



Clinical trial results:

An Open-Label, Multicenter Study to Evaluate Long-Term Outcomes With ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 With or Without Ribavirin (RBV) in Adults With Genotype 1 Chronic Hepatitis C Virus (HCV) Infection (TOPAZ-I)

Summary

| | |
|--------------------------|---|
| EudraCT number | 2014-001022-14 |
| Trial protocol | PT GB IE AT ES IT DE NO SE BE FI NL BG PL DK GR |
| Global end of trial date | 13 May 2021 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 29 March 2022 |
| First version publication date | 29 March 2022 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | M14-423 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|--------------------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02219490 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Companion study M14-222: NCT02167945 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | AbbVie |
| Sponsor organisation address | AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6-4UB |
| Public contact | Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com |
| Scientific contact | Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@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 | 13 May 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 13 May 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

This study (M14-423; TOPAZ-I), was a Phase 3b, open-label, multicenter study conducted at sites outside the United States which, together with its companion study M14-422 (TOPAZ-II, conducted in the United States), was designed with the primary objective of assessing the effect of treatment response on long-term clinical outcomes in adults with chronic HCV GT1 infection with or without compensated cirrhosis, who were either treatment-naïve or interferon/ribavirin (IFN/RBV) treatment-experienced. In both studies, participants were treated with the 3-DAA regimen with or without RBV. This study consisted of a screening period of up to 42 days, a treatment period of either 12 weeks for HCV GT1a-infected subjects without cirrhosis and for HCV GT1b-infected subjects without cirrhosis or with compensated cirrhosis or 24 weeks for GT1a-infected participants with compensated cirrhosis, and a 260-week post-treatment period.

Protection of trial subjects:

Subjects must have been able to understand and adhere to the study visit schedule and all other protocol requirements and must have voluntarily signed and dated an informed consent form, approved by an Institutional Review Board (IRB), prior to the initiation of any screening or study specific procedures.

Background therapy: -

Evidence for comparator:

Number of subjects ages 18-64: 1413 in Study M14-423 and 541 in Study M14-222

Number of subjects ages 65-84 years: 183 in Study M14-423 and 74 in Study M14-222

| | |
|---|-----------------|
| Actual start date of recruitment | 30 October 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Denmark: 21 |
| Country: Number of subjects enrolled | Finland: 14 |
| Country: Number of subjects enrolled | France: 120 |
| Country: Number of subjects enrolled | Germany: 83 |
| Country: Number of subjects enrolled | Greece: 21 |
| Country: Number of subjects enrolled | United States: 615 |
| Country: Number of subjects enrolled | Algeria: 25 |
| Country: Number of subjects enrolled | Australia: 80 |
| Country: Number of subjects enrolled | Austria: 21 |
| Country: Number of subjects enrolled | Belgium: 21 |

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Bulgaria: 35 |
| Country: Number of subjects enrolled | Canada: 105 |
| Country: Number of subjects enrolled | Ireland: 21 |
| Country: Number of subjects enrolled | Israel: 28 |
| Country: Number of subjects enrolled | Italy: 161 |
| Country: Number of subjects enrolled | Mexico: 77 |
| Country: Number of subjects enrolled | Netherlands: 21 |
| Country: Number of subjects enrolled | Norway: 27 |
| Country: Number of subjects enrolled | Poland: 42 |
| Country: Number of subjects enrolled | Portugal: 130 |
| Country: Number of subjects enrolled | Romania: 100 |
| Country: Number of subjects enrolled | Russian Federation: 113 |
| Country: Number of subjects enrolled | Saudi Arabia: 23 |
| Country: Number of subjects enrolled | Spain: 105 |
| Country: Number of subjects enrolled | Sweden: 21 |
| Country: Number of subjects enrolled | Switzerland: 21 |
| Country: Number of subjects enrolled | Turkey: 55 |
| Country: Number of subjects enrolled | United Kingdom: 105 |
| Worldwide total number of subjects | 2211 |
| EEA total number of subjects | 964 |

Notes:

Subjects enrolled per age group

| | |
|---|------|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 1954 |
| From 65 to 84 years | 257 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Safety population: All participants enrolled in this study (M14-423; TOPAZ-I) and in Study M14-222; TOPAZ-II who received at least one dose of study drug

Period 1

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

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | M14-423: ABT-450/r/ABT-267 plus ABT-333 +/- Ribavirin (RBV) |

Arm description:

Study M14-423: Participants with HCV GT1b without cirrhosis received the 3-DAA (ABT-450/ritonavir/ABT-267 and ABT-333) regimen: two 75 mg ABT-450/50 mg ritonavir/12.5 mg ABT-267 tablets taken orally every morning (QD) and one ABT-333 250 mg tablet taken orally twice a day (BID) for 12 weeks. Participants with HCV GT1a without cirrhosis and those with HCV GT1b with cirrhosis received the 3-DAA regimen and weight-based ribavirin (RBV; 1000 to 1200 mg divided twice daily per local label) for 12 weeks. Participants with HCV GT1a with cirrhosis received the 3-DAA regimen and weight-based RBV per local label for 24 weeks.

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

Dosage and administration details:

Participants with HCV GT1b without cirrhosis, those with HCV GT1a without cirrhosis, and those with HCV GT1b with cirrhosis received two 75 mg ABT-450/50 mg ritonavir/12.5 mg ABT-267 tablets taken orally every morning (QD) for 12 weeks. Participants with HCV GT1a with cirrhosis received this regimen for 24 weeks.

| | |
|--|--|
| Investigational medicinal product name | ABT-333 |
| Investigational medicinal product code | |
| Other name | ABT-333 also known as dasabuvir, ABT-333 also known as Exviera |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants with HCV GT1b without cirrhosis, those with HCV GT1a without cirrhosis, and those with HCV GT1b with cirrhosis received one ABT-333 250 mg tablet taken orally twice a day (BID) for 12 weeks. Participants with HCV GT1a with cirrhosis received one ABT-333 250 mg tablet taken orally twice a day (BID) mg/day for 24 weeks.

| | |
|--|--------------------|
| Investigational medicinal product name | Ribavirin (RBV) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |

| | |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

Participants with HCV GT1a without cirrhosis and those with HCV GT1b with cirrhosis received weight-based ribavirin (1000 to 1200 mg divided twice daily per local label) for 12 weeks. Participants with HCV GT1a with cirrhosis received weight-based RBV per local label for 24 weeks.

| | |
|------------------|---|
| Arm title | M14-222: ABT-450/r/ABT-267 plus ABT-333 +/- Ribavirin (RBV) |
|------------------|---|

Arm description:

Study M14-222: Participants with HCV GT1b without cirrhosis received the 3-DAA (ABT-450/ritonavir/ABT-267 and ABT-333) regimen: two 75 mg ABT-450/50 mg ritonavir/12.5 mg ABT-267 tablets taken orally every morning (QD) and one ABT-333 250 mg tablet taken orally twice a day (BID) for 12 weeks. Participants with HCV GT1a without cirrhosis and those with HCV GT1b with cirrhosis received the 3-DAA regimen and weight-based ribavirin (RBV; 1000 to 1200 mg divided twice daily per local label) for 12 weeks. Participants with HCV GT1a with cirrhosis received the 3-DAA regimen and weight-based RBV per local label for 24 weeks.

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

Dosage and administration details:

Participants with HCV GT1b without cirrhosis, those with HCV GT1a without cirrhosis, and those with HCV GT1b with cirrhosis received two 75 mg ABT-450/50 mg ritonavir/12.5 mg ABT-267 tablets taken orally every morning (QD) for 12 weeks. Participants with HCV GT1a with cirrhosis received this regimen for 24 weeks.

| | |
|--|--|
| Investigational medicinal product name | ABT-333 |
| Investigational medicinal product code | |
| Other name | ABT-333 also known as dasabuvir, ABT-333 also known as Exviera |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants with HCV GT1b without cirrhosis, those with HCV GT1a without cirrhosis, and those with HCV GT1b with cirrhosis received one ABT-333 250 mg tablet taken orally twice a day (BID) for 12 weeks. Participants with HCV GT1a with cirrhosis received one ABT-333 250 mg tablet taken orally twice a day (BID) mg/day for 24 weeks.

| | |
|--|--------------------|
| Investigational medicinal product name | Ribavirin (RBV) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants with HCV GT1a without cirrhosis and those with HCV GT1b with cirrhosis received weight-based ribavirin (1000 to 1200 mg divided twice daily per local label) for 12 weeks. Participants with HCV GT1a with cirrhosis received weight-based RBV per local label for 24 weeks.

| Number of subjects in period 1 | M14-423: ABT-450/r/ABT-267 plus ABT-333 +/- Ribavirin (RBV) | M14-222: ABT-450/r/ABT-267 plus ABT-333 +/- Ribavirin (RBV) |
|---------------------------------------|--|--|
| Started | 1596 | 615 |
| Completed | 1258 | 366 |
| Not completed | 338 | 249 |
| Adverse event, non-fatal | 24 | 16 |
| Other, not specified | 57 | 63 |
| COVID-19 logistical restrictions | 33 | 6 |
| Withdrew consent | 96 | 42 |
| Lost to follow-up | 126 | 122 |
| COVID-19 infection | 2 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | M14-423: ABT-450/r/ABT-267 plus ABT-333 +/- Ribavirin (RBV) |
|-----------------------|---|

Reporting group description:

Study M14-423: Participants with HCV GT1b without cirrhosis received the 3-DAA (ABT-450/ritonavir/ABT-267 and ABT-333) regimen: two 75 mg ABT-450/50 mg ritonavir/12.5 mg ABT-267 tablets taken orally every morning (QD) and one ABT-333 250 mg tablet taken orally twice a day (BID) for 12 weeks. Participants with HCV GT1a without cirrhosis and those with HCV GT1b with cirrhosis received the 3-DAA regimen and weight-based ribavirin (RBV; 1000 to 1200 mg divided twice daily per local label) for 12 weeks. Participants with HCV GT1a with cirrhosis received the 3-DAA regimen and weight-based RBV per local label for 24 weeks.

| | |
|-----------------------|---|
| Reporting group title | M14-222: ABT-450/r/ABT-267 plus ABT-333 +/- Ribavirin (RBV) |
|-----------------------|---|

Reporting group description:

Study M14-222: Participants with HCV GT1b without cirrhosis received the 3-DAA (ABT-450/ritonavir/ABT-267 and ABT-333) regimen: two 75 mg ABT-450/50 mg ritonavir/12.5 mg ABT-267 tablets taken orally every morning (QD) and one ABT-333 250 mg tablet taken orally twice a day (BID) for 12 weeks. Participants with HCV GT1a without cirrhosis and those with HCV GT1b with cirrhosis received the 3-DAA regimen and weight-based ribavirin (RBV; 1000 to 1200 mg divided twice daily per local label) for 12 weeks. Participants with HCV GT1a with cirrhosis received the 3-DAA regimen and weight-based RBV per local label for 24 weeks.

| Reporting group values | M14-423: ABT-450/r/ABT-267 plus ABT-333 +/- Ribavirin (RBV) | M14-222: ABT-450/r/ABT-267 plus ABT-333 +/- Ribavirin (RBV) | Total |
|---|---|---|-------|
| Number of subjects | 1596 | 615 | 2211 |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | 51.2 ± 11.62 | 54.5 ± 10.84 | - |
| Gender categorical Units: Subjects | | | |
| Female | 800 | 243 | 1043 |
| Male | 796 | 372 | 1168 |

End points

End points reporting groups

| | |
|-----------------------|---|
| Reporting group title | M14-423: ABT-450/r/ABT-267 plus ABT-333 +/- Ribavirin (RBV) |
|-----------------------|---|

Reporting group description:

Study M14-423: Participants with HCV GT1b without cirrhosis received the 3-DAA (ABT-450/ritonavir/ABT-267 and ABT-333) regimen: two 75 mg ABT-450/50 mg ritonavir/12.5 mg ABT-267 tablets taken orally every morning (QD) and one ABT-333 250 mg tablet taken orally twice a day (BID) for 12 weeks. Participants with HCV GT1a without cirrhosis and those with HCV GT1b with cirrhosis received the 3-DAA regimen and weight-based ribavirin (RBV; 1000 to 1200 mg divided twice daily per local label) for 12 weeks. Participants with HCV GT1a with cirrhosis received the 3-DAA regimen and weight-based RBV per local label for 24 weeks.

| | |
|-----------------------|---|
| Reporting group title | M14-222: ABT-450/r/ABT-267 plus ABT-333 +/- Ribavirin (RBV) |
|-----------------------|---|

Reporting group description:

Study M14-222: Participants with HCV GT1b without cirrhosis received the 3-DAA (ABT-450/ritonavir/ABT-267 and ABT-333) regimen: two 75 mg ABT-450/50 mg ritonavir/12.5 mg ABT-267 tablets taken orally every morning (QD) and one ABT-333 250 mg tablet taken orally twice a day (BID) for 12 weeks. Participants with HCV GT1a without cirrhosis and those with HCV GT1b with cirrhosis received the 3-DAA regimen and weight-based ribavirin (RBV; 1000 to 1200 mg divided twice daily per local label) for 12 weeks. Participants with HCV GT1a with cirrhosis received the 3-DAA regimen and weight-based RBV per local label for 24 weeks.

| | |
|----------------------------|--|
| Subject analysis set title | Subjects in studies M14-222 & M14-423 who didn't achieve SVR12 |
|----------------------------|--|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

SVR12 was defined as hepatitis C virus ribonucleic acid (HCV RNA) less than the lower limit of quantification (LLOQ) 12 weeks after the last actual dose of study drug.

| | |
|----------------------------|--|
| Subject analysis set title | Subjects in studies M14-222 & M14-423 who achieved SVR12 |
|----------------------------|--|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

SVR12 was defined as hepatitis C virus ribonucleic acid (HCV RNA) less than the lower limit of quantification (LLOQ) 12 weeks after the last actual dose of study drug.

| | |
|----------------------------|---|
| Subject analysis set title | Subjects in study M14-423 who did not achieve SVR12 |
|----------------------------|---|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

SVR12 was defined as hepatitis C virus ribonucleic acid (HCV RNA) less than the lower limit of quantification (LLOQ) 12 weeks after the last actual dose of study drug.

| | |
|----------------------------|--|
| Subject analysis set title | Subjects in study M14-423 who achieved SVR12 |
|----------------------------|--|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

SVR12 was defined as hepatitis C virus ribonucleic acid (HCV RNA) less than the lower limit of quantification (LLOQ) 12 weeks after the last actual dose of study drug.

Primary: All-Cause Death: Time to Event

| | |
|-----------------|--------------------------------|
| End point title | All-Cause Death: Time to Event |
|-----------------|--------------------------------|

End point description:

Time to all-cause death was defined as the number of days from the first day of study drug dosing for the participant to the date of death. All deaths were to be included, regardless of whether the death occurred while the participant was still taking study drug or had previously discontinued study drug. If the participant did not die, their data was to be censored at the date of their last available assessment of clinical outcomes. For participants with no post-baseline assessment, the participant's data was to be censored on the first day of study drug dosing. The event-free survival rates were estimated using Kaplan-Meier methodology and incidence estimates are presented with 95% confidence intervals. The

pre-specified analysis of all-cause death included pooled data from TOPAZ-I (this study) and the companion study TOPAZ-II (M14-222; NCT02167945).

| | |
|--|---------|
| End point type | Primary |
| End point timeframe: | |
| At Post-Treatment Weeks 52, 104, 156, 208, and 260 | |

| End point values | Subjects in studies M14-222 & M14-423 who didn't achieve SVR12 | Subjects in studies M14-222 & M14-423 who achieved SVR12 | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 77 ^[1] | 2134 ^[2] | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Kaplan-Meier estimate at PT Week 52 | 8.3 (3.1 to 21.2) | 0.1 (0.1 to 0.4) | | |
| Kaplan-Meier estimate at PT Week 104 | 8.3 (3.1 to 21.2) | 0.7 (0.4 to 1.1) | | |
| Kaplan-Meier estimate at PT Week 156 | 8.3 (3.1 to 21.2) | 1.2 (0.8 to 1.8) | | |
| Kaplan-Meier estimate at PT Week 208 | 8.3 (3.1 to 21.2) | 1.5 (1.1 to 2.2) | | |
| Kaplan-Meier estimate at PT Week 260 | 8.3 (3.1 to 21.2) | 2.0 (1.5 to 2.8) | | |

Notes:

[1] - ITT: enrolled subjects in this study (M14-423) and Study M14-222 who rcvd ≥ 1 dose of study drug

[2] - ITT: enrolled subjects in this study (M14-423) and Study M14-222 who rcvd ≥ 1 dose of study drug

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Log-rank test |
| Statistical analysis description: | |
| Comparisons between participants in studies M14-222 and M14-423 who achieved SVR12 and those who did not were performed using a log-rank test. | |
| Comparison groups | Subjects in studies M14-222 & M14-423 who didn't achieve SVR12 v Subjects in studies M14-222 & M14-423 who achieved SVR12 |
| Number of subjects included in analysis | 2211 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Log-rank test |

| | |
|----------------------------|--------------------------------|
| Statistical analysis title | Cox proportional hazards model |
|----------------------------|--------------------------------|

Statistical analysis description:

A Cox proportional hazards (PH) model was constructed. The covariates for the model included baseline age, BMI, HCV genotype 1 subtype (1b, non-1b), IL28B genotype (CC, non-CC), prior treatment history

(naive, experienced), baseline HCV RNA levels, baseline fibrosis stage (F0-1, F2, F3, F4), baseline albumin, baseline creatinine clearance, baseline platelet count, history of diabetes (yes, no), APRI, race (white, other), and alcohol use status (current, former, non-drinker).

| | |
|---|---|
| Comparison groups | Subjects in studies M14-222 & M14-423 who didn't achieve SVR12 v Subjects in studies M14-222 & M14-423 who achieved SVR12 |
| Number of subjects included in analysis | 2211 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[3] |
| P-value | < 0.001 |
| Method | Cox proportional hazards model |
| Parameter estimate | Cox Proportional Hazard Ratio |
| Point estimate | 0.126 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.044 |
| upper limit | 0.358 |

Notes:

[3] - The estimated value represents the hazard ratio for developing the event in the group of participants in studies M14-222 and M14-423 who achieved SVR12 compared to the group of participants in studies M14-222 and M14-423 who didn't achieve SVR12.

Primary: Liver-Related Death: Time to Event

| | |
|--|------------------------------------|
| End point title | Liver-Related Death: Time to Event |
| End point description: | |
| Time to liver-related death was defined as days from the 1st day of study drug dosing for the subject to date of liver-related death. All liver-related deaths were to be included, regardless of whether the death occurred while subject was still taking study drug or had previously discontinued study drug. If the subject didn't experience event of interest nor had died (all-cause death), their data was to be censored at date of last available assessment. For those with no post-baseline assessment, data was to be censored on 1st day of study drug dosing. All-cause death was a censoring event for liver-related death. The event-free survival rates were estimated using Kaplan-Meier methodology and incidence estimates are presented with 95% confidence intervals. The pre-specified analysis of liver-related death included pooled data from TOPAZ-I (this study) and the companion study TOPAZ-II (M14-222; NCT02167945). - 999 and 999 = confidence limits not calculable due to zero events at visit | |
| End point type | Primary |
| End point timeframe: | |
| At Post-Treatment Weeks 52, 104, 156, 208, and 260 | |

| End point values | Subjects in studies M14-222 & M14-423 who didn't achieve SVR12 | Subjects in studies M14-222 & M14-423 who achieved SVR12 | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 77 ^[4] | 2134 ^[5] | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Kaplan-Meier estimate at PT Week 52 | 1.4 (0.2 to 9.6) | 0 (-999 to 999) | | |
| Kaplan-Meier estimate at PT Week 104 | 1.4 (0.2 to 9.6) | 0 (-999 to 999) | | |
| Kaplan-Meier estimate at PT Week 156 | 1.4 (0.2 to 9.6) | 0.1 (0.1 to 0.4) | | |
| Kaplan-Meier estimate at PT Week 208 | 1.4 (0.2 to 9.6) | 0.1 (0.1 to 0.4) | | |
| Kaplan-Meier estimate at PT Week 260 | 1.4 (0.2 to 9.6) | 0.1 (0.1 to 0.4) | | |

Notes:

[4] - ITT: enrolled subjects in this study (M14-423) and Study M14-222 who rcvd ≥ 1 dose of study drug

[5] - ITT: enrolled subjects in this study (M14-423) and Study M14-222 who rcvd ≥ 1 dose of study drug

Statistical analyses

| | |
|-----------------------------------|---------------|
| Statistical analysis title | Log-rank test |
|-----------------------------------|---------------|

Statistical analysis description:

Comparisons between participants in studies M14-222 and M14-423 who achieved SVR12 and those who did not were performed using a log-rank test.

| | |
|---|---|
| Comparison groups | Subjects in studies M14-222 & M14-423 who didn't achieve SVR12 v Subjects in studies M14-222 & M14-423 who achieved SVR12 |
| Number of subjects included in analysis | 2211 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Log-rank test |

| | |
|-----------------------------------|--------------------------------|
| Statistical analysis title | Cox proportional hazards model |
|-----------------------------------|--------------------------------|

Statistical analysis description:

A Cox proportional hazards (PH) model was constructed. The covariates for the model included baseline age, BMI, HCV genotype 1 subtype (1b, non-1b), IL28B genotype (CC, non-CC), prior treatment history (naive, experienced), baseline HCV RNA levels, baseline fibrosis stage (F0-1, F2, F3, F4), baseline albumin, baseline creatinine clearance, baseline platelet count, history of diabetes (yes, no), APRI, race (white, other), and alcohol use status (current, former, non-drinker).

| | |
|---|---|
| Comparison groups | Subjects in studies M14-222 & M14-423 who didn't achieve SVR12 v Subjects in studies M14-222 & M14-423 who achieved SVR12 |
| Number of subjects included in analysis | 2211 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[6] |
| P-value | = 0.007 |
| Method | Cox proportional hazards model |
| Parameter estimate | Cox Proportional Hazard Ratio |
| Point estimate | 0.031 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.003 |
| upper limit | 0.38 |

Notes:

[6] - The estimated value represents the hazard ratio for developing the event in the group of participants in studies M14-222 and M14-423 who achieved SVR12 compared to the group of participants in studies M14-222 and M14-423 who didn't achieve SVR12.

Primary: Liver Decompensation: Time to Event

| | |
|-----------------|-------------------------------------|
| End point title | Liver Decompensation: Time to Event |
|-----------------|-------------------------------------|

End point description:

Time to liver decompensation was defined as number of days from the 1st day of study drug dosing for the participant to the date of liver decompensation. All liver decompensation was to be included, regardless of whether it occurred while the participant was still taking study drug or had previously discontinued study drug. If the participant didn't experience the event of interest nor had died (all-cause death), their data was to be censored at the date of their last available assessment of clinical outcomes. For participants with no post-baseline assessment, their data was to be censored on the 1st day of study drug dosing. All-cause death was a censoring event for liver decompensation. The event-free survival rates were estimated using Kaplan-Meier methodology and incidence estimates are presented with 95% confidence intervals. The pre-specified analysis of liver decompensation included pooled data from TOPAZ-I (this study) and the companion study TOPAZ-II (M14-222; NCT02167945).

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

At Post-Treatment Weeks 52, 104, 156, 208, and 260

| End point values | Subjects in studies M14-222 & M14-423 who didn't achieve SVR12 | Subjects in studies M14-222 & M14-423 who achieved SVR12 | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 77 ^[7] | 2134 ^[8] | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Kaplan-Meier estimate at PT Week 52 | 4.5 (1.5 to 13.4) | 0.2 (0.1 to 0.5) | | |
| Kaplan-Meier estimate at PT Week 104 | 4.5 (1.5 to 13.4) | 0.2 (0.1 to 0.5) | | |
| Kaplan-Meier estimate at PT Week 156 | 4.5 (1.5 to 13.4) | 0.3 (0.1 to 0.6) | | |
| Kaplan-Meier estimate at PT Week 208 | 4.5 (1.5 to 13.4) | 0.3 (0.2 to 0.7) | | |
| Kaplan-Meier estimate at PT Week 260 | 4.5 (1.5 to 13.4) | 0.5 (0.2 to 0.9) | | |

Notes:

[7] - ITT: enrolled subjects in this study (M14-423) and Study M14-222 who rcvd ≥ 1 dose of study drug

[8] - ITT: enrolled subjects in this study (M14-423) and Study M14-222 who rcvd ≥ 1 dose of study drug

Statistical analyses

| | |
|----------------------------|---------------|
| Statistical analysis title | Log-rank test |
|----------------------------|---------------|

Statistical analysis description:

Comparisons between participants in studies M14-222 and M14-423 who achieved SVR12 and those who did not were performed using a log-rank test.

| | |
|-------------------|--|
| Comparison groups | Subjects in studies M14-222 & M14-423 who achieved SVR12 v Subjects in studies M14-222 & M14-423 who didn't achieve SVR12 |
|-------------------|--|

| | |
|---|---------------|
| Number of subjects included in analysis | 2211 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Log-rank test |

| | |
|-----------------------------------|--------------------------------|
| Statistical analysis title | Cox proportional hazards model |
|-----------------------------------|--------------------------------|

Statistical analysis description:

A Cox proportional hazards (PH) model was constructed. The covariates for the model included baseline age, BMI, HCV genotype 1 subtype (1b, non-1b), IL28B genotype (CC, non-CC), prior treatment history (naive, experienced), baseline HCV RNA levels, baseline fibrosis stage (F0-1, F2, F3, F4), baseline albumin, baseline creatinine clearance, baseline platelet count, history of diabetes (yes, no), APRI, race (white, other), and alcohol use status (current, former, non-drinker).

| | |
|---|---|
| Comparison groups | Subjects in studies M14-222 & M14-423 who didn't achieve SVR12 v Subjects in studies M14-222 & M14-423 who achieved SVR12 |
| Number of subjects included in analysis | 2211 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[9] |
| P-value | < 0.001 |
| Method | Cox proportional hazards model |
| Parameter estimate | Cox Proportional Hazard Ratio |
| Point estimate | 0.038 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.009 |
| upper limit | 0.156 |

Notes:

[9] - The estimated value represents the hazard ratio for developing the event in the group of participants in studies M14-222 and M14-423 who achieved SVR12 compared to the group of participants in studies M14-222 and M14-423 who didn't achieve SVR12.

Primary: Liver Transplantation: Time to Event

| | |
|-----------------|--------------------------------------|
| End point title | Liver Transplantation: Time to Event |
|-----------------|--------------------------------------|

End point description:

Time to liver transplantation was defined as days from 1st day of study drug dosing for subject to date of liver transplantation. All liver transplantation was to be included, whether it occurred while the subject was still taking study drug or had previously discontinued study drug. If the subject didn't experience event of interest nor had died (all-cause death), their data was to be censored at the date of their last available assessment. For those with no post-baseline assessment, data was to be censored on 1st day of study drug dosing. All-cause death was a censoring event for liver transplantation. The event-free survival rates were estimated using Kaplan-Meier methodology and incidence estimates are presented with 95% confidence intervals. The pre-specified analysis of liver transplantation included pooled data from TOPAZ-I (this study) and the companion study TOPAZ-II (M14-222; NCT02167945). -999 and 999 = confidence limits not calculable due to zero events at visit

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

At Post-Treatment Weeks 52, 104, 156, 208, and 260

| End point values | Subjects in studies M14-222 & M14-423 who didn't achieve SVR12 | Subjects in studies M14-222 & M14-423 who achieved SVR12 | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 77 ^[10] | 2134 ^[11] | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Kaplan-Meier estimate at PT Week 52 | 0 (-999 to 999) | 0 (-999 to 999) | | |
| Kaplan-Meier estimate at PT Week 104 | 0 (-999 to 999) | 0 (-999 to 999) | | |
| Kaplan-Meier estimate at PT Week 156 | 0 (-999 to 999) | 0.1 (0.1 to 0.4) | | |
| Kaplan-Meier estimate at PT Week 208 | 0 (-999 to 999) | 0.1 (0.1 to 0.4) | | |
| Kaplan-Meier estimate at PT Week 260 | 0 (-999 to 999) | 0.2 (0.1 to 0.5) | | |

Notes:

[10] - ITT: enrolled subjects in this study (M14-423) and Study M14-222 who rcvd ≥ 1 dose of study drug

[11] - ITT: enrolled subjects in this study (M14-423) and Study M14-222 who rcvd ≥ 1 dose of study drug

Statistical analyses

| Statistical analysis title | Log-rank test |
|--|---|
| Statistical analysis description: | |
| Comparisons between participants in studies M14-222 and M14-423 who achieved SVR12 and those who did not were performed using a log-rank test. | |
| Comparison groups | Subjects in studies M14-222 & M14-423 who didn't achieve SVR12 v Subjects in studies M14-222 & M14-423 who achieved SVR12 |
| Number of subjects included in analysis | 2211 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.86 |
| Method | Log-rank test |

| Statistical analysis title | Cox proportional hazards model |
|---|---|
| Statistical analysis description: | |
| A Cox proportional hazards (PH) model was constructed. The covariates for the model included baseline age, BMI, HCV genotype 1 subtype (1b, non-1b), IL28B genotype (CC, non-CC), prior treatment history (naive, experienced), baseline HCV RNA levels, baseline fibrosis stage (F0-1, F2, F3, F4), baseline albumin, baseline creatinine clearance, baseline platelet count, history of diabetes (yes, no), APRI, race (white, other), and alcohol use status (current, former, non-drinker). | |
| Comparison groups | Subjects in studies M14-222 & M14-423 who didn't achieve SVR12 v Subjects in studies M14-222 & M14-423 who achieved SVR12 |
| Number of subjects included in analysis | 2211 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[12] |
| P-value | = 0.997 ^[13] |
| Method | Cox proportional hazards model |
| Parameter estimate | Cox Proportional Hazard Ratio |
| Point estimate | 999 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 999 |

Notes:

[12] - The estimated value represents the hazard ratio for developing the event in the group of participants in studies M14-222 and M14-423 who achieved SVR12 compared to the group of participants in studies M14-222 and M14-423 who didn't achieve SVR12.

[13] - The Hazard Ratio is infinite and CI is not bounded due to zero events in one of the groups.

Primary: Hepatocellular Carcinoma: Time to Event

| | |
|-----------------|---|
| End point title | Hepatocellular Carcinoma: Time to Event |
|-----------------|---|

End point description:

Time to hepatocellular carcinoma (HCC) was defined as number of days from 1st day of study drug dosing for subject to date of hepatocellular carcinoma. All HCC was to be included, whether it occurred while subject was still taking study drug or had previously discontinued study drug. If the subject didn't experience the event of interest nor had died (all-cause death), their data was to be censored at the date of their last available assessment. For those with no post-baseline assessment, their data was to be censored on the 1st day of study drug dosing. All-cause death was a censoring event for HCC. The event-free survival rates were estimated using Kaplan-Meier methodology and incidence estimates are presented with 95% confidence intervals. The pre-specified analysis of hepatocellular carcinoma included pooled data from TOPAZ-I (this study) and the companion study TOPAZ-II (M14-222; NCT02167945). - 999 and 999 = confidence limits not calculable due to zero events at visit

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

At Post-Treatment Weeks 52, 104, 156, 208, and 260

| End point values | Subjects in studies M14-222 & M14-423 who didn't achieve SVR12 | Subjects in studies M14-222 & M14-423 who achieved SVR12 | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 77 ^[14] | 2134 ^[15] | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Kaplan-Meier estimate at PT Week 52 | 0 (-999 to 999) | 0.2 (0.1 to 0.5) | | |
| Kaplan-Meier estimate at PT Week 104 | 0 (-999 to 999) | 0.4 (0.2 to 0.8) | | |
| Kaplan-Meier estimate at PT Week 156 | 0 (-999 to 999) | 0.5 (0.3 to 1.0) | | |
| Kaplan-Meier estimate at PT Week 208 | 0 (-999 to 999) | 0.6 (0.4 to 1.1) | | |
| Kaplan-Meier estimate at PT Week 260 | 0 (-999 to 999) | 0.9 (0.5 to 1.4) | | |

Notes:

[14] - ITT: enrolled subjects in this study (M14-423) and Study M14-222 who rcvd ≥ 1 dose of study drug

[15] - ITT: enrolled subjects in this study (M14-423) and Study M14-222 who rcvd ≥ 1 dose of study drug

Statistical analyses

| | |
|----------------------------|---------------|
| Statistical analysis title | Log-rank test |
|----------------------------|---------------|

Statistical analysis description:

Comparisons between participants in studies M14-222 and M14-423 who achieved SVR12 and those who did not were performed using a log-rank test.

| | |
|---|---|
| Comparison groups | Subjects in studies M14-222 & M14-423 who didn't achieve SVR12 v Subjects in studies M14-222 & M14-423 who achieved SVR12 |
| Number of subjects included in analysis | 2211 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.608 |
| Method | Log-rank test |

| | |
|-----------------------------------|--------------------------------|
| Statistical analysis title | Cox proportional hazards model |
|-----------------------------------|--------------------------------|

Statistical analysis description:

A Cox proportional hazards (PH) model was constructed. The covariates for the model included baseline age, BMI, HCV genotype 1 subtype (1b, non-1b), IL28B genotype (CC, non-CC), prior treatment history (naive, experienced), baseline HCV RNA levels, baseline fibrosis stage (F0-1, F2, F3, F4), baseline albumin, baseline creatinine clearance, baseline platelet count, history of diabetes (yes, no), APRI, race (white, other), and alcohol use status (current, former, non-drinker).

| | |
|---|---|
| Comparison groups | Subjects in studies M14-222 & M14-423 who didn't achieve SVR12 v Subjects in studies M14-222 & M14-423 who achieved SVR12 |
| Number of subjects included in analysis | 2211 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[16] |
| P-value | = 0.992 ^[17] |
| Method | Cox proportional hazards model |
| Parameter estimate | Cox Proportional Hazard Ratio |
| Point estimate | 999 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 999 |

Notes:

[16] - The estimated value represents the hazard ratio for developing the event in the group of participants in studies M14-222 and M14-423 who achieved SVR12 compared to the group of participants in studies M14-222 and M14-423 who didn't achieve SVR12.

[17] - The Hazard Ratio is infinite and CI is not bounded due to zero events in one of the groups.

Primary: All-Cause Death, Liver-Related Death, Liver Decompensation, Liver Transplantation, Hepatocellular Carcinoma: Time to Event

| | |
|-----------------|--|
| End point title | All-Cause Death, Liver-Related Death, Liver Decompensation, Liver Transplantation, Hepatocellular Carcinoma: Time to Event |
|-----------------|--|

End point description:

Time to the composite of clinical outcomes is the time to the first occurrence of all-cause death, liver-related death, liver decompensation, liver transplantation, or hepatocellular carcinoma. All first occurrences were to be included, regardless of whether it occurred while the participant was still taking study drug or had previously discontinued study drug. If the participant did not experience any of these events, their data was to be censored at the date of their last available assessment of clinical outcomes. For participants with no post-baseline assessment, the participant's data was to be censored on the first day of study drug dosing. The event-free survival rates were estimated using Kaplan-Meier methodology and incidence estimates are presented with 95% confidence intervals. Pre-specified analysis included pooled data from this study and from TOPAZ-II; NCT02167945.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

At Post-Treatment Weeks 52, 104, 156, 208, and 260

| End point values | Subjects in studies M14-222 & M14-423 who didn't achieve SVR12 | Subjects in studies M14-222 & M14-423 who achieved SVR12 | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 77 ^[18] | 2134 ^[19] | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Kaplan-Meier estimate at PT Week 52 | 11.4 (5.2 to 24.2) | 0.5 (0.3 to 0.9) | | |
| Kaplan-Meier estimate at PT Week 104 | 11.4 (5.2 to 24.2) | 1.2 (0.8 to 1.8) | | |
| Kaplan-Meier estimate at PT Week 156 | 11.4 (5.2 to 24.2) | 1.9 (1.4 to 2.6) | | |
| Kaplan-Meier estimate at PT Week 208 | 11.4 (5.2 to 24.2) | 2.3 (1.7 to 3.1) | | |
| Kaplan-Meier estimate at PT Week 260 | 11.4 (5.2 to 24.2) | 3.2 (2.5 to 4.1) | | |

Notes:

[18] - ITT: enrolled subjects in this study (M14-423) and Study M14-222 who rcvd ≥ 1 dose of study drug

[19] - ITT: enrolled subjects in this study (M14-423) and Study M14-222 who rcvd ≥ 1 dose of study drug

Statistical analyses

| Statistical analysis title | Log-rank test |
|--|---|
| Statistical analysis description: | |
| Comparisons between participants in studies M14-222 and M14-423 who achieved SVR12 and those who did not were performed using a log-rank test. | |
| Comparison groups | Subjects in studies M14-222 & M14-423 who didn't achieve SVR12 v Subjects in studies M14-222 & M14-423 who achieved SVR12 |
| Number of subjects included in analysis | 2211 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Log-rank test |

| Statistical analysis title | Cox proportional hazards model |
|---|---|
| Statistical analysis description: | |
| A Cox proportional hazards (PH) model was constructed. The covariates for the model included baseline age, BMI, HCV genotype 1 subtype (1b, non-1b), IL28B genotype (CC, non-CC), prior treatment history (naive, experienced), baseline HCV RNA levels, baseline fibrosis stage (F0-1, F2, F3, F4), baseline albumin, baseline creatinine clearance, baseline platelet count, history of diabetes (yes, no), APRI, race (white, other), and alcohol use status (current, former, non-drinker). | |
| Comparison groups | Subjects in studies M14-222 & M14-423 who didn't achieve SVR12 v Subjects in studies M14-222 & M14-423 who achieved |

| | |
|---|--------------------------------|
| | SVR12 |
| Number of subjects included in analysis | 2211 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[20] |
| P-value | < 0.001 |
| Method | Cox proportional hazards model |
| Parameter estimate | Cox Proportional Hazard Ratio |
| Point estimate | 0.133 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.057 |
| upper limit | 0.313 |

Notes:

[20] - The estimated value represents the hazard ratio for developing the event in the group of participants in studies M14-222 and M14-423 who achieved SVR12 compared to the group of participants in studies M14-222 and M14-423 who didn't achieve SVR12.

Secondary: Change from Baseline in FibroScan Score by SVR12 Status

| | |
|-----------------|---|
| End point title | Change from Baseline in FibroScan Score by SVR12 Status |
|-----------------|---|

End point description:

The FibroScan test is a validated non-invasive test used to assess liver fibrosis in participants with chronic liver disease, and it was performed at study sites where it was available. For participants with Hepatitis C infection, a FibroScan score of 2-7 kPa indicates no liver scarring or mild scarring; a score of 8 or 9 is associated with moderate liver scarring; 9-14 indicates severe liver scarring; and 14 or higher is indicative of advanced liver scarring, cirrhosis. Negative changes from baseline indicate improvement in liver fibrosis.

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

End point timeframe:

At the final treatment visit and Post-Treatment Weeks 12, 24, 52, 104, 156, 208, and 260

| End point values | Subjects in study M14-423 who did not achieve SVR12 | Subjects in study M14-423 who achieved SVR12 | | |
|--|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 22 ^[21] | 1187 ^[22] | | |
| Units: kPa | | | | |
| arithmetic mean (standard deviation) | | | | |
| At the final treatment visit (n= 22, 1015) | -2.55 (± 3.282) | -1.41 (± 4.283) | | |
| Post-Treatment Week 12 (n= 18, 1171) | -1.81 (± 2.624) | -1.76 (± 4.213) | | |
| Post-Treatment Week 24 (n= 18, 1175) | -1.26 (± 3.211) | -1.98 (± 4.363) | | |
| Post-Treatment Week 52 (n= 13, 1187) | -0.30 (± 1.986) | -2.46 (± 4.858) | | |
| Post-Treatment Week 104 (n= 13, 1122) | -0.35 (± 3.306) | -2.80 (± 5.195) | | |
| Post-Treatment Week 156 (n= 12, 1073) | -0.37 (± 3.999) | -2.92 (± 5.249) | | |
| Post-Treatment Week 208 (n= 12, 978) | -0.88 (± 2.445) | -3.08 (± 5.560) | | |

| | | | | |
|-------------------------------------|----------------------|----------------------|--|--|
| Post-Treatment Week 260 (n= 9, 860) | -1.31 (\pm 3.706) | -3.08 (\pm 5.662) | | |
|-------------------------------------|----------------------|----------------------|--|--|

Notes:

[21] - ITT-I: enrolled subjects in this study (M14-423) who rcvd \geq 1 dose of study drug

[22] - ITT-I: enrolled subjects in this study (M14-423) who rcvd \geq 1 dose of study drug

Statistical analyses

| | |
|-----------------------------------|-----------------------|
| Statistical analysis title | Final Treatment Visit |
|-----------------------------------|-----------------------|

Statistical analysis description:

The effect of sustained virologic response on change from baseline in FibroScan score was evaluated by comparing mean change from baseline between subjects who achieved SVR12 and those who did not using ANCOVA analyses. SVR12 status was included as a factor and baseline FibroScan score was included as a covariate in the ANCOVA model.

| | |
|---|---|
| Comparison groups | Subjects in study M14-423 who did not achieve SVR12 v Subjects in study M14-423 who achieved SVR12 |
| Number of subjects included in analysis | 1209 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[23] |
| P-value | = 0.151 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.37 |
| upper limit | 2.37 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.7 |

Notes:

[23] - Difference = with SVR12 minus without SVR12

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Post-Treatment Week 12 |
|-----------------------------------|------------------------|

Statistical analysis description:

The effect of sustained virologic response on change from baseline in FibroScan score was evaluated by comparing mean change from baseline between subjects who achieved SVR12 and those who did not using ANCOVA analyses. SVR12 status was included as a factor and baseline FibroScan score was included as a covariate in the ANCOVA model.

| | |
|---|---|
| Comparison groups | Subjects in study M14-423 who did not achieve SVR12 v Subjects in study M14-423 who achieved SVR12 |
| Number of subjects included in analysis | 1209 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[24] |
| P-value | = 0.878 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.64 |
| upper limit | 1.4 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.78 |

Notes:

[24] - Difference = with SVR12 minus without SVR12

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Post-Treatment Week 24 |
|-----------------------------------|------------------------|

Statistical analysis description:

The effect of sustained virologic response on change from baseline in FibroScan score was evaluated by comparing mean change from baseline between subjects who achieved SVR12 and those who did not using ANCOVA analyses. SVR12 status was included as a factor and baseline FibroScan score was included as a covariate in the ANCOVA model.

| | |
|---|---|
| Comparison groups | Subjects in study M14-423 who did not achieve SVR12 v Subjects in study M14-423 who achieved SVR12 |
| Number of subjects included in analysis | 1209 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[25] |
| P-value | = 0.199 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.33 |
| upper limit | 0.48 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.72 |

Notes:

[25] - Difference = with SVR12 minus without SVR12

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Post-Treatment Week 52 |
|-----------------------------------|------------------------|

Statistical analysis description:

The effect of sustained virologic response on change from baseline in FibroScan score was evaluated by comparing mean change from baseline between subjects who achieved SVR12 and those who did not using ANCOVA analyses. SVR12 status was included as a factor and baseline FibroScan score was included as a covariate in the ANCOVA model.

| | |
|---|---|
| Comparison groups | Subjects in study M14-423 who did not achieve SVR12 v Subjects in study M14-423 who achieved SVR12 |
| Number of subjects included in analysis | 1209 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[26] |
| P-value | = 0.021 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4 |
| upper limit | -0.33 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.93 |

Notes:

[26] - Difference = with SVR12 minus without SVR12

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Post-Treatment Week 104 |
|-----------------------------------|-------------------------|

Statistical analysis description:

The effect of sustained virologic response on change from baseline in FibroScan score was evaluated by comparing mean change from baseline between subjects who achieved SVR12 and those who did not using ANCOVA analyses. SVR12 status was included as a factor and baseline FibroScan score was included as a covariate in the ANCOVA model.

| | |
|---|---|
| Comparison groups | Subjects in study M14-423 who did not achieve SVR12 v Subjects in study M14-423 who achieved SVR12 |
| Number of subjects included in analysis | 1209 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[27] |
| P-value | = 0.006 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.47 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.22 |
| upper limit | -0.71 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.89 |

Notes:

[27] - Difference = with SVR12 minus without SVR12

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Post-Treatment Week 156 |
|-----------------------------------|-------------------------|

Statistical analysis description:

The effect of sustained virologic response on change from baseline in FibroScan score was evaluated by comparing mean change from baseline between subjects who achieved SVR12 and those who did not using ANCOVA analyses. SVR12 status was included as a factor and baseline FibroScan score was included as a covariate in the ANCOVA model.

| | |
|---|---|
| Comparison groups | Subjects in study M14-423 who did not achieve SVR12 v Subjects in study M14-423 who achieved SVR12 |
| Number of subjects included in analysis | 1209 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[28] |
| P-value | = 0.005 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -2.58 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.38 |
| upper limit | -0.79 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.92 |

Notes:

[28] - Difference = with SVR12 minus without SVR12

| | |
|---|---|
| Statistical analysis title | Post-Treatment Week 208 |
| Statistical analysis description: | |
| The effect of sustained virologic response on change from baseline in FibroScan score was evaluated by comparing mean change from baseline between subjects who achieved SVR12 and those who did not using ANCOVA analyses. SVR12 status was included as a factor and baseline FibroScan score was included as a covariate in the ANCOVA model. | |
| Comparison groups | Subjects in study M14-423 who did not achieve SVR12 v Subjects in study M14-423 who achieved SVR12 |
| Number of subjects included in analysis | 1209 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[29] |
| P-value | = 0.172 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.36 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.32 |
| upper limit | 0.59 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1 |

Notes:

[29] - Difference = with SVR12 minus without SVR12

| | |
|---|---|
| Statistical analysis title | Post-Treatment Week 260 |
| Statistical analysis description: | |
| The effect of sustained virologic response on change from baseline in FibroScan score was evaluated by comparing mean change from baseline between subjects who achieved SVR12 and those who did not using ANCOVA analyses. SVR12 status was included as a factor and baseline FibroScan score was included as a covariate in the ANCOVA model. | |
| Comparison groups | Subjects in study M14-423 who achieved SVR12 v Subjects in study M14-423 who did not achieve SVR12 |
| Number of subjects included in analysis | 1209 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[30] |
| P-value | = 0.322 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -1.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.35 |
| upper limit | 1.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.14 |

Notes:

[30] - Difference = with SVR12 minus without SVR12

Secondary: Percentage of Participants With Sustained Virologic Response 12 Weeks Post-treatment (SVR12)

| | |
|-----------------|--|
| End point title | Percentage of Participants With Sustained Virologic Response 12 Weeks Post-treatment (SVR12) ^[31] |
|-----------------|--|

End point description:

SVR12 is defined as hepatitis C virus ribonucleic acid (HCV RNA) less than the lower limit of quantification (LLOQ) 12 weeks after the last actual dose of study drug. Flanking imputation, where applicable, was used to impute missing data. After applying flanking imputation, if there was no value in the window but there was an HCV RNA value from a local laboratory present, then it was to be imputed into the SVR window. Otherwise, participants with missing data were counted as failures.

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

End point timeframe:

12 weeks after the last actual dose of study drug

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Per protocol, this is a secondary endpoint specific to study M14-423.

| | | | | |
|-----------------------------------|---|--|--|--|
| End point values | M14-423: ABT-450/r/ABT-267 plus ABT-333 +/- Ribavirin (RBV) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 1596 ^[32] | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 97.0 (96.0 to 97.7) | | | |

Notes:

[32] - All enrolled subjects in study M14-423 who received at least 1 dose of study drug

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality reported from study enrollment to end, up to 5 yrs. TEAEs and TESAEs collected from 1st dose of study drug until 30 d after the last administration, up to 203 d. From PT Week 4 to the end of the study, only SAE of death was collected.

Adverse event reporting additional description:

All-cause mortality and adverse events: all study M14-423 participants who received at least one dose of study drug

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | M14-423: ABT-450/r/ABT-267 plus ABT-333 +/- Ribavirin (RBV) |
|-----------------------|---|

Reporting group description:

Study M14-423: Participants with HCV GT1b without cirrhosis received the 3-DAA (ABT-450/ritonavir/ABT-267 and ABT-333) regimen: two 75 mg ABT 450/50 mg ritonavir/12.5 mg ABT-267 tablets taken orally every morning (QD) and one ABT-333 250 mg tablet taken orally twice a day (BID) for 12 weeks. Participants with HCV GT1a without cirrhosis and those with HCV GT1b with cirrhosis received the 3-DAA regimen for 12 weeks. Participants with HCV GT1a with cirrhosis received the 3-DAA regimen for 24 weeks.

| Serious adverse events | M14-423: ABT-450/r/ABT-267 plus ABT-333 +/- Ribavirin (RBV) | | |
|---|---|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 40 / 1596 (2.51%) | | |
| number of deaths (all causes) | 28 | | |
| number of deaths resulting from adverse events | 1 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| HEPATOCELLULAR CARCINOMA | | | |
| subjects affected / exposed | 2 / 1596 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| MALIGNANT MELANOMA | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PANCREATIC NEOPLASM | | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PAPILLARY THYROID CANCER | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| TUMOUR THROMBOSIS | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| HYPERTENSION | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pregnancy, puerperium and perinatal conditions | | | |
| ABORTION SPONTANEOUS | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DRUG INTERACTION | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| ANGER | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| AFFECT LABILITY | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| INSOMNIA | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SCHIZOAFFECTIVE DISORDER | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| MANIA | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| ALANINE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| HEAD INJURY | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| RADIUS FRACTURE | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|------------------|--|--|
| TENDON RUPTURE | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| ANGINA UNSTABLE | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PALPITATIONS | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| CEREBROVASCULAR ACCIDENT | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DIZZINESS POSTURAL | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ENCEPHALOPATHY | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PARAESTHESIA | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PSYCHOMOTOR SKILLS IMPAIRED | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|------------------|--|--|
| SYNCOPE | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| ABDOMINAL PAIN UPPER | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ANAL FISSURE | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ASCITES | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CONSTIPATION | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| COLITIS | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DENTAL CARIES | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|--|---|------------------|--|--|
| GASTRIC ULCER | subjects affected / exposed | 1 / 1596 (0.06%) | | |
| | occurrences causally related to treatment / all | 0 / 1 | | |
| | deaths causally related to treatment / all | 0 / 0 | | |
| DIARRHOEA | subjects affected / exposed | 1 / 1596 (0.06%) | | |
| | occurrences causally related to treatment / all | 0 / 1 | | |
| | deaths causally related to treatment / all | 0 / 0 | | |
| OESOPHAGEAL VARICES HAEMORRHAGE | subjects affected / exposed | 1 / 1596 (0.06%) | | |
| | occurrences causally related to treatment / all | 0 / 1 | | |
| | deaths causally related to treatment / all | 0 / 0 | | |
| VARICES OESOPHAGEAL | subjects affected / exposed | 1 / 1596 (0.06%) | | |
| | occurrences causally related to treatment / all | 1 / 1 | | |
| | deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | | |
| HEPATIC FAILURE | subjects affected / exposed | 1 / 1596 (0.06%) | | |
| | occurrences causally related to treatment / all | 1 / 1 | | |
| | deaths causally related to treatment / all | 0 / 0 | | |
| HEPATORENAL SYNDROME | subjects affected / exposed | 1 / 1596 (0.06%) | | |
| | occurrences causally related to treatment / all | 1 / 1 | | |
| | deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | | |
| ECZEMA | subjects affected / exposed | 1 / 1596 (0.06%) | | |
| | occurrences causally related to treatment / all | 0 / 1 | | |
| | deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | | |
| ACUTE KIDNEY INJURY | | | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CALCULUS URINARY | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| NEPHROLITHIASIS | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| RENAL COLIC | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| PATHOLOGICAL FRACTURE | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| APPENDICITIS | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DERMATITIS INFECTED | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ERYSIPELAS | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|------------------|--|--|
| INFLUENZA | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PERITONITIS BACTERIAL | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PNEUMONIA | | | |
| subjects affected / exposed | 2 / 1596 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| PYELONEPHRITIS | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| DEHYDRATION | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DIABETES MELLITUS | | | |
| subjects affected / exposed | 1 / 1596 (0.06%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| | | | |
|---|---|--|--|
| Non-serious adverse events | M14-423: ABT-450/r/ABT-267 plus ABT-333 +/- Ribavirin (RBV) | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 805 / 1596 (50.44%) | | |
| Nervous system disorders | | | |

| | | | |
|---|--|--|--|
| HEADACHE subjects affected / exposed occurrences (all) | 291 / 1596 (18.23%) 319 | | |
| General disorders and administration site conditions ASTHENIA subjects affected / exposed occurrences (all) | 165 / 1596 (10.34%) 179 | | |
| FATIGUE subjects affected / exposed occurrences (all) | 300 / 1596 (18.80%) 331 | | |
| Gastrointestinal disorders DIARRHOEA subjects affected / exposed occurrences (all) NAUSEA subjects affected / exposed occurrences (all) | 103 / 1596 (6.45%) 112 186 / 1596 (11.65%) 200 | | |
| Skin and subcutaneous tissue disorders PRURITUS subjects affected / exposed occurrences (all) | 199 / 1596 (12.47%) 209 | | |
| Psychiatric disorders INSOMNIA subjects affected / exposed occurrences (all) | 179 / 1596 (11.22%) 183 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 19 January 2015 | <p>Protocol Amendment 2</p> <ul style="list-style-type: none">• Updated treatment duration for subjects with GT1a infection and compensated cirrhosis (F4 fibrosis stage) from 12 to 24 weeks, with 12 weeks considered for some patients where consistent with the local label.• Updated Introduction to remove language detailing effects of ABT-450/ritonavir, ABT-267 (and its major, inactive human metabolites) and ABT-333 on embryo-fetal development.• Updated Introduction to refer investigators to locally approved labels for preclinical toxicology (including reproductive and development toxicity), metabolism, pharmacokinetics and drug-drug interactions in countries that have received marketing approval.• Clarified elevated ALT risk associated with ethinyl estradiol therapy in Section 3.0 Introduction; Integrated Safety Results.• Clarified enrollment caps for cirrhotic subjects.• Updated Contraindicated Medication list in Synopsis and Exclusion 3 (Table 6) to refer investigators to locally approved labels where AbbVie product containing the regimen for this study has been approved.• Updated Schedule of Activities (Table 7) removing duplicate "Study Drug Returned for IRT Reconciliation" entry.• Updated Schedule of Activities (Table 7, footnote "j.") and Section 5.3.1.1 to clarify urine pregnancy testing requirements for subjects on DAA regimen only.• Added AFP to the list of Clinical Laboratory Tests collected at the Screening Visit.• Updated Table 12 to allow for RBV dose modifications in management of hemoglobin decreases per local label.• Updated Section 9.1 to include submission of amendments to Regulatory Authority(ies) as applicable.• Updated Table 4 (Baseline Fibrosis Stage) to correct administrative error for F4 FibroScan range.• Added back-up Sponsor contact phone number to Title Page and Section 6.5. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported