



Clinical trial results:

An Open-Label Study to Evaluate the Safety and Efficacy of Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir with Ribavirin in Adults with Genotype 1 and Ombitasvir/Paritaprevir/Ritonavir with Ribavirin in Adults with Genotype 4 Chronic Hepatitis C Virus Infection and Decompensated Cirrhosis (TURQUOISE-CPB)

Summary

EudraCT number	2014-001477-13
Trial protocol	DE
Global end of trial date	03 March 2017

Results information

Result version number	v1 (current)
This version publication date	25 June 2017
First version publication date	25 June 2017

Trial information

Trial identification

Sponsor protocol code	M14-227
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02219477
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Abbvie Deutschland GmbH & Co.KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6-4UB
Public contact	Krystal Gibbons, BS, AbbVie, krystal.gibbons@abbvie.com
Scientific contact	Eric Cohen, MD, AbbVie, eric.cohen@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	03 March 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study were to assess the safety and the SVR12 rate of ombitasvir/paritaprevir/ritonavir and dasabuvir with RBV in GT1-infected subjects with decompensated cirrhosis.

Protection of trial subjects:

Participant and/or legal guardian read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 November 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects**Subjects enrolled per country**

Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	United States: 22
Worldwide total number of subjects	36
EEA total number of subjects	5

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)	29
From 65 to 84 years	7

85 years and over	0
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Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Eligible subjects had up to 42 days following the Screening Visit to enroll into the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1: GT1B

Arm description:

ombitasvir/paritaprevir/ritonavir 25/150/100 mg once daily (QD) + dasabuvir 250 mg twice daily (BID) + ribavirin (RBV) for 12 weeks in hepatitis C virus (HCV) genotype (GT) 1b-infected participants

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

Dosage and administration details:

Paritaprevir co-formulated with ritonavir and ombitasvir. Ombitasvir/paritaprevir/ritonavir was taken orally as 2 tablets QD which corresponds to a 25 mg ombitasvir/150 mg paritaprevir/100 mg ritonavir dose QD.

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

Dosage and administration details:

Dasabuvir was provided by AbbVie as 250 mg tablets. For GT1-infected subjects, dasabuvir was also taken orally as 1 tablet BID, which corresponds to a 250 mg dose BID.

Investigational medicinal product name	ribavirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

RBV was provided as 200 mg tablets and was taken orally. It is understood that RBV typically has weight-based dosing for subjects, 1000 to 1200 mg divided twice daily, per local label.

Arm title	Group 2: GT1 non-B
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Arm description:

ombitasvir/paritaprevir/ritonavir 25/150/100 mg QD + dasabuvir 250 mg BID + RBV for 24 weeks in HCV GT1non-b (including GT1a)-infected participants

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

Dosage and administration details:

Paritaprevir co-formulated with ritonavir and ombitasvir. Ombitasvir/paritaprevir/ritonavir was taken orally as 2 tablets QD which corresponds to a 25 mg ombitasvir/150 mg paritaprevir/100 mg ritonavir dose QD.

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

Dosage and administration details:

Dasabuvir was provided by AbbVie as 250 mg tablets. For GT1-infected subjects, dasabuvir was also taken orally as 1 tablet BID, which corresponds to a 250 mg dose BID.

Investigational medicinal product name	ribavirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

RBV was provided as 200 mg tablets and was taken orally. It is understood that RBV typically has weight-based dosing for subjects, 1000 to 1200 mg divided twice daily, per local label.

Arm title	Group 3: GT4
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Arm description:

ombitasvir/paritaprevir/ritonavir 25/150/100 mg QD + RBV for 24 weeks in HCV GT4-infected participants

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

Dosage and administration details:

Paritaprevir co-formulated with ritonavir and ombitasvir. Ombitasvir/paritaprevir/ritonavir was taken orally as 2 tablets QD which corresponds to a 25 mg ombitasvir/150 mg paritaprevir/100 mg ritonavir dose QD.

Investigational medicinal product name	ribavirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

RBV was provided as 200 mg tablets and was taken orally. It is understood that RBV typically has weight-based dosing for subjects, 1000 to 1200 mg divided twice daily, per local label.

Number of subjects in period 1	Group 1: GT1B	Group 2: GT1 non-B	Group 3: GT4
Started	9	24	3
Completed	9	22	2
Not completed	0	2	1
Consent withdrawn by subject	-	1	-
Adverse event	-	1	1

Baseline characteristics

Reporting groups

Reporting group title	Group 1: GT1B
Reporting group description: ombitasvir/paritaprevir/ritonavir 25/150/100 mg once daily (QD) + dasabuvir 250 mg twice daily (BID) + ribavirin (RBV) for 12 weeks in hepatitis C virus (HCV) genotype (GT) 1b-infected participants	
Reporting group title	Group 2: GT1 non-B
Reporting group description: ombitasvir/paritaprevir/ritonavir 25/150/100 mg QD + dasabuvir 250 mg BID + RBV for 24 weeks in HCV GT1non-b (including GT1a)-infected participants	
Reporting group title	Group 3: GT4
Reporting group description: ombitasvir/paritaprevir/ritonavir 25/150/100 mg QD + RBV for 24 weeks in HCV GT4-infected participants	

Reporting group values	Group 1: GT1B	Group 2: GT1 non-B	Group 3: GT4
Number of subjects	9	24	3
Age categorical			
Units: Subjects			
< 65 years	7	20	2
>= 65 years	2	4	1
Gender categorical			
Units: Subjects			
Female	2	7	1
Male	7	17	2

Reporting group values	Total		
Number of subjects	36		
Age categorical			
Units: Subjects			
< 65 years	29		
>= 65 years	7		
Gender categorical			
Units: Subjects			
Female	10		
Male	26		

End points

End points reporting groups

Reporting group title	Group 1: GT1B
Reporting group description: ombitasvir/paritaprevir/ritonavir 25/150/100 mg once daily (QD) + dasabuvir 250 mg twice daily (BID) + ribavirin (RBV) for 12 weeks in hepatitis C virus (HCV) genotype (GT) 1b-infected participants	
Reporting group title	Group 2: GT1 non-B
Reporting group description: ombitasvir/paritaprevir/ritonavir 25/150/100 mg QD + dasabuvir 250 mg BID + RBV for 24 weeks in HCV GT1non-b (including GT1a)-infected participants	
Reporting group title	Group 3: GT4
Reporting group description: ombitasvir/paritaprevir/ritonavir 25/150/100 mg QD + RBV for 24 weeks in HCV GT4-infected participants	

Primary: Percentages of Subjects with Sustained Virologic Response 12 Weeks Post-Treatment (SVR12) in Group 1 and in Group 2

End point title	Percentages of Subjects with Sustained Virologic Response 12 Weeks Post-Treatment (SVR12) in Group 1 and in Group 2 ^{[1][2]}
End point description: SVR12, defined as HCV RNA < lower limit of quantification (LLOQ) in the SVR12 window (12 weeks after the last actual dose of study drug) without any confirmed quantifiable (\geq LLOQ) post-treatment value before or during that SVR window. Flanking imputation: for participants with missing HCV RNA at a visit who have an undetectable HCV RNA or unquantifiable HCV RNA at the preceding visit and the succeeding visit, the missing value was imputed as undetectable or unquantifiable. For SVR analyses, if there was no value in the window after the flanking imputation but there was an HCV RNA value after the window, then it was imputed into the SVR window. After above imputations were applied, if there was still no value in the window but there was an HCV RNA value from a local laboratory present, then it was imputed into the SVR window. Otherwise, subjects with missing data were counted as failures. The 95% confidence interval was calculated using the Wilson score method.	
End point type	Primary
End point timeframe: 12 weeks after the last actual dose of study drug	

Notes:

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

Justification: Descriptive statistics are presented, per protocol.

[2] - 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: The primary endpoint was analyzed in Groups 1 and 2 only, per protocol.

End point values	Group 1: GT1B	Group 2: GT1 non-B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9 ^[3]	24 ^[4]		
Units: percentage of subjects				
number (confidence interval 95%)	100 (70.1 to 100)	95.8 (79.8 to 99.3)		

Notes:

[3] - ITT population: subjects who received ≥ 1 dose of study drug; subjects missing data = non-responders.

[4] - ITT population: subjects who received ≥ 1 dose of study drug; subjects missing data = non-responders.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With SVR12 in Group 3

End point title	Percentage of Subjects With SVR12 in Group 3 ^[5]
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End point description:

SVR12, defined as HCV RNA < LLOQ in the SVR12 window (12 weeks after the last actual dose of study drug) without any confirmed quantifiable (\geq LLOQ) post-treatment value before or during that SVR window. Flanking imputation: for participants with missing HCV RNA at a visit, who have an undetectable HCV RNA or unquantifiable HCV RNA at the preceding visit and the succeeding visit, the missing value was imputed as undetectable or unquantifiable. For SVR analyses, if there was no value in the window after the flanking imputation but there was an HCV RNA value after the window, then it was imputed into the SVR window. After above imputations were applied, if there was still no value in the window but there was an HCV RNA value from a local laboratory present, then it was imputed into the SVR window. Otherwise, subjects with missing data were counted as failures.

End point type	Secondary
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End point timeframe:

12 weeks after the last actual dose of study drug

Notes:

[5] - 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: This secondary endpoint was analyzed in Group 3 only, per protocol.

End point values	Group 3: GT4			
Subject group type	Reporting group			
Number of subjects analysed	3 ^[6]			
Units: percentage of subjects				
number (not applicable)	66.7			

Notes:

[6] - ITT population: subjects who received ≥ 1 dose of study drug; subjects missing data = non-responders.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With SVR12 Non-Response Due to Experiencing On-Treatment Virologic Failure

End point title	Percentage of Subjects With SVR12 Non-Response Due to Experiencing On-Treatment Virologic Failure
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End point description:

On-treatment virologic failure was defined as: confirmed HCV RNA \geq LLOQ after HCV RNA < LLOQ during treatment; confirmed increase from nadir in HCV RNA (two consecutive HCV RNA measurements > 1 log₁₀ IU/mL above nadir) at any time point during treatment; or HCV RNA \geq LLOQ persistently during treatment with at least 6 weeks (≥ 36 days) of treatment. The 95% confidence interval was calculated using Wilson score method. SVR12 was defined as HCV RNA < LLOQ in the SVR12 window (12 weeks after the last actual dose of study drug) without any confirmed quantifiable (\geq LLOQ) post-treatment value before or during that SVR window. +/-99999=not applicable; 95% confidence interval was not calculated for Group 3.

End point type	Secondary
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End point timeframe:

Up to 24 weeks during treatment

End point values	Group 1: GT1B	Group 2: GT1 non-B	Group 3: GT4	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9 ^[7]	24 ^[8]	3 ^[9]	
Units: percentage of subjects				
number (confidence interval 95%)	0 (0 to 29.9)	0 (0 to 13.8)	0 (-99999 to 99999)	

Notes:

[7] - Intent-to-treat population: subjects who received ≥ 1 dose of study drug.

[8] - Intent-to-treat population: subjects who received ≥ 1 dose of study drug.

[9] - Intent-to-treat population: subjects who received ≥ 1 dose of study drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With SVR12 Non-Response Due to Experiencing Relapse12

End point title	Percentage of Subjects With SVR12 Non-Response Due to Experiencing Relapse12
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End point description:

Relapse12 was defined as confirmed HCV RNA \geq LLOQ between end of treatment and 12 weeks after last actual dose of active study drug (up to and including the SVR12 window) for a subject with HCV RNA $<$ LLOQ at final treatment visit who completes treatment and has post-treatment HCV RNA data. Completion of treatment was defined as a study drug duration ≥ 77 days for subjects assigned to 12 weeks of treatment or ≥ 154 days for subjects assigned to 24 weeks of treatment. SVR12 was defined as HCV RNA $<$ LLOQ in the SVR12 window (12 weeks after the last actual dose of study drug) without any confirmed quantifiable (\geq LLOQ) post-treatment value before or during that SVR window. The 95% confidence interval was calculated using the Wilson score method. +/-99999=not applicable; 95% confidence interval was not calculated for Group 3.

End point type	Secondary
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End point timeframe:

Up to 12 weeks after the last actual dose of study drug

End point values	Group 1: GT1B	Group 2: GT1 non-B	Group 3: GT4	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7 ^[10]	19 ^[11]	2 ^[12]	
Units: percentage of subjects				
number (confidence interval 95%)	0 (0 to 35.4)	0 (0 to 16.8)	0 (-99999 to 99999)	

Notes:

[10] - Intent-to-treat population: subjects who received ≥ 1 dose of study drug and who had an assessment.

[11] - Intent-to-treat population: subjects who received ≥ 1 dose of study drug and who had an assessment.

[12] - Intent-to-treat population: subjects who received ≥ 1 dose of study drug and who had an assessment.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Improvement From Baseline to Post-Treatment Week 12 in Hepatic Function Tests

End point title	Percentage of Subjects With Improvement From Baseline to Post-Treatment Week 12 in Hepatic Function Tests
End point description:	
Improvement was defined as:	
<ul style="list-style-type: none"> increase of more than 0.2 g/L from baseline to post-treatment Week 12 in albumin decrease of more than 0.3 µmol/L from baseline to post-treatment Week 12 in bilirubin decrease of more than 5 ng/mL from baseline to post-treatment Week 12 in alpha-fetoprotein increase of more than 15×10^9/L from baseline to post-treatment Week 12 in platelet count decrease of more than 0.2 from baseline to post-treatment Week 12 in international normalized ratio. 	
99999=not applicable, since number of subjects=0.	
End point type	Secondary
End point timeframe:	
Up to post-treatment Week 12	

End point values	Group 1: GT1B	Group 2: GT1 non-B	Group 3: GT4	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9 ^[13]	22 ^[14]	2 ^[15]	
Units: percentage of subjects				
number (not applicable)				
Albumin; n=9, 22, 2	77.8	77.3	50	
Bilirubin; n=9, 22, 2	66.7	72.7	100	
Alpha-fetoprotein; n=9, 0, 0	33.3	99999	99999	
Platelet count; n=9, 21, 2	22.2	14.3	0	
International normalized ratio; n=9, 21, 2	0	0	0	

Notes:

[13] - ITT population: subjects who received ≥ 1 dose of study drug and who had assessments at BL & PT WK12.

[14] - ITT population: subjects who received ≥ 1 dose of study drug and who had assessments at BL & PT WK12.

[15] - ITT population: subjects who received ≥ 1 dose of study drug and who had assessments at BL & PT WK12.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Improvement From Baseline to Post-Treatment Week 12 in FibroTest

End point title	Percentage of Subjects With Improvement From Baseline to Post-Treatment Week 12 in FibroTest
End point description:	
The FibroTest score is used to assess liver fibrosis. Scores range from 0.00 to 1.00, with higher scores indicating a greater degree of fibrosis. Improvement was defined as a decrease of more than 0.2 from baseline (BL) to post-treatment (PT) Week 12 (WK12).	
End point type	Secondary
End point timeframe:	
Up to post-treatment Week 12	

End point values	Group 1: GT1B	Group 2: GT1 non-B	Group 3: GT4	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9 ^[16]	22 ^[17]	2 ^[18]	
Units: percentage of subjects				
number (not applicable)	0	9.1	50	

Notes:

[16] - ITT population: subjects who received ≥ 1 dose of study drug and who had assessments at BL & PT WK12.

[17] - ITT population: subjects who received ≥ 1 dose of study drug and who had assessments at BL & PT WK12.

[18] - ITT population: subjects who received ≥ 1 dose of study drug and who had assessments at BL & PT WK12.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Improvement From Baseline to Post-Treatment Week 12 in Child-Pugh Score

End point title	Percentage of Subjects With Improvement From Baseline to Post-Treatment Week 12 in Child-Pugh Score
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End point description:

The Child-Pugh score uses five clinical measures of liver disease (3 laboratory parameters and 2 clinical assessments) to measure severity of cirrhosis. Scores range from 5 to 15, with higher scores indicating more severity. Improvement was defined as a decrease of 1 or more from baseline to post-treatment Week 12.

End point type	Secondary
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End point timeframe:

Up to post-treatment Week 12

End point values	Group 1: GT1B	Group 2: GT1 non-B	Group 3: GT4	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9 ^[19]	22 ^[20]	2 ^[21]	
Units: percentage of subjects				
number (not applicable)	66.7	54.5	50	

Notes:

[19] - ITT population: subjects who received ≥ 1 dose of study drug and who had assessments at BL & PT WK12.

[20] - ITT population: subjects who received ≥ 1 dose of study drug and who had assessments at BL & PT WK12.

[21] - ITT population: subjects who received ≥ 1 dose of study drug and who had assessments at BL & PT WK12.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Improvement From Baseline to Post-Treatment Week 12 in Model for End-Stage Liver Disease (MELD) Score

End point title	Percentage of Subjects With Improvement From Baseline to Post-Treatment Week 12 in Model for End-Stage Liver Disease (MELD) Score
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End point description:

MELD is a scoring system for assessing the severity of chronic liver disease. Scores range from 6 to 40, with higher scores indicating more severity. Improvement was defined as a decrease of 1 or more from baseline to post-treatment Week 12.

End point type	Secondary
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End point timeframe:

Up to post-treatment Week 12

End point values	Group 1: GT1B	Group 2: GT1 non-B	Group 3: GT4	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8 ^[22]	21 ^[23]	2 ^[24]	
Units: percentage of subjects				
number (not applicable)	87.5	61.9	100	

Notes:

[22] - ITT population: subjects who received ≥ 1 dose of study drug and who had assessments at BL & PT WK12.

[23] - ITT population: subjects who received ≥ 1 dose of study drug and who had assessments at BL & PT WK12.

[24] - ITT population: subjects who received ≥ 1 dose of study drug and who had assessments at BL & PT WK12.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Protocol-related treatment-emergent adverse events and treatment-emergent serious adverse events were collected from the first dose of study drug until post treatment Day 30; treatment was up to Week 12 for Group 1, and up to Week 24 for Groups 2 and 3.

Adverse event reporting additional description:

A protocol-related event is defined as any event with onset or worsening reported by a subject from the first dose of study drug until 30 days have elapsed following discontinuation of study drug administration. Events were collected whether elicited or spontaneously reported by the subject.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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Reporting groups

Reporting group title	Group 1: GT1B
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Reporting group description:

ombitasvir/paritaprevir/ritonavir 25/150/100 mg QD + dasabuvir 250 mg BID + RBV for 12 weeks in HCV GT1b-infected participants

Reporting group title	Group 2: GT1 Non-B
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Reporting group description:

ombitasvir/paritaprevir/ritonavir 25/150/100 mg QD + dasabuvir 250 mg BID + RBV for 24 weeks in HCV GT1non-b (including GT1a)-infected participants

Reporting group title	Group 3: GT4
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Reporting group description:

ombitasvir/paritaprevir/ritonavir 25/150/100 mg QD + RBV for 24 weeks in HCV GT4-infected participants

Serious adverse events	Group 1: GT1B	Group 2: GT1 Non-B	Group 3: GT4
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)	10 / 24 (41.67%)	1 / 3 (33.33%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
HEPATOCELLULAR CARCINOMA			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
ACCIDENTAL OVERDOSE			

subjects affected / exposed	0 / 9 (0.00%)	0 / 24 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POST PROCEDURAL COMPLICATION			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
HAEMORRHAGE INTRACRANIAL			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATIC ENCEPHALOPATHY			
subjects affected / exposed	0 / 9 (0.00%)	2 / 24 (8.33%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SYNCOPE			
subjects affected / exposed	0 / 9 (0.00%)	0 / 24 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 9 (0.00%)	2 / 24 (8.33%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCYTOPENIA			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
GENERAL PHYSICAL HEALTH DETERIORATION			

subjects affected / exposed	0 / 9 (0.00%)	0 / 24 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ASCITES			
subjects affected / exposed	1 / 9 (11.11%)	1 / 24 (4.17%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			
subjects affected / exposed	0 / 9 (0.00%)	0 / 24 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMATEMESIS			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMATOOCHEZIA			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OESOPHAGEAL VARICES HAEMORRHAGE			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

HEPATIC FAILURE			
subjects affected / exposed	0 / 9 (0.00%)	0 / 24 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
HYPERBILIRUBINAEMIA			
subjects affected / exposed	1 / 9 (11.11%)	1 / 24 (4.17%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	0 / 9 (0.00%)	0 / 24 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
RENAL FAILURE			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
PERITONITIS BACTERIAL			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ELECTROLYTE IMBALANCE			
subjects affected / exposed	0 / 9 (0.00%)	0 / 24 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPONATRAEMIA			

subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Group 1: GT1B	Group 2: GT1 Non-B	Group 3: GT4
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 9 (88.89%)	24 / 24 (100.00%)	3 / 3 (100.00%)
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	1 / 9 (11.11%)	0 / 24 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
HYPOTENSION			
subjects affected / exposed	0 / 9 (0.00%)	3 / 24 (12.50%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	0 / 9 (0.00%)	4 / 24 (16.67%)	1 / 3 (33.33%)
occurrences (all)	0	4	1
CHILLS			
subjects affected / exposed	1 / 9 (11.11%)	2 / 24 (8.33%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
FATIGUE			
subjects affected / exposed	3 / 9 (33.33%)	11 / 24 (45.83%)	2 / 3 (66.67%)
occurrences (all)	3	11	3
OEDEMA PERIPHERAL			
subjects affected / exposed	0 / 9 (0.00%)	6 / 24 (25.00%)	1 / 3 (33.33%)
occurrences (all)	0	6	2
PYREXIA			
subjects affected / exposed	1 / 9 (11.11%)	3 / 24 (12.50%)	0 / 3 (0.00%)
occurrences (all)	1	4	0
Reproductive system and breast disorders			
BREAST PAIN			

subjects affected / exposed	0 / 9 (0.00%)	0 / 24 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
EJACULATION FAILURE			
subjects affected / exposed	0 / 9 (0.00%)	0 / 24 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
ERECTILE DYSFUNCTION			
subjects affected / exposed	0 / 9 (0.00%)	0 / 24 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	3 / 9 (33.33%)	1 / 24 (4.17%)	0 / 3 (0.00%)
occurrences (all)	3	1	0
DYSPNOEA			
subjects affected / exposed	0 / 9 (0.00%)	2 / 24 (8.33%)	1 / 3 (33.33%)
occurrences (all)	0	2	1
PRODUCTIVE COUGH			
subjects affected / exposed	0 / 9 (0.00%)	2 / 24 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	1 / 9 (11.11%)	1 / 24 (4.17%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
DEPRESSED MOOD			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
INSOMNIA			
subjects affected / exposed	0 / 9 (0.00%)	6 / 24 (25.00%)	2 / 3 (66.67%)
occurrences (all)	0	6	3
IRRITABILITY			
subjects affected / exposed	0 / 9 (0.00%)	2 / 24 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
MOOD SWINGS			
subjects affected / exposed	0 / 9 (0.00%)	0 / 24 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	3
PANIC ATTACK			

subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 24 (0.00%) 0	2 / 3 (66.67%) 2
Investigations			
BLOOD CREATININE INCREASED subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 24 (0.00%) 0	0 / 3 (0.00%) 0
CREATININE RENAL CLEARANCE DECREASED subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	2 / 24 (8.33%) 4	0 / 3 (0.00%) 0
HAEMOGLOBIN DECREASED subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	3 / 24 (12.50%) 4	1 / 3 (33.33%) 1
WEIGHT INCREASED subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 24 (0.00%) 0	1 / 3 (33.33%) 1
Injury, poisoning and procedural complications			
CONTUSION subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	2 / 24 (8.33%) 3	0 / 3 (0.00%) 0
FALL subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	3 / 24 (12.50%) 3	0 / 3 (0.00%) 0
Cardiac disorders			
TACHYCARDIA subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	2 / 24 (8.33%) 2	0 / 3 (0.00%) 0
Nervous system disorders			
DIZZINESS subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	7 / 24 (29.17%) 10	2 / 3 (66.67%) 2
HEADACHE subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	5 / 24 (20.83%) 5	0 / 3 (0.00%) 0
HEPATIC ENCEPHALOPATHY subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	4 / 24 (16.67%) 5	1 / 3 (33.33%) 1

HYPERAESTHESIA			
subjects affected / exposed	0 / 9 (0.00%)	0 / 24 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
HYPOTONIA			
subjects affected / exposed	0 / 9 (0.00%)	0 / 24 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
PARAESTHESIA			
subjects affected / exposed	0 / 9 (0.00%)	2 / 24 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
RADIAL NERVE PALSY			
subjects affected / exposed	0 / 9 (0.00%)	0 / 24 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
SYNCOPE			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
TREMOR			
subjects affected / exposed	1 / 9 (11.11%)	3 / 24 (12.50%)	0 / 3 (0.00%)
occurrences (all)	1	3	0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	2 / 9 (22.22%)	6 / 24 (25.00%)	0 / 3 (0.00%)
occurrences (all)	4	6	0
LEUKOCYTOSIS			
subjects affected / exposed	0 / 9 (0.00%)	0 / 24 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
PANCYTOPENIA			
subjects affected / exposed	0 / 9 (0.00%)	2 / 24 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 9 (0.00%)	3 / 24 (12.50%)	3 / 3 (100.00%)
occurrences (all)	0	3	4
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 9 (0.00%)	3 / 24 (12.50%)	1 / 3 (33.33%)
occurrences (all)	0	4	1
ASCITES			

subjects affected / exposed	0 / 9 (0.00%)	8 / 24 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	8	1
CONSTIPATION			
subjects affected / exposed	0 / 9 (0.00%)	5 / 24 (20.83%)	0 / 3 (0.00%)
occurrences (all)	0	6	0
DIARRHOEA			
subjects affected / exposed	3 / 9 (33.33%)	10 / 24 (41.67%)	1 / 3 (33.33%)
occurrences (all)	4	14	1
FLATULENCE			
subjects affected / exposed	0 / 9 (0.00%)	2 / 24 (8.33%)	1 / 3 (33.33%)
occurrences (all)	0	2	1
NAUSEA			
subjects affected / exposed	2 / 9 (22.22%)	13 / 24 (54.17%)	2 / 3 (66.67%)
occurrences (all)	2	19	3
VARICES OESOPHAGEAL			
subjects affected / exposed	0 / 9 (0.00%)	2 / 24 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
VOMITING			
subjects affected / exposed	1 / 9 (11.11%)	6 / 24 (25.00%)	1 / 3 (33.33%)
occurrences (all)	1	7	1
Hepatobiliary disorders			
BILE DUCT STENOSIS			
subjects affected / exposed	0 / 9 (0.00%)	0 / 24 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
HYPERBILIRUBINAEMIA			
subjects affected / exposed	2 / 9 (22.22%)	3 / 24 (12.50%)	1 / 3 (33.33%)
occurrences (all)	2	3	1
JAUNDICE			
subjects affected / exposed	2 / 9 (22.22%)	2 / 24 (8.33%)	1 / 3 (33.33%)
occurrences (all)	2	2	1
OCULAR ICTERUS			
subjects affected / exposed	2 / 9 (22.22%)	5 / 24 (20.83%)	0 / 3 (0.00%)
occurrences (all)	2	5	0
Skin and subcutaneous tissue disorders			
PRURITUS			

subjects affected / exposed	1 / 9 (11.11%)	7 / 24 (29.17%)	1 / 3 (33.33%)
occurrences (all)	1	12	1
PRURITUS GENERALISED			
subjects affected / exposed	0 / 9 (0.00%)	2 / 24 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
RASH			
subjects affected / exposed	0 / 9 (0.00%)	7 / 24 (29.17%)	1 / 3 (33.33%)
occurrences (all)	0	9	1
RASH GENERALISED			
subjects affected / exposed	0 / 9 (0.00%)	2 / 24 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	1 / 9 (11.11%)	2 / 24 (8.33%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
BACK PAIN			
subjects affected / exposed	1 / 9 (11.11%)	2 / 24 (8.33%)	0 / 3 (0.00%)
occurrences (all)	1	4	0
FISTULA			
subjects affected / exposed	0 / 9 (0.00%)	0 / 24 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
MUSCLE SPASMS			
subjects affected / exposed	0 / 9 (0.00%)	6 / 24 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	6	0
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	0 / 9 (0.00%)	2 / 24 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
CYSTITIS			
subjects affected / exposed	0 / 9 (0.00%)	0 / 24 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
DIVERTICULITIS			
subjects affected / exposed	0 / 9 (0.00%)	0 / 24 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
FUNGAL INFECTION			

subjects affected / exposed	0 / 9 (0.00%)	0 / 24 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
GASTROENTERITIS			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
NASOPHARYNGITIS			
subjects affected / exposed	0 / 9 (0.00%)	2 / 24 (8.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
SOFT TISSUE INFECTION			
subjects affected / exposed	0 / 9 (0.00%)	0 / 24 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
STAPHYLOCOCCAL INFECTION			
subjects affected / exposed	0 / 9 (0.00%)	1 / 24 (4.17%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 9 (0.00%)	2 / 24 (8.33%)	1 / 3 (33.33%)
occurrences (all)	0	2	1
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	0 / 9 (0.00%)	5 / 24 (20.83%)	0 / 3 (0.00%)
occurrences (all)	0	5	0
HYPERKALAEMIA			
subjects affected / exposed	0 / 9 (0.00%)	2 / 24 (8.33%)	1 / 3 (33.33%)
occurrences (all)	0	2	3
HYPERURICAEMIA			
subjects affected / exposed	0 / 9 (0.00%)	0 / 24 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
HYPOKALAEMIA			
subjects affected / exposed	0 / 9 (0.00%)	3 / 24 (12.50%)	1 / 3 (33.33%)
occurrences (all)	0	6	2
HYPOMAGNESAEMIA			
subjects affected / exposed	0 / 9 (0.00%)	3 / 24 (12.50%)	0 / 3 (0.00%)
occurrences (all)	0	4	0
HYPONATRAEMIA			
subjects affected / exposed	1 / 9 (11.11%)	7 / 24 (29.17%)	1 / 3 (33.33%)
occurrences (all)	1	7	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 June 2014	<p>The purpose of the amendment was to incorporate the changes summarized in the following text:</p> <ul style="list-style-type: none">• Amended the study title by adding the branded name of "TURQUOISE-CPB."• Amended inclusion criterion number 2 to specify that estrogen-containing contraceptives were not permitted.• Amended the prohibited meds table in Exclusion criterion 4 to include estrogen containing medications for systemic use.• Amended exclusion criterion number 10 for abnormal laboratory value for calculated creatinine clearance (by Cockcroft-Gault formula) to be ≤ 50 mL/min.• Amended exclusion criterion number 15 to clarify that subjects were to be excluded in the event subjects had a confirmed presence of HCC at Screening.• Modified the treatment period study activities table by adding the following: Child-Pugh Assessment and Score at Premature Discontinuation; liver ultrasound to be performed at Treatment Week 24; and removed the assessment of clinical outcomes at Treatment Day 1.• Removed the reference to creatinine clearance values for RBV dosing.• Updated the reference section for ombitasvir, paritaprevir, and dasabuvir Investigator Brochures.
10 October 2014	<p>The purpose of the amendment was to incorporate the changes summarized in the following text:</p> <ul style="list-style-type: none">• Updated the study title by removing the word "randomized".• Updated the Introduction.• Amended the study design and treatment based on regulatory feedback.• Updated sections impacted by the change in study design.• Updated the number of subjects in the sentinel cohort.• Revised the amount and format of data to be reviewed from the sentinel cohort.• Revised rescreening text.• Amended the RBV total daily dose to reflect that a subject may be initiated at a lower total daily dose upon approval.• Amended inclusion criterion number 2 to remove the example of "topical" estrogen-containing hormonal contraceptive.• Amended exclusion criterion number 3 to remove the method used to confirm human immunodeficiency virus (HIV)-1 and HIV-2 infections.• Amended exclusion criterion number 9 to reflect exclusion of subjects with MELD > 18 at time of screening.• Amended the Study Activities Table for the Treatment Period to provide additional visits for subjects receiving 24 weeks of treatment; to amend protocol procedures; to update the table footnotes.• Amended the Study Activities Table for the Post-Treatment Period to include clinical laboratory testing at Post-Treatment Weeks 2 and 8; and to update footnotes.• Amended the Informed Consent and RBV Information language in Study Procedures to remove the requirement to provide male subjects with an additional RBV Medication Guide and Partner Risk Fact Sheet for female partners.• Amended the pregnancy testing requirements to only include women of childbearing potential.• Updated treatment adjustment criteria to align with study design change.• Amended the ALT Toxicity Management section.• Added Subsection 6.7.6 "Increase in Child-Pugh Score."• Updated the "AE Reporting" section to reflect the central back-up number when the SDP was unavailable.• Updated the Reference section.

03 March 2015	<ul style="list-style-type: none"> • Updated the study title and add central backup contact information, and updated the information. • Updated the synopsis. • Updated the list of abbreviations. • Allowed inclusion of HCV genotype 4 (GT4) population and make appropriate updates through the protocol to reflect this addition. • Updated the introduction (Section 1.0), differences statement, and benefits/risks. • Expanded the primary and secondary objectives. • Revised inclusion criterion number 4. • Revised exclusion criterion number 4. • Revised exclusion criterion number 10. • Amended the study design and treatment. • Updated the study sample size. • Updated the list of prohibited therapy. • Revised the efficacy, pharmacokinetic, pharmacogenetic, and safety assessments/variables. • Updated the sentinel cohort data review. • Updated the treatments administered and specific dosing. • Updated the method of assigning subjects to treatment and randomization methods. • Amended study drug accountability documentation and study drug return requirements. • Amended management of creatinine clearance and decreases in hemoglobin. • Updated contacts for protocol deviations reporting. • Updated statistical methods and sample size. • Updated additional efficacy endpoints. • Updated references. • Minor clerical updates made throughout the document.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported