



Clinical trial results:

A phase II, randomized, double-blind, multicenter, active-controlled, parallel group study to evaluate the sustained virologic response of the HCV polymerase inhibitor prodrug RO5024048 in combination with Telaprevir and Pegasus/Copegus compared with Telaprevir and Pegasys/Copegus in patients with chronic Hepatitis C Genotype 1 virus infection who were prior null responders to treatment with Pegylated Interferon/Ribavirin.

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2011-002715-28 |
| Trial protocol | GB DE ES IT |
| Global end of trial date | 28 January 2014 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 22 April 2016 |
| First version publication date | 06 August 2015 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | NV27779 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01482390 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070 |
| Public contact | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 061 6878333, global.trial_information@roche.com |
| Scientific contact | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 061 6878333, global.trial_information@roche.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 | 28 January 2014 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 January 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To estimate the difference in sustained virologic response 12 weeks after treatment (SVR-12) between each of the following three experimental treatment groups (regimens containing RO5024048, telaprevir, Pegasys, and Copegus) and the control treatment group (regimen containing telaprevir, Pegasys, and Copegus) in patients with previous null response to pegylated interferon/ribavirin (PEG-IFN/RBV) combination therapy, defined as a $< 2 \log_{10}$ IU/mL decrease in viral titer after at least 12 weeks of treatment with PEG-IFN/RBV.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice. All subjects signed an informed consent form.

Background therapy:

There were no background therapies indicated for this study.

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 14 November 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Spain: 15 |
| Country: Number of subjects enrolled | United Kingdom: 14 |
| Country: Number of subjects enrolled | France: 9 |
| Country: Number of subjects enrolled | Germany: 5 |
| Country: Number of subjects enrolled | Canada: 17 |
| Country: Number of subjects enrolled | United States: 20 |
| Worldwide total number of subjects | 80 |
| EEA total number of subjects | 43 |

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) | 78 |
| From 65 to 84 years | 2 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screened over a period of 12 weeks

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|---------------------------------------|
| Arm title | Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS |
|------------------|---------------------------------------|

Arm description:

Twelve weeks of therapy with mericitabine (MCB), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB + Pegasys/Copegus (triple) (total treatment duration of 24 weeks), followed by a 24-week treatment-free follow-up period.

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

Dosage and administration details:

Total daily dose of 1000 mg (<75 kg) or 1200 mg (≥75 kg) taken orally within 30 minutes after meal or snack for 24 weeks

| | |
|--|--------------|
| Investigational medicinal product name | Mericitabine |
| Investigational medicinal product code | |
| Other name | RO5024048 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Administered at a dose of 1000 mg orally twice daily within 30 minutes of eating meal or snack for 24 weeks

| | |
|--|------------------|
| Investigational medicinal product name | Pegasys |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Administered at a dose of 180 µg via subcutaneous route once weekly for 24 weeks

| | |
|--|------------|
| Investigational medicinal product name | Telaprevir |
| Investigational medicinal product code | |
| Other name | |

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

Dosage and administration details:

Administered at a dose of 750 mg orally three times daily (at recommended intervals of 7-9 hours) within 30 minutes after meal or snack for 12 weeks

| | |
|------------------|---------------------------------------|
| Arm title | Arm B-TVR 12WKS, MCB 24WKS, P/R 48WKS |
|------------------|---------------------------------------|

Arm description:

Twelve weeks of therapy with mericitabine (MCB), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB + Pegasys/Copegus (triple), followed by 24 weeks of therapy with Pegasys/Copegus (total treatment duration of 48 weeks), followed by a 24-week treatment-free follow-up period.

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

Dosage and administration details:

Total daily dose of 1000 mg (<75 kg) or 1200 mg (≥75 kg) taken orally within 30 minutes after meal or snack for 48 weeks

| | |
|--|--------------|
| Investigational medicinal product name | Mericitabine |
| Investigational medicinal product code | |
| Other name | RO5024048 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Administered at a dose of 1000 mg orally twice daily within 30 minutes of eating meal or snack for 24 weeks

| | |
|--|------------------|
| Investigational medicinal product name | Pegasys |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Administered at a dose of 180 µg via subcutaneous route once weekly for 48 weeks

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

Dosage and administration details:

Administered at a dose of 750 mg orally three times daily (at recommended intervals of 7-9 hours) within 30 minutes after meal or snack for 12 weeks

| | |
|------------------|---|
| Arm title | Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS |
|------------------|---|

Arm description:

Twelve weeks of therapy with mericitabine (MCB), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB placebo (PLAC) + Pegasys/Copegus (triple), followed by 24 weeks of therapy with Pegasys/Copegus (total treatment duration of 48 weeks), followed by a 24-week treatment-free follow-up period.

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

Dosage and administration details:

Total daily dose of 1000 mg (<75 kg) or 1200 mg (≥75 kg) taken orally within 30 minutes after meal or snack for 48 weeks

| | |
|--|--------------|
| Investigational medicinal product name | Mericitabine |
| Investigational medicinal product code | |
| Other name | RO5024048 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Administered at a dose of 1000 mg orally twice daily within 30 minutes of eating meal or snack for 12 weeks

| | |
|--|------------------|
| Investigational medicinal product name | Pegasys |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Administered at a dose of 180 µg via subcutaneous route once weekly for 48 weeks

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

Dosage and administration details:

Administered at a dose of 750 mg orally three times daily (at recommended intervals of 7-9 hours) within 30 minutes after meal or snack for 12 weeks

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

Dosage and administration details:

Administered 1000 mg orally twice daily for 12 weeks

| | |
|------------------|--|
| Arm title | Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS |
|------------------|--|

Arm description:

Twelve weeks of therapy with mericitabine (MCB) placebo (PLAC), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB placebo + Pegasys/Copegus (triple), followed by 24 weeks of therapy with Pegasys/Copegus (total treatment duration of 48 weeks), followed by a 24-week treatment-free follow-up period.

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

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

Dosage and administration details:

Total daily dose of 1000 mg (<75 kg) or 1200 mg (≥75 kg) taken orally within 30 minutes after meal or snack for 48 weeks

| | |
|--|------------------|
| Investigational medicinal product name | Pegasys |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Administered at a dose of 180 µg via subcutaneous route once weekly for 48 weeks

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

Dosage and administration details:

Administered at a dose of 750 mg orally three times daily (at recommended intervals of 7-9 hours) within 30 minutes after meal or snack for 12 weeks

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

Dosage and administration details:

Administered 1000 mg orally twice daily for 24 weeks

| Number of subjects in period 1 | Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS | Arm B-TVR 12WKS, MCB 24WKS, P/R 48WKS | Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS |
|---------------------------------------|---|---|--|
| Started | 21 | 24 | 24 |
| Completed | 18 | 22 | 24 |
| Not completed | 3 | 2 | 0 |
| Physician decision | 1 | - | - |
| Not specified | 1 | - | - |
| Did not receive study drug | - | 1 | - |
| Lost to follow-up | - | 1 | - |
| Withdrawal by subject | 1 | - | - |

| | |
|---------------------------------------|--|
| Number of subjects in period 1 | Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS |
|---------------------------------------|--|

| | |
|----------------------------|----|
| Started | 11 |
| Completed | 11 |
| Not completed | 0 |
| Physician decision | - |
| Not specified | - |
| Did not receive study drug | - |
| Lost to follow-up | - |
| Withdrawal by subject | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------------------------------|
| Reporting group title | Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS |
|-----------------------|---------------------------------------|

Reporting group description:

Twelve weeks of therapy with mericitabine (MCB), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB + Pegasys/Copegus (triple) (total treatment duration of 24 weeks), followed by a 24-week treatment-free follow-up period.

| | |
|-----------------------|---------------------------------------|
| Reporting group title | Arm B-TVR 12WKS, MCB 24WKS, P/R 48WKS |
|-----------------------|---------------------------------------|

Reporting group description:

Twelve weeks of therapy with mericitabine (MCB), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB + Pegasys/Copegus (triple), followed by 24 weeks of therapy with Pegasys/Copegus (total treatment duration of 48 weeks), followed by a 24-week treatment-free follow-up period.

| | |
|-----------------------|---|
| Reporting group title | Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS |
|-----------------------|---|

Reporting group description:

Twelve weeks of therapy with mericitabine (MCB), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB placebo (PLAC) + Pegasys/Copegus (triple), followed by 24 weeks of therapy with Pegasys/Copegus (total treatment duration of 48 weeks), followed by a 24-week treatment-free follow-up period.

| | |
|-----------------------|--|
| Reporting group title | Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS |
|-----------------------|--|

Reporting group description:

Twelve weeks of therapy with mericitabine (MCB) placebo (PLAC), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB placebo + Pegasys/Copegus (triple), followed by 24 weeks of therapy with Pegasys/Copegus (total treatment duration of 48 weeks), followed by a 24-week treatment-free follow-up period.

| Reporting group values | Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS | Arm B-TVR 12WKS, MCB 24WKS, P/R 48WKS | Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS |
|---------------------------------------|---------------------------------------|---------------------------------------|---|
| Number of subjects | 21 | 24 | 24 |
| Age categorical Units: Subjects | | | |
| <18 years | 0 | 0 | 0 |
| >=18-<=65 years | 20 | 24 | 23 |
| >65 | 1 | 0 | 1 |
| Age continuous Units: years | | | |
| arithmetic mean | 51.9 | 54 | 53.5 |
| standard deviation | ± 10.1 | ± 7.6 | ± 7.7 |
| Gender categorical Units: Subjects | | | |
| Female | 6 | 7 | 7 |
| Male | 15 | 17 | 17 |

| Reporting group values | Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS | Total | |
|------------------------|--|-------|--|
| Number of subjects | 11 | 80 | |

| | | | |
|---------------------------------------|-------|----|--|
| Age categorical Units: Subjects | | | |
| <18 years | 0 | 0 | |
| >=18-<=65 years | 11 | 78 | |
| >65 | 0 | 2 | |
| Age continuous Units: years | | | |
| arithmetic mean | 52.8 | | |
| standard deviation | ± 6.7 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 2 | 22 | |
| Male | 9 | 58 | |

End points

End points reporting groups

| | |
|-----------------------|---------------------------------------|
| Reporting group title | Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS |
|-----------------------|---------------------------------------|

Reporting group description:

Twelve weeks of therapy with mericitabine (MCB), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB + Pegasys/Copegus (triple) (total treatment duration of 24 weeks), followed by a 24-week treatment-free follow-up period.

| | |
|-----------------------|---------------------------------------|
| Reporting group title | Arm B-TVR 12WKS, MCB 24WKS, P/R 48WKS |
|-----------------------|---------------------------------------|

Reporting group description:

Twelve weeks of therapy with mericitabine (MCB), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB + Pegasys/Copegus (triple), followed by 24 weeks of therapy with Pegasys/Copegus (total treatment duration of 48 weeks), followed by a 24-week treatment-free follow-up period.

| | |
|-----------------------|---|
| Reporting group title | Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS |
|-----------------------|---|

Reporting group description:

Twelve weeks of therapy with mericitabine (MCB), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB placebo (PLAC) + Pegasys/Copegus (triple), followed by 24 weeks of therapy with Pegasys/Copegus (total treatment duration of 48 weeks), followed by a 24-week treatment-free follow-up period.

| | |
|-----------------------|--|
| Reporting group title | Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS |
|-----------------------|--|

Reporting group description:

Twelve weeks of therapy with mericitabine (MCB) placebo (PLAC), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB placebo + Pegasys/Copegus (triple), followed by 24 weeks of therapy with Pegasys/Copegus (total treatment duration of 48 weeks), followed by a 24-week treatment-free follow-up period.

| | |
|----------------------------|---|
| Subject analysis set title | Hepatitis C Virus (HCV)-resistance Monitoring Set |
|----------------------------|---|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

All patients who received therapy were monitored for the presence of resistance mutations.

Primary: Percent of Subjects With Sustained Virological Response 12 Weeks After Treatment (SVR12)

| | |
|-----------------|---|
| End point title | Percent of Subjects With Sustained Virological Response 12 Weeks After Treatment (SVR12) ^[1] |
|-----------------|---|

End point description:

Response was defined as an unquantifiable (less than the lower limit of quantification [LLOQ]; <25 International Units [IU]/mL) serum HCV-RNA 12 weeks after the actual end of treatment (EOT) (a single last unquantifiable HCV-RNA within 8-20 weeks after the last day of study drug administration). Serum HCV RNA was assessed in all randomized patients by polymerase chain reaction (PCR) techniques using the Roche COBAS TaqMan HCV v2.0 Test.

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

End point timeframe:

Up to 60 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: No formal hypothesis testing was conducted in this exploratory study. The primary efficacy endpoint (SVR12 [actual]) for each of the treatment groups was summarized by using descriptive statistics.

| End point values | Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS | Arm B-TVR 12WKS, MCB 24WKS, P/R 48WKS | Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS | Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS |
|-----------------------------|--|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 21 | 23 | 24 | 11 |
| Units: percentage | | | | |
| number (not applicable) | 81 | 95.7 | 70.8 | 90.9 |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects With SVR4

| | |
|---|-------------------------------|
| End point title | Percent of Subjects With SVR4 |
| End point description: Response was defined as an unquantifiable (less than the lower limit of quantification [LLOQ]; <25 International Units [IU]/mL) serum HCV-RNA within 2 – 8 weeks after the last day of study drug administration. Serum HCV RNA was assessed in all randomized patients by polymerase chain reaction (PCR) techniques using the Roche COBAS TaqMan HCV v2.0 Test. | |
| End point type | Secondary |
| End point timeframe: Up to 52 weeks | |

| End point values | Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS | Arm B-TVR 12WKS, MCB 24WKS, P/R 48WKS | Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS | Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS |
|-----------------------------|--|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 21 | 23 | 24 | 11 |
| Units: percentage | | | | |
| number (not applicable) | 85.7 | 95.7 | 70.8 | 90.9 |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects With SVR24

| | |
|--|--------------------------------|
| End point title | Percent of Subjects With SVR24 |
| End point description: Response was defined as an unquantifiable (less than the lower limit of quantification [LLOQ]; <25 International Units [IU]/mL) serum HCV-RNA \geq 20 weeks after the last day of study drug administration. Serum HCV RNA was assessed in all randomized patients by polymerase chain reaction (PCR) techniques using the Roche COBAS TaqMan HCV v2.0 Test. | |
| End point type | Secondary |

End point timeframe:

Up to 72 weeks

| End point values | Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS | Arm B-TVR 12WKS, MCB 24WKS, P/R 48WKS | Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS | Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS |
|-----------------------------|--|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 21 | 23 | 24 | 11 |
| Units: percentage | | | | |
| number (not applicable) | 76.2 | 95.7 | 70.8 | 90.9 |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects With Virologic Response Over Time From Week 2 to Week 48

| | |
|-----------------|--|
| End point title | Percent of Subjects With Virologic Response Over Time From Week 2 to Week 48 |
|-----------------|--|

End point description:

Response was defined as an unquantifiable (less than the lower limit of quantification [LLOQ]; <25 International Units [IU]/mL) serum HCV-RNA. Serum HCV RNA was assessed in all randomized patients by polymerase chain reaction (PCR) techniques using the Roche COBAS TaqMan HCV v2.0 Test.

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

End point timeframe:

Up to 48 weeks

| End point values | Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS | Arm B-TVR 12WKS, MCB 24WKS, P/R 48WKS | Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS | Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS |
|-----------------------------|--|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 21 | 23 | 24 | 11 |
| Units: percentage | | | | |
| number (not applicable) | | | | |
| Week 2 | 85.7 | 65.2 | 70.8 | 54.5 |
| Week 4 | 100 | 95.7 | 91.7 | 100 |
| Week 12 | 100 | 95.7 | 91.7 | 90.9 |
| Week 24 | 100 | 91.3 | 75 | 90.9 |
| Week 48 | 0 | 78.3 | 54.2 | 81.8 |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-resistant Mutations

| | |
|-----------------|---|
| End point title | Number of Subjects With Treatment-resistant Mutations |
|-----------------|---|

End point description:

Blood samples were collected throughout the study to monitor for the development of drug resistance. During the course of the study, phenotypic and/or sequence analyses were performed on samples from patients who experienced virologic breakthrough, partial response, non-response, or relapse. Patients who developed resistance to MCB and/or to telaprevir were monitored for the persistence of resistant mutation(s) during the follow-up period. The genotype of samples from telaprevir- and/or RO5024048-resistant subjects were determined through population sequencing of the non-structural protein 3/non-structural protein 4a (NS3-4a) and nonstructural protein 5B (NS5B) coding regions by using standard sequencing technology.

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

End point timeframe:

60 weeks

| End point values | Hepatitis C Virus (HCV)-resistance Monitoring Set | | | |
|---|---|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 79 | | | |
| Units: subjects | | | | |
| Subjects with telaprevir resistance mutations | 10 | | | |
| Subjects with MCB resistance mutations | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events

| | |
|-----------------|--|
| End point title | Number of Subjects With Adverse Events |
|-----------------|--|

End point description:

Adverse events were systematically monitored throughout the study.

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

End point timeframe:

60 weeks

| End point values | Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS | Arm B-TVR 12WKS, MCB 24WKS, P/R 48WKS | Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS | Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS |
|-----------------------------|--|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 21 | 23 | 24 | 11 |
| Units: Subjects | | | | |
| Serious adverse events | 4 | 6 | 3 | 0 |
| Non-serious adverse events | 20 | 23 | 24 | 11 |

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration of RO4995855

| | |
|--|-----------------------------------|
| End point title | Trough Concentration of RO4995855 |
| End point description: | |
| Trough concentration was defined as the minimum observed drug concentration during a dosing interval. Pharmacokinetic (PK) plasma and serum samples were collected from all patients to measure RO4995855, its metabolite (RO5012433), and telaprevir before the morning dose of all study drugs on Day 1 (baseline) and at Week 8. Plasma concentrations for RO4995855, RO5012433, and telaprevir were measured by specific and validated liquid chromatography tandem mass spectrometry methods. The value reported is the average trough plasma concentration for Week 8. | |
| End point type | Secondary |
| End point timeframe: | |
| Day 1 and Week 8 | |

| End point values | Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS | Arm B-TVR 12WKS, MCB 24WKS, P/R 48WKS | Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS | Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS |
|--------------------------------------|--|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 20 | 22 | 23 | 4 |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 3147.75 (± 1711.91) | 2716.77 (± 1508.75) | 3933.09 (± 1938.6) | 1277 (± 2068) |

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration of RO5012433

| | |
|---|-----------------------------------|
| End point title | Trough Concentration of RO5012433 |
| End point description: | |
| Trough concentration was defined as the minimum observed drug concentration during a dosing interval. Pharmacokinetic (PK) plasma and serum samples were collected from all patients to measure | |

RO4995855, its metabolite (RO5012433), and telaprevir before the morning dose of all study drugs on Day 1 (baseline) and at Week 8. Plasma concentrations for RO4995855, RO5012433, and telaprevir were measured by specific and validated liquid chromatography tandem mass spectrometry methods. The value reported is the average trough plasma concentration for Week 8.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day 1 and week 8 | |

| End point values | Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS | Arm B-TVR 12WKS, MCB 24WKS, P/R 48WKS | Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS | Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS |
|--------------------------------------|--|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 20 | 22 | 23 | 4 |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 727.4 (± 373.47) | 638.68 (± 307.73) | 853.3 (± 407.2) | 394 (± 669.8) |

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration of Telaprevir

| | |
|--|------------------------------------|
| End point title | Trough Concentration of Telaprevir |
| End point description: | |
| Trough concentration was defined as the minimum observed drug concentration during a dosing interval. Pharmacokinetic (PK) plasma and serum samples were collected from all patients to measure RO4995855, its metabolite (RO5012433), and telaprevir before the morning dose of all study drugs on Day 1 (baseline) and at Week 8. Plasma concentrations for RO4995855, RO5012433, and telaprevir were measured by specific and validated liquid chromatography tandem mass spectrometry methods. The value reported is the average trough plasma concentration for Week 8. | |
| End point type | Secondary |
| End point timeframe: | |
| Day 1 and week 8 | |

| End point values | Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS | Arm B-TVR 12WKS, MCB 24WKS, P/R 48WKS | Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS | Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS |
|--------------------------------------|--|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 9 | 12 | 9 | 4 |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 2070.56 (± 1240.77) | 2020.83 (± 465.31) | 2288.89 (± 623.83) | 1663.25 (± 614.95) |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

48 week timeframe for reporting adverse events

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------------------------|
| Reporting group title | Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS |
|-----------------------|---------------------------------------|

Reporting group description:

Twelve weeks of therapy with mericitabine (MCB), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB + Pegasys/Copegus (triple) (total treatment duration of 24 weeks), followed by a 24-week treatment-free follow-up period.

| | |
|-----------------------|---------------------------------------|
| Reporting group title | Arm B-TVR 12WKS, MCB 24WKS, P/R 48WKS |
|-----------------------|---------------------------------------|

Reporting group description:

Twelve weeks of therapy with mericitabine (MCB), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB + Pegasys/Copegus (triple), followed by 24 weeks of therapy with Pegasys/Copegus (total treatment duration of 48 weeks), followed by a 24-week treatment-free follow-up period.

| | |
|-----------------------|---|
| Reporting group title | Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS |
|-----------------------|---|

Reporting group description:

Twelve weeks of therapy with mericitabine (MCB), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB placebo (PLAC) + Pegasys/Copegus (triple), followed by 24 weeks of therapy with Pegasys/Copegus (total treatment duration of 48 weeks), followed by a 24-week treatment-free follow-up period.

| | |
|-----------------------|--|
| Reporting group title | Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS |
|-----------------------|--|

Reporting group description:

Twelve weeks of therapy with mericitabine (MCB) placebo (PLAC), telaprevir (TVR), Pegasys and Copegus (P/R), followed by 12 weeks of therapy with MCB placebo + Pegasys/Copegus (triple), followed by 24 weeks of therapy with Pegasys/Copegus (total treatment duration of 48 weeks), followed by a 24-week treatment-free follow-up period.

| Serious adverse events | Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS | Arm B-TVR 12WKS, MCB 24WKS, P/R 48WKS | Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS |
|---|---------------------------------------|---------------------------------------|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 21 (19.05%) | 6 / 23 (26.09%) | 3 / 24 (12.50%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Thyroid cancer | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 23 (4.35%) | 0 / 24 (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 |

| | | | |
|---|----------------|----------------|----------------|
| Hepatocellular carcinoma | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 1 / 24 (4.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 23 (0.00%) | 0 / 24 (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 | | | |
| Amnesia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 23 (4.35%) | 0 / 24 (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 |
| Blood and lymphatic system disorders | | | |
| Anemia | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 23 (4.35%) | 1 / 24 (4.17%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 23 (4.35%) | 0 / 24 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Ophthalmoplegia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 1 / 24 (4.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 23 (0.00%) | 0 / 24 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Major depression | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 23 (4.35%) | 0 / 24 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abdominal wall abscess | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 23 (0.00%) | 0 / 24 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 23 (4.35%) | 0 / 24 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|--|--|--|
| Serious adverse events | Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Thyroid cancer | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatocellular carcinoma | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Amnesia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Ophthalmoplegia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Major depression | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Abdominal wall abscess | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis viral | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Arm A-TVR 12WKS, MCB 24WKS, P/R 24WKS | Arm B-TVR 12WKS, MCB 24WKS, P/R 48WKS | Arm C-TVR 12WKS, MCB 12WKS, PLAC MCB 12WKS, P/R 48WKS |
|---|---|---|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 20 / 21 (95.24%) | 23 / 23 (100.00%) | 24 / 24 (100.00%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 23 (4.35%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Phlebitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 4 / 21 (19.05%) | 5 / 23 (21.74%) | 6 / 24 (25.00%) |
| occurrences (all) | 4 | 5 | 7 |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 23 (4.35%) | 1 / 24 (4.17%) |
| occurrences (all) | 0 | 1 | 1 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 23 (8.70%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Chills | | | |
| subjects affected / exposed | 4 / 21 (19.05%) | 3 / 23 (13.04%) | 2 / 24 (8.33%) |
| occurrences (all) | 4 | 3 | 2 |
| Fatigue | | | |
| subjects affected / exposed | 12 / 21 (57.14%) | 14 / 23 (60.87%) | 12 / 24 (50.00%) |
| occurrences (all) | 13 | 15 | 12 |
| Feeling abnormal | | | |

| | | | |
|--|----------------------|----------------------|------------------------|
| subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 1 / 23 (4.35%) 1 | 1 / 24 (4.17%) 1 |
| Feeling hot subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 | 0 / 23 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Influenza like illness subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 5 / 23 (21.74%) 5 | 2 / 24 (8.33%) 2 |
| Injection site rash subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 2 / 23 (8.70%) 2 | 0 / 24 (0.00%) 0 |
| Irritability subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 6 / 23 (26.09%) 6 | 4 / 24 (16.67%) 4 |
| Local swelling subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 2 / 23 (8.70%) 2 | 2 / 24 (8.33%) 2 |
| Malaise subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 | 1 / 23 (4.35%) 1 | 0 / 24 (0.00%) 0 |
| Pain subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 2 / 23 (8.70%) 2 | 1 / 24 (4.17%) 1 |
| Pyrexia subjects affected / exposed occurrences (all) | 3 / 21 (14.29%) 3 | 4 / 23 (17.39%) 4 | 4 / 24 (16.67%) 5 |
| Reproductive system and breast disorders Erectile dysfunction subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 23 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 | 7 / 23 (30.43%) 7 | 10 / 24 (41.67%) 11 |
| Dyspnoea | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 21 (4.76%) | 2 / 23 (8.70%) | 3 / 24 (12.50%) |
| occurrences (all) | 1 | 2 | 3 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 7 / 23 (30.43%) | 4 / 24 (16.67%) |
| occurrences (all) | 3 | 7 | 4 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 23 (4.35%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 23 (0.00%) | 2 / 24 (8.33%) |
| occurrences (all) | 1 | 0 | 2 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 23 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Sinus congestion | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 1 / 23 (4.35%) | 2 / 24 (8.33%) |
| occurrences (all) | 2 | 1 | 2 |
| Depressed mood | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 3 / 23 (13.04%) | 2 / 24 (8.33%) |
| occurrences (all) | 1 | 3 | 2 |
| Depression | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 4 / 23 (17.39%) | 2 / 24 (8.33%) |
| occurrences (all) | 1 | 4 | 2 |
| Emotional disorder | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Initial insomnia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 4 / 23 (17.39%) | 5 / 24 (20.83%) |
| occurrences (all) | 2 | 4 | 5 |

| | | | |
|--|---------------------|---------------------|----------------------|
| Libido decreased subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 23 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Mood altered subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 2 / 23 (8.70%) 2 | 0 / 24 (0.00%) 0 |
| Mood swings subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 0 / 23 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Restlessness subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 | 0 / 23 (0.00%) 0 | 1 / 24 (4.17%) 1 |
| Sleep disorder subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 2 / 23 (8.70%) 2 | 2 / 24 (8.33%) 2 |
| Stress subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 23 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Investigations Glomerular filtration rate decreased subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 23 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Weight decreased subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 0 / 23 (0.00%) 0 | 3 / 24 (12.50%) 3 |
| Injury, poisoning and procedural complications Arthropod bite subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 23 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Contusion subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 23 (4.35%) 1 | 0 / 24 (0.00%) 0 |
| Cardiac disorders Atrioventricular block first degree subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 23 (0.00%) 0 | 0 / 24 (0.00%) 0 |

| | | | |
|--|----------------------|-----------------------|-----------------------|
| Tachycardia subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 23 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Nervous system disorders | | | |
| Amnesia subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 23 (0.00%) 0 | 1 / 24 (4.17%) 1 |
| Disturbance in attention subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 3 / 23 (13.04%) 3 | 2 / 24 (8.33%) 2 |
| Dizziness subjects affected / exposed occurrences (all) | 3 / 21 (14.29%) 3 | 5 / 23 (21.74%) 5 | 2 / 24 (8.33%) 2 |
| Dysgeusia subjects affected / exposed occurrences (all) | 5 / 21 (23.81%) 5 | 2 / 23 (8.70%) 2 | 2 / 24 (8.33%) 2 |
| Headache subjects affected / exposed occurrences (all) | 9 / 21 (42.86%) 9 | 9 / 23 (39.13%) 10 | 9 / 24 (37.50%) 10 |
| Hyperaesthesia subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 2 / 23 (8.70%) 2 | 0 / 24 (0.00%) 0 |
| Hypoaesthesia subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 3 / 23 (13.04%) 3 | 0 / 24 (0.00%) 0 |
| Lethargy subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 23 (0.00%) 0 | 1 / 24 (4.17%) 1 |
| Memory impairment subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 23 (0.00%) 0 | 2 / 24 (8.33%) 2 |
| Paraesthesia subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 23 (0.00%) 0 | 2 / 24 (8.33%) 2 |
| Parosmia | | | |

| | | | |
|--|----------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 23 (4.35%) 1 | 0 / 24 (0.00%) 0 |
| Syncope subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 23 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 6 / 21 (28.57%) 6 | 10 / 23 (43.48%) 10 | 10 / 24 (41.67%) 10 |
| Leukopenia subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 23 (4.35%) 1 | 0 / 24 (0.00%) 0 |
| Lymph node pain subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 23 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Lymphopenia subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 3 / 23 (13.04%) 3 | 1 / 24 (4.17%) 1 |
| Neutropenia subjects affected / exposed occurrences (all) | 4 / 21 (19.05%) 4 | 6 / 23 (26.09%) 7 | 3 / 24 (12.50%) 3 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 4 / 23 (17.39%) 4 | 1 / 24 (4.17%) 1 |
| Ear and labyrinth disorders | | | |
| Ear discomfort subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 23 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Hyperacusis subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 23 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Eye disorders | | | |
| Dry eye subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 2 / 23 (8.70%) 3 | 2 / 24 (8.33%) 2 |
| Ocular hyperaemia | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Photophobia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 23 (8.70%) | 2 / 24 (8.33%) |
| occurrences (all) | 0 | 2 | 2 |
| Visual acuity reduced | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 3 / 24 (12.50%) |
| occurrences (all) | 0 | 0 | 3 |
| Visual impairment | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 23 (4.35%) | 1 / 24 (4.17%) |
| occurrences (all) | 0 | 1 | 1 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 23 (8.70%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 23 (0.00%) | 1 / 24 (4.17%) |
| occurrences (all) | 2 | 0 | 1 |
| Anal pruritus | | | |
| subjects affected / exposed | 5 / 21 (23.81%) | 3 / 23 (13.04%) | 6 / 24 (25.00%) |
| occurrences (all) | 5 | 4 | 6 |
| Anorectal discomfort | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 1 / 24 (4.17%) |
| occurrences (all) | 0 | 0 | 1 |
| Cheilitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 1 / 24 (4.17%) |
| occurrences (all) | 0 | 0 | 1 |
| Constipation | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 1 / 23 (4.35%) | 2 / 24 (8.33%) |
| occurrences (all) | 2 | 1 | 3 |
| Dental caries | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 23 (4.35%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| Diarrhoea | | | |
| subjects affected / exposed | 5 / 21 (23.81%) | 8 / 23 (34.78%) | 4 / 24 (16.67%) |
| occurrences (all) | 6 | 10 | 4 |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 4 / 23 (17.39%) | 3 / 24 (12.50%) |
| occurrences (all) | 0 | 4 | 3 |
| Dyspepsia | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 0 / 23 (0.00%) | 3 / 24 (12.50%) |
| occurrences (all) | 3 | 0 | 3 |
| Frequent bowel movements | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 23 (4.35%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gingival pain | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 23 (0.00%) | 1 / 24 (4.17%) |
| occurrences (all) | 2 | 0 | 1 |
| Haemorrhoids | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 1 / 23 (4.35%) | 3 / 24 (12.50%) |
| occurrences (all) | 2 | 1 | 3 |
| Nausea | | | |
| subjects affected / exposed | 9 / 21 (42.86%) | 8 / 23 (34.78%) | 7 / 24 (29.17%) |
| occurrences (all) | 9 | 13 | 7 |
| Oral pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Painful defaecation | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tongue disorder | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|--|----------------------|----------------------|----------------------|
| Tongue dry subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 23 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Vomiting subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 | 4 / 23 (17.39%) 6 | 6 / 24 (25.00%) 6 |
| Hepatobiliary disorders Jaundice subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 2 / 23 (8.70%) 2 | 1 / 24 (4.17%) 1 |
| Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) | 3 / 21 (14.29%) 3 | 3 / 23 (13.04%) 3 | 2 / 24 (8.33%) 2 |
| Dermatitis subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 23 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Dermatitis psoriasiform subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 23 (4.35%) 1 | 0 / 24 (0.00%) 0 |
| Dry skin subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 | 3 / 23 (13.04%) 3 | 3 / 24 (12.50%) 3 |
| Eczema subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 2 / 23 (8.70%) 2 | 3 / 24 (12.50%) 3 |
| Erythema subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 23 (0.00%) 0 | 2 / 24 (8.33%) 2 |
| Night sweats subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 2 / 23 (8.70%) 2 | 1 / 24 (4.17%) 1 |
| Photosensitivity reaction subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 23 (0.00%) 0 | 2 / 24 (8.33%) 2 |
| Pruritus | | | |

| | | | |
|-----------------------------|-----------------|------------------|------------------|
| subjects affected / exposed | 7 / 21 (33.33%) | 12 / 23 (52.17%) | 9 / 24 (37.50%) |
| occurrences (all) | 8 | 13 | 11 |
| Pruritus generalised | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 3 / 23 (13.04%) | 4 / 24 (16.67%) |
| occurrences (all) | 2 | 3 | 5 |
| Psoriasis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 1 / 24 (4.17%) |
| occurrences (all) | 0 | 0 | 1 |
| Rash | | | |
| subjects affected / exposed | 6 / 21 (28.57%) | 7 / 23 (30.43%) | 14 / 24 (58.33%) |
| occurrences (all) | 7 | 7 | 21 |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash generalised | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 23 (0.00%) | 2 / 24 (8.33%) |
| occurrences (all) | 1 | 0 | 2 |
| Rash macular | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 23 (0.00%) | 1 / 24 (4.17%) |
| occurrences (all) | 2 | 0 | 1 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 2 / 23 (8.70%) | 1 / 24 (4.17%) |
| occurrences (all) | 1 | 3 | 2 |
| Skin discolouration | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin irritation | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 23 (4.35%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|----------------------|----------------------|----------------------|
| Renal colic subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 23 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 4 / 21 (19.05%) 4 | 6 / 23 (26.09%) 8 | 1 / 24 (4.17%) 1 |
| Back pain subjects affected / exposed occurrences (all) | 4 / 21 (19.05%) 4 | 4 / 23 (17.39%) 4 | 3 / 24 (12.50%) 3 |
| Flank pain subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 23 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Muscle spasms subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 23 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Muscular weakness subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 | 1 / 23 (4.35%) 1 | 2 / 24 (8.33%) 2 |
| Myalgia subjects affected / exposed occurrences (all) | 5 / 21 (23.81%) 5 | 6 / 23 (26.09%) 6 | 4 / 24 (16.67%) 4 |
| Pain in jaw subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 23 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Infections and infestations | | | |
| Ear infection subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 23 (4.35%) 1 | 0 / 24 (0.00%) 0 |
| Eye infection subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 23 (4.35%) 1 | 0 / 24 (0.00%) 0 |
| Hordeolum subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 23 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Infection | | | |

| | | | |
|------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 23 (8.70%) | 2 / 24 (8.33%) |
| occurrences (all) | 0 | 2 | 2 |
| Oral herpes | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 23 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Staphylococcal skin infection | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 3 / 23 (13.04%) | 1 / 24 (4.17%) |
| occurrences (all) | 0 | 3 | 1 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 23 (4.35%) | 4 / 24 (16.67%) |
| occurrences (all) | 1 | 1 | 6 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 5 / 21 (23.81%) | 5 / 23 (21.74%) | 3 / 24 (12.50%) |
| occurrences (all) | 5 | 5 | 3 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 23 (0.00%) | 1 / 24 (4.17%) |
| occurrences (all) | 0 | 0 | 1 |
| Gout | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 23 (8.70%) | 0 / 24 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 23 (0.00%) | 1 / 24 (4.17%) |
| occurrences (all) | 1 | 0 | 1 |

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| Non-serious adverse events | Arm D-TVR 12WKS, MCB or PLAC MCB, 24WKS, P/R 48WKS | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 11 / 11 (100.00%) | | |
| Vascular disorders | | | |

| | | | |
|--|-----------------|--|--|
| Hypertension | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Phlebitis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 4 / 11 (36.36%) | | |
| occurrences (all) | 4 | | |
| Chest discomfort | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Chills | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | | |
| occurrences (all) | 2 | | |
| Fatigue | | | |
| subjects affected / exposed | 4 / 11 (36.36%) | | |
| occurrences (all) | 6 | | |
| Feeling abnormal | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Feeling hot | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Injection site rash | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Irritability | | | |

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|---|-----------------|--|--|
| subjects affected / exposed | 3 / 11 (27.27%) | | |
| occurrences (all) | 3 | | |
| Local swelling | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Malaise | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pain | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | | |
| occurrences (all) | 4 | | |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 11 (36.36%) | | |
| occurrences (all) | 5 | | |
| Reproductive system and breast disorders | | | |
| Erectile dysfunction | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 3 / 11 (27.27%) | | |
| occurrences (all) | 3 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | | |
| occurrences (all) | 2 | | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | | |
| occurrences (all) | 2 | | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | | |
| occurrences (all) | 2 | | |
| Rhinorrhoea | | | |

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| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Sinus congestion | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Depressed mood | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Depression | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Emotional disorder | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Initial insomnia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Libido decreased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Mood altered | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Mood swings | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Restlessness | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |

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| Sleep disorder subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | | |
| Stress subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | | |
| Investigations Glomerular filtration rate decreased subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | | |
| Weight decreased subjects affected / exposed occurrences (all) | 2 / 11 (18.18%) 2 | | |
| Injury, poisoning and procedural complications Arthropod bite subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | | |
| Contusion subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 2 | | |
| Cardiac disorders Atrioventricular block first degree subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | | |
| Tachycardia subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | | |
| Nervous system disorders Amnesia subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | | |
| Disturbance in attention subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | | |
| Dizziness | | | |

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|--------------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Dysgeusia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Headache | | | |
| subjects affected / exposed | 5 / 11 (45.45%) | | |
| occurrences (all) | 5 | | |
| Hyperaesthesia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Lethargy | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Memory impairment | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Parosmia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 2 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 6 / 11 (54.55%) | | |
| occurrences (all) | 7 | | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |

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|---|---------------------|--|--|
| Lymph node pain subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | | |
| Lymphopenia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | | |
| Neutropenia subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 3 | | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | | |
| Ear and labyrinth disorders Ear discomfort subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | | |
| Hyperacusis subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | | |
| Eye disorders Dry eye subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | | |
| Ocular hyperaemia subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | | |
| Photophobia subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | | |
| Vision blurred subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | | |
| Visual acuity reduced subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | | |
| Visual impairment | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Anal pruritus | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | | |
| occurrences (all) | 2 | | |
| Anorectal discomfort | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | | |
| occurrences (all) | 2 | | |
| Cheilitis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Constipation | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Dental caries | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | | |
| occurrences (all) | 2 | | |
| Dry mouth | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | | |
| occurrences (all) | 2 | | |
| Frequent bowel movements | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |

| | | | |
|--|-----------------|--|--|
| Gingival pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Haemorrhoids | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | | |
| occurrences (all) | 2 | | |
| Nausea | | | |
| subjects affected / exposed | 3 / 11 (27.27%) | | |
| occurrences (all) | 3 | | |
| Oral pain | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Painful defaecation | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Tongue disorder | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | | |
| occurrences (all) | 2 | | |
| Tongue dry | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hepatobiliary disorders | | | |
| Jaundice | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| Alopecia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dermatitis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Dermatitis psoriasiform | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Dry skin | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Eczema | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | | |
| occurrences (all) | 2 | | |
| Erythema | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Night sweats | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Photosensitivity reaction | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Pruritus | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | | |
| occurrences (all) | 9 | | |
| Pruritus generalised | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | | |
| occurrences (all) | 2 | | |
| Psoriasis | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | | |
| occurrences (all) | 2 | | |
| Rash | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | | |
| occurrences (all) | 2 | | |

| | | | |
|---|----------------------|--|--|
| Rash erythematous subjects affected / exposed occurrences (all) | 2 / 11 (18.18%) 9 | | |
| Rash generalised subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | | |
| Rash macular subjects affected / exposed occurrences (all) | 2 / 11 (18.18%) 4 | | |
| Rash maculo-papular subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 3 | | |
| Skin discolouration subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 2 | | |
| Skin irritation subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | | |
| Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | | |
| Pollakiuria subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | | |
| Renal colic subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | | |
| Back pain subjects affected / exposed occurrences (all) | 2 / 11 (18.18%) 2 | | |
| Flank pain | | | |

| | | | |
|-------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | | |
| occurrences (all) | 2 | | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pain in jaw | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Infections and infestations | | | |
| Ear infection | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Eye infection | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Hordeolum | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Infection | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 2 | | |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oral herpes | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Staphylococcal skin infection | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |

| | | | |
|---|----------------------|--|--|
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 4 / 11 (36.36%) 4 | | |
| Dehydration subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | | |
| Gout subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 02 March 2012 | This amendment included the following changes: <ul style="list-style-type: none">- Additional assessments were added for urine protein analyses- Safety follow-up measures during the study were clarified- Study drug-stopping rules were updated- The definition of the primary efficacy analysis population was revised- SVR4 and SVR24 were specified as secondary efficacy endpoints- Fibroscan assessment allowed to define a liver status- Number of 'cirrhotic' patients raised up to 50%- Screening period extended to 24 weeks.- Study changed from active controlled to placebo controlled. |
| 10 July 2012 | This amendment included the following changes: <ul style="list-style-type: none">- Control Arm D (MCB-free arm) was removed. Patients enrolled to this arm were offered the option to switch to MCB in addition to their current medications- The 50% cap on patients with a prior null response and compensated cirrhosis was removed- Intensive PK/pharmacodynamic sampling was deleted. Sparse PK sampling from all patients (Week 8 trough concentration) was scheduled to enable the measurement of drug exposure- IP-10 samples were collected only at baseline- The SVR24 analysis was removed and treatment free follow-up was decreased from 24 to 12 weeks- The SAE reporting window was reduced from 1 working day to immediately (i.e., within 24 hours) |
| 13 November 2012 | This amendment included the following changes: <ul style="list-style-type: none">- SVR24 was added as the secondary endpoint- The treatment-free follow-up Week 24 visit was reinstated |
| 15 February 2013 | The primary reason for the amendment was the addition of a Week 42 visit to the Schedule of Assessments, with the same procedures as the Week 30 visit. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported