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	51.2	54.5	
standard deviation	± 11.62	± 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 (± 3.706)	-3.08 (± 5.662)		

Notes:

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

[22] - ITT-I: enrolled subjects in this study (M14-423) who rcvd ≥ 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	291 / 1596 (18.23%)		
occurrences (all)	319		
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	165 / 1596 (10.34%)		
occurrences (all)	179		
FATIGUE			
subjects affected / exposed	300 / 1596 (18.80%)		
occurrences (all)	331		
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	103 / 1596 (6.45%)		
occurrences (all)	112		
NAUSEA			
subjects affected / exposed	186 / 1596 (11.65%)		
occurrences (all)	200		
Skin and subcutaneous tissue disorders			
PRURITUS			
subjects affected / exposed	199 / 1596 (12.47%)		
occurrences (all)	209		
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	179 / 1596 (11.22%)		
occurrences (all)	183		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 January 2015	Protocol Amendment 2 ● 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 it 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 were 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