



Clinical trial results:

A Randomized, Open-Label, Multicenter Study to Evaluate the Antiviral Activity, Safety, and Pharmacokinetics, of ABT-450 with Ritonavir (ABT-450/r) in Combination with ABT-267 and/or ABT-333 With and Without Ribavirin (RBV) for 8, 12 or 24 Weeks in Treatment-Naïve and Null Responder Subjects with Genotype 1 Chronic Hepatitis C Virus Infection

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2010-022455-31 |
| Trial protocol | GB ES |
| Global end of trial date | 19 September 2013 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 20 April 2016 |
| First version publication date | 13 June 2015 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | M11-652 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01464827 |
| 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, 011 800-633-9110, |
| Scientific contact | Daniel Cohen, MD, AbbVie , daniel.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 | 19 September 2013 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 19 September 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Assess the safety of all treatment regimens and the percentage of subjects achieving 24-week sustained virologic response (SVR24; hepatitis C virus [HCV] ribonucleic acid [RNA] less than the lower limit of quantitation [LLOQ] at post-treatment Week 24) following treatment for 8 weeks versus 12 weeks with 3 direct-acting antiviral agents (DAA) and ribavirin (RBV) in HCV genotype 1-infected treatment-naïve adults.

Protection of trial subjects:

The study was conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct, and the ethical principles that have their origin in the Declaration of Helsinki. All subjects entering the study had to sign an informed consent that was explained to them and questions encouraged.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 03 October 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

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

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Spain: 36 |
| Country: Number of subjects enrolled | United Kingdom: 33 |
| Country: Number of subjects enrolled | France: 58 |
| Country: Number of subjects enrolled | Germany: 39 |
| Country: Number of subjects enrolled | Australia: 8 |
| Country: Number of subjects enrolled | New Zealand: 1 |
| Country: Number of subjects enrolled | United States: 400 |
| Country: Number of subjects enrolled | Canada: 5 |
| Worldwide total number of subjects | 580 |
| EEA total number of subjects | 166 |

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) | 548 |
| From 65 to 84 years | 32 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects underwent screening procedures within 35 days prior to enrollment. HCV genotype 1-infected adult male and female subjects who were either treatment-naïve or previous null responders to pegylated interferon (pegIFN) and RBV were eligible to participate.

Period 1

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

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Group A |

Arm description:

Treatment-naïve participants received ABT-450 150 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily for 8 weeks.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | ABT-450 |
| Investigational medicinal product code | |
| Other name | Paritaprevir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

50 mg tablets

| | |
|--|------------|
| Investigational medicinal product name | ABT-267 |
| Investigational medicinal product code | |
| Other name | Ombitasvir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

25 mg tablets

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

Dosage and administration details:

400 mg tablets

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

Dosage and administration details:

Ribavirin tablets administered at a weight-based dose, between 1,000 to 1,200 mg daily (divided).

| | |
|--|-----------|
| Investigational medicinal product name | Ritonavir |
| Investigational medicinal product code | |
| Other name | Norvir |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

100 mg capsules

| | |
|------------------|---------|
| Arm title | Group B |
|------------------|---------|

Arm description:

Treatment-naïve participants received ABT-450 150 mg and ritonavir 100 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily for 12 weeks.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | ABT-450 |
| Investigational medicinal product code | |
| Other name | Paritaprevir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

50 mg tablets

| | |
|--|-----------|
| Investigational medicinal product name | Ritonavir |
| Investigational medicinal product code | |
| Other name | Norvir |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

100 mg capsules

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

Dosage and administration details:

400 mg tablets

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

Dosage and administration details:

Ribavirin tablets administered at a weight-based dose, between 1,000 to 1,200 mg daily (divided).

| | |
|------------------|---------|
| Arm title | Group C |
|------------------|---------|

Arm description:

Treatment-naïve participants received ABT-450 100 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, and ribavirin dosed by weight, twice daily for 12 weeks.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | ABT-450 |
| Investigational medicinal product code | |
| Other name | Paritaprevir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

50 mg tablets

| | |
|--|--------------|
| Investigational medicinal product name | Ritonavir |
| Investigational medicinal product code | |
| Other name | Norvir |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |
| Dosage and administration details: 100 mg capsules | |
| Investigational medicinal product name | ABT-267 |
| Investigational medicinal product code | |
| Other name | Ombitasvir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: 25 mg tablets | |
| Investigational medicinal product name | Ribavirin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: Ribavirin tablets administered at a weight-based dose, between 1,000 to 1,200 mg daily (divided). | |
| Arm title | Group D |
| Arm description: Treatment-naïve participants received ABT-450 200 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, and ribavirin dosed by weight, twice daily for 12 weeks. | |
| Arm type | Experimental |
| Investigational medicinal product name | ABT-450 |
| Investigational medicinal product code | |
| Other name | Paritaprevir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: 50 mg tablets | |
| Investigational medicinal product name | ABT-267 |
| Investigational medicinal product code | |
| Other name | Ombitasvir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: 25 mg tablets | |
| Investigational medicinal product name | Ribavirin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: Ribavirin tablets administered at a weight-based dose, between 1,000 to 1,200 mg daily (divided). | |
| Investigational medicinal product name | Ritonavir |
| Investigational medicinal product code | |
| Other name | Norvir |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

100 mg capsules

| | |
|------------------|---------|
| Arm title | Group E |
|------------------|---------|

Arm description:

Treatment-naïve participants received ABT-450 150 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, and ABT-333 400 mg twice daily for 12 weeks.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | ABT-450 |
| Investigational medicinal product code | |
| Other name | Paritaprevir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

50 mg tablets

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

Dosage and administration details:

400 mg tablets

| | |
|--|------------|
| Investigational medicinal product name | ABT-267 |
| Investigational medicinal product code | |
| Other name | Ombitasvir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

25 mg tablets

| | |
|--|-----------|
| Investigational medicinal product name | Ritonavir |
| Investigational medicinal product code | |
| Other name | Norvir |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

100 mg capsules

| | |
|------------------|---------|
| Arm title | Group F |
|------------------|---------|

Arm description:

Treatment-naïve participants received ABT-450 100 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily for 12 weeks.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | ABT-450 |
| Investigational medicinal product code | |
| Other name | Paritaprevir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

50 mg tablets

| | |
|---|--------------|
| Investigational medicinal product name | ABT-333 |
| Investigational medicinal product code | |
| Other name | Dasabuvir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Other use |
| Dosage and administration details: | |
| 400 mg tablets | |
| Investigational medicinal product name | ABT-267 |
| Investigational medicinal product code | |
| Other name | Ombitasvir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 25 mg tablets | |
| Investigational medicinal product name | Ritonavir |
| Investigational medicinal product code | |
| Other name | Norvir |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 100 mg capsules | |
| Investigational medicinal product name | Ribavirin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Ribavirin tablets administered at a weight-based dose, between 1,000 to 1,200 mg daily (divided). | |
| Arm title | Group G |
| Arm description: | |
| Treatment-naïve participants received ABT-450 150 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 12 weeks. | |
| Arm type | Experimental |
| Investigational medicinal product name | ABT-450 |
| Investigational medicinal product code | |
| Other name | Paritaprevir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 50 mg tablets | |
| Investigational medicinal product name | ABT-333 |
| Investigational medicinal product code | |
| Other name | Dasabuvir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Other use |
| Dosage and administration details: | |
| 400 mg tablets | |
| Investigational medicinal product name | ABT-267 |
| Investigational medicinal product code | |
| Other name | Ombitasvir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

| | |
|---|--------------|
| Dosage and administration details: | |
| 25 mg tablets | |
| Investigational medicinal product name | Ritonavir |
| Investigational medicinal product code | |
| Other name | Norvir |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 100 mg capsules | |
| Investigational medicinal product name | Ribavirin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Ribavirin tablets administered at a weight-based dose, between 1,000 to 1,200 mg daily (divided). | |
| Arm title | Group H |
| Arm description: | |
| Treatment-naïve participants received ABT-450 100 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 24 weeks. | |
| Arm type | Experimental |
| Investigational medicinal product name | ABT-450 |
| Investigational medicinal product code | |
| Other name | Paritaprevir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 50 mg tablets | |
| Investigational medicinal product name | ABT-333 |
| Investigational medicinal product code | |
| Other name | Dasabuvir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Other use |
| Dosage and administration details: | |
| 400 mg tablets | |
| Investigational medicinal product name | ABT-267 |
| Investigational medicinal product code | |
| Other name | Ombitasvir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 25 mg tablets | |
| Investigational medicinal product name | Ritonavir |
| Investigational medicinal product code | |
| Other name | Norvir |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 100 mg capsules | |
| Investigational medicinal product name | Ribavirin |
| Investigational medicinal product code | |
| Other name | |

| | |
|--------------------------|----------|
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Ribavirin tablets administered at a weight-based dose, between 1,000 to 1,200 mg daily (divided).

| | |
|------------------|---------|
| Arm title | Group I |
|------------------|---------|

Arm description:

Treatment-naïve participants received ABT-450 150 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 24 weeks.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | ABT-450 |
| Investigational medicinal product code | |
| Other name | Paritaprevir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

50 mg tablets

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

Dosage and administration details:

400 mg tablets

| | |
|--|------------|
| Investigational medicinal product name | ABT-267 |
| Investigational medicinal product code | |
| Other name | Ombitasvir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

25 mg tablets

| | |
|--|-----------|
| Investigational medicinal product name | Ritonavir |
| Investigational medicinal product code | |
| Other name | Norvir |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

100 mg capsules

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

Dosage and administration details:

Ribavirin tablets administered at a weight-based dose, between 1,000 to 1,200 mg daily (divided).

| | |
|------------------|---------|
| Arm title | Group J |
|------------------|---------|

Arm description:

Participants who were null-responders to previous HCV treatment received ABT-450 200 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, and ribavirin dosed by weight, twice daily, for 12 weeks.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|--------------|
| Investigational medicinal product name | ABT-450 |
| Investigational medicinal product code | |
| Other name | Paritaprevir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 50 mg tablets | |
| Investigational medicinal product name | ABT-267 |
| Investigational medicinal product code | |
| Other name | Ombitasvir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 25 mg tablets | |
| Investigational medicinal product name | Ritonavir |
| Investigational medicinal product code | |
| Other name | Norvir |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 100 mg capsules | |
| Investigational medicinal product name | Ribavirin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Ribavirin tablets administered at a weight-based dose, between 1,000 to 1,200 mg daily (divided). | |
| Arm title | Group K |
| Arm description: | |
| Participants who were null-responders to previous HCV treatment received ABT-450 100 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 12 weeks. | |
| Arm type | Experimental |
| Investigational medicinal product name | ABT-450 |
| Investigational medicinal product code | |
| Other name | Paritaprevir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 50 mg tablets | |
| Investigational medicinal product name | ABT-333 |
| Investigational medicinal product code | |
| Other name | Dasabuvir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Other use |
| Dosage and administration details: | |
| 400 mg tablets | |
| Investigational medicinal product name | ABT-267 |
| Investigational medicinal product code | |
| Other name | Ombitasvir |
| Pharmaceutical forms | Tablet |

| | |
|--|--------------|
| Routes of administration | Oral use |
| Dosage and administration details: 25 mg tablets | |
| Investigational medicinal product name | Ritonavir |
| Investigational medicinal product code | |
| Other name | Norvir |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |
| Dosage and administration details: 100 mg capsules | |
| Investigational medicinal product name | Ribavirin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: Ribavirin tablets administered at a weight-based dose, between 1,000 to 1,200 mg daily (divided). | |
| Arm title | Group L |
| Arm description: Participants who were null-responders to previous HCV treatment received ABT-450 150 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 12 weeks. | |
| Arm type | Experimental |
| Investigational medicinal product name | ABT-450 |
| Investigational medicinal product code | |
| Other name | Paritaprevir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: 50 mg tablets | |
| Investigational medicinal product name | ABT-333 |
| Investigational medicinal product code | |
| Other name | Dasabuvir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Other use |
| Dosage and administration details: 400 mg tablets | |
| Investigational medicinal product name | ABT-267 |
| Investigational medicinal product code | |
| Other name | Ombitasvir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: 25 mg tablets | |
| Investigational medicinal product name | Ritonavir |
| Investigational medicinal product code | |
| Other name | Norvir |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |
| Dosage and administration details: 100 mg capsules | |

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

Dosage and administration details:

Ribavirin tablets administered at a weight-based dose, between 1,000 to 1,200 mg daily (divided).

| | |
|------------------|---------|
| Arm title | Group M |
|------------------|---------|

Arm description:

Participants who were null-responders to previous HCV treatment received ABT-450 100 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 24 weeks.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | ABT-450 |
| Investigational medicinal product code | |
| Other name | Paritaprevir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

50 mg tablets

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

Dosage and administration details:

400 mg tablets

| | |
|--|------------|
| Investigational medicinal product name | ABT-267 |
| Investigational medicinal product code | |
| Other name | Ombitasvir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

25 mg tablets

| | |
|--|-----------|
| Investigational medicinal product name | Ritonavir |
| Investigational medicinal product code | |
| Other name | Norvir |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

100 mg capsules

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

Dosage and administration details:

Ribavirin tablets administered at a weight-based dose, between 1,000 to 1,200 mg daily (divided).

| | |
|------------------|---------|
| Arm title | Group N |
|------------------|---------|

Arm description:

Participants who were null-responders to previous HCV treatment received ABT-450 150 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin

dosed by weight, twice daily, for 24 weeks.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | ABT-450 |
| Investigational medicinal product code | |
| Other name | Paritaprevir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

50 mg tablets

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

Dosage and administration details:

400 mg tablets

| | |
|--|------------|
| Investigational medicinal product name | ABT-267 |
| Investigational medicinal product code | |
| Other name | Ombitasvir |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

25 mg tablets

| | |
|--|-----------|
| Investigational medicinal product name | Ritonavir |
| Investigational medicinal product code | |
| Other name | Norvir |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

100 mg capsules

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

Dosage and administration details:

Ribavirin tablets administered at a weight-based dose, between 1,000 to 1,200 mg daily (divided).

| Number of subjects in period 1 | Group A | Group B | Group C |
|---------------------------------------|---------|---------|---------|
| Started | 80 | 43 | 39 |
| Treated | 80 | 41 | 39 |
| Completed | 77 | 36 | 39 |
| Not completed | 3 | 7 | 0 |
| Consent withdrawn by subject | 1 | - | - |
| Adverse event, non-fatal | - | - | - |
| Other | 2 | 3 | - |

| | | | |
|-------------------|---|---|---|
| Lost to follow-up | - | 2 | - |
| Not treated | - | 2 | - |

| Number of subjects in period 1 | Group D | Group E | Group F |
|--------------------------------|---------|---------|---------|
| Started | 40 | 80 | 39 |
| Treated | 40 | 79 | 39 |
| Completed | 36 | 72 | 38 |
| Not completed | 4 | 8 | 1 |
| Consent withdrawn by subject | - | 1 | - |
| Adverse event, non-fatal | - | - | - |
| Other | 2 | 3 | - |
| Lost to follow-up | 2 | 3 | 1 |
| Not treated | - | 1 | - |

| Number of subjects in period 1 | Group G | Group H | Group I |
|--------------------------------|---------|---------|---------|
| Started | 41 | 40 | 40 |
| Treated | 40 | 40 | 40 |
| Completed | 37 | 37 | 37 |
| Not completed | 4 | 3 | 3 |
| Consent withdrawn by subject | - | 1 | - |
| Adverse event, non-fatal | - | - | - |
| Other | 1 | - | 3 |
| Lost to follow-up | 2 | 2 | - |
| Not treated | 1 | - | - |

| Number of subjects in period 1 | Group J | Group K | Group L |
|--------------------------------|---------|---------|---------|
| Started | 47 | 23 | 23 |
| Treated | 45 | 23 | 22 |
| Completed | 44 | 21 | 21 |
| Not completed | 3 | 2 | 2 |
| Consent withdrawn by subject | - | - | - |
| Adverse event, non-fatal | - | - | - |
| Other | 1 | 2 | - |
| Lost to follow-up | - | - | 1 |
| Not treated | 2 | - | 1 |

| Number of subjects in period 1 | Group M | Group N |
|--------------------------------|---------|---------|
| Started | 23 | 22 |
| Treated | 23 | 20 |
| Completed | 21 | 19 |
| Not completed | 2 | 3 |
| Consent withdrawn by subject | - | - |

| | | |
|--------------------------|---|---|
| Adverse event, non-fatal | 1 | - |
| Other | 1 | - |
| Lost to follow-up | - | 1 |
| Not treated | - | 2 |

Baseline characteristics

Reporting groups

| | |
|--|---------|
| Reporting group title | Group A |
| Reporting group description: Treatment-naïve participants received ABT-450 150 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily for 8 weeks. | |
| Reporting group title | Group B |
| Reporting group description: Treatment-naïve participants received ABT-450 150 mg and ritonavir 100 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily for 12 weeks. | |
| Reporting group title | Group C |
| Reporting group description: Treatment-naïve participants received ABT-450 100 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, and ribavirin dosed by weight, twice daily for 12 weeks. | |
| Reporting group title | Group D |
| Reporting group description: Treatment-naïve participants received ABT-450 200 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, and ribavirin dosed by weight, twice daily for 12 weeks. | |
| Reporting group title | Group E |
| Reporting group description: Treatment-naïve participants received ABT-450 150 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, and ABT-333 400 mg twice daily for 12 weeks. | |
| Reporting group title | Group F |
| Reporting group description: Treatment-naïve participants received ABT-450 100 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily for 12 weeks. | |
| Reporting group title | Group G |
| Reporting group description: Treatment-naïve participants received ABT-450 150 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 12 weeks. | |
| Reporting group title | Group H |
| Reporting group description: Treatment-naïve participants received ABT-450 100 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 24 weeks. | |
| Reporting group title | Group I |
| Reporting group description: Treatment-naïve participants received ABT-450 150 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 24 weeks. | |
| Reporting group title | Group J |
| Reporting group description: Participants who were null-responders to previous HCV treatment received ABT-450 200 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, and ribavirin dosed by weight, twice daily, for 12 weeks. | |
| Reporting group title | Group K |
| Reporting group description: Participants who were null-responders to previous HCV treatment received ABT-450 100 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 12 weeks. | |
| Reporting group title | Group L |
| Reporting group description: Participants who were null-responders to previous HCV treatment received ABT-450 150 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 12 weeks. | |
| Reporting group title | Group M |

Reporting group description:

Participants who were null-responders to previous HCV treatment received ABT-450 100 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 24 weeks.

| | |
|-----------------------|---------|
| Reporting group title | Group N |
|-----------------------|---------|

Reporting group description:

Participants who were null-responders to previous HCV treatment received ABT-450 150 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 24 weeks.

| Reporting group values | Group A | Group B | Group C |
|------------------------|---------|---------|---------|
| Number of subjects | 80 | 43 | 39 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|--------|--------|--------|
| Age continuous | | | |
| Data are provided for the safety population (participants who received at least 1 dose of direct-acting antiviral agent). | | | |
| Units: years | | | |
| arithmetic mean | 50.1 | 50.8 | 51.1 |
| standard deviation | ± 9.99 | ± 9.84 | ± 8.07 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 34 | 24 | 14 |
| Male | 46 | 19 | 25 |

| Reporting group values | Group D | Group E | Group F |
|------------------------|---------|---------|---------|
| Number of subjects | 40 | 80 | 39 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|---------|---------|--------|
| Age continuous | | | |
| Data are provided for the safety population (participants who received at least 1 dose of direct-acting antiviral agent). | | | |
| Units: years | | | |
| arithmetic mean | 49 | 48.3 | 49.4 |
| standard deviation | ± 10.59 | ± 10.53 | ± 9.72 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 20 | 34 | 19 |
| Male | 20 | 46 | 20 |

| Reporting group values | Group G | Group H | Group I |
|------------------------|---------|---------|---------|
| Number of subjects | 41 | 40 | 40 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|--|--|--|
| Age continuous | | | |
| Data are provided for the safety population (participants who received at least 1 dose of direct-acting antiviral agent). | | | |
| Units: years | | | |

| | | | |
|--------------------|---------|---------|--------|
| arithmetic mean | 51 | 51.5 | 51.5 |
| standard deviation | ± 11.08 | ± 11.95 | ± 9.78 |

| | | | |
|---------------------------------------|----|----|----|
| Gender categorical Units: Subjects | | | |
| Female | 16 | 22 | 24 |
| Male | 25 | 18 | 16 |

| | | | |
|------------------------------------|---------|---------|---------|
| Reporting group values | Group J | Group K | Group L |
| Number of subjects | 47 | 23 | 23 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|---------|---------|---------|
| Age continuous | | | |
| Data are provided for the safety population (participants who received at least 1 dose of direct-acting antiviral agent). | | | |
| Units: years | | | |
| arithmetic mean | 50.6 | 48.5 | 51.2 |
| standard deviation | ± 11.19 | ± 12.91 | ± 12.07 |
| Gender categorical Units: Subjects | | | |
| Female | 19 | 7 | 10 |
| Male | 28 | 16 | 13 |

| | | | |
|------------------------------------|---------|---------|-------|
| Reporting group values | Group M | Group N | Total |
| Number of subjects | 23 | 22 | 580 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|--------|---------|-----|
| Age continuous | | | |
| Data are provided for the safety population (participants who received at least 1 dose of direct-acting antiviral agent). | | | |
| Units: years | | | |
| arithmetic mean | 51.5 | 54.6 | |
| standard deviation | ± 9.06 | ± 11.78 | - |
| Gender categorical Units: Subjects | | | |
| Female | 8 | 9 | 260 |
| Male | 15 | 13 | 320 |

End points

End points reporting groups

| | |
|--|---------|
| Reporting group title | Group A |
| Reporting group description: Treatment-naïve participants received ABT-450 150 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily for 8 weeks. | |
| Reporting group title | Group B |
| Reporting group description: Treatment-naïve participants received ABT-450 150 mg and ritonavir 100 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily for 12 weeks. | |
| Reporting group title | Group C |
| Reporting group description: Treatment-naïve participants received ABT-450 100 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, and ribavirin dosed by weight, twice daily for 12 weeks. | |
| Reporting group title | Group D |
| Reporting group description: Treatment-naïve participants received ABT-450 200 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, and ribavirin dosed by weight, twice daily for 12 weeks. | |
| Reporting group title | Group E |
| Reporting group description: Treatment-naïve participants received ABT-450 150 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, and ABT-333 400 mg twice daily for 12 weeks. | |
| Reporting group title | Group F |
| Reporting group description: Treatment-naïve participants received ABT-450 100 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily for 12 weeks. | |
| Reporting group title | Group G |
| Reporting group description: Treatment-naïve participants received ABT-450 150 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 12 weeks. | |
| Reporting group title | Group H |
| Reporting group description: Treatment-naïve participants received ABT-450 100 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 24 weeks. | |
| Reporting group title | Group I |
| Reporting group description: Treatment-naïve participants received ABT-450 150 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 24 weeks. | |
| Reporting group title | Group J |
| Reporting group description: Participants who were null-responders to previous HCV treatment received ABT-450 200 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, and ribavirin dosed by weight, twice daily, for 12 weeks. | |
| Reporting group title | Group K |
| Reporting group description: Participants who were null-responders to previous HCV treatment received ABT-450 100 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 12 weeks. | |
| Reporting group title | Group L |
| Reporting group description: Participants who were null-responders to previous HCV treatment received ABT-450 150 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 12 weeks. | |
| Reporting group title | Group M |

Reporting group description:

Participants who were null-responders to previous HCV treatment received ABT-450 100 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 24 weeks.

| | |
|-----------------------|---------|
| Reporting group title | Group N |
|-----------------------|---------|

Reporting group description:

Participants who were null-responders to previous HCV treatment received ABT-450 150 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 24 weeks.

| | |
|----------------------------|---------|
| Subject analysis set title | Group A |
|----------------------------|---------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Treatment-naïve participants received ABT-450 150 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 8 weeks.

| | |
|----------------------------|---------|
| Subject analysis set title | Group B |
|----------------------------|---------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Treatment-naïve participants received ABT-450 150 mg and ritonavir 100 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily for 12 weeks.

| | |
|----------------------------|-------------|
| Subject analysis set title | Group C + D |
|----------------------------|-------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Treatment-naïve participants received ABT-450 (100 mg or 200 mg) and ritonavir 100 mg once daily, ABT-267 25 mg once daily, and ribavirin dosed by weight, twice daily, for 12 weeks.

| | |
|----------------------------|---------|
| Subject analysis set title | Group E |
|----------------------------|---------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Treatment-naïve participants received ABT-450 150 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, and ABT-333 400 mg twice daily for 12 weeks.

| | |
|----------------------------|-------------|
| Subject analysis set title | Group F + G |
|----------------------------|-------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Treatment-naïve participants received ABT-450 (100 mg or 150 mg) and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 12 weeks.

| | |
|----------------------------|-------------|
| Subject analysis set title | Group H + I |
|----------------------------|-------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Treatment-naïve participants received ABT-450 (100 mg or 150 mg) and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 24 weeks.

| | |
|----------------------------|---------|
| Subject analysis set title | Group J |
|----------------------------|---------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Participants who were null-responders to previous HCV treatment received ABT-450 200 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, and ribavirin dosed by weight, twice daily, for 12 weeks.

| | |
|----------------------------|-------------|
| Subject analysis set title | Group K + L |
|----------------------------|-------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Participants who were null-responders to previous HCV treatment received ABT-450 (100 mg or 150 mg) and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 12 weeks.

| | |
|----------------------------|-------------|
| Subject analysis set title | Group M + N |
|----------------------------|-------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Participants who were null-responders to previous HCV treatment received ABT-450 (100 mg or 150

mg) and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 24 weeks.

| | |
|----------------------------|----------------------|
| Subject analysis set title | Groups F + G + K + L |
|----------------------------|----------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Participants (treatment-naïve and null-responders) received ABT-450 (100 mg or 150 mg) and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 12 weeks.

| | |
|----------------------------|----------------------|
| Subject analysis set title | Groups H + I + M + N |
|----------------------------|----------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Participants (treatment-naïve and null-responders) received ABT-450 (100 mg or 150 mg) and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 24 weeks.

| | |
|----------------------------|------------------|
| Subject analysis set title | Groups C + D + J |
|----------------------------|------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Participants (treatment-naïve and null-responders) received ABT-450 (100 mg or 200 mg) and ritonavir 100 mg once daily, ABT-267 25 mg once daily, and ribavirin dosed by weight, twice daily, for 12 weeks.

| | |
|----------------------------|----------------------|
| Subject analysis set title | Groups F + G + H + I |
|----------------------------|----------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Treatment-naïve participants received ABT-450 (100 mg or 150 mg) and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 12 or 24 weeks.

| | |
|----------------------------|----------------------|
| Subject analysis set title | Groups K + L + M + N |
|----------------------------|----------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Participants who were null-responders to previous HCV treatment received ABT-450 (100 mg or 150 mg) and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 12 or 24 weeks.

Primary: Number of Participants With Adverse Events (AEs)

| | |
|-----------------|---|
| End point title | Number of Participants With Adverse Events (AEs) ^[1] |
|-----------------|---|

End point description:

An adverse event was defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and that did not necessarily have a causal relationship with this treatment.

The investigator assessed the relationship of each AE to the use of direct-acting antiviral agents (DAAs) and to ribavirin, and rated the severity of each event as either:

Mild: The AE was transient and easily tolerated by the participant; Moderate: The AE caused the participant discomfort and interrupted usual activities; Severe: The AE caused considerable interference with the participant's usual activities and could have been incapacitating or life-threatening.

A serious adverse event was any event that resulted in death, was life-threatening, resulted in or prolonged hospitalization, resulted in a congenital anomaly or persistent or significant disability or was any other important medical event requiring medical or surgical intervention.

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

End point timeframe:

From the time of study drug administration until 30 days following discontinuation of study drug administration (up to 28 weeks).

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: Safety was assessed by summarizing the incidence of adverse events.

| End point values | Group A | Group B | Group C + D | Group E |
|---|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 80 | 41 | 79 | 79 |
| Units: participants | | | | |
| Any adverse event | 67 | 36 | 71 | 68 |
| Any adverse event at least possibly DAARelated | 58 | 29 | 53 | 51 |
| Any severe adverse event | 3 | 0 | 3 | 5 |
| Any serious adverse event | 0 | 0 | 2 | 2 |
| Any AE leading to discontinuation of study drug | 1 | 0 | 0 | 0 |
| Any AE leading to interruption of study drug | 0 | 1 | 2 | 1 |
| Any AE leading to ribavirin dose modification | 2 | 2 | 4 | 0 |
| Any fatal adverse events | 0 | 0 | 0 | 0 |

| End point values | Group F + G | Group H + I | Group J | Group K + L |
|---|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 79 | 80 | 45 | 45 |
| Units: participants | | | | |
| Any adverse event | 71 | 77 | 42 | 39 |
| Any adverse event at least possibly DAARelated | 57 | 68 | 35 | 30 |
| Any severe adverse event | 3 | 3 | 1 | 1 |
| Any serious adverse event | 1 | 1 | 0 | 0 |
| Any AE leading to discontinuation of study drug | 3 | 3 | 1 | 0 |
| Any AE leading to interruption of study drug | 0 | 1 | 0 | 0 |
| Any AE leading to ribavirin dose modification | 9 | 10 | 3 | 1 |
| Any fatal adverse events | 0 | 0 | 0 | 0 |

| End point values | Group M + N | | | |
|---|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 45 | | | |
| Units: participants | | | | |
| Any adverse event | 37 | | | |
| Any adverse event at least possibly DAARelated | 28 | | | |
| Any severe adverse event | 1 | | | |
| Any serious adverse event | 2 | | | |
| Any AE leading to discontinuation of study drug | 1 | | | |
| Any AE leading to interruption of study drug | 0 | | | |
| Any AE leading to ribavirin dose modification | 3 | | | |

| | | | | |
|--------------------------|---|--|--|--|
| Any fatal adverse events | 0 | | | |
|--------------------------|---|--|--|--|

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With Sustained Virologic Response 24 Weeks Post-dose for 8 Weeks Versus 12 Weeks of Treatment With 3 DAAs and Ribavirin

| | |
|---|--|
| End point title | Percentage of Participants With Sustained Virologic Response 24 Weeks Post-dose for 8 Weeks Versus 12 Weeks of Treatment With 3 DAAs and Ribavirin |
| End point description: | |
| <p>The percentage of participants achieving sustained virologic response 24 weeks after the last dose of study drug (SVR24), defined as hepatitis C virus (HCV) ribonucleic acid (RNA) less than the lower limit of quantitation (LLOQ), without any confirmed quantifiable (\geq LLOQ) post-treatment value before that time point. HCV RNA levels were measured from plasma by a central laboratory. The LLOQ for the assay was 25 IU/mL.</p> <p>The primary efficacy endpoint was the comparison between treatment-naïve participants following 8 weeks of treatment with 3 DAAs and ribavirin and those with 12 weeks of treatment with 3 DAAs and ribavirin (Group A versus Group G).</p> <p>Participants with missing data were counted as non-responders.</p> | |
| End point type | Primary |
| End point timeframe: | |
| Post Treatment Week 24 | |

| End point values | Group A | Group B | Group C | Group D |
|-----------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 80 | 41 | 39 | 40 |
| Units: percentage of participants | | | | |
| number (not applicable) | 87.5 | 82.9 | 84.6 | 92.5 |

| End point values | Group E | Group F | Group G | Group H |
|-----------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 79 | 39 | 40 | 40 |
| Units: percentage of participants | | | | |
| number (not applicable) | 88.6 | 97.4 | 95 | 92.5 |

| End point values | Group I | Group J | Group K | Group L |
|-----------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 40 | 45 | 23 | 22 |
| Units: percentage of participants | | | | |

| | | | | |
|-------------------------|----|------|------|------|
| number (not applicable) | 90 | 88.9 | 91.3 | 95.5 |
|-------------------------|----|------|------|------|

| End point values | Group M | Group N | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 23 | 20 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 91.3 | 100 | | |

Statistical analyses

| Statistical analysis title | Primary analysis |
|----------------------------|------------------|
|----------------------------|------------------|

Statistical analysis description:

The primary efficacy endpoint was the comparison of the percentage of treatment-naïve participants with SVR24 after treatment with 3 DAAs (at the 150 mg ABT-450 dose) and ribavirin for 8 weeks (Group A) versus 12 weeks (Group G).

| | |
|---|----------------------------|
| Comparison groups | Group G v Group A |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[2] |
| P-value | = 0.406 ^[3] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.09 |
| upper limit | 2.61 |

Notes:

[2] - Pre-specified 2-sided significance level of 0.05.

[3] - Logistic regression with baseline log10 HCV RNA level, treatment group, Interleukin 28B genotype (CC or non-CC), HCV subgenotype (1a or non-1a), and geographic region (US or non-US) as predictors. No adjustment for multiple comparison.

Secondary: Percentage of Participants With Sustained Virologic Response 24 Weeks Post-dose Following Treatment of Different Durations With 3 Direct-acting Antiviral Agents (DAAs) and Ribavirin

| | |
|-----------------|---|
| End point title | Percentage of Participants With Sustained Virologic Response 24 Weeks Post-dose Following Treatment of Different Durations With 3 Direct-acting Antiviral Agents (DAAs) and Ribavirin |
|-----------------|---|

End point description:

This endpoint compares the percentage of participants achieving sustained virologic response 24 weeks after the last dose of study drug (HCV RNA < LLOQ at post-treatment Week 24) following treatment with 3 DAAs (ABT-450/ritonavir, ABT-267, and ABT-333) and ribavirin in both treatment naïve and null-responder participants for 8 weeks (Group A) versus 12 weeks (Groups F + G + K + L) versus 24 weeks (Groups H + I + M + N).

Participants with missing data were counted as non-responders.

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

End point timeframe:

Post-Treatment Week 24

| End point values | Group A | Groups F + G + K + L | Groups H + I + M + N | |
|-----------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 80 | 124 | 123 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 87.5 | 95.2 | 92.7 | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|--------------------------------|
| Statistical analysis description: | |
| The percentage of participants with SVR24 after treatment for 8 weeks versus 12 weeks was compared using logistic regression with treatment group, baseline log10 HCV RNA level, HCV subgenotype (1a or non-1a), geographic region (US or non-US), Interleukin 28B genotype (CC or non-CC), and ABT-450/ritonavir dose and population (treatment-naïve or null-responders) as predictors. | |
| Comparison groups | Group A v Groups F + G + K + L |
| Number of subjects included in analysis | 204 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[4] |
| P-value | = 0.266 ^[5] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.08 |
| upper limit | 2.02 |

Notes:

[4] - Pre-specified 2-sided significance level of 0.05.

[5] - No adjustment for multiple comparison.

| Statistical analysis title | Statistical Analysis 2 |
|---|--------------------------------|
| Statistical analysis description: | |
| The percentage of participants with SVR24 after treatment for 8 weeks versus 24 weeks was compared using logistic regression with treatment group, baseline log10 HCV RNA level, HCV subgenotype (1a or non-1a), geographic region (US or non-US), Interleukin 28B genotype (CC or non-CC), ABT-450/ritonavir dose and population (treatment-naïve or null-responders) as predictors. | |
| Comparison groups | Group A v Groups H + I + M + N |
| Number of subjects included in analysis | 203 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[6] |
| P-value | = 0.525 ^[7] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.66 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.18 |
| upper limit | 2.4 |

Notes:

[6] - Pre-specified 2-sided significance level of 0.05.

[7] - No adjustment for multiple comparison.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

The percentage of participants with SVR24 after treatment for 12 weeks versus 24 weeks was compared using logistic regression with treatment group, baseline log10 HCV RNA level, HCV subgenotype (1a or non-1a), geographic region (US or non-US), Interleukin 28B genotype (CC or non-CC), ABT-450/ritonavir dose and population (treatment-naïve or null-responders) as predictors.

| | |
|---|---|
| Comparison groups | Groups F + G + K + L v Groups H + I + M + N |
| Number of subjects included in analysis | 247 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[8] |
| P-value | = 0.375 ^[9] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.64 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.55 |
| upper limit | 4.92 |

Notes:

[8] - Pre-specified 2-sided significance level of 0.05.

[9] - No adjustment for multiple comparison.

Secondary: Percentage of Participants With Sustained Virologic Response 24 Weeks Post-dose Following Treatment for 12 Weeks With 2 DAAs and Ribavirin Versus 3 DAAs and Ribavirin

| | |
|-----------------|--|
| End point title | Percentage of Participants With Sustained Virologic Response 24 Weeks Post-dose Following Treatment for 12 Weeks With 2 DAAs and Ribavirin Versus 3 DAAs and Ribavirin |
|-----------------|--|

End point description:

This endpoint compares the percentage of participants achieving sustained virologic response 24 weeks post-dose (HCV RNA < LLOQ at post-treatment Week 24) following treatment with 2 DAAs (ABT-450/ritonavir plus ABT-333 [Group B] or ABT-450/ritonavir plus ABT-267 [Groups C + D + J]) and ribavirin versus 3 DAAs (ABT-450/ritonavir plus ABT-333 and ABT-267) and ribavirin (Groups F + G + K + L).

Participants with missing data were counted as non-responders.

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

End point timeframe:

Post-Treatment Week 24

| End point values | Group B | Groups F + G + K + L | Groups C + D + J | |
|-----------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 41 | 124 | 124 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 82.9 | 95.2 | 88.7 | |

Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|--|--|
| Statistical analysis description: | |
| The percentage of participants with SVR24 after treatment with 2 DAAs and ribavirin versus 3 DAAs and ribavirin was compared using stratum-adjusted Mantel-Haenszel (MH) method with Interleukin 28B genotype (CC or non-CC) and HCV subgenotype (1a or non-1a). | |
| Comparison groups | Group B v Groups F + G + K + L |
| Number of subjects included in analysis | 165 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[10] |
| P-value | = 0.068 ^[11] |
| Method | Mantel-Haenszel |
| Parameter estimate | Difference (Group B - Groups F + G + K) |
| Point estimate | -12.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -25.2 |
| upper limit | 0.88 |

Notes:

[10] - Pre-specified 2-sided significance level of 0.05.

[11] - The Mantel-Haenszel method was used because logistic regression failed due to separation or quasi-separation. There was no adjustment for multiple comparison.

| Statistical analysis title | Statistical Analysis 2 |
|--|--|
| Statistical analysis description: | |
| The percentage of participants with SVR24 after treatment with 2 DAAs and ribavirin versus 3 DAAs and ribavirin was compared using stratum-adjusted Mantel-Haenszel (MH) method with Interleukin 28B genotype (CC or non-CC) and HCV subgenotype (1a or non-1a). | |
| Comparison groups | Groups F + G + K + L v Groups C + D + J |
| Number of subjects included in analysis | 248 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[12] |
| P-value | = 0.065 ^[13] |
| Method | Mantel-Haenszel |
| Parameter estimate | Difference (Group C+D+J - Group F+G+K+L) |
| Point estimate | -6.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -13.93 |
| upper limit | 0.43 |

Notes:

[12] - Pre-specified 2-sided significance level of 0.05.

[13] - The Mantel-Haenszel method was used because logistic regression failed due to separation or quasi-separation. No adjustment for multiple comparison.

Secondary: Percentage of Participants With Sustained Virologic Response 24 Weeks Post-dose Following Treatment for 12 Weeks With 3 DAAs With Versus Without Ribavirin

| | |
|-----------------|--|
| End point title | Percentage of Participants With Sustained Virologic Response 24 Weeks Post-dose Following Treatment for 12 Weeks With 3 DAAs With Versus Without Ribavirin |
|-----------------|--|

End point description:

This endpoint compares the percentage of participants achieving sustained virologic response 24 weeks post-dose (HCV RNA < LLOQ at post-treatment Week 24) following treatment with 3 DAAs with or without ribavirin (Group E versus Groups F + G + K + L).

Participants with missing data were counted as non-responders.

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

End point timeframe:

Post-Treatment Week 24

| End point values | Group E | Groups F + G + K + L | | |
|-----------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 79 | 124 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 88.6 | 95.2 | | |

Statistical analyses

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

Statistical analysis description:

The percentage of participants with SVR24 after treatment with 3 DAAs with and without ribavirin was compared using a stratum-adjusted Mantel-Haenszel (MH) method with Interleukin 28B genotype (CC or non-CC) and HCV subgenotype (1a or non-1a).

| | |
|---|--------------------------------------|
| Comparison groups | Group E v Groups F + G + K + L |
| Number of subjects included in analysis | 203 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[14] |
| P-value | = 0.106 ^[15] |
| Method | Mantel-Haenszel |
| Parameter estimate | Difference (Group E - Group F+G+K+L) |
| Point estimate | -7.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -15.77 |
| upper limit | 1.51 |

Notes:

[14] - Pre-specified 2-sided significance level of 0.05.

[15] - The Mantel-Haenszel method was used because logistic regression failed due to separation or quasi-separation. No adjustment for multiple comparison.

Secondary: Percentage of Participants With Sustained Virologic Response 24 Weeks Post-dose in Treatment-naïve Versus Null-responders

| | |
|-----------------|---|
| End point title | Percentage of Participants With Sustained Virologic Response 24 Weeks Post-dose in Treatment-naïve Versus Null-responders |
|-----------------|---|

End point description:

This endpoint compares the percentage of participants achieving sustained virologic response 24 weeks post-dose (HCV RNA < LLOQ at post-treatment Week 24) following treatment with 3 DAAs and ribavirin in participants who were treatment-naïve versus those who were null-responders to previous HCV therapy (Groups F + G + H + I versus Groups K + L + M + N). Participants with missing data were counted as non-responders.

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

End point timeframe:

Post-Treatment Week 24

| End point values | Groups F + G + H + I | Groups K + L + M + N | | |
|-----------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 159 | 88 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 93.7 | 94.3 | | |

Statistical analyses

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

Statistical analysis description:

The percentage of participants with SVR24 after treatment with 3 DAAs and ribavirin in treatment-naïve versus null-responders was compared using logistic regression with treatment group, baseline log10 HCV RNA level, HCV subgenotype (1a or non-1a), geographic region (US or non-US), Interleukin 28B genotype (CC or non-CC), and ABT-450/ritonavir dose as predictors.

| | |
|---|---|
| Comparison groups | Groups F + G + H + I v Groups K + L + M + N |
| Number of subjects included in analysis | 247 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[16] |
| P-value | = 0.616 ^[17] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.41 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.37 |
| upper limit | 5.34 |

Notes:

[16] - Pre-specified 2-sided significance level of 0.05.

[17] - No adjustment for multiple comparison.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 28 weeks

Adverse event reporting additional description:

Treatment groups differing only in ABT-450 dose (100 mg, 150 mg or 200 mg) were combined for safety analyses.

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

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Group A |
|-----------------------|---------|

Reporting group description:

Treatment-naïve participants received ABT-450 150 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 8 weeks.

| | |
|-----------------------|---------|
| Reporting group title | Group B |
|-----------------------|---------|

Reporting group description:

Treatment-naïve participants received ABT-450 150 mg and ritonavir 100 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily for 12 weeks.

| | |
|-----------------------|-------------|
| Reporting group title | Group C + D |
|-----------------------|-------------|

Reporting group description:

Treatment-naïve participants received ABT-450 (100 mg or 200 mg) and ritonavir 100 mg once daily, ABT-267 25 mg once daily, and ribavirin dosed by weight, twice daily, for 12 weeks.

| | |
|-----------------------|---------|
| Reporting group title | Group E |
|-----------------------|---------|

Reporting group description:

Treatment-naïve participants received ABT-450 150 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, and ABT-333 400 mg twice daily for 12 weeks.

| | |
|-----------------------|-------------|
| Reporting group title | Group F + G |
|-----------------------|-------------|

Reporting group description:

Treatment-naïve participants received ABT-450 (100 mg or 150 mg) and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 12 weeks.

| | |
|-----------------------|-------------|
| Reporting group title | Group H + I |
|-----------------------|-------------|

Reporting group description:

Treatment-naïve participants received ABT-450 (100 mg or 150 mg) and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 24 weeks.

| | |
|-----------------------|---------|
| Reporting group title | Group J |
|-----------------------|---------|

Reporting group description:

Participants who were null-responders to previous HCV treatment received ABT-450 200 mg and ritonavir 100 mg once daily, ABT-267 25 mg once daily, and ribavirin dosed by weight, twice daily, for 12 weeks.

| | |
|-----------------------|-------------|
| Reporting group title | Group K + L |
|-----------------------|-------------|

Reporting group description:

Participants who were null-responders to previous HCV treatment received ABT-450 (100 mg or 150 mg) and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 12 weeks.

| | |
|-----------------------|-------------|
| Reporting group title | Group M + N |
|-----------------------|-------------|

Reporting group description:

Participants who were null-responders to previous HCV treatment received ABT-450 (100 mg or 150 mg) and ritonavir 100 mg once daily, ABT-267 25 mg once daily, ABT-333 400 mg twice daily, and ribavirin dosed by weight, twice daily, for 24 weeks.

| Serious adverse events | Group A | Group B | Group C + D |
|---|----------------|----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 41 (0.00%) | 2 / 79 (2.53%) |
| number of deaths (all causes) | 0 | 1 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 41 (0.00%) | 1 / 79 (1.27%) |
| 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 | | | |
| Animal bite | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 41 (0.00%) | 0 / 79 (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 | | | |
| Cervicobrachial syndrome | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 41 (0.00%) | 0 / 79 (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 |
| Facial paresis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 41 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 41 (0.00%) | 0 / 79 (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 | | | |
| Lung disorder | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 41 (0.00%) | 0 / 79 (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 |
| Psychiatric disorders | | | |
| Affective disorder | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 41 (0.00%) | 0 / 79 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 41 (0.00%) | 0 / 79 (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 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 41 (0.00%) | 0 / 79 (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 |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 41 (0.00%) | 0 / 79 (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 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 41 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 41 (0.00%) | 0 / 79 (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 E | Group F + G | Group H + I |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 1 / 79 (1.27%) | 1 / 80 (1.25%) |
| number of deaths (all causes) | 1 | 0 | 0 |

| | | | |
|---|----------------|----------------|----------------|
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 0 / 79 (0.00%) | 0 / 80 (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 | | | |
| Animal bite | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 79 (0.00%) | 0 / 80 (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 |
| Nervous system disorders | | | |
| Cervicobrachial syndrome | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 0 / 79 (0.00%) | 0 / 80 (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 |
| Facial paresis | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 0 / 79 (0.00%) | 0 / 80 (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 |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 0 / 79 (0.00%) | 0 / 80 (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 | | | |
| Lung disorder | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 79 (0.00%) | 0 / 80 (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 |
| Psychiatric disorders | | | |
| Affective disorder | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 79 (1.27%) | 0 / 80 (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 |

| | | | |
|---|----------------|----------------|----------------|
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 0 / 79 (0.00%) | 1 / 80 (1.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 0 / 79 (0.00%) | 0 / 80 (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 |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 0 / 79 (0.00%) | 0 / 80 (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 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 0 / 79 (0.00%) | 0 / 80 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 79 (0.00%) | 0 / 80 (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 |

| Serious adverse events | Group J | Group K + L | Group M + N |
|---|----------------|----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 45 (0.00%) | 2 / 43 (4.65%) |
| number of deaths (all causes) | 0 | 0 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 45 (0.00%) | 0 / 43 (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 | | | |
| Animal bite | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 45 (0.00%) | 0 / 43 (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 | | | |
| Cervicobrachial syndrome | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 45 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial paresis | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 45 (0.00%) | 0 / 43 (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 |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 45 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Lung disorder | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 45 (0.00%) | 0 / 43 (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 |
| Psychiatric disorders | | | |
| Affective disorder | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 45 (0.00%) | 0 / 43 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 45 (0.00%) | 0 / 43 (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 |
| Neck pain | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 45 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 45 (0.00%) | 1 / 43 (2.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 45 (0.00%) | 0 / 43 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 45 (0.00%) | 0 / 43 (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 |

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

| Non-serious adverse events | Group A | Group B | Group C + D |
|---|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 64 / 80 (80.00%) | 33 / 41 (80.49%) | 66 / 79 (83.54%) |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 7 / 80 (8.75%) | 1 / 41 (2.44%) | 8 / 79 (10.13%) |
| occurrences (all) | 7 | 1 | 8 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 41 (2.44%) | 2 / 79 (2.53%) |
| occurrences (all) | 0 | 1 | 2 |
| Chills | | | |
| subjects affected / exposed | 4 / 80 (5.00%) | 1 / 41 (2.44%) | 1 / 79 (1.27%) |
| occurrences (all) | 4 | 1 | 1 |
| Fatigue | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 29 / 80 (36.25%) | 13 / 41 (31.71%) | 22 / 79 (27.85%) |
| occurrences (all) | 33 | 13 | 25 |
| Irritability | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 4 / 41 (9.76%) | 5 / 79 (6.33%) |
| occurrences (all) | 1 | 5 | 5 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 12 / 80 (15.00%) | 5 / 41 (12.20%) | 11 / 79 (13.92%) |
| occurrences (all) | 12 | 5 | 11 |
| Dyspnoea | | | |
| subjects affected / exposed | 8 / 80 (10.00%) | 3 / 41 (7.32%) | 4 / 79 (5.06%) |
| occurrences (all) | 8 | 3 | 4 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 0 / 41 (0.00%) | 3 / 79 (3.80%) |
| occurrences (all) | 2 | 0 | 3 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | 0 / 41 (0.00%) | 4 / 79 (5.06%) |
| occurrences (all) | 3 | 0 | 4 |
| Sinus congestion | | | |
| subjects affected / exposed | 4 / 80 (5.00%) | 0 / 41 (0.00%) | 0 / 79 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Psychiatric disorders | | | |
| Abnormal dreams | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 2 / 41 (4.88%) | 2 / 79 (2.53%) |
| occurrences (all) | 1 | 2 | 2 |
| Anxiety | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 2 / 41 (4.88%) | 0 / 79 (0.00%) |
| occurrences (all) | 3 | 2 | 0 |
| Depressed mood | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 3 / 41 (7.32%) | 1 / 79 (1.27%) |
| occurrences (all) | 1 | 3 | 1 |
| Depression | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | 3 / 41 (7.32%) | 3 / 79 (3.80%) |
| occurrences (all) | 3 | 3 | 3 |
| Insomnia | | | |

| | | | |
|--|------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 10 / 80 (12.50%) 10 | 8 / 41 (19.51%) 8 | 9 / 79 (11.39%) 9 |
| Sleep disorder subjects affected / exposed occurrences (all) | 1 / 80 (1.25%) 1 | 0 / 41 (0.00%) 0 | 0 / 79 (0.00%) 0 |
| Investigations Haemoglobin decreased subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 0 / 41 (0.00%) 0 | 0 / 79 (0.00%) 0 |
| Nervous system disorders Disturbance in attention subjects affected / exposed occurrences (all) | 2 / 80 (2.50%) 2 | 1 / 41 (2.44%) 1 | 2 / 79 (2.53%) 2 |
| Dizziness subjects affected / exposed occurrences (all) | 5 / 80 (6.25%) 5 | 7 / 41 (17.07%) 8 | 2 / 79 (2.53%) 2 |
| Dysgeusia subjects affected / exposed occurrences (all) | 2 / 80 (2.50%) 2 | 1 / 41 (2.44%) 1 | 3 / 79 (3.80%) 3 |
| Headache subjects affected / exposed occurrences (all) | 28 / 80 (35.00%) 31 | 13 / 41 (31.71%) 18 | 23 / 79 (29.11%) 30 |
| Lethargy subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 0 / 41 (0.00%) 0 | 2 / 79 (2.53%) 2 |
| Memory impairment subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 0 / 41 (0.00%) 0 | 1 / 79 (1.27%) 1 |
| Paraesthesia subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 0 / 41 (0.00%) 0 | 3 / 79 (3.80%) 3 |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 5 / 80 (6.25%) 5 | 1 / 41 (2.44%) 1 | 3 / 79 (3.80%) 3 |
| Ear and labyrinth disorders | | | |

| | | | |
|----------------------------------|------------------|------------------|------------------|
| Tinnitus | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 3 / 41 (7.32%) | 0 / 79 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 41 (2.44%) | 1 / 79 (1.27%) |
| occurrences (all) | 0 | 1 | 1 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 3 / 41 (7.32%) | 4 / 79 (5.06%) |
| occurrences (all) | 1 | 3 | 4 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 2 / 41 (4.88%) | 5 / 79 (6.33%) |
| occurrences (all) | 0 | 2 | 5 |
| Constipation | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | 1 / 41 (2.44%) | 5 / 79 (6.33%) |
| occurrences (all) | 4 | 1 | 5 |
| Diarrhoea | | | |
| subjects affected / exposed | 8 / 80 (10.00%) | 10 / 41 (24.39%) | 8 / 79 (10.13%) |
| occurrences (all) | 8 | 12 | 8 |
| Dry mouth | | | |
| subjects affected / exposed | 4 / 80 (5.00%) | 0 / 41 (0.00%) | 2 / 79 (2.53%) |
| occurrences (all) | 4 | 0 | 3 |
| Dyspepsia | | | |
| subjects affected / exposed | 7 / 80 (8.75%) | 1 / 41 (2.44%) | 9 / 79 (11.39%) |
| occurrences (all) | 8 | 1 | 9 |
| Flatulence | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 41 (2.44%) | 4 / 79 (5.06%) |
| occurrences (all) | 0 | 1 | 4 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 41 (0.00%) | 2 / 79 (2.53%) |
| occurrences (all) | 1 | 0 | 2 |
| Nausea | | | |
| subjects affected / exposed | 12 / 80 (15.00%) | 7 / 41 (17.07%) | 16 / 79 (20.25%) |
| occurrences (all) | 13 | 9 | 16 |
| Vomiting | | | |

| | | | |
|--|------------------------|----------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 7 / 80 (8.75%) 8 | 4 / 41 (9.76%) 4 | 4 / 79 (5.06%) 4 |
| Hepatobiliary disorders | | | |
| Jaundice | | | |
| subjects affected / exposed occurrences (all) | 3 / 80 (3.75%) 3 | 0 / 41 (0.00%) 0 | 1 / 79 (1.27%) 1 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 0 / 41 (0.00%) 0 | 0 / 79 (0.00%) 0 |
| Dry skin | | | |
| subjects affected / exposed occurrences (all) | 4 / 80 (5.00%) 4 | 3 / 41 (7.32%) 4 | 3 / 79 (3.80%) 3 |
| Pruritus | | | |
| subjects affected / exposed occurrences (all) | 12 / 80 (15.00%) 13 | 3 / 41 (7.32%) 3 | 8 / 79 (10.13%) 10 |
| Pruritus generalised | | | |
| subjects affected / exposed occurrences (all) | 2 / 80 (2.50%) 2 | 5 / 41 (12.20%) 5 | 0 / 79 (0.00%) 0 |
| Rash | | | |
| subjects affected / exposed occurrences (all) | 10 / 80 (12.50%) 12 | 2 / 41 (4.88%) 2 | 6 / 79 (7.59%) 8 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed occurrences (all) | 2 / 80 (2.50%) 2 | 2 / 41 (4.88%) 3 | 6 / 79 (7.59%) 6 |
| Back pain | | | |
| subjects affected / exposed occurrences (all) | 2 / 80 (2.50%) 2 | 1 / 41 (2.44%) 1 | 3 / 79 (3.80%) 3 |
| Muscle spasms | | | |
| subjects affected / exposed occurrences (all) | 2 / 80 (2.50%) 2 | 1 / 41 (2.44%) 1 | 2 / 79 (2.53%) 2 |
| Myalgia | | | |
| subjects affected / exposed occurrences (all) | 4 / 80 (5.00%) 4 | 3 / 41 (7.32%) 3 | 5 / 79 (6.33%) 5 |
| Pain in extremity | | | |

| | | | |
|--|----------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 2 / 80 (2.50%) 2 | 1 / 41 (2.44%) 1 | 1 / 79 (1.27%) 1 |
| Infections and infestations | | | |
| Influenza | | | |
| subjects affected / exposed occurrences (all) | 1 / 80 (1.25%) 1 | 0 / 41 (0.00%) 0 | 1 / 79 (1.27%) 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed occurrences (all) | 4 / 80 (5.00%) 4 | 3 / 41 (7.32%) 3 | 4 / 79 (5.06%) 4 |
| Oral herpes | | | |
| subjects affected / exposed occurrences (all) | 2 / 80 (2.50%) 3 | 0 / 41 (0.00%) 0 | 2 / 79 (2.53%) 2 |
| Rhinitis | | | |
| subjects affected / exposed occurrences (all) | 1 / 80 (1.25%) 1 | 0 / 41 (0.00%) 0 | 5 / 79 (6.33%) 6 |
| Sinusitis | | | |
| subjects affected / exposed occurrences (all) | 4 / 80 (5.00%) 4 | 0 / 41 (0.00%) 0 | 7 / 79 (8.86%) 8 |
| Tooth infection | | | |
| subjects affected / exposed occurrences (all) | 2 / 80 (2.50%) 2 | 0 / 41 (0.00%) 0 | 0 / 79 (0.00%) 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed occurrences (all) | 5 / 80 (6.25%) 5 | 1 / 41 (2.44%) 2 | 5 / 79 (6.33%) 5 |
| Urinary tract infection | | | |
| subjects affected / exposed occurrences (all) | 4 / 80 (5.00%) 4 | 3 / 41 (7.32%) 3 | 2 / 79 (2.53%) 2 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed occurrences (all) | 8 / 80 (10.00%) 8 | 1 / 41 (2.44%) 1 | 5 / 79 (6.33%) 5 |

| | | | |
|---|------------------|------------------|------------------|
| Non-serious adverse events | Group E | Group F + G | Group H + I |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 59 / 79 (74.68%) | 66 / 79 (83.54%) | 74 / 80 (92.50%) |
| General disorders and administration site conditions | | | |

| | | | |
|---|------------------|------------------|------------------|
| Asthenia | | | |
| subjects affected / exposed | 5 / 79 (6.33%) | 3 / 79 (3.80%) | 12 / 80 (15.00%) |
| occurrences (all) | 7 | 4 | 17 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 79 (1.27%) | 4 / 80 (5.00%) |
| occurrences (all) | 0 | 1 | 4 |
| Chills | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 1 / 79 (1.27%) | 3 / 80 (3.75%) |
| occurrences (all) | 1 | 1 | 3 |
| Fatigue | | | |
| subjects affected / exposed | 16 / 79 (20.25%) | 22 / 79 (27.85%) | 30 / 80 (37.50%) |
| occurrences (all) | 17 | 23 | 35 |
| Irritability | | | |
| subjects affected / exposed | 5 / 79 (6.33%) | 1 / 79 (1.27%) | 10 / 80 (12.50%) |
| occurrences (all) | 5 | 1 | 11 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 8 / 79 (10.13%) | 12 / 80 (15.00%) |
| occurrences (all) | 2 | 8 | 14 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 5 / 79 (6.33%) | 8 / 80 (10.00%) |
| occurrences (all) | 1 | 5 | 8 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 4 / 79 (5.06%) | 9 / 80 (11.25%) |
| occurrences (all) | 0 | 4 | 11 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 79 (1.27%) | 4 / 80 (5.00%) |
| occurrences (all) | 0 | 1 | 4 |
| Sinus congestion | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 1 / 79 (1.27%) | 2 / 80 (2.50%) |
| occurrences (all) | 1 | 1 | 2 |
| Psychiatric disorders | | | |
| Abnormal dreams | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 1 / 79 (1.27%) | 5 / 80 (6.25%) |
| occurrences (all) | 1 | 1 | 5 |
| Anxiety | | | |

| | | | |
|-----------------------------|------------------|------------------|------------------|
| subjects affected / exposed | 3 / 79 (3.80%) | 4 / 79 (5.06%) | 6 / 80 (7.50%) |
| occurrences (all) | 3 | 4 | 6 |
| Depressed mood | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 0 / 79 (0.00%) | 0 / 80 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Depression | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 3 / 79 (3.80%) | 12 / 80 (15.00%) |
| occurrences (all) | 1 | 4 | 13 |
| Insomnia | | | |
| subjects affected / exposed | 6 / 79 (7.59%) | 16 / 79 (20.25%) | 20 / 80 (25.00%) |
| occurrences (all) | 6 | 17 | 22 |
| Sleep disorder | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 0 / 79 (0.00%) | 2 / 80 (2.50%) |
| occurrences (all) | 0 | 0 | 2 |
| Investigations | | | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 1 / 79 (1.27%) | 0 / 80 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Nervous system disorders | | | |
| Disturbance in attention | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 2 / 79 (2.53%) | 9 / 80 (11.25%) |
| occurrences (all) | 1 | 2 | 9 |
| Dizziness | | | |
| subjects affected / exposed | 4 / 79 (5.06%) | 3 / 79 (3.80%) | 8 / 80 (10.00%) |
| occurrences (all) | 4 | 3 | 8 |
| Dysgeusia | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 3 / 79 (3.80%) | 4 / 80 (5.00%) |
| occurrences (all) | 2 | 3 | 4 |
| Headache | | | |
| subjects affected / exposed | 15 / 79 (18.99%) | 21 / 79 (26.58%) | 28 / 80 (35.00%) |
| occurrences (all) | 15 | 22 | 29 |
| Lethargy | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 79 (0.00%) | 1 / 80 (1.25%) |
| occurrences (all) | 1 | 0 | 1 |
| Memory impairment | | | |

| | | | |
|--|------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 3 / 79 (3.80%) 3 | 0 / 79 (0.00%) 0 | 5 / 80 (6.25%) 5 |
| Paraesthesia subjects affected / exposed occurrences (all) | 1 / 79 (1.27%) 1 | 1 / 79 (1.27%) 1 | 2 / 80 (2.50%) 2 |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 1 / 79 (1.27%) 1 | 7 / 79 (8.86%) 7 | 6 / 80 (7.50%) 6 |
| Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all) | 1 / 79 (1.27%) 1 | 0 / 79 (0.00%) 0 | 3 / 80 (3.75%) 3 |
| Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) | 3 / 79 (3.80%) 3 | 3 / 79 (3.80%) 3 | 5 / 80 (6.25%) 5 |
| Abdominal pain subjects affected / exposed occurrences (all) | 3 / 79 (3.80%) 4 | 3 / 79 (3.80%) 4 | 7 / 80 (8.75%) 8 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 3 / 79 (3.80%) 3 | 4 / 79 (5.06%) 4 | 4 / 80 (5.00%) 4 |
| Constipation subjects affected / exposed occurrences (all) | 5 / 79 (6.33%) 5 | 1 / 79 (1.27%) 2 | 9 / 80 (11.25%) 11 |
| Diarrhoea subjects affected / exposed occurrences (all) | 13 / 79 (16.46%) 15 | 10 / 79 (12.66%) 11 | 11 / 80 (13.75%) 13 |
| Dry mouth subjects affected / exposed occurrences (all) | 2 / 79 (2.53%) 2 | 1 / 79 (1.27%) 1 | 2 / 80 (2.50%) 2 |
| Dyspepsia subjects affected / exposed occurrences (all) | 2 / 79 (2.53%) 2 | 4 / 79 (5.06%) 4 | 6 / 80 (7.50%) 6 |
| Flatulence | | | |

| | | | |
|---|------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 4 / 79 (5.06%) 4 | 2 / 79 (2.53%) 2 | 1 / 80 (1.25%) 1 |
| Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) | 3 / 79 (3.80%) 3 | 2 / 79 (2.53%) 2 | 2 / 80 (2.50%) 2 |
| Nausea subjects affected / exposed occurrences (all) | 11 / 79 (13.92%) 12 | 19 / 79 (24.05%) 21 | 20 / 80 (25.00%) 23 |
| Vomiting subjects affected / exposed occurrences (all) | 4 / 79 (5.06%) 4 | 4 / 79 (5.06%) 5 | 4 / 80 (5.00%) 5 |
| Hepatobiliary disorders Jaundice subjects affected / exposed occurrences (all) | 0 / 79 (0.00%) 0 | 3 / 79 (3.80%) 3 | 3 / 80 (3.75%) 3 |
| Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) | 2 / 79 (2.53%) 2 | 0 / 79 (0.00%) 0 | 6 / 80 (7.50%) 7 |
| Dry skin subjects affected / exposed occurrences (all) | 1 / 79 (1.27%) 1 | 4 / 79 (5.06%) 4 | 6 / 80 (7.50%) 7 |
| Pruritus subjects affected / exposed occurrences (all) | 3 / 79 (3.80%) 3 | 6 / 79 (7.59%) 6 | 11 / 80 (13.75%) 12 |
| Pruritus generalised subjects affected / exposed occurrences (all) | 1 / 79 (1.27%) 2 | 4 / 79 (5.06%) 4 | 3 / 80 (3.75%) 3 |
| Rash subjects affected / exposed occurrences (all) | 6 / 79 (7.59%) 6 | 11 / 79 (13.92%) 11 | 15 / 80 (18.75%) 18 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 7 / 79 (8.86%) 8 | 5 / 79 (6.33%) 6 | 8 / 80 (10.00%) 9 |
| Back pain | | | |

| | | | |
|---|----------------------|---------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 4 / 79 (5.06%) 4 | 2 / 79 (2.53%) 2 | 5 / 80 (6.25%) 5 |
| Muscle spasms subjects affected / exposed occurrences (all) | 1 / 79 (1.27%) 1 | 5 / 79 (6.33%) 5 | 2 / 80 (2.50%) 2 |
| Myalgia subjects affected / exposed occurrences (all) | 2 / 79 (2.53%) 2 | 3 / 79 (3.80%) 3 | 9 / 80 (11.25%) 10 |
| Pain in extremity subjects affected / exposed occurrences (all) | 1 / 79 (1.27%) 1 | 0 / 79 (0.00%) 0 | 3 / 80 (3.75%) 3 |
| Infections and infestations | | | |
| Influenza subjects affected / exposed occurrences (all) | 2 / 79 (2.53%) 2 | 1 / 79 (1.27%) 2 | 1 / 80 (1.25%) 1 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 8 / 79 (10.13%) 8 | 7 / 79 (8.86%) 7 | 7 / 80 (8.75%) 8 |
| Oral herpes subjects affected / exposed occurrences (all) | 2 / 79 (2.53%) 2 | 1 / 79 (1.27%) 1 | 3 / 80 (3.75%) 3 |
| Rhinitis subjects affected / exposed occurrences (all) | 2 / 79 (2.53%) 2 | 0 / 79 (0.00%) 0 | 0 / 80 (0.00%) 0 |
| Sinusitis subjects affected / exposed occurrences (all) | 2 / 79 (2.53%) 2 | 5 / 79 (6.33%) 5 | 3 / 80 (3.75%) 3 |
| Tooth infection subjects affected / exposed occurrences (all) | 1 / 79 (1.27%) 1 | 4 / 79 (5.06%) 4 | 4 / 80 (5.00%) 4 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 5 / 79 (6.33%) 5 | 4 / 79 (5.06%) 4 | 5 / 80 (6.25%) 5 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 1 / 79 (1.27%) 2 | 0 / 79 (0.00%) 0 | 6 / 80 (7.50%) 6 |

| | | | |
|--|---------------------|---------------------|---------------------|
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 3 / 79 (3.80%) 3 | 3 / 79 (3.80%) 3 | 6 / 80 (7.50%) 7 |
|--|---------------------|---------------------|---------------------|

| Non-serious adverse events | Group J | Group K + L | Group M + N |
|--|------------------------|------------------------|-----------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 40 / 45 (88.89%) | 36 / 45 (80.00%) | 34 / 43 (79.07%) |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 10 / 45 (22.22%) 11 | 4 / 45 (8.89%) 4 | 4 / 43 (9.30%) 4 |
| Chest pain subjects affected / exposed occurrences (all) | 1 / 45 (2.22%) 1 | 3 / 45 (6.67%) 3 | 0 / 43 (0.00%) 0 |
| Chills subjects affected / exposed occurrences (all) | 1 / 45 (2.22%) 1 | 0 / 45 (0.00%) 0 | 2 / 43 (4.65%) 2 |
| Fatigue subjects affected / exposed occurrences (all) | 12 / 45 (26.67%) 13 | 12 / 45 (26.67%) 15 | 9 / 43 (20.93%) 12 |
| Irritability subjects affected / exposed occurrences (all) | 7 / 45 (15.56%) 7 | 2 / 45 (4.44%) 2 | 3 / 43 (6.98%) 3 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 7 / 45 (15.56%) 7 | 3 / 45 (6.67%) 3 | 9 / 43 (20.93%) 12 |
| Dyspnoea subjects affected / exposed occurrences (all) | 4 / 45 (8.89%) 4 | 3 / 45 (6.67%) 3 | 3 / 43 (6.98%) 4 |
| Dyspnoea exertional subjects affected / exposed occurrences (all) | 0 / 45 (0.00%) 0 | 0 / 45 (0.00%) 0 | 2 / 43 (4.65%) 2 |
| Oropharyngeal pain | | | |

| | | | |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 2 / 45 (4.44%) 3 | 4 / 45 (8.89%) 4 | 2 / 43 (4.65%) 2 |
| Sinus congestion subjects affected / exposed occurrences (all) | 1 / 45 (2.22%) 1 | 0 / 45 (0.00%) 0 | 0 / 43 (0.00%) 0 |
| Psychiatric disorders | | | |
| Abnormal dreams subjects affected / exposed occurrences (all) | 1 / 45 (2.22%) 1 | 1 / 45 (2.22%) 1 | 1 / 43 (2.33%) 1 |
| Anxiety subjects affected / exposed occurrences (all) | 4 / 45 (8.89%) 4 | 1 / 45 (2.22%) 1 | 3 / 43 (6.98%) 4 |
| Depressed mood subjects affected / exposed occurrences (all) | 0 / 45 (0.00%) 0 | 2 / 45 (4.44%) 2 | 1 / 43 (2.33%) 1 |
| Depression subjects affected / exposed occurrences (all) | 2 / 45 (4.44%) 2 | 5 / 45 (11.11%) 5 | 1 / 43 (2.33%) 1 |
| Insomnia subjects affected / exposed occurrences (all) | 8 / 45 (17.78%) 8 | 6 / 45 (13.33%) 6 | 7 / 43 (16.28%) 8 |
| Sleep disorder subjects affected / exposed occurrences (all) | 0 / 45 (0.00%) 0 | 4 / 45 (8.89%) 4 | 2 / 43 (4.65%) 2 |
| Investigations | | | |
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 0 / 45 (0.00%) 0 | 1 / 45 (2.22%) 1 | 4 / 43 (9.30%) 4 |
| Nervous system disorders | | | |
| Disturbance in attention subjects affected / exposed occurrences (all) | 3 / 45 (6.67%) 4 | 3 / 45 (6.67%) 3 | 3 / 43 (6.98%) 4 |
| Dizziness subjects affected / exposed occurrences (all) | 4 / 45 (8.89%) 4 | 1 / 45 (2.22%) 1 | 4 / 43 (9.30%) 5 |
| Dysgeusia | | | |

| | | | |
|--------------------------------------|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 45 (0.00%) | 4 / 45 (8.89%) | 4 / 43 (9.30%) |
| occurrences (all) | 0 | 4 | 4 |
| Headache | | | |
| subjects affected / exposed | 15 / 45 (33.33%) | 13 / 45 (28.89%) | 14 / 43 (32.56%) |
| occurrences (all) | 17 | 13 | 20 |
| Lethargy | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 3 / 45 (6.67%) | 2 / 43 (4.65%) |
| occurrences (all) | 1 | 4 | 2 |
| Memory impairment | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 45 (0.00%) | 2 / 43 (4.65%) |
| occurrences (all) | 1 | 0 | 2 |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 0 / 45 (0.00%) | 5 / 43 (11.63%) |
| occurrences (all) | 1 | 0 | 5 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 45 (6.67%) | 3 / 45 (6.67%) | 2 / 43 (4.65%) |
| occurrences (all) | 3 | 3 | 2 |
| Ear and labyrinth disorders | | | |
| Tinnitus | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 45 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 2 / 45 (4.44%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 6 / 45 (13.33%) | 0 / 43 (0.00%) |
| occurrences (all) | 1 | 7 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 45 (2.22%) | 2 / 43 (4.65%) |
| occurrences (all) | 0 | 1 | 2 |
| Constipation | | | |
| subjects affected / exposed | 2 / 45 (4.44%) | 1 / 45 (2.22%) | 4 / 43 (9.30%) |
| occurrences (all) | 2 | 2 | 4 |
| Diarrhoea | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 7 / 45 (15.56%) | 8 / 45 (17.78%) | 8 / 43 (18.60%) |
| occurrences (all) | 9 | 10 | 12 |
| Dry mouth | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 2 / 45 (4.44%) | 2 / 43 (4.65%) |
| occurrences (all) | 1 | 2 | 2 |
| Dyspepsia | | | |
| subjects affected / exposed | 2 / 45 (4.44%) | 2 / 45 (4.44%) | 2 / 43 (4.65%) |
| occurrences (all) | 3 | 2 | 2 |
| Flatulence | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 1 / 45 (2.22%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 1 / 45 (2.22%) | 4 / 43 (9.30%) |
| occurrences (all) | 1 | 1 | 4 |
| Nausea | | | |
| subjects affected / exposed | 6 / 45 (13.33%) | 9 / 45 (20.00%) | 8 / 43 (18.60%) |
| occurrences (all) | 6 | 11 | 8 |
| Vomiting | | | |
| subjects affected / exposed | 4 / 45 (8.89%) | 4 / 45 (8.89%) | 3 / 43 (6.98%) |
| occurrences (all) | 4 | 4 | 3 |
| Hepatobiliary disorders | | | |
| Jaundice | | | |
| subjects affected / exposed | 1 / 45 (2.22%) | 3 / 45 (6.67%) | 1 / 43 (2.33%) |
| occurrences (all) | 1 | 3 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 0 / 45 (0.00%) | 0 / 45 (0.00%) | 4 / 43 (9.30%) |
| occurrences (all) | 0 | 0 | 4 |
| Dry skin | | | |
| subjects affected / exposed | 6 / 45 (13.33%) | 4 / 45 (8.89%) | 4 / 43 (9.30%) |
| occurrences (all) | 6 | 4 | 4 |
| Pruritus | | | |
| subjects affected / exposed | 6 / 45 (13.33%) | 7 / 45 (15.56%) | 6 / 43 (13.95%) |
| occurrences (all) | 8 | 7 | 6 |
| Pruritus generalised | | | |

| | | | |
|---|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 5 / 45 (11.11%) 6 | 0 / 45 (0.00%) 0 | 1 / 43 (2.33%) 1 |
| Rash subjects affected / exposed occurrences (all) | 2 / 45 (4.44%) 5 | 4 / 45 (8.89%) 4 | 6 / 43 (13.95%) 6 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 3 / 45 (6.67%) 3 | 5 / 45 (11.11%) 5 | 7 / 43 (16.28%) 7 |
| Back pain subjects affected / exposed occurrences (all) | 2 / 45 (4.44%) 3 | 2 / 45 (4.44%) 2 | 4 / 43 (9.30%) 4 |
| Muscle spasms subjects affected / exposed occurrences (all) | 2 / 45 (4.44%) 2 | 0 / 45 (0.00%) 0 | 0 / 43 (0.00%) 0 |
| Myalgia subjects affected / exposed occurrences (all) | 5 / 45 (11.11%) 5 | 4 / 45 (8.89%) 4 | 6 / 43 (13.95%) 7 |
| Pain in extremity subjects affected / exposed occurrences (all) | 0 / 45 (0.00%) 0 | 3 / 45 (6.67%) 3 | 0 / 43 (0.00%) 0 |
| Infections and infestations | | | |
| Influenza subjects affected / exposed occurrences (all) | 1 / 45 (2.22%) 1 | 3 / 45 (6.67%) 3 | 0 / 43 (0.00%) 0 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 2 / 45 (4.44%) 2 | 4 / 45 (8.89%) 4 | 3 / 43 (6.98%) 4 |
| Oral herpes subjects affected / exposed occurrences (all) | 3 / 45 (6.67%) 5 | 3 / 45 (6.67%) 4 | 2 / 43 (4.65%) 2 |
| Rhinitis subjects affected / exposed occurrences (all) | 0 / 45 (0.00%) 0 | 1 / 45 (2.22%) 1 | 0 / 43 (0.00%) 0 |
| Sinusitis | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 45 (2.22%) 1 | 2 / 45 (4.44%) 2 | 3 / 43 (6.98%) 3 |
| Tooth infection subjects affected / exposed occurrences (all) | 1 / 45 (2.22%) 1 | 1 / 45 (2.22%) 1 | 0 / 43 (0.00%) 0 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 3 / 45 (6.67%) 3 | 4 / 45 (8.89%) 4 | 0 / 43 (0.00%) 0 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 2 / 45 (4.44%) 2 | 3 / 45 (6.67%) 4 | 2 / 43 (4.65%) 2 |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 3 / 45 (6.67%) 3 | 1 / 45 (2.22%) 1 | 1 / 43 (2.33%) 2 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 19 October 2011 | <p>The purpose of this amendment was to:</p> <ul style="list-style-type: none">• modify the post-treatment pregnancy monitoring to be in compliance with local labeling requirements for RBV;• clarify that the RBV Pregnancy Registry Brochure and RBV Medication Guide were to be distributed where applicable/locally available;• define the primary and secondary endpoints of SVR24 as HCV RNA < LLOQ 24 weeks after the last dose of study drug;• incorporate Administrative Change 1; and• address inconsistencies throughout the protocol |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported