



Clinical trial results:

A Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Coadministration of ABT-450 with Ritonavir (ABT-450/r) and ABT-267 in Adults with Chronic Hepatitis C Virus Infection (PEARL-I)

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2011-005762-38 |
| Trial protocol | ES HU IT |
| Global end of trial date | 17 February 2015 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 18 May 2016 |
| First version publication date | 18 May 2016 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | M13-393 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01685203 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | AbbVie Deutschland GmbH & Co. KG |
| Sponsor organisation address | Abbott House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire , United Kingdom, SL6 4XE |
| Public contact | Global Medical Information, AbbVie, +001 800-633-9110, |
| Scientific contact | Nilou Mobashery, MD, AbbVie, nilou.mobashery@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 | 17 February 2015 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 17 February 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the safety and efficacy of co-administration of ABT-450 (also known as paritaprevir) with ritonavir (ABT-450/r) and ABT-267 (also known as ombitasvir) in adults with chronic hepatitis C virus infection.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 14 August 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Poland: 19 |
| Country: Number of subjects enrolled | Spain: 60 |
| Country: Number of subjects enrolled | France: 74 |
| Country: Number of subjects enrolled | Hungary: 18 |
| Country: Number of subjects enrolled | Italy: 24 |
| Country: Number of subjects enrolled | Romania: 49 |
| Country: Number of subjects enrolled | Turkey: 9 |
| Country: Number of subjects enrolled | United States: 63 |
| Worldwide total number of subjects | 316 |
| EEA total number of subjects | 244 |

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) | 291 |
| From 65 to 84 years | 25 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Group 5 (Genotype 4 (GT4) treatment-experienced, ABT-450 150 mg + ritonavir 100 mg + ABT-267 25 mg (2-DAA) regimen for 12 weeks) was not open to enrollment, based on a protocol-specified interim review of results from the treatment-naïve GT4 Groups 1 and 4 that indicated higher SVR rates among subjects receiving the 2-DAA regimen with ribavirin.

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 |
|------------------|---------|

Arm description:

ABT-450 150 mg/ r 100 mg, and ABT-267 25 mg once daily for 12 weeks to adult noncirrhotic, treatment-naïve, HCV GT4-infected participants

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

Dosage and administration details:

Tablet; ABT-450; Capsule; ritonavir

ABT-450 150 mg/ritonavir 100 mg once daily for 12 weeks

| | |
|--|----------------------------------|
| Investigational medicinal product name | ABT-267 |
| Investigational medicinal product code | |
| Other name | ABT-267 also known as ombitasvir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

25 mg once daily for 12 weeks

| | |
|------------------|---------|
| Arm title | Group 2 |
|------------------|---------|

Arm description:

ABT-450 150 mg/ r 100 mg, and ABT-267 25 mg once daily for 12 weeks to adult noncirrhotic, treatment-naïve HCV GT1b-infected participants

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

Dosage and administration details:

Tablet; ABT-450; Capsule; ritonavir

ABT-450 150 mg/ritonavir 100 mg once daily for 12 weeks

| | |
|--|------------------------------------|
| Investigational medicinal product name | ABT-267 |
| Investigational medicinal product code | |
| Other name | ABT-267 also known as ombitasvir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: 25 mg once daily for 12 weeks | |
| Arm title | Group 3 |
| Arm description: ABT-450 150 mg/ r 100 mg, and ABT-267 25 mg once daily for 12 weeks to adult noncirrhotic, HCV GT1b-infected, pegylated-interferon/ribavirin (pegIFN/RBV) treatment null responder participants | |
| Arm type | Experimental |
| Investigational medicinal product name | ABT-450/ritonavir |
| Investigational medicinal product code | |
| Other name | ABT-450 also known as paritaprevir |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: Tablet; ABT-450; Capsule; ritonavir ABT-450 150 mg/ritonavir 100 mg once daily for 12 weeks | |
| Investigational medicinal product name | ABT-267 |
| Investigational medicinal product code | |
| Other name | ABT-267 also known as ombitasvir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: 25 mg once daily for 12 weeks | |
| Arm title | Group 4 |
| Arm description: ABT-450 150 mg/ r 100 mg, ABT-267 25 mg , once daily and weight-based ribavirin (RBV; 1,000 mg/day if < 75 kg or 1,200 mg/day if ≥ 75 kg, divided twice daily) for 12 weeks to adult noncirrhotic, treatment-naïve, HCV GT4 -infected participants | |
| Arm type | Experimental |
| Investigational medicinal product name | ABT-450/ritonavir |
| Investigational medicinal product code | |
| Other name | ABT-450 also known as paritaprevir |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: Tablet; ABT-450; Capsule; ritonavir ABT-450 150 mg/ritonavir 100 mg once daily for 12 weeks | |
| Investigational medicinal product name | ABT-267 |
| Investigational medicinal product code | |
| Other name | ABT-267 also known as ombitasvir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: 25 mg once daily for 12 weeks | |
| Investigational medicinal product name | Ribavirin (RBV) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

1,000 mg/day if body weight < 75 kg or 1,200 mg/day if body weight ≥ 75 kg, divided twice daily, for 12 weeks

| | |
|------------------|---------|
| Arm title | Group 6 |
|------------------|---------|

Arm description:

ABT-450 150 mg/ r 100 mg, ABT-267 25 mg , once daily and weight-based ribavirin (RBV; 1,000 mg/day if < 75 kg or 1,200 mg/day if ≥ 75 kg, divided twice daily) for 12 weeks to adult noncirrhotic, HCV GT4-infected, pegylated-interferon/RBV (pegIFN/RBV) treatment-experienced participants

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

Dosage and administration details:

Tablet; ABT-450; Capsule; ritonavir

ABT-450 150 mg/ritonavir 100 mg once daily for 12 weeks

| | |
|--|----------------------------------|
| Investigational medicinal product name | ABT-267 |
| Investigational medicinal product code | |
| Other name | ABT-267 also known as ombitasvir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

25 mg once daily for 12 weeks

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

Dosage and administration details:

1,000 mg/day if body weight < 75 kg or 1,200 mg/day if body weight ≥ 75 kg, divided twice daily, for 12 weeks

| | |
|------------------|---------|
| Arm title | Group 7 |
|------------------|---------|

Arm description:

ABT-450 150 mg/ r 100 mg, and ABT-267 25 mg once daily for 24 weeks to adult, HCV GT1b-infected, treatment-naïve participants with compensated cirrhosis

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

Dosage and administration details:

Tablet; ABT-450; Capsule; ritonavir

ABT-450 150 mg/ritonavir 100 mg once daily for 24 weeks

| | |
|--|----------------------------------|
| Investigational medicinal product name | ABT-267 |
| Investigational medicinal product code | |
| Other name | ABT-267 also known as ombitasvir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

25 mg once daily for 24 weeks

| | |
|------------------|---------|
| Arm title | Group 8 |
|------------------|---------|

Arm description:

ABT-450 150 mg/ r 100 mg, and ABT-267 25 mg once daily for 24 weeks to adult, HCV GT1b-infected, pegylated-interferon/RBV(pegIFN/RBV) treatment-experienced participants with compensated cirrhosis

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

Dosage and administration details:

Tablet; ABT-450; Capsule; ritonavir

ABT-450 150 mg/ritonavir 100 mg once daily for 24 weeks

| | |
|--|----------------------------------|
| Investigational medicinal product name | ABT-267 |
| Investigational medicinal product code | |
| Other name | ABT-267 also known as ombitasvir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

25 mg once daily for 24 weeks

| Number of subjects in period 1 | Group 1 | Group 2 | Group 3 |
|---------------------------------------|---------|---------|-------------------|
| Started | 44 | 42 | 40 |
| Completed study drug | 42 | 40 | 39 ^[1] |
| Completed | 40 | 39 | 40 |
| Not completed | 4 | 3 | 0 |
| Adverse event, non-fatal | - | - | - |
| Adverse event and withdrew consent | 1 | - | - |
| Patient's decision | - | - | - |
| Lost to follow-up | 3 | 3 | - |

| Number of subjects in period 1 | Group 4 | Group 6 | Group 7 |
|---------------------------------------|---------|---------|-------------------|
| Started | 42 | 49 | 47 |
| Completed study drug | 42 | 49 | 43 ^[2] |
| Completed | 41 | 49 | 44 |
| Not completed | 1 | 0 | 3 |
| Adverse event, non-fatal | - | - | 2 |
| Adverse event and withdrew consent | - | - | - |

| | | | |
|--------------------|---|---|---|
| Patient's decision | - | - | 1 |
| Lost to follow-up | 1 | - | - |

| Number of subjects in period 1 | Group 8 |
|------------------------------------|---------|
| Started | 52 |
| Completed study drug | 52 |
| Completed | 52 |
| Not completed | 0 |
| Adverse event, non-fatal | - |
| Adverse event and withdrew consent | - |
| Patient's decision | - |
| Lost to follow-up | - |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: One subject discontinued study drug but continued the study in the post-treatment period.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: One subject discontinued study drug but continued the study in the post-treatment period.

Baseline characteristics

Reporting groups

| | |
|---|---------|
| Reporting group title | Group 1 |
| Reporting group description: ABT-450 150 mg/ r 100 mg, and ABT-267 25 mg once daily for 12 weeks to adult noncirrhotic, treatment-naïve, HCV GT4-infected participants | |
| Reporting group title | Group 2 |
| Reporting group description: ABT-450 150 mg/ r 100 mg, and ABT-267 25 mg once daily for 12 weeks to adult noncirrhotic, treatment-naïve HCV GT1b-infected participants | |
| Reporting group title | Group 3 |
| Reporting group description: ABT-450 150 mg/ r 100 mg, and ABT-267 25 mg once daily for 12 weeks to adult noncirrhotic, HCV GT1b-infected, pegylated-interferon/ribavirin (pegIFN/RBV) treatment null responder participants | |
| Reporting group title | Group 4 |
| Reporting group description: ABT-450 150 mg/ r 100 mg, ABT-267 25 mg , once daily and weight-based ribavirin (RBV; 1,000 mg/day if < 75 kg or 1,200 mg/day if ≥ 75 kg, divided twice daily) for 12 weeks to adult noncirrhotic, treatment-naïve, HCV GT4 -infected participants | |
| Reporting group title | Group 6 |
| Reporting group description: ABT-450 150 mg/ r 100 mg, ABT-267 25 mg , once daily and weight-based ribavirin (RBV; 1,000 mg/day if < 75 kg or 1,200 mg/day if ≥ 75 kg, divided twice daily) for 12 weeks to adult noncirrhotic, HCV GT4-infected, pegylated-interferon/RBV (pegIFN/RBV) treatment-experienced participants | |
| Reporting group title | Group 7 |
| Reporting group description: ABT-450 150 mg/ r 100 mg, and ABT-267 25 mg once daily for 24 weeks to adult, HCV GT1b-infected, treatment-naïve participants with compensated cirrhosis | |
| Reporting group title | Group 8 |
| Reporting group description: ABT-450 150 mg/ r 100 mg, and ABT-267 25 mg once daily for 24 weeks to adult, HCV GT1b-infected, pegylated-interferon/RBV(pegIFN/RBV) treatment-experienced participants with compensated cirrhosis | |

| Reporting group values | Group 1 | Group 2 | Group 3 |
|--|---------|---------|---------|
| Number of subjects | 44 | 42 | 40 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 42 | 42 | 36 |
| From 65-84 years | 2 | 0 | 4 |
| 85 years and over | 0 | 0 | 0 |

| | | | |
|---|-----------------|----------------|----------------|
| Age continuous Units: years arithmetic mean standard deviation | 48.9 ± 10.03 | 55.8 ± 6.88 | 54.2 ± 9.61 |
| Gender categorical Units: Subjects | | | |
| Female | 20 | 17 | 25 |
| Male | 24 | 25 | 15 |

| Reporting group values | Group 4 | Group 6 | Group 7 |
|---|-----------------|-----------------|----------------|
| Number of subjects | 42 | 49 | 47 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 41 | 48 | 40 |
| From 65-84 years | 1 | 1 | 7 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous Units: years arithmetic mean standard deviation | 44.2 ± 12.67 | 50.9 ± 10.13 | 57.8 ± 7.12 |
| Gender categorical Units: Subjects | | | |
| Female | 14 | 13 | 24 |
| Male | 28 | 36 | 23 |

| Reporting group values | Group 8 | Total | |
|---|----------------|-------|--|
| Number of subjects | 52 | 316 | |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 42 | 291 | |
| From 65-84 years | 10 | 25 | |
| 85 years and over | 0 | 0 | |
| Age continuous Units: years arithmetic mean standard deviation | 57.1 ± 6.02 | - | |

| | | | |
|---------------------------------------|----|-----|--|
| Gender categorical Units: Subjects | | | |
| Female | 19 | 132 | |
| Male | 33 | 184 | |

Subject analysis sets

| | |
|----------------------------|---------------|
| Subject analysis set title | Overall study |
| Subject analysis set type | Full analysis |

Subject analysis set description:

All participants who received at least 1 dose of study drug.

| Reporting group values | Overall study | | |
|---|---------------|--|--|
| Number of subjects | 316 | | |
| Age categorical Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 291 | | |
| From 65-84 years | 25 | | |
| 85 years and over | 0 | | |
| Age continuous Units: years | | | |
| arithmetic mean | 52.8 | | |
| standard deviation | ± 10.1 | | |
| Gender categorical Units: Subjects | | | |
| Female | 132 | | |
| Male | 184 | | |

End points

End points reporting groups

| | |
|---|---------------|
| Reporting group title | Group 1 |
| Reporting group description: ABT-450 150 mg/ r 100 mg, and ABT-267 25 mg once daily for 12 weeks to adult noncirrhotic, treatment-naïve, HCV GT4-infected participants | |
| Reporting group title | Group 2 |
| Reporting group description: ABT-450 150 mg/ r 100 mg, and ABT-267 25 mg once daily for 12 weeks to adult noncirrhotic, treatment-naïve HCV GT1b-infected participants | |
| Reporting group title | Group 3 |
| Reporting group description: ABT-450 150 mg/ r 100 mg, and ABT-267 25 mg once daily for 12 weeks to adult noncirrhotic, HCV GT1b-infected, pegylated-interferon/ribavirin (pegIFN/RBV) treatment null responder participants | |
| Reporting group title | Group 4 |
| Reporting group description: ABT-450 150 mg/ r 100 mg, ABT-267 25 mg , once daily and weight-based ribavirin (RBV; 1,000 mg/day if < 75 kg or 1,200 mg/day if ≥ 75 kg, divided twice daily) for 12 weeks to adult noncirrhotic, treatment-naïve, HCV GT4 -infected participants | |
| Reporting group title | Group 6 |
| Reporting group description: ABT-450 150 mg/ r 100 mg, ABT-267 25 mg , once daily and weight-based ribavirin (RBV; 1,000 mg/day if < 75 kg or 1,200 mg/day if ≥ 75 kg, divided twice daily) for 12 weeks to adult noncirrhotic, HCV GT4-infected, pegylated-interferon/RBV (pegIFN/RBV) treatment-experienced participants | |
| Reporting group title | Group 7 |
| Reporting group description: ABT-450 150 mg/ r 100 mg, and ABT-267 25 mg once daily for 24 weeks to adult, HCV GT1b-infected, treatment-naïve participants with compensated cirrhosis | |
| Reporting group title | Group 8 |
| Reporting group description: ABT-450 150 mg/ r 100 mg, and ABT-267 25 mg once daily for 24 weeks to adult, HCV GT1b-infected, pegylated-interferon/RBV(pegIFN/RBV) treatment-experienced participants with compensated cirrhosis | |
| Subject analysis set title | Overall study |
| Subject analysis set type | Full analysis |
| Subject analysis set description: All participants who received at least 1 dose of study drug. | |

Primary: Percentage of participants in each treatment group with sustained virologic response 12 weeks post-treatment

| | |
|--|--|
| End point title | Percentage of participants in each treatment group with sustained virologic response 12 weeks post-treatment |
| End point description: The percentage of participants with sustained virologic response (plasma Hepatitis C virus ribonucleic acid [HCV RNA] level less than the lower limit of quantitation [<LLOQ]) 12 weeks after the last dose of study drug. | |
| End point type | Primary |
| End point timeframe: 12 weeks after the last actual dose of study drug | |

| End point values | Group 1 | Group 2 | Group 3 | Group 4 |
|-----------------------------------|---------------------|---------------------|-------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 44 ^[1] | 42 ^[2] | 40 ^[3] | 42 ^[4] |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 90.9 (78.3 to 97.5) | 95.2 (83.8 to 99.4) | 90 (76.3 to 97.2) | 100 (91.6 to 100) |

Notes:

[1] - All randomized participants who received at least 1 dose of study drug.

[2] - All participants who received at least 1 dose of study drug.

[3] - All participants who received at least 1 dose of study drug.

[4] - All randomized participants who received at least 1 dose of study drug.

| End point values | Group 6 | Group 7 | Group 8 | |
|-----------------------------------|-------------------|---------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 49 ^[5] | 47 ^[6] | 52 ^[7] | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 100 (92.7 to 100) | 97.9 (88.7 to 99.9) | 98.1 (89.7 to 100) | |

Notes:

[5] - All participants who received at least 1 dose of study drug.

[6] - All participants who received at least 1 dose of study drug.

[7] - All participants who received at least 1 dose of study drug.

Statistical analyses

| Statistical analysis title | Pairwise comparison between Groups 2 and 3 |
|---|--|
| Comparison groups | Group 2 v Group 3 |
| Number of subjects included in analysis | 82 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.381 ^[8] |
| Method | Regression, Logistic |

Notes:

[8] - Treatment group, baseline log(subscript)10(subscript) HCV RNA level and Interleukin-28B (IL28B) genotype (CC or non-CC) were used as predictors

| Statistical analysis title | Additional comparison, Group 1 vs Group 4 |
|---|---|
| Comparison groups | Group 1 v Group 4 |
| Number of subjects included in analysis | 86 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.086 ^[9] |
| Method | Stratum-adjusted Mantel-Haenszel |

Notes:

[9] - Difference in rates after adjusting for Interleukin-28 (IL28) genotype (CC or Non-CC) using stratum-adjusted Mantel-Haenszel proportions and continuity-corrected variances.

Secondary: Percentage of Participants in Each Treatment Group With Sustained Virologic Response 24 Weeks Post-treatment

| End point title | Percentage of Participants in Each Treatment Group With Sustained Virologic Response 24 Weeks Post-treatment |
|-----------------|--|
|-----------------|--|

End point description:

The percentage of participants with sustained virologic response (plasma Hepatitis C virus ribonucleic acid [HCV RNA] level less than the lower limit of quantitation [$<LLOQ$]) 24 weeks after the last dose of

study drug.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 24 weeks after the last actual dose of study drug | |

| End point values | Group 1 | Group 2 | Group 3 | Group 4 |
|-----------------------------------|---------------------|---------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 44 ^[10] | 42 ^[11] | 40 ^[12] | 42 ^[13] |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 86.4 (72.6 to 94.8) | 92.9 (80.5 to 98.5) | 90 (76.3 to 97.2) | 100 (91.6 to 100) |

Notes:

[10] - All randomized participants who received at least 1 dose of study drug.

[11] - All participants who received at least 1 dose of study drug.

[12] - All participants who received at least 1 dose of study drug.

[13] - All randomized participants who received at least 1 dose of study drug.

| End point values | Group 6 | Group 7 | Group 8 | |
|-----------------------------------|--------------------|---------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 49 ^[14] | 47 ^[15] | 52 ^[16] | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 100 (92.7 to 100) | 97.9 (88.7 to 99.9) | 98.1 (89.7 to 100) | |

Notes:

[14] - All participants who received at least 1 dose of study drug.

[15] - All participants who received at least 1 dose of study drug.

[16] - All participants who received at least 1 dose of study drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants in Each Treatment Group With On-treatment Virologic Failure

| | |
|-----------------|--|
| End point title | Percentage of Participants in Each Treatment Group With On-treatment Virologic Failure |
|-----------------|--|

End point description:

Virologic failure during treatment was defined as rebound (confirmed HCV RNA greater than or equal to the lower limit of quantitation [\geq LLOQ] after HCV RNA < LLOQ during treatment, or confirmed increase from the lowest value post baseline in HCV RNA [2 consecutive HCV RNA measurements > 1 log(subscript)10(subscript) IU/mL above the lowest value post baseline] at any time point during treatment), or failure to suppress (HCV RNA \geq LLOQ persistently during treatment with at least 6 weeks [\geq 36 days] of treatment).

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

End point timeframe:

Baseline (Day 1), Day 3, and Treatment Weeks 1, 2, 3, 4, 6, 8, 10, and 12 for all participants and Treatment Weeks 16, 20 and 24 for Groups 7 and 8

| End point values | Group 1 | Group 2 | Group 3 | Group 4 |
|-----------------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 44 ^[17] | 42 ^[18] | 40 ^[19] | 42 ^[20] |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 2.3 (0.1 to 12) | 0 (0 to 8.4) | 2.5 (0.1 to 13.2) | 0 (0 to 8.4) |

Notes:

[17] - All randomized participants who received at least 1 dose of study drug.

[18] - All participants who received at least 1 dose of study drug.

[19] - All participants who received at least 1 dose of study drug.

[20] - All randomized participants who received at least 1 dose of study drug.

| End point values | Group 6 | Group 7 | Group 8 | |
|-----------------------------------|--------------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 49 ^[21] | 47 ^[22] | 52 ^[23] | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 0 (0 to 7.3) | 0 (0 to 7.5) | 0 (0 to 6.8) | |

Notes:

[21] - All participants who received at least 1 dose of study drug.

[22] - All participants who received at least 1 dose of study drug.

[23] - All participants who received at least 1 dose of study drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants in Each Treatment Group With Post-treatment Virologic Relapse.

| | |
|-----------------|---|
| End point title | Percentage of Participants in Each Treatment Group With Post-treatment Virologic Relapse. |
|-----------------|---|

End point description:

Participants were considered to have virologic relapse after treatment if they had confirmed quantifiable plasma Hepatitis C virus ribonucleic acid (HCV RNA) \geq lower limit of quantification (LLOQ) between the end of treatment and 12 weeks after the last dose of study drug among participants who completed treatment with HCV RNA < LLOQ at the end of treatment.

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

End point timeframe:

Within 12 weeks after the last dose of study drug

| End point values | Group 1 | Group 2 | Group 3 | Group 4 |
|-----------------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 42 ^[24] | 40 ^[25] | 39 ^[26] | 42 ^[27] |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 4.8 (0.6 to 16.2) | 0 (0 to 8.8) | 7.7 (1.6 to 20.9) | 0 (0 to 8.4) |

Notes:

[24] - Subjects who rcvd at least 1 dose of study drug and ended Tx with HCV RNA <LLOQ at the last Tx visit

[25] - Subjects who rcvd at least 1 dose of study drug and ended Tx with HCV RNA <LLOQ at the last Tx visit

[26] - Subjects who rcvd at least 1 dose of study drug and ended Tx with HCV RNA <LLOQ at the last Tx visit

[27] - Subjects who rcvd at least 1 dose of study drug and ended Tx with HCV RNA <LLOQ at the last Tx visit

| End point values | Group 6 | Group 7 | Group 8 | |
|-----------------------------------|--------------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 49 ^[28] | 44 ^[29] | 52 ^[30] | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 0 (0 to 7.3) | 0 (0 to 8) | 1.9 (0 to 10.3) | |

Notes:

[28] - Subjects who rcvd at least 1 dose of study drug and ended Tx with HCV RNA <LLOQ at the last Tx visit

[29] - Subjects who rcvd at least 1 dose of study drug and ended Tx with HCV RNA <LLOQ at the last Tx visit

[30] - Subjects who rcvd at least 1 dose of study drug and ended Tx with HCV RNA <LLOQ at the last Tx visit

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants in each treatment group with treatment-emergent adverse events

| | |
|-----------------|---|
| End point title | Percentage of participants in each treatment group with treatment-emergent adverse events |
|-----------------|---|

End point description:

Treatment-emergent adverse events were defined as any event that began or worsened in severity after initiation of study drug through 30 days after the last dose of study drug.

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

End point timeframe:

From the time of study drug administration until 30 days after the last dose, up to 16 weeks for Groups 1, 2, 3, 4, and 6, and up to 28 weeks for Groups 7 and 8

| End point values | Group 1 | Group 2 | Group 3 | Group 4 |
|-----------------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 44 ^[31] | 42 ^[32] | 40 ^[33] | 42 ^[34] |
| Units: Percentage of participants | | | | |
| number (not applicable) | 77.3 | 73.8 | 80 | 88.1 |

Notes:

[31] - All randomized participants who received at least one dose of study drug.

[32] - All participants who received at least one dose of study drug.

[33] - All participants who received at least one dose of study drug.

[34] - All randomized participants who received at least one dose of study drug.

| End point values | Group 6 | Group 7 | Group 8 | |
|-----------------------------------|--------------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 49 ^[35] | 47 ^[36] | 52 ^[37] | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 85.7 | 85.1 | 71.2 | |

Notes:

[35] - All participants who received at least one dose of study drug.

[36] - All participants who received at least one dose of study drug.

[37] - All participants who received at least one dose of study drug.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from study drug administration until 30 days after the last dose, up to 16 wks for Groups 1-4, & 6, and up to 28 wks for Groups 7 & 8. Serious AEs were collected from informed consent until the end of the study, up to 65 wks

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Group 1 |
|-----------------------|---------|

Reporting group description:

ABT-450 150 mg/ r 100 mg, and ABT-267 25 mg once daily for 12 weeks to adult noncirrhotic, treatment-naïve, HCV GT4-infected participants

| | |
|-----------------------|---------|
| Reporting group title | Group 2 |
|-----------------------|---------|

Reporting group description:

ABT-450 150 mg/ r 100 mg, and ABT-267 25 mg once daily for 12 weeks to adult noncirrhotic, treatment-naïve HCV GT1b-infected participants

| | |
|-----------------------|---------|
| Reporting group title | Group 3 |
|-----------------------|---------|

Reporting group description:

ABT-450 150 mg/ r 100 mg, and ABT-267 25 mg once daily for 12 weeks to adult noncirrhotic, HCV GT1b-infected, pegylated-interferon/ribavirin (pegIFN/RBV) treatment null responder participants

| | |
|-----------------------|---------|
| Reporting group title | Group 4 |
|-----------------------|---------|

Reporting group description:

ABT-450 150 mg/ r 100 mg, ABT-267 25 mg , once daily and weight-based ribavirin (RBV; 1,000 mg/day if < 75 kg or 1,200 mg/day if ≥ 75 kg, divided twice daily) for 12 weeks to adult noncirrhotic, treatment-naïve, HCV GT4 -infected participants

| | |
|-----------------------|---------|
| Reporting group title | Group 6 |
|-----------------------|---------|

Reporting group description:

ABT-450 150 mg/ r 100 mg, ABT-267 25 mg , once daily and weight-based ribavirin (RBV; 1,000 mg/day if < 75 kg or 1,200 mg/day if ≥ 75 kg, divided twice daily) for 12 weeks to adult noncirrhotic, HCV GT4-infected, pegylated-interferon/RBV (pegIFN/RBV) treatment-experienced participants

| | |
|-----------------------|---------|
| Reporting group title | Group 7 |
|-----------------------|---------|

Reporting group description:

ABT-450 150 mg/ r 100 mg, and ABT-267 25 mg once daily for 24 weeks to adult, HCV GT1b-infected, treatment-naïve participants with compensated cirrhosis

| | |
|-----------------------|---------|
| Reporting group title | Group 8 |
|-----------------------|---------|

Reporting group description:

ABT-450 150 mg/ r 100 mg, and ABT-267 25 mg once daily for 24 weeks to adult, HCV GT1b-infected, pegylated-interferon/RBV(pegIFN/RBV) treatment-experienced participants with compensated cirrhosis

| Serious adverse events | Group 1 | Group 2 | Group 3 |
|---|----------------|----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 1 / 42 (2.38%) | 1 / 40 (2.50%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| | | | |
|---|----------------|----------------|----------------|
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 42 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 42 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Hepatic neoplasm | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 42 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 42 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 42 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Road traffic accident | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 42 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Peripheral artery aneurysm | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 42 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |

| | | | |
|--|----------------|----------------|----------------|
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 42 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Partial seizures | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 42 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Device extrusion | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 42 (0.00%) | 1 / 40 (2.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Oesophageal varices haemorrhage | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 42 (0.00%) | 0 / 40 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 42 (2.38%) | 0 / 40 (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 |

| Serious adverse events | Group 4 | Group 6 | Group 7 |
|---|----------------|----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 49 (0.00%) | 3 / 47 (6.38%) |
| number of deaths (all causes) | 0 | 0 | 2 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 49 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 49 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Hepatic neoplasm | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 49 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 49 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 49 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 49 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Peripheral artery aneurysm | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 49 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 49 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |

| | | | |
|--|----------------|----------------|----------------|
| Partial seizures | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 49 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Device extrusion | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 49 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Oesophageal varices haemorrhage | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 49 (0.00%) | 1 / 47 (2.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 49 (0.00%) | 0 / 47 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|--|--|
| Serious adverse events | Group 8 | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Hepatic neoplasm | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Peripheral artery aneurysm | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Partial seizures | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |

| | | | |
|---|----------------|--|--|
| Device extrusion | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Oesophageal varices haemorrhage | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Group 1 | Group 2 | Group 3 |
|---|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 30 / 44 (68.18%) | 24 / 42 (57.14%) | 26 / 40 (65.00%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 42 (0.00%) | 1 / 40 (2.50%) |
| occurrences (all) | 0 | 0 | 1 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 11 / 44 (25.00%) | 3 / 42 (7.14%) | 2 / 40 (5.00%) |
| occurrences (all) | 12 | 6 | 2 |
| Fatigue | | | |
| subjects affected / exposed | 3 / 44 (6.82%) | 6 / 42 (14.29%) | 0 / 40 (0.00%) |
| occurrences (all) | 4 | 6 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 42 (2.38%) | 2 / 40 (5.00%) |
| occurrences (all) | 0 | 1 | 2 |
| Irritability | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 3 / 44 (6.82%) 3 | 0 / 42 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Oedema peripheral subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 3 / 42 (7.14%) 3 | 0 / 40 (0.00%) 0 |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 42 (2.38%) 1 | 0 / 40 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 2 / 42 (4.76%) 2 | 2 / 40 (5.00%) 2 |
| Dyspnoea exertional subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 42 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Epistaxis subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 42 (0.00%) 0 | 2 / 40 (5.00%) 2 |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 42 (2.38%) 1 | 0 / 40 (0.00%) 0 |
| Psychiatric disorders | | | |
| Anxiety subjects affected / exposed occurrences (all) | 2 / 44 (4.55%) 2 | 0 / 42 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Insomnia subjects affected / exposed occurrences (all) | 2 / 44 (4.55%) 2 | 1 / 42 (2.38%) 1 | 0 / 40 (0.00%) 0 |
| Depression subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 42 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Investigations | | | |
| Blood pressure increased subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 42 (0.00%) 0 | 2 / 40 (5.00%) 2 |
| Cardiac disorders | | | |

| | | | |
|--|------------------------|------------------------|------------------------|
| Tachycardia subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 42 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 1 / 42 (2.38%) 1 | 3 / 40 (7.50%) 3 |
| Headache subjects affected / exposed occurrences (all) | 13 / 44 (29.55%) 16 | 14 / 42 (33.33%) 16 | 10 / 40 (25.00%) 11 |
| Ear and labyrinth disorders | | | |
| Vertigo subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 3 / 42 (7.14%) 4 | 1 / 40 (2.50%) 1 |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 42 (2.38%) 1 | 0 / 40 (0.00%) 0 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 1 / 42 (2.38%) 1 | 0 / 40 (0.00%) 0 |
| Diarrhoea subjects affected / exposed occurrences (all) | 2 / 44 (4.55%) 2 | 6 / 42 (14.29%) 6 | 0 / 40 (0.00%) 0 |
| Dyspepsia subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 42 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Flatulence subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 42 (2.38%) 1 | 0 / 40 (0.00%) 0 |
| Nausea subjects affected / exposed occurrences (all) | 4 / 44 (9.09%) 4 | 8 / 42 (19.05%) 9 | 0 / 40 (0.00%) 0 |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 3 / 42 (7.14%) 4 | 0 / 40 (0.00%) 0 |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|---------------------|----------------------|---------------------|
| Dry skin subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 7 / 42 (16.67%) 7 | 0 / 40 (0.00%) 0 |
| Pruritus subjects affected / exposed occurrences (all) | 2 / 44 (4.55%) 2 | 6 / 42 (14.29%) 8 | 0 / 40 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 42 (2.38%) 1 | 0 / 40 (0.00%) 0 |
| Back pain subjects affected / exposed occurrences (all) | 3 / 44 (6.82%) 3 | 0 / 42 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Myalgia subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 2 / 42 (4.76%) 2 | 2 / 40 (5.00%) 2 |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 42 (0.00%) 0 | 1 / 40 (2.50%) 1 |
| Influenza subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 1 / 42 (2.38%) 1 | 2 / 40 (5.00%) 2 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 2 / 44 (4.55%) 2 | 1 / 42 (2.38%) 1 | 2 / 40 (5.00%) 3 |
| Rhinitis subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 42 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 42 (0.00%) 0 | 0 / 40 (0.00%) 0 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 3 / 44 (6.82%) 3 | 2 / 42 (4.76%) 2 | 2 / 40 (5.00%) 2 |
| Gastroenteritis | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 42 (0.00%) 0 | 2 / 40 (5.00%) 2 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 1 / 42 (2.38%) | 0 / 40 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 42 (0.00%) | 2 / 40 (5.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Increased appetite | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 42 (2.38%) | 0 / 40 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| Non-serious adverse events | Group 4 | Group 6 | Group 7 |
|---|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 32 / 42 (76.19%) | 38 / 49 (77.55%) | 34 / 47 (72.34%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 1 / 49 (2.04%) | 7 / 47 (14.89%) |
| occurrences (all) | 1 | 2 | 7 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 10 / 42 (23.81%) | 16 / 49 (32.65%) | 10 / 47 (21.28%) |
| occurrences (all) | 14 | 21 | 12 |
| Fatigue | | | |
| subjects affected / exposed | 5 / 42 (11.90%) | 9 / 49 (18.37%) | 4 / 47 (8.51%) |
| occurrences (all) | 7 | 11 | 4 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 49 (2.04%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Irritability | | | |
| subjects affected / exposed | 6 / 42 (14.29%) | 2 / 49 (4.08%) | 1 / 47 (2.13%) |
| occurrences (all) | 6 | 2 | 1 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 2 / 49 (4.08%) | 2 / 47 (4.26%) |
| occurrences (all) | 1 | 2 | 2 |
| Pyrexia | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | 3 / 49 (6.12%) 3 | 1 / 47 (2.13%) 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 4 / 49 (8.16%) | 3 / 47 (6.38%) |
| occurrences (all) | 2 | 4 | 3 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 3 / 49 (6.12%) | 0 / 47 (0.00%) |
| occurrences (all) | 2 | 5 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 1 / 49 (2.04%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 49 (0.00%) | 2 / 47 (4.26%) |
| occurrences (all) | 0 | 0 | 2 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 4 / 42 (9.52%) | 2 / 49 (4.08%) | 1 / 47 (2.13%) |
| occurrences (all) | 4 | 2 | 1 |
| Insomnia | | | |
| subjects affected / exposed | 4 / 42 (9.52%) | 8 / 49 (16.33%) | 3 / 47 (6.38%) |
| occurrences (all) | 4 | 8 | 4 |
| Depression | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 3 / 49 (6.12%) | 1 / 47 (2.13%) |
| occurrences (all) | 1 | 3 | 1 |
| Investigations | | | |
| Blood pressure increased | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 49 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 0 / 49 (0.00%) | 3 / 47 (6.38%) |
| occurrences (all) | 1 | 0 | 3 |
| Nervous system disorders | | | |
| Dizziness | | | |

| | | | |
|--|------------------------|------------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 3 / 49 (6.12%) 3 | 0 / 47 (0.00%) 0 |
| Headache subjects affected / exposed occurrences (all) | 14 / 42 (33.33%) 18 | 14 / 49 (28.57%) 16 | 9 / 47 (19.15%) 11 |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 0 / 49 (0.00%) 0 | 2 / 47 (4.26%) 2 |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) | 2 / 42 (4.76%) 2 | 1 / 49 (2.04%) 1 | 3 / 47 (6.38%) 3 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 2 | 1 / 49 (2.04%) 1 | 1 / 47 (2.13%) 1 |
| Diarrhoea subjects affected / exposed occurrences (all) | 6 / 42 (14.29%) 7 | 3 / 49 (6.12%) 4 | 7 / 47 (14.89%) 8 |
| Dyspepsia subjects affected / exposed occurrences (all) | 2 / 42 (4.76%) 2 | 4 / 49 (8.16%) 4 | 0 / 47 (0.00%) 0 |
| Flatulence subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 0 / 49 (0.00%) 0 | 1 / 47 (2.13%) 1 |
| Nausea subjects affected / exposed occurrences (all) | 7 / 42 (16.67%) 9 | 6 / 49 (12.24%) 7 | 5 / 47 (10.64%) 5 |
| Vomiting subjects affected / exposed occurrences (all) | 2 / 42 (4.76%) 6 | 0 / 49 (0.00%) 0 | 2 / 47 (4.26%) 2 |
| Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 3 / 49 (6.12%) 5 | 1 / 47 (2.13%) 1 |
| Pruritus | | | |

| | | | |
|--|---------------------|----------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | 5 / 49 (10.20%) 7 | 8 / 47 (17.02%) 10 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 1 / 49 (2.04%) | 4 / 47 (8.51%) |
| occurrences (all) | 2 | 1 | 4 |
| Back pain | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 4 / 49 (8.16%) | 6 / 47 (12.77%) |
| occurrences (all) | 2 | 4 | 6 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 5 / 49 (10.20%) | 3 / 47 (6.38%) |
| occurrences (all) | 0 | 5 | 4 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 2 / 49 (4.08%) | 3 / 47 (6.38%) |
| occurrences (all) | 1 | 2 | 5 |
| Influenza | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 2 / 49 (4.08%) | 1 / 47 (2.13%) |
| occurrences (all) | 0 | 2 | 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 6 / 49 (12.24%) | 4 / 47 (8.51%) |
| occurrences (all) | 2 | 6 | 4 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 3 / 49 (6.12%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | 1 / 49 (2.04%) | 2 / 47 (4.26%) |
| occurrences (all) | 2 | 1 | 2 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | 2 / 49 (4.08%) | 2 / 47 (4.26%) |
| occurrences (all) | 1 | 3 | 3 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 42 (0.00%) | 0 / 49 (0.00%) | 0 / 47 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| Decreased appetite subjects affected / exposed occurrences (all) | 1 / 42 (2.38%) 1 | 3 / 49 (6.12%) 3 | 2 / 47 (4.26%) 2 |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 0 / 49 (0.00%) 0 | 0 / 47 (0.00%) 0 |
| Increased appetite subjects affected / exposed occurrences (all) | 0 / 42 (0.00%) 0 | 0 / 49 (0.00%) 0 | 3 / 47 (6.38%) 3 |

| | | | |
|--|----------------------|--|--|
| Non-serious adverse events | Group 8 | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 33 / 52 (63.46%) | | |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 1 / 52 (1.92%) 1 | | |
| General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) | 7 / 52 (13.46%) 9 | | |
| Fatigue subjects affected / exposed occurrences (all) | 6 / 52 (11.54%) 6 | | |
| Influenza like illness subjects affected / exposed occurrences (all) | 2 / 52 (3.85%) 2 | | |
| Irritability subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 2 / 52 (3.85%) 3 | | |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | | |
| Respiratory, thoracic and mediastinal | | | |

| | | | |
|-----------------------------|----------------|--|--|
| disorders | | | |
| Cough | | | |
| subjects affected / exposed | 5 / 52 (9.62%) | | |
| occurrences (all) | 6 | | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences (all) | 0 | | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | | |
| occurrences (all) | 1 | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 3 / 52 (5.77%) | | |
| occurrences (all) | 3 | | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | | |
| occurrences (all) | 2 | | |
| Insomnia | | | |
| subjects affected / exposed | 4 / 52 (7.69%) | | |
| occurrences (all) | 4 | | |
| Depression | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | | |
| occurrences (all) | 1 | | |
| Investigations | | | |
| Blood pressure increased | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences (all) | 0 | | |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | | |
| occurrences (all) | 1 | | |
| Headache | | | |

| | | | |
|--|--|--|--|
| subjects affected / exposed occurrences (all) | 10 / 52 (19.23%) 11 | | |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 | | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Flatulence subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) | 1 / 52 (1.92%) 1 4 / 52 (7.69%) 4 7 / 52 (13.46%) 8 0 / 52 (0.00%) 0 3 / 52 (5.77%) 3 5 / 52 (9.62%) 6 1 / 52 (1.92%) 1 | | |
| Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) | 0 / 52 (0.00%) 0 9 / 52 (17.31%) 9 | | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|------------------------------------|----------------|--|--|
| Arthralgia | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences (all) | 0 | | |
| Back pain | | | |
| subjects affected / exposed | 5 / 52 (9.62%) | | |
| occurrences (all) | 5 | | |
| Myalgia | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | | |
| occurrences (all) | 2 | | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | | |
| occurrences (all) | 1 | | |
| Influenza | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | | |
| occurrences (all) | 4 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 4 / 52 (7.69%) | | |
| occurrences (all) | 4 | | |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences (all) | 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 52 (7.69%) | | |
| occurrences (all) | 4 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | | |
| occurrences (all) | 1 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences (all) | 0 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | | |
| occurrences (all) | 1 | | |
| Hyperglycaemia | | | |

| | | | |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences (all) | 0 | | |
| Increased appetite | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | | |
| occurrences (all) | 0 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 27 June 2012 | <p>Protocol Amendment No. 1 was dated 27 June 2012, and 86 subjects were enrolled into the study under this amendment. The purpose of Amendment No. 1 is summarized as follows:</p> <ul style="list-style-type: none">• Modify the study design, by removing the HCV GT1a 8-week treatment group.• Revise the study objectives based on the modified study design.• Revise the efficacy variables based on the modified study design.• Revise the efficacy endpoints based on the modified study design.• Revise how study enrollment would occur.• Update the data required for review prior to opening Group 1 and/or Group 4.• Clarify post study treatment information.• Clarify the efficacy stopping criteria.• Include the collection of optional mRNA study samples.• Incorporate Administrative Change 1.• Address any inconsistencies throughout the protocol. |
| 21 January 2013 | <p>Protocol Amendment No. 2 was dated 21 January 2013, and 127 subjects were enrolled into the study under this amendment. The purpose of Amendment No. 2 is summarized as follows:</p> <ul style="list-style-type: none">• Modify the study design by:<ul style="list-style-type: none">Removing the HCV GT1a 12-week treatment group.Removing the HCV GT1b 8-week treatment group.Adding 2 GT4 treatment-naïve treatment arms (Groups 1 and 4).Adding 2 GT4 treatment-experienced treatment arms (Groups 5 and 6).Adding GT1b treatment-naïve and treatment-experienced subjects with compensated cirrhosis (Groups 7 and 8).• Revise the study objectives based on the modified study design.• Revise the efficacy variables based on the modified study design.• Revise the statistical analyses based on the modified study design.• Revise how study enrollment will occur.• Add the data required for review prior to opening Groups 5 – 8.• Clarify the efficacy stopping criteria.• Change the primary Study Designated Physician.• Incorporate Administrative Change 2.• Update Section 1.0 – Title Page.• Update Section 1.2 – Synopsis, Section 1.3 – List of Abbreviations and Definition of Terms, and Section 2.0 – Table of Contents.• Update Section 3.0 – Introduction, Section 4.0 – Study Objectives, Section 5.0 – Investigational Plan, and Section 6.0 – Adverse Events and all subsections under each of these sections.• Update Section 8.0 – Statistical Methods and Determination of Sample Size and all subsections under this section.• Update Section 15.0 – Reference List.• Added Appendix C – Clinical Toxicity Grades.• Address any inconsistencies throughout the protocol. |
| 08 April 2013 | <p>Protocol Amendment No. 3 was dated 08 April 2013, and 95 subjects were enrolled into the study under this amendment. The purpose of Amendment No. 3 is summarized as follows:</p> <ul style="list-style-type: none">• Prohibit the use of hormonal contraceptives during study drug administration. |

| | |
|-----------------|---|
| 13 August 2013 | <p>Protocol Amendment No. 4 was dated 13 August 2013, and 6 subjects were enrolled into the study under this amendment. The purpose of Amendment No. 4 is summarized as follows:</p> <ul style="list-style-type: none"> • Address inconsistencies throughout the protocol. • Modify Inclusion Criterion No. 2 and corresponding contraception language throughout the protocol to specify contraindication of hormone eluting IUDs. • Modify Inclusion Criterion No. 11 to include FibroTest/APRI. • Modify Exclusion Criterion No. 8 to allow for rescreening of subjects who test positive for alcohol on their initial drug/alcohol screening. • Modify Exclusion Criterion No. 20 to exclude an Absolute Neutrophil Count (ANC) < 1200 cells/μL for subjects of African descent who are black. • Modify Section 5.1.1.1 Rescreening language. • Remove language prohibiting the use of inhibitors of CYP2C8 from Section 5.2.3.3 Prohibited Therapy. • Add a laboratory collection at Post-Treatment Week 12 visit in Table 2 for subjects participating in Substudy 2. • Remove requirement that sites maintain a MEMS cap accountability form provided by AbbVie. • Modify Section 5.3.2.3 Disposition of Samples to remove "An inventory of the samples included will accompany the package." • Modify Section 5.5.7 Drug Accountability language. • Modify Section 6.7.3 to include additional language regarding the management of bilirubin elevations. • Modify definition of on-treatment virologic failure. • Add footnotes for Ascites to Table 4. • Modify Section 8.1.3.2 Secondary Efficacy Endpoints. |
| 17 October 2013 | <p>Amendment No. 5 was dated 17 October 2013, and 2 subjects were enrolled under this amendment. The purpose of Amendment No. 5 is summarized as follows:</p> <ul style="list-style-type: none"> • Modify the text to reflect the decision to extend the treatment period for Groups 7 and 8 subjects to 24 weeks. • Modify study design to reflect the decision to open enrollment for Group 6 (the HCV GT4 treatment-experienced group to be treated with the 2-DAA regimen plus RBV) but not Group 5 (the HCV GT4 treatment-experienced group to be treated with the 2-DAA regimen without RBV). • Remove the interim analyses for all subjects who have completed treatment. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Not applicable

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/25837829>

<http://www.ncbi.nlm.nih.gov/pubmed/26170136>