



Clinical trial results:

A multicenter, randomized, double-blind, placebocontrolled, parallel-group phase II study on efficacy and safety of DEB025 combined with pegIFNalpha2a and ribavirin in chronic hepatitis C genotype 1 relapsers and non-responders to previous pegIFN plus ribavirin treatment

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2010-020033-14 |
| Trial protocol | GB HU DE FR ES BE IT PL |
| Global end of trial date | 09 May 2013 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 29 September 2016 |
| First version publication date | 29 September 2016 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CDEB025A2210 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01183169 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, +41 613241111 , |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, +41 613241111 , |

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 | 09 May 2013 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 09 May 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to demonstrate that in chronic hepatitis C G1 patients with previous non-response to pegIFN/RBV or with previous relapse after pegIFN/RBV treatment:

- triple therapy with DEB025 600 mg BID (loading dose) / 600 mg QD plus pegIFNa2a/RBV leads to a superior cEVR (by Limit of Quantification [LOQ] i.e. HCV RNA < 25 IU/mL) rate as compared to pegIFNa2a/RBV AND/OR
- triple therapy with DEB025 600 mg BID (loading dose) / 800 mg QD plus pegIFNa2a/RBV leads to a superior cEVR rate (by LOQ) as compared to pegIFNa2a/RBV AND/OR
- triple therapy with DEB025 400 mg BID plus pegIFNa2a/RBV leads to a superior cEVR rate (by LOQ) as compared to pegIFNa2a/RBV

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 30 August 2010 |
| 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 | Poland: 29 |
| Country: Number of subjects enrolled | Romania: 76 |
| Country: Number of subjects enrolled | Spain: 29 |
| Country: Number of subjects enrolled | United Kingdom: 15 |
| Country: Number of subjects enrolled | Belgium: 2 |
| Country: Number of subjects enrolled | France: 8 |
| Country: Number of subjects enrolled | Germany: 37 |
| Country: Number of subjects enrolled | Hungary: 29 |
| Country: Number of subjects enrolled | Italy: 36 |
| Country: Number of subjects enrolled | United States: 59 |
| Country: Number of subjects enrolled | Australia: 29 |
| Country: Number of subjects enrolled | Taiwan: 80 |
| Country: Number of subjects enrolled | Turkey: 30 |

| | |
|------------------------------------|-----|
| Worldwide total number of subjects | 459 |
| EEA total number of subjects | 261 |

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) | 444 |
| From 65 to 84 years | 15 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

It was planned to enroll 344 patients. A total of 459 patients were randomized and included in the Full Analysis Set (FAS).

Period 1

| | |
|------------------------------|---|
| Period 1 title | Initial treatment period |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Data analyst, Assessor |

Blinding implementation details:

At Visit 2 (baseline visit) all eligible patients were randomized via Interactive Response Technology (IRT) to one of the four treatment arms. In order to blind all treatment arms, the placebo-treated patients of arm C were split into two sub-arms of (C1 and C2) in 1:1 ratio.

Arms

| | |
|------------------------------|-------------------------|
| Are arms mutually exclusive? | No |
| Arm title | Arm A: DEB025 600 mg QD |

Arm description:

DEB025 600 mg once daily (QD) with PEG and RBV for up to 48 weeks

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | DEB025 |
| Investigational medicinal product code | |
| Other name | Alisporivir |
| Pharmaceutical forms | Capsule, soft |
| Routes of administration | Oral use |

Dosage and administration details:

DEB025 was supplied as 200 mg soft gel capsules.

| | |
|--|-----------------------|
| Investigational medicinal product name | Peginterferon alfa-2a |
| Investigational medicinal product code | |
| Other name | Pegasys® |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

PEG 180 µg administered via subcutaneous (s.c.) injection once weekly

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

Dosage and administration details:

RBV 200 mg tablets (weight-based dose: < 75 mg = 1000 mg/day; ≥ 75 kg = 1200 mg/day) administered orally in a divided daily dose.

| | |
|---|-------------------|
| Arm title | Arm B: DEB 800 QD |
| Arm description: | |
| DEB025 800 mg QD with PEG and RBV for up to 48 weeks. | |
| Arm type | Experimental |

| | |
|--|---------------|
| Investigational medicinal product name | DEB025 |
| Investigational medicinal product code | |
| Other name | Alisporivir |
| Pharmaceutical forms | Capsule, soft |
| Routes of administration | Oral use |

Dosage and administration details:

DEB025 was supplied as 200 mg soft gel capsules.

| | |
|--|-----------------------|
| Investigational medicinal product name | Peginterferon alfa-2a |
| Investigational medicinal product code | |
| Other name | Pegasys® |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

PEG 180 µg administered via subcutaneous (s.c.) injection once weekly

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

Dosage and administration details:

RBV 200 mg tablets (weight-based dose: < 75 kg = 1000 mg/day; ≥ 75 kg = 1200 mg/day) administered orally in a divided daily dose.

| | |
|------------------|--------------------|
| Arm title | Arm C1- Placebo QD |
|------------------|--------------------|

Arm description:

Placebo with PEG and RBV for up to 48 weeks; participants not achieving complete early virologic response (cEVR: HCV RNA <LOQ after 12 weeks of treatment) may switch to active ALV 600 mg QD with PEG and RBV.

Note: For one patient in arm C the corresponding end-of treatment CRF page was by mistake not entered into the database before the database was locked (the patient completed the treatment phase on 31-Mar-2012). Therefore, this patient is not included or in other summaries dependent on end-of-treatment status.

| | |
|--|-----------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Peginterferon alfa-2a |
| Investigational medicinal product code | |
| Other name | Pegasys® |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

PEG 180 µg administered via subcutaneous (s.c.) injection once weekly

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

Dosage and administration details:

RBV 200 mg tablets (weight-based dose: < 75 kg = 1000 mg/day; ≥ 75 kg = 1200 mg/day) administered orally in a divided daily dose.

| | |
|--|-------------------|
| Investigational medicinal product name | Placebo to DEB025 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, soft |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo soft gel capsules administered orally

| | |
|---|-----------------------|
| Arm title | Arm C2- Placebo BID |
| Arm description: Placebo with PEG and RBV for up to 48 weeks; participants not achieving cEVR may switch to active ALV 400 mg twice daily (BID) with PEG and RBV. | |
| Arm type | Placebo |
| Investigational medicinal product name | Placebo to DEB025 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, soft |
| Routes of administration | Oral use |
| Dosage and administration details: Placebo soft gel capsules administered orally | |
| Investigational medicinal product name | Ribavirin |
| Investigational medicinal product code | |
| Other name | Copegus® |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: RBV 200 mg tablets (weight-based dose: < 75 mg = 1000 mg/day; ≥ 75 kg = 1200 mg/day) administered orally in a divided daily dose. | |
| Investigational medicinal product name | Peginterferon alfa-2a |
| Investigational medicinal product code | |
| Other name | Pegasys® |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: PEG 180 µg administered via subcutaneous (s.c.) injection once weekly | |
| Arm title | Arm D DEB 400 BID |
| Arm description: DEB025 400 mg twice daily BID with PEG and RBV for up to 48 weeks | |
| Arm type | Experimental |
| Investigational medicinal product name | DEB025 |
| Investigational medicinal product code | |
| Other name | Alisporivir |
| Pharmaceutical forms | Capsule, soft |
| Routes of administration | Oral use |
| Dosage and administration details: DEB025 was supplied as 200 mg soft gel capsules. | |
| Investigational medicinal product name | Peginterferon alfa-2a |
| Investigational medicinal product code | |
| Other name | Pegasys® |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: PEG 180 µg administered via subcutaneous (s.c.) injection once weekly | |
| Investigational medicinal product name | Ribavirin |
| Investigational medicinal product code | |
| Other name | Copegus® |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: RBV 200 mg tablets (weight-based dose: < 75 mg = 1000 mg/day; ≥ 75 kg = 1200 mg/day) | |

administered orally in a divided daily dose.

| | |
|------------------|----------------|
| Arm title | Arm C- Placebo |
|------------------|----------------|

Arm description:

Placebo with PEG and RBV for up to 48 weeks; participants not achieving complete early virologic response (cEVR: HCV RNA <LOQ after 12 weeks of treatment) may switch to active ALV 600 mg QD with PEG and RBV.

Note: For one patient in arm C the corresponding end-of treatment CRF page was by mistake not entered into the database before the database was locked (the patient completed the treatment phase on 31-Mar-2012). Therefore, this patient is not included in Table 10-1 or in other summaries dependent on end-of-treatment status.

| | |
|--|-------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo to DEB025 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, soft |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo soft gel capsules administered orally

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

Dosage and administration details:

RBV 200 mg tablets (weight-based dose: < 75 kg = 1000 mg/day; ≥ 75 kg = 1200 mg/day) administered orally in a divided daily dose.

| | |
|--|-----------------------|
| Investigational medicinal product name | Peginterferon alfa-2a |
| Investigational medicinal product code | |
| Other name | Pegasys® |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

PEG 180 µg administered via subcutaneous (s.c.) injection once weekly

| Number of subjects in period 1 | Arm A: DEB025 600 mg QD | Arm B: DEB 800 QD | Arm C1- Placebo QD |
|---------------------------------------|-------------------------|-------------------|--------------------|
| Started | 121 | 115 | 59 |
| Completed | 72 | 78 | 18 |
| Not completed | 49 | 37 | 41 |
| Abnormal laboratory value(s) | - | 2 | 1 |
| Consent withdrawn by subject | 7 | 5 | 1 |
| Disease progression | 1 | - | - |
| Adverse event, non-fatal | 12 | 9 | 3 |
| Unsatisfactory therapeutic effect | 25 | 20 | 1 |

| | | | |
|-------------------------|---|---|----|
| Administrative problems | 2 | - | - |
| Non-compliance | 1 | - | - |
| Protocol deviation | 1 | 1 | - |
| Switch to DEB025 | - | - | 35 |

| Number of subjects in period 1 | Arm C2- Placebo BID | Arm D DEB 400 BID | Arm C- Placebo |
|-----------------------------------|------------------------|-------------------|----------------|
| Started | 55 | 109 | 114 |
| Completed | 17 | 77 | 35 |
| Not completed | 38 | 32 | 79 |
| Abnormal laboratory value(s) | 1 | 1 | 2 |
| Consent withdrawn by subject | 2 | 9 | 3 |
| Disease progression | - | - | - |
| Adverse event, non-fatal | 2 | 18 | 5 |
| Unsatisfactory therapeutic effect | 3 | 3 | 4 |
| Administrative problems | - | 1 | - |
| Non-compliance | - | - | - |
| Protocol deviation | - | - | - |
| Switch to DEB025 | 30 | - | 65 |

Period 2

| | |
|------------------------------|---|
| Period 2 title | After week 16 switch to DEB025 |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Data analyst, Assessor |

Arms

| | |
|------------------------------|----------|
| Are arms mutually exclusive? | No |
| Arm title | Arm C1-A |

Arm description:

Placebo to DEB 600 QD

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | DEB025 |
| Investigational medicinal product code | |
| Other name | Alisporivir |
| Pharmaceutical forms | Capsule, soft |
| Routes of administration | Oral use |

Dosage and administration details:

DEB025 was supplied as 200 mg soft gel capsules.

| | |
|--|-----------------------|
| Investigational medicinal product name | Peginterferon alfa-2a |
| Investigational medicinal product code | |
| Other name | Pegasys® |
| Pharmaceutical forms | Injection |

| | |
|---|-----------------------|
| Routes of administration | Subcutaneous use |
| Dosage and administration details: PEG 180 µg administered via subcutaneous (s.c.) injection once weekly | |
| Investigational medicinal product name | Ribavirin |
| Investigational medicinal product code | |
| Other name | Copegus® |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: RBV 200 mg tablets (weight-based dose: < 75 mg = 1000 mg/day; ≥ 75 kg = 1200 mg/day) administered orally in a divided daily dose. | |
| Arm title | Arm C2-A |
| Arm description: Placebo to DEB 400 BID | |
| Arm type | Experimental |
| Investigational medicinal product name | DEB025 |
| Investigational medicinal product code | |
| Other name | Alisporivir |
| Pharmaceutical forms | Capsule, soft |
| Routes of administration | Oral use |
| Dosage and administration details: DEB025 was supplied as 200 mg soft gel capsules. | |
| Investigational medicinal product name | Peginterferon alfa-2a |
| Investigational medicinal product code | |
| Other name | Pegasys® |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: PEG 180 µg administered via subcutaneous (s.c.) injection once weekly | |
| Investigational medicinal product name | Ribavirin |
| Investigational medicinal product code | |
| Other name | Copegus® |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: RBV 200 mg tablets (weight-based dose: < 75 mg = 1000 mg/day; ≥ 75 kg = 1200 mg/day) administered orally in a divided daily dose. | |

| Number of subjects in period 2 | Arm C1-A | Arm C2-A |
|---------------------------------------|----------|----------|
| Started | 35 | 30 |
| Completed | 12 | 13 |
| Not completed | 23 | 17 |
| Abnormal laboratory value(s) | - | 1 |
| Consent withdrawn by subject | 2 | - |
| Adverse event, non-fatal | 3 | 3 |
| Unsatisfactory therapeutic effect | 17 | 9 |
| Administrative problems | 1 | 4 |

Baseline characteristics

Reporting groups

| | |
|------------------------------|---|
| Reporting group title | Arm A: DEB025 600 mg QD |
| Reporting group description: | DEB025 600 mg once daily (QD) with PEG and RBV for up to 48 weeks |
| Reporting group title | Arm B: DEB 800 QD |
| Reporting group description: | DEB025 800 mg QD with PEG and RBV for up to 48 weeks. |
| Reporting group title | Arm C1- Placebo QD |
| Reporting group description: | Placebo with PEG and RBV for up to 48 weeks; participants not achieving complete early virologic response (cEVR: HCV RNA <LOQ after 12 weeks of treatment) may switch to active ALV 600 mg QD with PEG and RBV. Note: For one patient in arm C the corresponding end-of treatment CRF page was by mistake not entered into the database before the database was locked (the patient completed the treatment phase on 31-Mar-2012). Therefore, this patient is not included or in other summaries dependent on end-of-treatment status. |
| Reporting group title | Arm C2- Placebo BID |
| Reporting group description: | Placebo with PEG and RBV for up to 48 weeks; participants not achieving cEVR may switch to active ALV 400 mg twice daily (BID) with PEG and RBV. |
| Reporting group title | Arm D DEB 400 BID |
| Reporting group description: | DEB025 400 mg twice daily BID with PEG and RBV for up to 48 weeks |
| Reporting group title | Arm C- Placebo |
| Reporting group description: | Placebo with PEG and RBV for up to 48 weeks; participants not achieving complete early virologic response (cEVR: HCV RNA <LOQ after 12 weeks of treatment) may switch to active ALV 600 mg QD with PEG and RBV. Note: For one patient in arm C the corresponding end-of treatment CRF page was by mistake not entered into the database before the database was locked (the patient completed the treatment phase on 31-Mar-2012). Therefore, this patient is not included in Table 10-1 or in other summaries dependent on end-of-treatment status. |

| Reporting group values | Arm A: DEB025 600 mg QD | Arm B: DEB 800 QD | Arm C1- Placebo QD |
|---------------------------------------|-------------------------|-------------------|--------------------|
| Number of subjects | 121 | 115 | 59 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 118 | 111 | 57 |
| From 65-84 years | 3 | 4 | 2 |
| Age continuous Units: years | | | |
| arithmetic mean | 50.2 | 50.9 | 51.5 |
| standard deviation | ± 9.24 | ± 10.11 | ± 8.99 |
| Gender categorical Units: Subjects | | | |
| Female | 58 | 47 | 19 |
| Male | 63 | 68 | 40 |

| Reporting group values | Arm C2- Placebo BID | Arm D DEB 400 BID | Arm C- Placebo |
|------------------------|---------------------|-------------------|----------------|
| Number of subjects | 55 | 109 | 114 |

| | | | |
|----------------------|---------|--------|--------|
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 55 | 103 | 112 |
| From 65-84 years | 0 | 6 | 2 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 49.4 | 51 | 50.5 |
| standard deviation | ± 11.91 | ± 9.68 | ± 10.5 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 17 | 40 | 36 |
| Male | 38 | 69 | 78 |

| | | | |
|-------------------------------|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 459 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 444 | | |
| From 65-84 years | 15 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 181 | | |
| Male | 278 | | |

End points

End points reporting groups

| | |
|---|-------------------------|
| Reporting group title | Arm A: DEB025 600 mg QD |
| Reporting group description: DEB025 600 mg once daily (QD) with PEG and RBV for up to 48 weeks | |
| Reporting group title | Arm B: DEB 800 QD |
| Reporting group description: DEB025 800 mg QD with PEG and RBV for up to 48 weeks. | |
| Reporting group title | Arm C1- Placebo QD |
| Reporting group description: Placebo with PEG and RBV for up to 48 weeks; participants not achieving complete early virologic response (cEVR: HCV RNA <LOQ after 12 weeks of treatment) may switch to active ALV 600 mg QD with PEG and RBV. Note: For one patient in arm C the corresponding end-of treatment CRF page was by mistake not entered into the database before the database was locked (the patient completed the treatment phase on 31-Mar-2012). Therefore, this patient is not included or in other summaries dependent on end-of-treatment status. | |
| Reporting group title | Arm C2- Placebo BID |
| Reporting group description: Placebo with PEG and RBV for up to 48 weeks; participants not achieving cEVR may switch to active ALV 400 mg twice daily (BID) with PEG and RBV. | |
| Reporting group title | Arm D DEB 400 BID |
| Reporting group description: DEB025 400 mg twice daily BID with PEG and RBV for up to 48 weeks | |
| Reporting group title | Arm C- Placebo |
| Reporting group description: Placebo with PEG and RBV for up to 48 weeks; participants not achieving complete early virologic response (cEVR: HCV RNA <LOQ after 12 weeks of treatment) may switch to active ALV 600 mg QD with PEG and RBV. Note: For one patient in arm C the corresponding end-of treatment CRF page was by mistake not entered into the database before the database was locked (the patient completed the treatment phase on 31-Mar-2012). Therefore, this patient is not included in Table 10-1 or in other summaries dependent on end-of-treatment status. | |
| Reporting group title | Arm C1-A |
| Reporting group description: Placebo to DEB 600 QD | |
| Reporting group title | Arm C2-A |
| Reporting group description: Placebo to DEB 400 BID | |

Primary: Percentage of Participants With Complete Early Viral Response (cEVR)-LOQ

| | |
|--|---|
| End point title | Percentage of Participants With Complete Early Viral Response (cEVR)-LOQ ^[1] |
| End point description: cEVR-LOQ was defined as serum HCV RNA below the limit of quantification (< LOQ; i.e., 25 IU/mL) after 12 weeks of treatment. Post-switch groups were assessed 12 weeks after the switch. | |
| End point type | Primary |
| End point timeframe: 12 weeks | |

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics are represented for all arms. The Placebo arm is represented one arm (total) and as the two arms as a result of the switch at week 16.

| End point values | Arm A: DEB025 600 mg QD | Arm B: DEB 800 QD | Arm D DEB 400 BID | Arm C1-A |
|-----------------------------|-------------------------------|----------------------|----------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 110 ^[2] | 108 ^[3] | 109 ^[4] | 33 ^[5] |
| Units: percent | | | | |
| number (not applicable) | 48.2 | 61.1 | 74.3 | 45.5 |

Notes:

[2] - Full Analysis Set (FAS): all patients to whom study treatment had been assigned

[3] - FAS

[4] - FAS

[5] - FAS

| End point values | Arm C2-A | Arm C- Placebo | | |
|-----------------------------|-------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 ^[6] | 110 ^[7] | | |
| Units: percent | | | | |
| number (not applicable) | 80 | 35.5 | | |

Notes:

[6] - FAS

[7] - FAS

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Arm A: Comparison with Arm C (Placebo) |
| Comparison groups | Arm A: DEB025 600 mg QD v Arm C- Placebo |
| Number of subjects included in analysis | 220 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.0131 |
| Method | Hochberg |
| Parameter estimate | Cochran-Mantel-Haenszel test |
| Point estimate | 1.45 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.082 |
| upper limit | 1.951 |

| | |
|----------------------------|--|
| Statistical analysis title | Arm B: Comparison with Arm C (Placebo) |
| Comparison groups | Arm B: DEB 800 QD v Arm C- Placebo |

| | |
|---|------------------------------|
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.0001 |
| Method | Hochberg |
| Parameter estimate | Cochran-Mantel-Haenszel test |
| Point estimate | 1.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.358 |
| upper limit | 2.325 |

| | |
|---|--|
| Statistical analysis title | Arm D: Comparison with Arm C (Placebo) |
| Comparison groups | Arm C- Placebo v Arm D DEB 400 BID |
| Number of subjects included in analysis | 219 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.0001 |
| Method | Hochberg |
| Parameter estimate | Cochran-Mantel-Haenszel test |
| Point estimate | 2.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.656 |
| upper limit | 2.889 |

Secondary: Percentage of participants who achieved sustained virologic response (SVR) 12 weeks post treatment

| | |
|-----------------|---|
| End point title | Percentage of participants who achieved sustained virologic response (SVR) 12 weeks post treatment ^[8] |
|-----------------|---|

End point description:

Data is based on patients randomized after the 2nd protocol amendment only.

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

End point timeframe:

12 weeks post treatment

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Statistics are represented for all arms. The Placebo arm is represented one arm (total) and as the two arms as a result of the switch at week 16.

| End point values | Arm A: DEB025 600 mg QD | Arm B: DEB 800 QD | Arm D DEB 400 BID | Arm C1-A |
|-----------------------------|-------------------------------|----------------------|----------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 110 ^[9] | 108 ^[10] | 109 | 33 ^[11] |
| Units: percent | | | | |
| number (not applicable) | 42.7 | 51.9 | 65.1 | 18.2 |

Notes:

[9] - FAS

[10] - FAS

[11] - FAS

| End point values | Arm C2-A | Arm C- Placebo | | |
|-----------------------------|--------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 ^[12] | 110 ^[13] | | |
| Units: percent | | | | |
| number (not applicable) | 53.3 | 14.5 | | |

Notes:

[12] - FAS

[13] - FAS

Statistical analyses

| Statistical analysis title | Arm A: Comparison with Arm C (Placebo) |
|---|--|
| Comparison groups | Arm A: DEB025 600 mg QD v Arm C- Placebo |
| Number of subjects included in analysis | 220 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.0001 |
| Method | Hochberg |
| Parameter estimate | Cochran-Mantel-Haenszel test |
| Point estimate | 3.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.917 |
| upper limit | 5.063 |

| Statistical analysis title | Arm B: Comparison with Arm C (Placebo) |
|---|--|
| Comparison groups | Arm C- Placebo v Arm B: DEB 800 QD |
| Number of subjects included in analysis | 218 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.0001 |
| Method | Hochberg |
| Parameter estimate | Cochran-Mantel-Haenszel test |
| Point estimate | 3.7 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.31 |
| upper limit | 5.963 |

| | |
|---|--|
| Statistical analysis title | Arm D: Comparison with Arm C (Placebo) |
| Comparison groups | Arm C- Placebo v Arm D DEB 400 BID |
| Number of subjects included in analysis | 219 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.0001 |
| Method | Hochberg |
| Parameter estimate | Cochran-Mantel-Haenszel test |
| Point estimate | 4.55 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.799 |
| upper limit | 7.41 |

Secondary: Percentage of participants who achieved virologic response by level of quantification (LOQ)

| | |
|-----------------|---|
| End point title | Percentage of participants who achieved virologic response by level of quantification (LOQ) ^[14] |
|-----------------|---|

End point description:

Data is based on patients randomized after the 2nd protocol amendment only.

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

End point timeframe:

12 weeks post treatment

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistics are represented for all arms. The Placebo arm is represented one arm (total) and as the two arms as a result of the switch at week 16.

| End point values | Arm A: DEB025 600 mg QD | Arm B: DEB 800 QD | Arm D DEB 400 BID | Arm C- Placebo |
|--|-------------------------------|----------------------|----------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 110 ^[15] | 108 ^[16] | 109 ^[17] | 110 ^[18] |
| Units: percent | | | | |
| number (not applicable) | | | | |
| RVR (rapid virologic response) | 20.9 | 25 | 41.3 | 7.3 |
| cEVR (complete early virologic response) | 48.2 | 61.1 | 74.3 | 35.5 |

| | | | | |
|---|------|------|------|------|
| EDTR (end of DEB025-treatment virologic response) | 72.7 | 77.8 | 87.2 | 33.6 |
| ETR (end of treatment virologic response) | 68.2 | 74.1 | 82.6 | 33.6 |
| SVR4 (sustained virologic response 4 weeks) | 50 | 57.4 | 69.7 | 21.8 |
| SVR12 (sustained virologic response 12 weeks) | 42.7 | 51.9 | 65.1 | 14.5 |
| SVR24 (sustained virologic response 24 weeks) | 41.8 | 51.9 | 65.1 | 14.5 |

Notes:

[15] - FAS

[16] - FAS

[17] - FAS

[18] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who achieved virologic response by LOQ by response status to previous treatment

| | |
|-----------------|--|
| End point title | Percentage of participants who achieved virologic response by LOQ by response status to previous treatment ^[19] |
|-----------------|--|

End point description:

Data is based on patients randomized after the 2nd protocol amendment only.

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

End point timeframe:

12 weeks post treatment

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistics are represented for all arms. The Placebo arm is represented one arm (total) and as the two arms as a result of the switch at week 16.

| End point values | Arm A: DEB025 600 mg QD | Arm B: DEB 800 QD | Arm D DEB 400 BID | Arm C- Placebo |
|-----------------------------|-------------------------------|----------------------|----------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 110 ^[20] | 108 ^[21] | 109 ^[22] | 110 ^[23] |
| Units: percent | | | | |
| number (not applicable) | | | | |
| Relapser - cEVR | 64.6 | 77.6 | 77.1 | 57.4 |
| Relapser - EDTR | 85.4 | 83.7 | 85.4 | 59.3 |
| Relapser - ETR | 87.5 | 83.7 | 85.4 | 59.3 |
| Relapser - SVR12 | 60.4 | 63.3 | 64.6 | 25.9 |
| Relapser - SVR24 | 58.3 | 65.3 | 64.6 | 25.9 |
| Non-responder - cEVR | 35.5 | 47.35 | 72.1 | 14.3 |
| Non-responder - EDTR | 62.9 | 72.9 | 88.5 | 8.9 |
| Non-responder - ETR | 53.2 | 66.1 | 80.3 | 8.9 |
| Non-responder - SVR12 | 29 | 42.4 | 65.6 | 3.6 |
| Non-responder - SVR24 | 29 | 40.7 | 65.6 | 3.6 |
| Null non-responder - cEVR | 33.3 | 40.5 | 70.6 | 11.1 |
| Null non-responder - EDTR | 60.4 | 70.3 | 82.4 | 8.3 |
| Null non-responder - ETR | 50 | 64.9 | 73.5 | 8.3 |

| | | | | |
|---|------|------|------|-----|
| Null non-responder - SVR12 | 22.9 | 40.5 | 67.6 | 2.8 |
| Null non-responder - SVR24 | 22.9 | 37.8 | 67.6 | 2.8 |
| Partial non-responder / unspecified – cEVR | 42.9 | 59.1 | 74.1 | 20 |
| Partial non-responder / unspecified – EDTR | 71.4 | 77.3 | 96.3 | 10 |
| Partial non-responder / unspecified – ETR | 64.3 | 68.2 | 88.9 | 10 |
| Partial non-responder / unspecified – SVR12 | 50 | 45.5 | 63 | 5 |
| Partial non-responder / unspecified – SVR24 | 50 | 45.5 | 63 | 5 |

Notes:

[20] - FAS: n= 48, 62, 48, 14

[21] - FAS: n = 49, 59, 37, 22

[22] - FAS: n = 48, 61, 34, 27

[23] - FAS: n = 54, 56, 36, 20

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who achieved virologic response by LOQ by IL28B polymorphism

| | |
|-----------------|---|
| End point title | Percentage of participants who achieved virologic response by LOQ by IL28B polymorphism ^[24] |
|-----------------|---|

End point description:

Data is based on patients randomized after the 2nd protocol amendment only.

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

End point timeframe:

12 weeks post treatment

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistics are represented for all arms. The Placebo arm is represented one arm (total) and as the two arms as a result of the switch at week 16.

| End point values | Arm A: DEB025 600 mg QD | Arm B: DEB 800 QD | Arm D DEB 400 BID | Arm C- Placebo |
|-----------------------------|-------------------------------|----------------------|----------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 110 ^[25] | 108 ^[26] | 109 ^[27] | 110 ^[28] |
| Units: percent | | | | |
| number (not applicable) | | | | |
| CC - cEVR | 71.4 | 90.5 | 85 | 60.9 |
| CC - EDTR | 81 | 95.2 | 100 | 65.2 |
| CC - ETR | 81 | 95.2 | 100 | 65.2 |
| CC - SVR12 | 66.7 | 85.7 | 65 | 26.1 |
| CC - SVR24 | 66.7 | 81 | 65 | 26.1 |
| CT/TT - cEVR | 42.7 | 54 | 71.9 | 28.7 |
| CT/TT - EDTR | 70.8 | 73.6 | 84.3 | 25.3 |
| CT/TT - ETR | 65.2 | 69 | 78.7 | 25.3 |
| CT/TT - SVR12 | 37.1 | 43.7 | 65.2 | 11.5 |
| CT/TT - SVR24 | 36 | 44.8 | 65.2 | 11.5 |

Notes:

[25] - FAS: n = 21, 89

[26] - FAS: n = 21, 87

[27] - FAS: n = 20, 89

[28] - FAS: n = 23, 87

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who achieved virologic response by LOQ by cirrhosis or transition to cirrhosis

| | |
|-----------------|---|
| End point title | Percentage of participants who achieved virologic response by LOQ by cirrhosis or transition to cirrhosis ^[29] |
|-----------------|---|

End point description:

Data is based on patients randomized after the 2nd protocol amendment only.

| | |
|-------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 12 weeks post treatment | |

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistics are represented for all arms. The Placebo arm is represented one arm (total) and as the two arms as a result of the switch at week 16.

| End point values | Arm A: DEB025 600 mg QD | Arm B: DEB 800 QD | Arm D DEB 400 BID | Arm C- Placebo |
|---|-------------------------------|----------------------|----------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 110 ^[30] | 108 ^[31] | 109 ^[32] | 110 ^[33] |
| Units: percent | | | | |
| number (not applicable) | | | | |
| Cirrhosis or transition to cirrhosis - cEVR | 40.7 | 57.1 | 60.9 | 20.7 |
| Cirrhosis or transition to cirrhosis - EDTR | 70.4 | 68.6 | 73.9 | 17.2 |
| Cirrhosis or transition to cirrhosis - ETR | 55.6 | 65.7 | 69.6 | 17.2 |
| Cirrhosis or transition to cirrhosis - SVR12 | 33.3 | 40 | 52.2 | 0 |
| Cirrhosis or transition to cirrhosis - SVR24 | 33.3 | 40 | 52.2 | 0 |
| No cirrhosis or transition to cirrhosis - cEVR | 51.2 | 64.3 | 78 | 39.2 |
| No cirrhosis or transition to cirrhosis - EDTR | 74.4 | 81.4 | 91.5 | 38 |
| No cirrhosis or transition to cirrhosis - ETR | 73.2 | 78.6 | 86.6 | 38 |
| No cirrhosis or transition to cirrhosis - SVR12 | 46.3 | 58.6 | 68.3 | 20.3 |
| No cirrhosis or transition to cirrhosis - SVR24 | 45.1 | 58.6 | 68.3 | 20.3 |

Notes:

[30] - FAS: n= 27, 82

[31] - FAS: n= 35, 70

[32] - FAS: n= 23, 82

[33] - FAS: n= 29, 79

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who achieved virologic response by LOQ by HCV genotype 1 subtype

| | |
|-----------------|---|
| End point title | Percentage of participants who achieved virologic response by LOQ by HCV genotype 1 subtype ^[34] |
|-----------------|---|

End point description:

Data is based on patients randomized after the 2nd protocol amendment only.

| | |
|-------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 12 weeks post treatment | |

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistics are represented for all arms. The Placebo arm is represented one arm (total) and as the two arms as a result of the switch at week 16.

| End point values | Arm A: DEB025 600 mg QD | Arm B: DEB 800 QD | Arm D DEB 400 BID | Arm C- Placebo |
|-----------------------------|-------------------------------|----------------------|----------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 110 ^[35] | 108 ^[36] | 109 ^[37] | 110 ^[38] |
| Units: percent | | | | |
| number (not applicable) | | | | |
| 1a - cEVR | 50 | 63 | 66.7 | 32.3 |
| 1a - EDTR | 73.3 | 74.1 | 86.1 | 35.5 |
| 1a - ETR | 73.3 | 66.7 | 77.8 | 35.5 |
| 1a - SVR12 | 46.7 | 59.3 | 55.6 | 12.9 |
| 1a - SVR24 | 46.7 | 59.3 | 55.6 | 12.9 |
| 1b - cEVR | 47.5 | 60.5 | 78.1 | 36.7 |
| 1b - EDTR | 72.5 | 79 | 87.7 | 32.9 |
| 1b - ETR | 66.3 | 76.5 | 84.9 | 32.9 |
| 1b - SVR12 | 41.3 | 49.4 | 69.9 | 15.2 |
| 1b - SVR24 | 40 | 49.4 | 69.9 | 15.2 |

Notes:

[35] - FAS: n= 30, 80

[36] - FAS: n= 27, 81

[37] - FAS: n= 36, 73

[38] - FAS: n= 31, 79

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

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

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Arm A DEB 600 QD |
|-----------------------|------------------|

Reporting group description:

Arm A DEB 600 QD

| | |
|-----------------------|------------------|
| Reporting group title | Arm B DEB 800 QD |
|-----------------------|------------------|

Reporting group description:

Arm B DEB 800 QD

| | |
|-----------------------|-------------------|
| Reporting group title | Arm C1 Placebo QD |
|-----------------------|-------------------|

Reporting group description:

Arm C1 Placebo QD

| | |
|-----------------------|--------------------|
| Reporting group title | Arm C2 Placebo BID |
|-----------------------|--------------------|

Reporting group description:

Arm C2 Placebo BID

| | |
|-----------------------|---------------|
| Reporting group title | Arm C Placebo |
|-----------------------|---------------|

Reporting group description:

Arm C Placebo

| | |
|-----------------------|-------------------|
| Reporting group title | Arm D DEB 400 BID |
|-----------------------|-------------------|

Reporting group description:

Arm D DEB 400 BID

| | |
|-----------------------|-------|
| Reporting group title | Total |
|-----------------------|-------|

Reporting group description:

Total

| Serious adverse events | Arm A DEB 600 QD | Arm B DEB 800 QD | Arm C1 Placebo QD |
|---|------------------|------------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 120 (5.83%) | 11 / 115 (9.57%) | 5 / 59 (8.47%) |
| 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) | | | |
| Malignant melanoma | | | |

| | | | |
|--|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 115 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-small cell lung cancer stage I | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 115 (0.00%) | 0 / 59 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 1 / 115 (0.87%) | 0 / 59 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 115 (0.87%) | 0 / 59 (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 |
| Chest pain | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 115 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug interaction | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 115 (0.00%) | 0 / 59 (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 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 115 (0.00%) | 0 / 59 (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 |
| Multi-organ failure | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 115 (0.00%) | 0 / 59 (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 |

| | | | |
|---|-----------------|-----------------|----------------|
| Pyrexia | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 115 (0.00%) | 0 / 59 (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 |
| Reproductive system and breast disorders | | | |
| Endometriosis | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 115 (0.87%) | 0 / 59 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 115 (0.00%) | 0 / 59 (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 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 115 (0.87%) | 0 / 59 (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 |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 115 (0.00%) | 0 / 59 (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 |
| Pulmonary mass | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 115 (0.00%) | 0 / 59 (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 |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 115 (0.00%) | 0 / 59 (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 | | | |
| Disorientation | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 115 (0.87%) | 0 / 59 (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 |
| Psychotic disorder | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 115 (0.00%) | 0 / 59 (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 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 115 (0.00%) | 0 / 59 (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 | | | |
| Vascular pseudoaneurysm | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 115 (0.00%) | 0 / 59 (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 |
| Cardiac disorders | | | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 115 (0.00%) | 0 / 59 (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 | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 115 (0.00%) | 0 / 59 (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 |
| Headache | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 115 (0.00%) | 0 / 59 (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 |
| Loss of consciousness | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 115 (0.00%) | 0 / 59 (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 |
| Syncope | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 115 (0.00%) | 0 / 59 (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 |
| Vertebrobasilar insufficiency | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 115 (0.00%) | 0 / 59 (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 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 2 / 115 (1.74%) | 0 / 59 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 5 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 115 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 115 (0.87%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 115 (0.87%) | 0 / 59 (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 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 115 (0.87%) | 0 / 59 (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 |
| Diarrhoea | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 115 (0.00%) | 0 / 59 (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 |
| Nausea | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 115 (0.00%) | 0 / 59 (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 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 115 (0.00%) | 0 / 59 (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 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 115 (0.87%) | 0 / 59 (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 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 115 (0.00%) | 0 / 59 (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 / 120 (0.00%) | 1 / 115 (0.87%) | 0 / 59 (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 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 115 (0.87%) | 0 / 59 (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 |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 115 (0.00%) | 0 / 59 (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 |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| Psoriasis | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 115 (0.87%) | 0 / 59 (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 |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 115 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 115 (0.00%) | 0 / 59 (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 |
| Endocrine disorders | | | |
| Hypopituitarism | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 115 (0.87%) | 0 / 59 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthritis | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 115 (0.87%) | 0 / 59 (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 | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 2 / 115 (1.74%) | 0 / 59 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis viral | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 115 (0.87%) | 0 / 59 (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 |
| Cystitis | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 115 (0.87%) | 0 / 59 (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 |
| Ear infection | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 115 (0.87%) | 0 / 59 (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 |
| Hepatitis C | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 115 (0.00%) | 0 / 59 (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 |
| Orchitis | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 115 (0.00%) | 0 / 59 (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 |
| Osteomyelitis | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 115 (0.00%) | 0 / 59 (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 |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 115 (0.87%) | 0 / 59 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 115 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 115 (0.00%) | 0 / 59 (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 |
| Urinary tract infection | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 115 (0.00%) | 0 / 59 (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 |
| Metabolism and nutrition disorders | | | |
| Hyperamylasaemia | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 115 (0.00%) | 0 / 59 (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 |
| Hyperlipasaemia | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 115 (0.00%) | 0 / 59 (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 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 115 (0.00%) | 0 / 59 (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 | Arm C2 Placebo BID | Arm C Placebo | Arm D DEB 400 BID |
|---|--------------------|-----------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 6 / 114 (5.26%) | 18 / 108 (16.67%) |
| number of deaths (all causes) | 0 | 0 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant melanoma | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 114 (0.88%) | 0 / 108 (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 |
| Non-small cell lung cancer stage I | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypertension | | | |

| | | | |
|--|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 2 / 108 (1.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 0 / 108 (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 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 114 (0.88%) | 2 / 108 (1.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug interaction | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multi-organ failure | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Endometriosis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|-----------------|-----------------|
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary mass | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 0 / 108 (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 distress | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Disorientation | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 0 / 108 (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 |
| Psychotic disorder | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Vascular pseudoaneurysm | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 0 / 108 (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 |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 2 / 108 (1.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 0 / 108 (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 |
| Vertebrobasilar insufficiency | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 1 / 114 (0.88%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|-----------------|-----------------|
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 114 (0.88%) | 0 / 108 (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 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 114 (0.88%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 0 / 108 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 0 / 108 (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 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|-----------------|-----------------|
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 0 / 108 (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 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 0 / 108 (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 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 0 / 108 (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 |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Psoriasis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 0 / 108 (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 |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 1 / 114 (0.88%) | 0 / 108 (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 |
| Renal and urinary disorders | | | |
| Renal failure | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Hypopituitarism | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 0 / 108 (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 | | | |
| Arthritis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 0 / 108 (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 | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 0 / 108 (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 |
| Arthritis viral | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 0 / 108 (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 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 0 / 108 (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 |
| Ear infection | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 0 / 108 (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 |
| Hepatitis C | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 0 / 108 (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 |

| | | | |
|---|----------------|-----------------|-----------------|
| Orchitis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 0 / 108 (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 |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 0 / 108 (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 / 55 (0.00%) | 1 / 114 (0.88%) | 3 / 108 (2.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 0 / 108 (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 |
| Metabolism and nutrition disorders | | | |
| Hyperamylasaemia | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperlipasaemia | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 55 (0.00%) | 0 / 114 (0.00%) | 1 / 108 (0.93%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Total | | |
|---|------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 42 / 457 (9.19%) | | |
| number of deaths (all causes) | 1 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant melanoma | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Non-small cell lung cancer stage I | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 4 / 457 (0.88%) | | |
| occurrences causally related to treatment / all | 4 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Chest discomfort | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest pain | | | |
| subjects affected / exposed | 4 / 457 (0.88%) | | |
| occurrences causally related to treatment / all | 2 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug interaction | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Multi-organ failure | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 457 (0.44%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Endometriosis | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 457 (0.44%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonitis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary mass | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory distress | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Disorientation | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychotic disorder | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Vascular pseudoaneurysm | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Supraventricular tachycardia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 457 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Headache | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Loss of consciousness | | | |
| subjects affected / exposed | 2 / 457 (0.44%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vertebrobasilar insufficiency | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 457 (0.66%) | | |
| occurrences causally related to treatment / all | 6 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 3 / 457 (0.66%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |

| | | | |
|---|-----------------|--|--|
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Psoriasis | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rash erythematous | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Hypopituitarism | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthritis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 2 / 457 (0.44%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arthritis viral | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cystitis | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear infection | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatitis C | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Orchitis | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteomyelitis | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peritonitis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 4 / 457 (0.88%) | | |
| occurrences causally related to treatment / all | 3 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Hyperamylasaemia | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperlipasaemia | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 457 (0.22%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Arm A DEB 600 QD | Arm B DEB 800 QD | Arm C1 Placebo QD |
|---|--------------------|--------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 116 / 120 (96.67%) | 108 / 115 (93.91%) | 54 / 59 (91.53%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 21 / 120 (17.50%) | 22 / 115 (19.13%) | 0 / 59 (0.00%) |
| occurrences (all) | 21 | 24 | 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 19 / 120 (15.83%) | 30 / 115 (26.09%) | 9 / 59 (15.25%) |
| occurrences (all) | 19 | 31 | 11 |
| Chest pain | | | |
| subjects affected / exposed | 3 / 120 (2.50%) | 4 / 115 (3.48%) | 1 / 59 (1.69%) |
| occurrences (all) | 3 | 4 | 1 |
| Chills | | | |
| subjects affected / exposed | 14 / 120 (11.67%) | 13 / 115 (11.30%) | 6 / 59 (10.17%) |
| occurrences (all) | 19 | 15 | 7 |
| Fatigue | | | |
| subjects affected / exposed | 47 / 120 (39.17%) | 45 / 115 (39.13%) | 21 / 59 (35.59%) |
| occurrences (all) | 53 | 48 | 23 |
| Influenza like illness | | | |
| subjects affected / exposed | 13 / 120 (10.83%) | 10 / 115 (8.70%) | 15 / 59 (25.42%) |
| occurrences (all) | 18 | 11 | 18 |
| Injection site erythema | | | |
| subjects affected / exposed | 8 / 120 (6.67%) | 11 / 115 (9.57%) | 5 / 59 (8.47%) |
| occurrences (all) | 8 | 13 | 5 |
| Injection site rash | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 1 / 115 (0.87%) | 4 / 59 (6.78%) |
| occurrences (all) | 1 | 1 | 4 |
| Irritability | | | |
| subjects affected / exposed | 8 / 120 (6.67%) | 7 / 115 (6.09%) | 3 / 59 (5.08%) |
| occurrences (all) | 8 | 7 | 3 |
| Malaise | | | |
| subjects affected / exposed | 9 / 120 (7.50%) | 8 / 115 (6.96%) | 1 / 59 (1.69%) |
| occurrences (all) | 14 | 8 | 2 |
| Pyrexia | | | |

| | | | |
|--|-------------------------|-------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 32 / 120 (26.67%) 48 | 34 / 115 (29.57%) 48 | 16 / 59 (27.12%) 20 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 38 / 120 (31.67%) | 29 / 115 (25.22%) | 17 / 59 (28.81%) |
| occurrences (all) | 43 | 33 | 19 |
| Dyspnoea | | | |
| subjects affected / exposed | 21 / 120 (17.50%) | 8 / 115 (6.96%) | 6 / 59 (10.17%) |
| occurrences (all) | 21 | 8 | 6 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 6 / 120 (5.00%) | 9 / 115 (7.83%) | 3 / 59 (5.08%) |
| occurrences (all) | 9 | 11 | 3 |
| Epistaxis | | | |
| subjects affected / exposed | 5 / 120 (4.17%) | 3 / 115 (2.61%) | 3 / 59 (5.08%) |
| occurrences (all) | 6 | 4 | 3 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 9 / 120 (7.50%) | 8 / 115 (6.96%) | 5 / 59 (8.47%) |
| occurrences (all) | 11 | 9 | 6 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 19 / 120 (15.83%) | 8 / 115 (6.96%) | 3 / 59 (5.08%) |
| occurrences (all) | 19 | 8 | 3 |
| Depression | | | |
| subjects affected / exposed | 22 / 120 (18.33%) | 14 / 115 (12.17%) | 8 / 59 (13.56%) |
| occurrences (all) | 24 | 14 | 10 |
| Insomnia | | | |
| subjects affected / exposed | 35 / 120 (29.17%) | 24 / 115 (20.87%) | 10 / 59 (16.95%) |
| occurrences (all) | 45 | 25 | 10 |
| Nervousness | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 1 / 115 (0.87%) | 2 / 59 (3.39%) |
| occurrences (all) | 1 | 1 | 2 |
| Restlessness | | | |
| subjects affected / exposed | 7 / 120 (5.83%) | 4 / 115 (3.48%) | 1 / 59 (1.69%) |
| occurrences (all) | 10 | 5 | 1 |
| Sleep disorder | | | |

| | | | |
|--|----------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 2 / 120 (1.67%) 2 | 4 / 115 (3.48%) 4 | 3 / 59 (5.08%) 3 |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 6 / 120 (5.00%) | 1 / 115 (0.87%) | 0 / 59 (0.00%) |
| occurrences (all) | 9 | 1 | 0 |
| Lipase increased | | | |
| subjects affected / exposed | 2 / 120 (1.67%) | 1 / 115 (0.87%) | 4 / 59 (6.78%) |
| occurrences (all) | 3 | 1 | 4 |
| Total bile acids increased | | | |
| subjects affected / exposed | 5 / 120 (4.17%) | 3 / 115 (2.61%) | 1 / 59 (1.69%) |
| occurrences (all) | 7 | 4 | 1 |
| Weight decreased | | | |
| subjects affected / exposed | 9 / 120 (7.50%) | 9 / 115 (7.83%) | 2 / 59 (3.39%) |
| occurrences (all) | 10 | 9 | 2 |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 11 / 120 (9.17%) | 7 / 115 (6.09%) | 3 / 59 (5.08%) |
| occurrences (all) | 12 | 7 | 3 |
| Nervous system disorders | | | |
| Disturbance in attention | | | |
| subjects affected / exposed | 9 / 120 (7.50%) | 10 / 115 (8.70%) | 3 / 59 (5.08%) |
| occurrences (all) | 10 | 10 | 3 |
| Dizziness | | | |
| subjects affected / exposed | 20 / 120 (16.67%) | 22 / 115 (19.13%) | 10 / 59 (16.95%) |
| occurrences (all) | 27 | 30 | 12 |
| Dysgeusia | | | |
| subjects affected / exposed | 5 / 120 (4.17%) | 7 / 115 (6.09%) | 3 / 59 (5.08%) |
| occurrences (all) | 5 | 7 | 3 |
| Headache | | | |
| subjects affected / exposed | 59 / 120 (49.17%) | 47 / 115 (40.87%) | 23 / 59 (38.98%) |
| occurrences (all) | 92 | 69 | 30 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 6 / 120 (5.00%) | 2 / 115 (1.74%) | 1 / 59 (1.69%) |
| occurrences (all) | 7 | 2 | 1 |
| Memory impairment | | | |

| | | | |
|--|----------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 5 / 120 (4.17%) 5 | 4 / 115 (3.48%) 4 | 2 / 59 (3.39%) 2 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 49 / 120 (40.83%) | 41 / 115 (35.65%) | 17 / 59 (28.81%) |
| occurrences (all) | 79 | 63 | 24 |
| Leukopenia | | | |
| subjects affected / exposed | 17 / 120 (14.17%) | 13 / 115 (11.30%) | 7 / 59 (11.86%) |
| occurrences (all) | 33 | 27 | 14 |
| Lymphopenia | | | |
| subjects affected / exposed | 5 / 120 (4.17%) | 2 / 115 (1.74%) | 3 / 59 (5.08%) |
| occurrences (all) | 5 | 4 | 5 |
| Neutropenia | | | |
| subjects affected / exposed | 49 / 120 (40.83%) | 40 / 115 (34.78%) | 15 / 59 (25.42%) |
| occurrences (all) | 88 | 72 | 25 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 24 / 120 (20.00%) | 19 / 115 (16.52%) | 3 / 59 (5.08%) |
| occurrences (all) | 39 | 28 | 4 |
| Eye disorders | | | |
| Dry eye | | | |
| subjects affected / exposed | 7 / 120 (5.83%) | 7 / 115 (6.09%) | 2 / 59 (3.39%) |
| occurrences (all) | 7 | 7 | 2 |
| Ocular icterus | | | |
| subjects affected / exposed | 5 / 120 (4.17%) | 8 / 115 (6.96%) | 1 / 59 (1.69%) |
| occurrences (all) | 8 | 13 | 1 |
| Vision blurred | | | |
| subjects affected / exposed | 4 / 120 (3.33%) | 8 / 115 (6.96%) | 1 / 59 (1.69%) |
| occurrences (all) | 4 | 10 | 1 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 2 / 120 (1.67%) | 5 / 115 (4.35%) | 0 / 59 (0.00%) |
| occurrences (all) | 3 | 6 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 9 / 120 (7.50%) | 7 / 115 (6.09%) | 6 / 59 (10.17%) |
| occurrences (all) | 9 | 9 | 6 |
| Abdominal pain upper | | | |

| | | | |
|-----------------------------|-------------------|-------------------|------------------|
| subjects affected / exposed | 15 / 120 (12.50%) | 8 / 115 (6.96%) | 5 / 59 (8.47%) |
| occurrences (all) | 15 | 9 | 5 |
| Aphthous stomatitis | | | |
| subjects affected / exposed | 6 / 120 (5.00%) | 3 / 115 (2.61%) | 3 / 59 (5.08%) |
| occurrences (all) | 6 | 5 | 4 |
| Cheilitis | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 6 / 115 (5.22%) | 1 / 59 (1.69%) |
| occurrences (all) | 1 | 7 | 1 |
| Constipation | | | |
| subjects affected / exposed | 10 / 120 (8.33%) | 7 / 115 (6.09%) | 1 / 59 (1.69%) |
| occurrences (all) | 11 | 7 | 1 |
| Diarrhoea | | | |
| subjects affected / exposed | 19 / 120 (15.83%) | 18 / 115 (15.65%) | 8 / 59 (13.56%) |
| occurrences (all) | 27 | 18 | 8 |
| Dry mouth | | | |
| subjects affected / exposed | 15 / 120 (12.50%) | 10 / 115 (8.70%) | 5 / 59 (8.47%) |
| occurrences (all) | 17 | 11 | 5 |
| Dyspepsia | | | |
| subjects affected / exposed | 15 / 120 (12.50%) | 4 / 115 (3.48%) | 5 / 59 (8.47%) |
| occurrences (all) | 18 | 4 | 6 |
| Mouth ulceration | | | |
| subjects affected / exposed | 7 / 120 (5.83%) | 10 / 115 (8.70%) | 2 / 59 (3.39%) |
| occurrences (all) | 16 | 11 | 2 |
| Nausea | | | |
| subjects affected / exposed | 46 / 120 (38.33%) | 35 / 115 (30.43%) | 17 / 59 (28.81%) |
| occurrences (all) | 57 | 55 | 22 |
| Toothache | | | |
| subjects affected / exposed | 3 / 120 (2.50%) | 3 / 115 (2.61%) | 3 / 59 (5.08%) |
| occurrences (all) | 3 | 4 | 3 |
| Vomiting | | | |
| subjects affected / exposed | 19 / 120 (15.83%) | 18 / 115 (15.65%) | 4 / 59 (6.78%) |
| occurrences (all) | 39 | 27 | 5 |
| Hepatobiliary disorders | | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 19 / 120 (15.83%) | 14 / 115 (12.17%) | 2 / 59 (3.39%) |
| occurrences (all) | 25 | 16 | 2 |

| | | | |
|--|-------------------------|-------------------------|------------------------|
| Jaundice subjects affected / exposed occurrences (all) | 14 / 120 (11.67%) 17 | 11 / 115 (9.57%) 12 | 3 / 59 (5.08%) 4 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia subjects affected / exposed occurrences (all) | 22 / 120 (18.33%) 22 | 23 / 115 (20.00%) 23 | 6 / 59 (10.17%) 6 |
| Dermatitis subjects affected / exposed occurrences (all) | 3 / 120 (2.50%) 4 | 2 / 115 (1.74%) 2 | 3 / 59 (5.08%) 3 |
| Dry skin subjects affected / exposed occurrences (all) | 15 / 120 (12.50%) 20 | 16 / 115 (13.91%) 17 | 8 / 59 (13.56%) 8 |
| Erythema subjects affected / exposed occurrences (all) | 6 / 120 (5.00%) 6 | 7 / 115 (6.09%) 7 | 0 / 59 (0.00%) 0 |
| Hyperhidrosis subjects affected / exposed occurrences (all) | 2 / 120 (1.67%) 3 | 1 / 115 (0.87%) 1 | 4 / 59 (6.78%) 4 |
| Pruritus subjects affected / exposed occurrences (all) | 36 / 120 (30.00%) 52 | 30 / 115 (26.09%) 42 | 20 / 59 (33.90%) 24 |
| Rash subjects affected / exposed occurrences (all) | 23 / 120 (19.17%) 29 | 22 / 115 (19.13%) 29 | 14 / 59 (23.73%) 16 |
| Endocrine disorders | | | |
| Hypothyroidism subjects affected / exposed occurrences (all) | 7 / 120 (5.83%) 7 | 6 / 115 (5.22%) 7 | 0 / 59 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 19 / 120 (15.83%) 21 | 19 / 115 (16.52%) 21 | 7 / 59 (11.86%) 7 |
| Back pain subjects affected / exposed occurrences (all) | 20 / 120 (16.67%) 24 | 5 / 115 (4.35%) 5 | 4 / 59 (6.78%) 4 |

| | | | |
|---|-------------------------|-------------------------|------------------------|
| Muscle spasms subjects affected / exposed occurrences (all) | 14 / 120 (11.67%) 15 | 12 / 115 (10.43%) 14 | 3 / 59 (5.08%) 4 |
| Myalgia subjects affected / exposed occurrences (all) | 23 / 120 (19.17%) 29 | 21 / 115 (18.26%) 28 | 15 / 59 (25.42%) 16 |
| Neck pain subjects affected / exposed occurrences (all) | 4 / 120 (3.33%) 4 | 1 / 115 (0.87%) 1 | 3 / 59 (5.08%) 3 |
| Osteopenia subjects affected / exposed occurrences (all) | 5 / 120 (4.17%) 5 | 6 / 115 (5.22%) 6 | 0 / 59 (0.00%) 0 |
| Pain in extremity subjects affected / exposed occurrences (all) | 7 / 120 (5.83%) 8 | 5 / 115 (4.35%) 5 | 2 / 59 (3.39%) 2 |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 6 / 120 (5.00%) 7 | 5 / 115 (4.35%) 5 | 1 / 59 (1.69%) 1 |
| Oral herpes subjects affected / exposed occurrences (all) | 4 / 120 (3.33%) 4 | 7 / 115 (6.09%) 7 | 2 / 59 (3.39%) 2 |
| Pharyngitis subjects affected / exposed occurrences (all) | 4 / 120 (3.33%) 4 | 3 / 115 (2.61%) 6 | 2 / 59 (3.39%) 2 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 12 / 120 (10.00%) 17 | 5 / 115 (4.35%) 5 | 2 / 59 (3.39%) 3 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 7 / 120 (5.83%) 9 | 2 / 115 (1.74%) 2 | 3 / 59 (5.08%) 3 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 31 / 120 (25.83%) 35 | 23 / 115 (20.00%) 26 | 8 / 59 (13.56%) 9 |
| Hypertriglyceridaemia | | | |

| | | | |
|-----------------------------|-------------------|-------------------|----------------|
| subjects affected / exposed | 16 / 120 (13.33%) | 21 / 115 (18.26%) | 2 / 59 (3.39%) |
| occurrences (all) | 19 | 22 | 2 |

| Non-serious adverse events | Arm C2 Placebo BID | Arm C Placebo | Arm D DEB 400 BID |
|---|--------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 50 / 55 (90.91%) | 104 / 114 (91.23%) | 106 / 108 (98.15%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 55 (3.64%) | 2 / 114 (1.75%) | 28 / 108 (25.93%) |
| occurrences (all) | 2 | 2 | 31 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 12 / 55 (21.82%) | 21 / 114 (18.42%) | 17 / 108 (15.74%) |
| occurrences (all) | 13 | 24 | 18 |
| Chest pain | | | |
| subjects affected / exposed | 4 / 55 (7.27%) | 5 / 114 (4.39%) | 4 / 108 (3.70%) |
| occurrences (all) | 4 | 5 | 4 |
| Chills | | | |
| subjects affected / exposed | 3 / 55 (5.45%) | 9 / 114 (7.89%) | 14 / 108 (12.96%) |
| occurrences (all) | 4 | 11 | 18 |
| Fatigue | | | |
| subjects affected / exposed | 20 / 55 (36.36%) | 41 / 114 (35.96%) | 45 / 108 (41.67%) |
| occurrences (all) | 24 | 47 | 50 |
| Influenza like illness | | | |
| subjects affected / exposed | 6 / 55 (10.91%) | 21 / 114 (18.42%) | 11 / 108 (10.19%) |
| occurrences (all) | 6 | 24 | 14 |
| Injection site erythema | | | |
| subjects affected / exposed | 3 / 55 (5.45%) | 8 / 114 (7.02%) | 3 / 108 (2.78%) |
| occurrences (all) | 3 | 8 | 4 |
| Injection site rash | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 5 / 114 (4.39%) | 0 / 108 (0.00%) |
| occurrences (all) | 1 | 5 | 0 |
| Irritability | | | |
| subjects affected / exposed | 2 / 55 (3.64%) | 5 / 114 (4.39%) | 6 / 108 (5.56%) |
| occurrences (all) | 2 | 5 | 6 |
| Malaise | | | |

| | | | |
|---|------------------|-------------------|-------------------|
| subjects affected / exposed | 2 / 55 (3.64%) | 3 / 114 (2.63%) | 9 / 108 (8.33%) |
| occurrences (all) | 4 | 6 | 12 |
| Pyrexia | | | |
| subjects affected / exposed | 16 / 55 (29.09%) | 32 / 114 (28.07%) | 28 / 108 (25.93%) |
| occurrences (all) | 49 | 69 | 48 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 12 / 55 (21.82%) | 29 / 114 (25.44%) | 16 / 108 (14.81%) |
| occurrences (all) | 13 | 32 | 18 |
| Dyspnoea | | | |
| subjects affected / exposed | 4 / 55 (7.27%) | 10 / 114 (8.77%) | 16 / 108 (14.81%) |
| occurrences (all) | 4 | 10 | 17 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 4 / 55 (7.27%) | 7 / 114 (6.14%) | 8 / 108 (7.41%) |
| occurrences (all) | 5 | 8 | 8 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 3 / 114 (2.63%) | 10 / 108 (9.26%) |
| occurrences (all) | 0 | 3 | 13 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 3 / 55 (5.45%) | 8 / 114 (7.02%) | 8 / 108 (7.41%) |
| occurrences (all) | 3 | 9 | 8 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 3 / 55 (5.45%) | 6 / 114 (5.26%) | 11 / 108 (10.19%) |
| occurrences (all) | 3 | 6 | 12 |
| Depression | | | |
| subjects affected / exposed | 4 / 55 (7.27%) | 12 / 114 (10.53%) | 13 / 108 (12.04%) |
| occurrences (all) | 4 | 14 | 14 |
| Insomnia | | | |
| subjects affected / exposed | 15 / 55 (27.27%) | 25 / 114 (21.93%) | 17 / 108 (15.74%) |
| occurrences (all) | 19 | 29 | 22 |
| Nervousness | | | |
| subjects affected / exposed | 4 / 55 (7.27%) | 6 / 114 (5.26%) | 2 / 108 (1.85%) |
| occurrences (all) | 4 | 6 | 2 |
| Restlessness | | | |

| | | | |
|---|------------------------|-------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 2 / 55 (3.64%) 2 | 3 / 114 (2.63%) 3 | 1 / 108 (0.93%) 1 |
| Sleep disorder subjects affected / exposed occurrences (all) | 0 / 55 (0.00%) 0 | 3 / 114 (2.63%) 3 | 2 / 108 (1.85%) 2 |
| Investigations Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 1 / 55 (1.82%) 1 | 1 / 114 (0.88%) 1 | 3 / 108 (2.78%) 3 |
| Lipase increased subjects affected / exposed occurrences (all) | 1 / 55 (1.82%) 2 | 5 / 114 (4.39%) 6 | 5 / 108 (4.63%) 6 |
| Total bile acids increased subjects affected / exposed occurrences (all) | 1 / 55 (1.82%) 2 | 2 / 114 (1.75%) 3 | 8 / 108 (7.41%) 17 |
| Weight decreased subjects affected / exposed occurrences (all) | 2 / 55 (3.64%) 2 | 4 / 114 (3.51%) 4 | 9 / 108 (8.33%) 10 |
| Cardiac disorders Palpitations subjects affected / exposed occurrences (all) | 1 / 55 (1.82%) 1 | 4 / 114 (3.51%) 4 | 2 / 108 (1.85%) 2 |
| Nervous system disorders Disturbance in attention subjects affected / exposed occurrences (all) | 3 / 55 (5.45%) 3 | 6 / 114 (5.26%) 6 | 4 / 108 (3.70%) 5 |
| Dizziness subjects affected / exposed occurrences (all) | 4 / 55 (7.27%) 5 | 14 / 114 (12.28%) 17 | 15 / 108 (13.89%) 18 |
| Dysgeusia subjects affected / exposed occurrences (all) | 2 / 55 (3.64%) 2 | 5 / 114 (4.39%) 5 | 9 / 108 (8.33%) 10 |
| Headache subjects affected / exposed occurrences (all) | 18 / 55 (32.73%) 23 | 41 / 114 (35.96%) 53 | 38 / 108 (35.19%) 53 |
| Hypoaesthesia | | | |

| | | | |
|--|------------------------|-------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 1 / 55 (1.82%) 1 | 2 / 114 (1.75%) 2 | 2 / 108 (1.85%) 2 |
| Memory impairment subjects affected / exposed occurrences (all) | 3 / 55 (5.45%) 3 | 5 / 114 (4.39%) 5 | 3 / 108 (2.78%) 4 |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 10 / 55 (18.18%) 17 | 27 / 114 (23.68%) 41 | 51 / 108 (47.22%) 87 |
| Leukopenia subjects affected / exposed occurrences (all) | 5 / 55 (9.09%) 5 | 12 / 114 (10.53%) 19 | 20 / 108 (18.52%) 50 |
| Lymphopenia subjects affected / exposed occurrences (all) | 0 / 55 (0.00%) 0 | 3 / 114 (2.63%) 5 | 8 / 108 (7.41%) 21 |
| Neutropenia subjects affected / exposed occurrences (all) | 12 / 55 (21.82%) 19 | 27 / 114 (23.68%) 44 | 46 / 108 (42.59%) 97 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 1 / 55 (1.82%) 3 | 4 / 114 (3.51%) 7 | 28 / 108 (25.93%) 45 |
| Eye disorders | | | |
| Dry eye subjects affected / exposed occurrences (all) | 0 / 55 (0.00%) 0 | 2 / 114 (1.75%) 2 | 3 / 108 (2.78%) 3 |
| Ocular icterus subjects affected / exposed occurrences (all) | 2 / 55 (3.64%) 4 | 3 / 114 (2.63%) 5 | 14 / 108 (12.96%) 18 |
| Vision blurred subjects affected / exposed occurrences (all) | 0 / 55 (0.00%) 0 | 1 / 114 (0.88%) 1 | 3 / 108 (2.78%) 6 |
| Gastrointestinal disorders | | | |
| Abdominal distension subjects affected / exposed occurrences (all) | 1 / 55 (1.82%) 1 | 1 / 114 (0.88%) 1 | 7 / 108 (6.48%) 8 |
| Abdominal pain | | | |

| | | | |
|-----------------------------|------------------|-------------------|-------------------|
| subjects affected / exposed | 3 / 55 (5.45%) | 9 / 114 (7.89%) | 6 / 108 (5.56%) |
| occurrences (all) | 3 | 9 | 6 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 4 / 55 (7.27%) | 9 / 114 (7.89%) | 13 / 108 (12.04%) |
| occurrences (all) | 5 | 10 | 15 |
| Aphthous stomatitis | | | |
| subjects affected / exposed | 2 / 55 (3.64%) | 5 / 114 (4.39%) | 6 / 108 (5.56%) |
| occurrences (all) | 2 | 6 | 9 |
| Cheilitis | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 2 / 114 (1.75%) | 3 / 108 (2.78%) |
| occurrences (all) | 1 | 2 | 3 |
| Constipation | | | |
| subjects affected / exposed | 3 / 55 (5.45%) | 4 / 114 (3.51%) | 15 / 108 (13.89%) |
| occurrences (all) | 3 | 4 | 16 |
| Diarrhoea | | | |
| subjects affected / exposed | 6 / 55 (10.91%) | 14 / 114 (12.28%) | 10 / 108 (9.26%) |
| occurrences (all) | 7 | 15 | 13 |
| Dry mouth | | | |
| subjects affected / exposed | 6 / 55 (10.91%) | 11 / 114 (9.65%) | 10 / 108 (9.26%) |
| occurrences (all) | 9 | 14 | 10 |
| Dyspepsia | | | |
| subjects affected / exposed | 2 / 55 (3.64%) | 7 / 114 (6.14%) | 15 / 108 (13.89%) |
| occurrences (all) | 2 | 8 | 17 |
| Mouth ulceration | | | |
| subjects affected / exposed | 5 / 55 (9.09%) | 7 / 114 (6.14%) | 3 / 108 (2.78%) |
| occurrences (all) | 5 | 7 | 3 |
| Nausea | | | |
| subjects affected / exposed | 12 / 55 (21.82%) | 29 / 114 (25.44%) | 51 / 108 (47.22%) |
| occurrences (all) | 12 | 34 | 59 |
| Toothache | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 4 / 114 (3.51%) | 2 / 108 (1.85%) |
| occurrences (all) | 2 | 5 | 2 |
| Vomiting | | | |
| subjects affected / exposed | 5 / 55 (9.09%) | 9 / 114 (7.89%) | 19 / 108 (17.59%) |
| occurrences (all) | 7 | 12 | 32 |
| Hepatobiliary disorders | | | |

| | | | |
|---|------------------------|-------------------------|-------------------------|
| Hyperbilirubinaemia subjects affected / exposed occurrences (all) | 0 / 55 (0.00%) 0 | 2 / 114 (1.75%) 2 | 36 / 108 (33.33%) 56 |
| Jaundice subjects affected / exposed occurrences (all) | 2 / 55 (3.64%) 2 | 5 / 114 (4.39%) 6 | 18 / 108 (16.67%) 19 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia subjects affected / exposed occurrences (all) | 5 / 55 (9.09%) 5 | 11 / 114 (9.65%) 11 | 19 / 108 (17.59%) 19 |
| Dermatitis subjects affected / exposed occurrences (all) | 2 / 55 (3.64%) 4 | 5 / 114 (4.39%) 7 | 0 / 108 (0.00%) 0 |
| Dry skin subjects affected / exposed occurrences (all) | 9 / 55 (16.36%) 9 | 17 / 114 (14.91%) 17 | 16 / 108 (14.81%) 16 |
| Erythema subjects affected / exposed occurrences (all) | 0 / 55 (0.00%) 0 | 0 / 114 (0.00%) 0 | 5 / 108 (4.63%) 5 |
| Hyperhidrosis subjects affected / exposed occurrences (all) | 2 / 55 (3.64%) 3 | 6 / 114 (5.26%) 7 | 3 / 108 (2.78%) 3 |
| Pruritus subjects affected / exposed occurrences (all) | 12 / 55 (21.82%) 14 | 32 / 114 (28.07%) 38 | 32 / 108 (29.63%) 39 |
| Rash subjects affected / exposed occurrences (all) | 6 / 55 (10.91%) 6 | 20 / 114 (17.54%) 22 | 17 / 108 (15.74%) 20 |
| Endocrine disorders | | | |
| Hypothyroidism subjects affected / exposed occurrences (all) | 3 / 55 (5.45%) 3 | 3 / 114 (2.63%) 3 | 14 / 108 (12.96%) 15 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 6 / 55 (10.91%) 9 | 13 / 114 (11.40%) 16 | 9 / 108 (8.33%) 9 |

| | | | |
|------------------------------------|------------------|-------------------|-------------------|
| Back pain | | | |
| subjects affected / exposed | 5 / 55 (9.09%) | 9 / 114 (7.89%) | 10 / 108 (9.26%) |
| occurrences (all) | 5 | 9 | 15 |
| Muscle spasms | | | |
| subjects affected / exposed | 3 / 55 (5.45%) | 6 / 114 (5.26%) | 17 / 108 (15.74%) |
| occurrences (all) | 4 | 8 | 24 |
| Myalgia | | | |
| subjects affected / exposed | 11 / 55 (20.00%) | 26 / 114 (22.81%) | 18 / 108 (16.67%) |
| occurrences (all) | 16 | 32 | 20 |
| Neck pain | | | |
| subjects affected / exposed | 2 / 55 (3.64%) | 5 / 114 (4.39%) | 3 / 108 (2.78%) |
| occurrences (all) | 3 | 6 | 3 |
| Osteopenia | | | |
| subjects affected / exposed | 2 / 55 (3.64%) | 2 / 114 (1.75%) | 6 / 108 (5.56%) |
| occurrences (all) | 2 | 2 | 6 |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 3 / 114 (2.63%) | 5 / 108 (4.63%) |
| occurrences (all) | 2 | 4 | 5 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 3 / 55 (5.45%) | 4 / 114 (3.51%) | 4 / 108 (3.70%) |
| occurrences (all) | 3 | 4 | 7 |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 55 (0.00%) | 2 / 114 (1.75%) | 3 / 108 (2.78%) |
| occurrences (all) | 0 | 2 | 3 |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 55 (1.82%) | 3 / 114 (2.63%) | 6 / 108 (5.56%) |
| occurrences (all) | 1 | 3 | 6 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 55 (7.27%) | 6 / 114 (5.26%) | 6 / 108 (5.56%) |
| occurrences (all) | 4 | 7 | 6 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 55 (3.64%) | 5 / 114 (4.39%) | 9 / 108 (8.33%) |
| occurrences (all) | 2 | 5 | 10 |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|----------------------|-------------------------|-------------------------|
| Decreased appetite subjects affected / exposed occurrences (all) | 8 / 55 (14.55%) 8 | 16 / 114 (14.04%) 17 | 26 / 108 (24.07%) 26 |
| Hypertriglyceridaemia subjects affected / exposed occurrences (all) | 2 / 55 (3.64%) 2 | 4 / 114 (3.51%) 4 | 18 / 108 (16.67%) 23 |

| Non-serious adverse events | Total | | |
|--|---------------------------|--|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 434 / 457 (94.97%) | | |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 73 / 457 (15.97%) 78 | | |
| General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) | 87 / 457 (19.04%) 92 | | |
| Chest pain subjects affected / exposed occurrences (all) | 16 / 457 (3.50%) 16 | | |
| Chills subjects affected / exposed occurrences (all) | 50 / 457 (10.94%) 63 | | |
| Fatigue subjects affected / exposed occurrences (all) | 178 / 457 (38.95%) 198 | | |
| Influenza like illness subjects affected / exposed occurrences (all) | 55 / 457 (12.04%) 67 | | |
| Injection site erythema subjects affected / exposed occurrences (all) | 30 / 457 (6.56%) 33 | | |
| Injection site rash subjects affected / exposed occurrences (all) | 7 / 457 (1.53%) 7 | | |
| Irritability | | | |

| | | | |
|---|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Malaise</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pyrexia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>26 / 457 (5.69%)</p> <p>26</p> <p>29 / 457 (6.35%)</p> <p>40</p> <p>126 / 457 (27.57%)</p> <p>213</p> | | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnoea exertional</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Epistaxis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Oropharyngeal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>112 / 457 (24.51%)</p> <p>126</p> <p>55 / 457 (12.04%)</p> <p>56</p> <p>30 / 457 (6.56%)</p> <p>36</p> <p>21 / 457 (4.60%)</p> <p>26</p> <p>33 / 457 (7.22%)</p> <p>37</p> | | |
| <p>Psychiatric disorders</p> <p>Anxiety</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Depression</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Insomnia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nervousness</p> | <p>44 / 457 (9.63%)</p> <p>45</p> <p>61 / 457 (13.35%)</p> <p>66</p> <p>101 / 457 (22.10%)</p> <p>121</p> | | |

| | | | |
|--------------------------------------|-------------------|--|--|
| subjects affected / exposed | 10 / 457 (2.19%) | | |
| occurrences (all) | 10 | | |
| Restlessness | | | |
| subjects affected / exposed | 15 / 457 (3.28%) | | |
| occurrences (all) | 19 | | |
| Sleep disorder | | | |
| subjects affected / exposed | 11 / 457 (2.41%) | | |
| occurrences (all) | 11 | | |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 11 / 457 (2.41%) | | |
| occurrences (all) | 14 | | |
| Lipase increased | | | |
| subjects affected / exposed | 13 / 457 (2.84%) | | |
| occurrences (all) | 16 | | |
| Total bile acids increased | | | |
| subjects affected / exposed | 18 / 457 (3.94%) | | |
| occurrences (all) | 31 | | |
| Weight decreased | | | |
| subjects affected / exposed | 31 / 457 (6.78%) | | |
| occurrences (all) | 33 | | |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 24 / 457 (5.25%) | | |
| occurrences (all) | 25 | | |
| Nervous system disorders | | | |
| Disturbance in attention | | | |
| subjects affected / exposed | 29 / 457 (6.35%) | | |
| occurrences (all) | 31 | | |
| Dizziness | | | |
| subjects affected / exposed | 71 / 457 (15.54%) | | |
| occurrences (all) | 92 | | |
| Dysgeusia | | | |
| subjects affected / exposed | 26 / 457 (5.69%) | | |
| occurrences (all) | 27 | | |
| Headache | | | |

| | | | |
|--------------------------------------|--------------------|--|--|
| subjects affected / exposed | 185 / 457 (40.48%) | | |
| occurrences (all) | 267 | | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 12 / 457 (2.63%) | | |
| occurrences (all) | 13 | | |
| Memory impairment | | | |
| subjects affected / exposed | 17 / 457 (3.72%) | | |
| occurrences (all) | 18 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 168 / 457 (36.76%) | | |
| occurrences (all) | 270 | | |
| Leukopenia | | | |
| subjects affected / exposed | 62 / 457 (13.57%) | | |
| occurrences (all) | 129 | | |
| Lymphopenia | | | |
| subjects affected / exposed | 18 / 457 (3.94%) | | |
| occurrences (all) | 35 | | |
| Neutropenia | | | |
| subjects affected / exposed | 162 / 457 (35.45%) | | |
| occurrences (all) | 301 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 75 / 457 (16.41%) | | |
| occurrences (all) | 119 | | |
| Eye disorders | | | |
| Dry eye | | | |
| subjects affected / exposed | 19 / 457 (4.16%) | | |
| occurrences (all) | 19 | | |
| Ocular icterus | | | |
| subjects affected / exposed | 30 / 457 (6.56%) | | |
| occurrences (all) | 44 | | |
| Vision blurred | | | |
| subjects affected / exposed | 16 / 457 (3.50%) | | |
| occurrences (all) | 21 | | |
| Gastrointestinal disorders | | | |

| | | | |
|-----------------------------|--------------------|--|--|
| Abdominal distension | | | |
| subjects affected / exposed | 15 / 457 (3.28%) | | |
| occurrences (all) | 18 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 31 / 457 (6.78%) | | |
| occurrences (all) | 33 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 45 / 457 (9.85%) | | |
| occurrences (all) | 49 | | |
| Aphthous stomatitis | | | |
| subjects affected / exposed | 20 / 457 (4.38%) | | |
| occurrences (all) | 26 | | |
| Cheilitis | | | |
| subjects affected / exposed | 12 / 457 (2.63%) | | |
| occurrences (all) | 13 | | |
| Constipation | | | |
| subjects affected / exposed | 36 / 457 (7.88%) | | |
| occurrences (all) | 38 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 61 / 457 (13.35%) | | |
| occurrences (all) | 73 | | |
| Dry mouth | | | |
| subjects affected / exposed | 46 / 457 (10.07%) | | |
| occurrences (all) | 52 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 41 / 457 (8.97%) | | |
| occurrences (all) | 47 | | |
| Mouth ulceration | | | |
| subjects affected / exposed | 27 / 457 (5.91%) | | |
| occurrences (all) | 37 | | |
| Nausea | | | |
| subjects affected / exposed | 161 / 457 (35.23%) | | |
| occurrences (all) | 205 | | |
| Toothache | | | |
| subjects affected / exposed | 12 / 457 (2.63%) | | |
| occurrences (all) | 14 | | |

| | | | |
|--|---------------------------|--|--|
| Vomiting subjects affected / exposed occurrences (all) | 65 / 457 (14.22%) 110 | | |
| Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all) | 71 / 457 (15.54%) 99 | | |
| Jaundice subjects affected / exposed occurrences (all) | 48 / 457 (10.50%) 54 | | |
| Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) | 75 / 457 (16.41%) 75 | | |
| Dermatitis subjects affected / exposed occurrences (all) | 10 / 457 (2.19%) 13 | | |
| Dry skin subjects affected / exposed occurrences (all) | 64 / 457 (14.00%) 70 | | |
| Erythema subjects affected / exposed occurrences (all) | 18 / 457 (3.94%) 18 | | |
| Hyperhidrosis subjects affected / exposed occurrences (all) | 12 / 457 (2.63%) 14 | | |
| Pruritus subjects affected / exposed occurrences (all) | 130 / 457 (28.45%) 171 | | |
| Rash subjects affected / exposed occurrences (all) | 82 / 457 (17.94%) 100 | | |
| Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) | 30 / 457 (6.56%) 32 | | |
| Musculoskeletal and connective tissue | | | |

| | | | |
|-----------------------------------|-------------------|--|--|
| disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 60 / 457 (13.13%) | | |
| occurrences (all) | 67 | | |
| Back pain | | | |
| subjects affected / exposed | 44 / 457 (9.63%) | | |
| occurrences (all) | 53 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 49 / 457 (10.72%) | | |
| occurrences (all) | 61 | | |
| Myalgia | | | |
| subjects affected / exposed | 88 / 457 (19.26%) | | |
| occurrences (all) | 109 | | |
| Neck pain | | | |
| subjects affected / exposed | 13 / 457 (2.84%) | | |
| occurrences (all) | 14 | | |
| Osteopenia | | | |
| subjects affected / exposed | 19 / 457 (4.16%) | | |
| occurrences (all) | 19 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 20 / 457 (4.38%) | | |
| occurrences (all) | 22 | | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 19 / 457 (4.16%) | | |
| occurrences (all) | 23 | | |
| Oral herpes | | | |
| subjects affected / exposed | 16 / 457 (3.50%) | | |
| occurrences (all) | 16 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 16 / 457 (3.50%) | | |
| occurrences (all) | 19 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 29 / 457 (6.35%) | | |
| occurrences (all) | 35 | | |
| Urinary tract infection | | | |

| | | | |
|--|--------------------------|--|--|
| subjects affected / exposed occurrences (all) | 23 / 457 (5.03%) 26 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed occurrences (all) | 96 / 457 (21.01%) 104 | | |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed occurrences (all) | 59 / 457 (12.91%) 68 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 30 November 2010 | The amendment introduced the following change(s): <ul style="list-style-type: none">• Exclusion criteria were changed to make sure women of child-bearing potential used highly effective contraception i.e. total abstinence, sterilization, male partner sterilization, or a combination of two specified methods.• A rationale for birth control to be used in this study was added• Substrates of cytochrome P450 3A for which a clinically important drug-drug interactions with DEB025 could not be excluded because it was not yet investigated (e.g., hormonal contraceptives, etc.) had been added to the list of prohibited treatment |
| 14 December 2010 | The amendment introduced the following change(s): <ul style="list-style-type: none">• Changes were made to the protocol in the inclusion of HCV genotype 1 patients that have relapsed after pegIFNα2a/RBV treatment, as well as the addition of a further treatment arm to allow 400mg BID treatment with the study medication.• inconsistencies and typos in the original protocol were corrected. |
| 26 April 2012 | The amendment introduced the following change(s): <ul style="list-style-type: none">• Patients on treatment with DEB025/placebo in combination with pegIFNα2a /RBV had already been requested to immediately discontinue DEB025/placebo treatment. These patients were asked to continue their treatment with the combination of pegIFNα2a and RBV and to continue in the study as scheduled in the protocol in order to achieve SVR.• All patients were to receive an addendum to the Informed Consent Form they have already signed. The addendum provided the most recent safety information and all patients were expected to sign that they have received and understood the addendum. Investigators were previously sent a safety alert to discontinue patients from DEB025/placebo with triglyceride levels above 350 mg/dL. This alert meanwhile became redundant due to the discontinuation of DEB025/placebo in all patients. However, since patients were still treated with pegIFNα2a, it was recommended that the management of triglyceride levels should follow the ATPIII guideline (NIH 2001).• According to the requirements of the study protocol, all patients who were still on study treatment by 18-Apr-2012, had responded to treatment and had reached a viral load for HCV RNA < 25 IU/mL.• To better understand the benefit-risk profile for the patients, a second Interim Analysis was to be performed on Week 24 data.• Furthermore, investigators were to be unblinded to the HCV RNA data i.e. they would have access to all HCV RNA data from their patients.• End-of-treatment assessments were to be performed at the next visit after DEB025/placebo discontinuation, including bone density X-ray assessments. |
| 14 August 2012 | This amendment was a follow-up to the urgent safety Amendment 3, i.e. the termination of the DEB025/placebo treatment in all patients as a result of the partial clinical hold. As planned at the time protocol Amendment 3 was issued, the protocol sections which were affected were fully updated after the impact of these safety measures had been assessed in detail. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------|--------------|--------------|
|------|--------------|--------------|

| | | |
|---------------|--|---|
| 18 April 2012 | Upon request from the US FDA, the study design was modified to immediately discontinue DEB025/placebo treatment in all patients (urgent safety measure). Patients remained on pegIFNa2a/RBV treatment. | - |
|---------------|--|---|

Notes:

Limitations and caveats

None reported