%)  |  |
| occurrences (all)                     | 3                 | 6                |  |
| Fatigue                               |                   |                  |  |
| subjects affected / exposed           | 12 / 101 (11.88%) | 12 / 47 (25.53%) |  |
| occurrences (all)                     | 14                | 13               |  |
| General physical health deterioration |                   |                  |  |
| subjects affected / exposed           | 0 / 101 (0.00%)   | 3 / 47 (6.38%)   |  |
| occurrences (all)                     | 0                 | 3                |  |
| influenza like illness                |                   |                  |  |
| subjects affected / exposed           | 0 / 101 (0.00%)   | 4 / 47 (8.51%)   |  |
| occurrences (all)                     | 0                 | 5                |  |
| Injection site erythema               |                   |                  |  |
| subjects affected / exposed           | 0 / 101 (0.00%)   | 3 / 47 (6.38%)   |  |
| occurrences (all)                     | 0                 | 3                |  |
| Pyrexia                               |                   |                  |  |
| subjects affected / exposed           | 2 / 101 (1.98%)   | 15 / 47 (31.91%) |  |
| occurrences (all)                     | 2                 | 19               |  |
| Gastrointestinal disorders            |                   |                  |  |
| Abdominal pain                        |                   |                  |  |
| subjects affected / exposed           | 3 / 101 (2.97%)   | 4 / 47 (8.51%)   |  |
| occurrences (all)                     | 3                 | 4                |  |
| Abdominal pain upper                  |                   |                  |  |
| subjects affected / exposed           | 3 / 101 (2.97%)   | 4 / 47 (8.51%)   |  |
| occurrences (all)                     | 3                 | 4                |  |
| Anal pruritus                         |                   |                  |  |
| subjects affected / exposed           | 0 / 101 (0.00%)   | 12 / 47 (25.53%) |  |
| occurrences (all)                     | 0                 | 12               |  |
| Aphthous stomatitis                   |                   |                  |  |
| subjects affected / exposed           | 0 / 101 (0.00%)   | 3 / 47 (6.38%)   |  |
| occurrences (all)                     | 0                 | 4                |  |
| Haemorrhoids                          |                   |                  |  |
| subjects affected / exposed           | 0 / 101 (0.00%)   | 3 / 47 (6.38%)   |  |
| occurrences (all)                     | 0                 | 4                |  |
| Nausea                                |                   |                  |  |
| subjects affected / exposed           | 10 / 101 (9.90%)  | 20 / 47 (42.55%) |  |
| occurrences (all)                     | 11                | 22               |  |



|  |   |  |  |
|--|---|--|--|
| Vomiting<br>subjects affected / exposed<br>occurrences (all)   | 3 / 101 (2.97%)<br>3  | 7 / 47 (14.89%)<br>8   |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)<br><br>Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)   | 7 / 101 (6.93%)<br>8<br><br>1 / 101 (0.99%)<br>1  | 12 / 47 (25.53%)<br>16<br><br>3 / 47 (6.38%)<br>3  |  |
| Skin and subcutaneous tissue disorders<br>Alopecia<br>subjects affected / exposed<br>occurrences (all)<br><br>Dry skin<br>subjects affected / exposed<br>occurrences (all)<br><br>Eczema<br>subjects affected / exposed<br>occurrences (all)<br><br>Pruritus<br>subjects affected / exposed<br>occurrences (all)<br><br>Pruritus generalised<br>subjects affected / exposed<br>occurrences (all)<br><br>Rash<br>subjects affected / exposed<br>occurrences (all) | 0 / 101 (0.00%)<br>0<br><br>0 / 101 (0.00%)<br>0<br><br>0 / 101 (0.00%)<br>0<br><br>13 / 101 (12.87%)<br>19<br><br>0 / 101 (0.00%)<br>0<br><br>3 / 101 (2.97%)<br>4 | 6 / 47 (12.77%)<br>6<br><br>7 / 47 (14.89%)<br>7<br><br>3 / 47 (6.38%)<br>3<br><br>19 / 47 (40.43%)<br>21<br><br>3 / 47 (6.38%)<br>3<br><br>12 / 47 (25.53%)<br>15 |  |
| Psychiatric disorders<br>Depressed mood<br>subjects affected / exposed<br>occurrences (all)<br><br>Depression<br>subjects affected / exposed<br>occurrences (all)  | 0 / 101 (0.00%)<br>0<br><br>0 / 101 (0.00%)<br>0  | 3 / 47 (6.38%)<br>3<br><br>3 / 47 (6.38%)<br>3   |  |

|   |                      |                        |  |
|---|----------------------|------------------------|--|
| Insomnia<br>subjects affected / exposed<br>occurrences (all)  | 6 / 101 (5.94%)<br>6 | 10 / 47 (21.28%)<br>10 |  |
| Irritability<br>subjects affected / exposed<br>occurrences (all)  | 2 / 101 (1.98%)<br>2 | 5 / 47 (10.64%)<br>5   |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 3 / 101 (2.97%)<br>3 | 8 / 47 (17.02%)<br>10  |  |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)   | 2 / 101 (1.98%)<br>2 | 3 / 47 (6.38%)<br>3    |  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)   | 3 / 101 (2.97%)<br>3 | 9 / 47 (19.15%)<br>14  |  |
| Infections and infestations<br>Gastroenteritis<br>subjects affected / exposed<br>occurrences (all)                | 2 / 101 (1.98%)<br>2 | 3 / 47 (6.38%)<br>3    |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)   | 5 / 101 (4.95%)<br>5 | 5 / 47 (10.64%)<br>9   |  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all)      | 3 / 101 (2.97%)<br>3 | 8 / 47 (17.02%)<br>8   |  |
| Hypertriglyceridaemia<br>subjects affected / exposed<br>occurrences (all)   | 1 / 101 (0.99%)<br>1 | 3 / 47 (6.38%)<br>5    |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 28 December 2012 | The purpose of this amendment was to clarify the definition of relapser and study activities and procedures.   |
| 10 April 2013    | The purpose of this amendment was to prohibit the use of hormonal contraceptives during study drug administration.   |
| 18 June 2013     | The purpose of this amendment was to adjust the stratification proportion of genotype 1a versus non-1a subjects, clarify re-screening criteria, allow enrollment of subjects with a borderline pregnancy test result under certain circumstances, and allow appropriate use of over-the-counter and prescription medication. |
| 30 October 2013  | The purpose of this amendment was to adjust the stratification proportion of genotype 1a versus non-1a subjects and include the option of conducting certain visits in the home.   |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported