



Clinical trial results:

A Phase 3b, Randomized, Double-Blind Study to Evaluate Switching from a Regimen Consisting of Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate (EFV/FTC/TDF) Fixed Dose Combination (FDC) to Emtricitabine/Rilpivirine/Tenofovir Alafenamide (FTC/RPV/TAF) FDC in Virologically-Suppressed, HIV-1 Infected Subjects

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2014-004779-21 |
| Trial protocol | DE GB BE ES NL |
| Global end of trial date | 02 January 2019 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 01 January 2020 |
| First version publication date | 01 January 2020 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | GS-US-366-1160 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02345226 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Gilead Sciences |
| Sponsor organisation address | 333 Lakeside Drive, Foster City, CA, United States, 94404 |
| Public contact | Gilead Clinical Study Information Center, Gilead Sciences, Inc., GileadClinicalTrials@gilead.com |
| Scientific contact | Gilead Clinical Study Information Center, Gilead Sciences, Inc., GileadClinicalTrials@gilead.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 02 January 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 29 June 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 02 January 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the non-inferiority of switching to emtricitabine/rilpivirine/tenofovir alafenamide (FTC/RPV/TAF) fixed dose combination (FDC) as compared to continuing the non-nucleoside reverse transcriptase inhibitor (NNRTI) regimen of efavirenz /FTC/tenofovir disoproxil fumarate (EFV/FTC/TDF) FDC in virologically-suppressed HIV-1 infected participants.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 26 January 2015 |
| 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 | Canada: 44 |
| Country: Number of subjects enrolled | Puerto Rico: 18 |
| Country: Number of subjects enrolled | Switzerland: 11 |
| Country: Number of subjects enrolled | United States: 683 |
| Country: Number of subjects enrolled | Spain: 29 |
| Country: Number of subjects enrolled | United Kingdom: 16 |
| Country: Number of subjects enrolled | Belgium: 7 |
| Country: Number of subjects enrolled | France: 13 |
| Country: Number of subjects enrolled | Germany: 60 |
| Worldwide total number of subjects | 881 |
| EEA total number of subjects | 125 |

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) | 849 |
| From 65 to 84 years | 32 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in Europe and North America. The first participant was screened on 26

January 2015. The last study visit occurred on 02 January 2019.

Pre-assignment

Screening details:

974 participants were screened.

Period 1

| | |
|------------------------------|--|
| Period 1 title | Double-Blind Phase |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Carer, Assessor |

Arms

| | |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes |
| Arm title | FTC/RPV/TAF |

Arm description:

Double-Blind Phase: FTC/RPV/TAF (200/25/25 mg) FDC tablet + EFV/FTC/TDF placebo tablet orally once daily for up to 96 weeks.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Emtricitabine/Rilpivirine/Tenofovir Alafenamide |
| Investigational medicinal product code | |
| Other name | FTC/RPV/TAF, Odefsey® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

200/25/25 mg FDC tablets administered orally once daily

| | |
|--|---|
| Investigational medicinal product name | Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Tablets administered orally once daily

| | |
|------------------|-------------|
| Arm title | EFV/FTC/TDF |
|------------------|-------------|

Arm description:

Double-Blind Phase: EFV/FTC/TDF (600/200/300 mg) FDC tablet + FTC/RPV/TAF placebo to match FTC/RPV/TAF tablet orally once daily for up to 96 weeks.

| | |
|--|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate |
| Investigational medicinal product code | |
| Other name | EFV/FTC/TDF, Atripla® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

600/200/300 mg FDC tablets administered orally once daily

| | |
|--|---|
| Investigational medicinal product name | Emtricitabine/Rilpivirine/Tenofovir Alafenamide Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Tablets administered orally once daily

| Number of subjects in period 1^[1] | FTC/RPV/TAF | EFV/FTC/TDF |
|---|-------------|-------------|
| Started | 438 | 437 |
| Completed | 371 | 370 |
| Not completed | 67 | 67 |
| Withdrew Consent | 41 | 39 |
| Adverse Event | 5 | 6 |
| Non-Compliance with Study Drug | 1 | 2 |
| Death | 3 | - |
| Investigator's Discretion | 4 | 3 |
| Pregnancy | - | 1 |
| Lost to follow-up | 12 | 16 |
| Lack of efficacy | 1 | - |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 6 participants (FTC/RPV/TAF: N= 2; EFV/FTC/TDF; N= 4) who were randomized but not treated are not included in the subject disposition table.

Period 2

| | |
|------------------------------|-----------------------------|
| Period 2 title | Open-Label Extension Phase |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|----------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | FTC/RPV/TAF To FTC/RPV/TAF |

Arm description:

Open-Label Extension Phase: After the Week 96 visit, participants were given the option to receive open label FTC/RPV/TAF FDC for up to an additional 48 weeks. In countries where FTC/RPV/TAF FDC was not yet commercially available, participants were given the option to receive open-label FTC/RPV/TAF FDC orally once daily and attend visits every 12 weeks until FTC/RPV/TAF FDC became commercially available, or until Gilead elected to discontinue the study, whichever occurred first.

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

| | |
|---|---|
| Investigational medicinal product name | Emtricitabine/Rilpivirine/Tenofovir Alafenamide |
| Investigational medicinal product code | |
| Other name | FTC/RPV/TAF, Odefsey® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: 200/25/25 mg FDC tablets administered orally once daily | |
| Arm title | EFV/FTC/TDF To FTC/RPV/TAF |

Arm description:

Open-Label Extension Phase: After the Week 96 visit, participants were given the option to receive open label FTC/RPV/TAF FDC for up to an additional 48 weeks. In countries where FTC/RPV/TAF FDC was not yet commercially available, participants were given the option to receive open-label FTC/RPV/TAF FDC orally once daily and attend visits every 12 weeks until FTC/RPV/TAF FDC became commercially available, or until Gilead elected to discontinue the study, whichever occurred first.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Emtricitabine/Rilpivirine/Tenofovir Alafenamide |
| Investigational medicinal product code | |
| Other name | FTC/RPV/TAF, Odefsey® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

200/25/25 mg FDC tablets administered orally once daily

| Number of subjects in period 2^[2] | FTC/RPV/TAF To FTC/RPV/TAF | EFV/FTC/TDF To FTC/RPV/TAF |
|---|----------------------------|----------------------------|
| Started | 25 | 21 |
| Completed | 25 | 20 |
| Not completed | 0 | 1 |
| Lost to follow-up | - | 1 |

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 695 participants (FTC/RPV/TAF: N = 346; EFV/FTC/TDF: N = 349) completed the Double-Blind Phase, but did not enter the Open-Label Extension Phase.

Baseline characteristics

Reporting groups

| | |
|---|-------------|
| Reporting group title | FTC/RPV/TAF |
| Reporting group description: | |
| Double-Blind Phase: FTC/RPV/TAF (200/25/25 mg) FDC tablet + EFV/FTC/TDF placebo tablet orally once daily for up to 96 weeks. | |
| Reporting group title | EFV/FTC/TDF |
| Reporting group description: | |
| Double-Blind Phase: EFV/FTC/TDF (600/200/300 mg) FDC tablet + FTC/RPV/TAF placebo to match FTC/RPV/TAF tablet orally once daily for up to 96 weeks. | |

| Reporting group values | FTC/RPV/TAF | EFV/FTC/TDF | Total |
|-------------------------------------|-------------|-------------|-------|
| Number of subjects | 438 | 437 | 875 |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 48 | 47 | |
| standard deviation | ± 9.8 | ± 10.5 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 373 | 390 | 763 |
| Male | 65 | 47 | 112 |
| Race | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 3 | 2 | 5 |
| Asian | 9 | 8 | 17 |
| Black | 118 | 120 | 238 |
| Native Hawaiian or Pacific Islander | 1 | 0 | 1 |
| White | 291 | 292 | 583 |
| Not Permitted | 6 | 3 | 9 |
| Other | 10 | 12 | 22 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 79 | 78 | 157 |
| Not Hispanic or Latino | 358 | 359 | 717 |
| Not Permitted | 1 | 0 | 1 |
| HIV-1 RNA Category | | | |
| Units: Subjects | | | |
| < 50 copies/mL | 430 | 432 | 862 |
| ≥ 50 copies/mL | 8 | 5 | 13 |
| CD4 Cell Count Category | | | |
| Units: Subjects | | | |
| ≥ 50 to < 200 cells/μL | 2 | 5 | 7 |
| ≥ 200 to < 350 cells/μL | 41 | 26 | 67 |
| ≥ 350 to < 500 cells/μL | 63 | 74 | 137 |
| ≥ 500 cells/ μL | 332 | 332 | 664 |

| | | | |
|-----------------------|-------------|-------------|---|
| CD4 Cell Count | | | |
| Units: cells/ μ L | | | |
| arithmetic mean | 711 | 688 | |
| standard deviation | ± 292.3 | ± 263.5 | - |

End points

End points reporting groups

| | |
|---|----------------------------|
| Reporting group title | FTC/RPV/TAF |
| Reporting group description: Double-Blind Phase: FTC/RPV/TAF (200/25/25 mg) FDC tablet + EFV/FTC/TDF placebo tablet orally once daily for up to 96 weeks. | |
| Reporting group title | EFV/FTC/TDF |
| Reporting group description: Double-Blind Phase: EFV/FTC/TDF (600/200/300 mg) FDC tablet + FTC/RPV/TAF placebo to match FTC/RPV/TAF tablet orally once daily for up to 96 weeks. | |
| Reporting group title | FTC/RPV/TAF To FTC/RPV/TAF |
| Reporting group description: Open-Label Extension Phase: After the Week 96 visit, participants were given the option to receive open label FTC/RPV/TAF FDC for up to an additional 48 weeks. In countries where FTC/RPV/TAF FDC was not yet commercially available, participants were given the option to receive open-label FTC/RPV/TAF FDC orally once daily and attend visits every 12 weeks until FTC/RPV/TAF FDC became commercially available, or until Gilead elected to discontinue the study, whichever occurred first. | |
| Reporting group title | EFV/FTC/TDF To FTC/RPV/TAF |
| Reporting group description: Open-Label Extension Phase: After the Week 96 visit, participants were given the option to receive open label FTC/RPV/TAF FDC for up to an additional 48 weeks. In countries where FTC/RPV/TAF FDC was not yet commercially available, participants were given the option to receive open-label FTC/RPV/TAF FDC orally once daily and attend visits every 12 weeks until FTC/RPV/TAF FDC became commercially available, or until Gilead elected to discontinue the study, whichever occurred first. | |

Primary: Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Week 48 as Defined by the US FDA-defined Snapshot Algorithm

| | |
|---|---|
| End point title | Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Week 48 as Defined by the US FDA-defined Snapshot Algorithm |
| End point description: The percentage of participants achieving HIV-1 RNA < 50 copies/mL at Week 48 was analyzed using the snapshot algorithm, which defines a patient's virologic response status using only the viral load at the predefined time point within an allowed window of time, along with study drug discontinuation status. The Full Analysis Set included participants who were randomized and received at least 1 dose of study drug and were on EFV/FTC/TDF prior to the screening visit. | |
| End point type | Primary |
| End point timeframe: Week 48 | |

| End point values | FTC/RPV/TAF | EFV/FTC/TDF | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 438 | 437 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 90.0 | 92.0 | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Statistical Analysis 1- FTC/RPV/TAF vs EFV/FTC/TDF |
| Statistical analysis description: | |
| The null hypothesis was that the percentage of participants with HIV-1 RNA < 50 copies/mL at Week 48 in the FTC/RPV/TAF group was at least 8% lower than the rate in the EFV/FTC/TDF group; the alternative hypothesis was that the percentage of participants with HIV-1 RNA < 50 copies/mL in FTC/RPV/TAF group was less than 8% lower than that in the EFV/FTC/TDF group. The difference in percentages and its 95.001% CI were calculated based on an unconditional exact method using 2 inverted 1-sided tests. | |
| Comparison groups | FTC/RPV/TAF v EFV/FTC/TDF |
| Number of subjects included in analysis | 875 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[1] |
| Parameter estimate | Difference in Percentages |
| Point estimate | -2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.9 |
| upper limit | 1.8 |

Notes:

[1] - A sample size of 400 HIV-1 infected participants per treatment group would provide 95% power to detect a non-inferiority margin of 8% in the Week 48 response rate difference between the FTC/RPV/TAF group and EFV/FTC/TDF group. For sample size and power computation, it is assumed that both treatment groups will have a response rate of 89% (based on Gilead Study GS-US-292-0109), that a noninferiority margin is 8%, and that the significance level of the test is at a one-sided alpha level of 0.025.

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 2- FTC/RPV/TAF vs EFV/FTC/TDF |
| Comparison groups | FTC/RPV/TAF v EFV/FTC/TDF |
| Number of subjects included in analysis | 875 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.35 |
| Method | Fisher exact |

Secondary: Percentage of Participants With HIV-1 RNA ≥ 50 Copies/mL at Week 48 as Defined by the US FDA-defined Snapshot Algorithm

| | |
|--|---|
| End point title | Percentage of Participants With HIV-1 RNA ≥ 50 Copies/mL at Week 48 as Defined by the US FDA-defined Snapshot Algorithm |
| End point description: | |
| The percentage of participants with HIV-1 RNA ≥ 50 copies/mL at Week 48 was analyzed using the snapshot algorithm, which defines a patient's virologic response status using only the viral load at the predefined time point within an allowed window of time, along with study drug discontinuation status. Participants in the Full Analysis Set were analyzed. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 48 | |

| End point values | FTC/RPV/TAF | EFV/FTC/TDF | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 438 | 437 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 1.1 | 0.9 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HIV-1 RNA \geq 50 Copies/mL at Week 96 as Defined by the US FDA-defined Snapshot Algorithm

| | |
|-----------------|--|
| End point title | Percentage of Participants With HIV-1 RNA \geq 50 Copies/mL at Week 96 as Defined by the US FDA-defined Snapshot Algorithm |
|-----------------|--|

End point description:

The percentage of participants with HIV-1 RNA \geq 50 copies/mL at Week 96 was analyzed using the snapshot algorithm, which defines a patient's virologic response status using only the viral load at the predefined time point within an allowed window of time, along with study drug discontinuation status. Participants in the Full Analysis Set were analyzed.

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

End point timeframe:

Week 96

| End point values | FTC/RPV/TAF | EFV/FTC/TDF | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 438 | 437 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 0.7 | 0.9 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Week 96 as Defined by the US FDA-defined Snapshot

| | |
|-----------------|---|
| End point title | Percentage of Participants With HIV-1 RNA < 50 Copies/mL at Week 96 as Defined by the US FDA-defined Snapshot |
|-----------------|---|

End point description:

The percentage of participants with HIV-1 RNA < 50 copies/mL at Week 96 was analyzed using the snapshot algorithm, which defines a patient's virologic response status using only the viral load at the predefined time point within an allowed window of time, along with study drug discontinuation status. Participants in the Full Analysis Set were analyzed.

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

End point timeframe:

Week 96

| End point values | FTC/RPV/TAF | EFV/FTC/TDF | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 438 | 437 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 85.2 | 85.1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CD4+ Cell Count at Week 48

| | |
|------------------------|---|
| End point title | Change From Baseline in CD4+ Cell Count at Week 48 |
| End point description: | Participants in the Full Analysis Set with on-treatment data were analyzed. |
| End point type | Secondary |
| End point timeframe: | Baseline; Week 48 |

| End point values | FTC/RPV/TAF | EFV/FTC/TDF | | |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 390 | 403 | | |
| Units: cells/ μ L | | | | |
| arithmetic mean (standard deviation) | 23 (\pm 156.4) | 12 (\pm 153.3) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CD4+ Cell Count at Week 96

| | |
|------------------------|---|
| End point title | Change From Baseline in CD4+ Cell Count at Week 96 |
| End point description: | Participants in the Full Analysis Set with on-treatment data were analyzed. |
| End point type | Secondary |
| End point timeframe: | Baseline; Week 96 |

| End point values | FTC/RPV/TAF | EFV/FTC/TDF | | |
|--------------------------------------|-------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 370 | 371 | | |
| Units: cells/ μ L | | | | |
| arithmetic mean (standard deviation) | 12 (\pm 199.8) | 6 (\pm 153.2) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Hip Bone Mineral Density (BMD) at Week 48

| | |
|-----------------|---|
| End point title | Percent Change From Baseline in Hip Bone Mineral Density (BMD) at Week 48 |
|-----------------|---|

End point description:

Hip BMD was assessed by dual energy x-ray absorptiometry (DXA) scan. Participants in the Hip DXA Analysis Set (all randomized participants received at least 1 dose of study drug, and had nonmissing baseline hip BMD value) with available data were analyzed.

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

End point timeframe:

Baseline; Week 48

| End point values | FTC/RPV/TAF | EFV/FTC/TDF | | |
|--------------------------------------|-----------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 347 | 367 | | |
| Units: percentage change | | | | |
| arithmetic mean (standard deviation) | 1.279 (\pm 2.3800) | -0.134 (\pm 2.4930) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Hip BMD at Week 96

| | |
|-----------------|--|
| End point title | Percent Change From Baseline in Hip BMD at Week 96 |
|-----------------|--|

End point description:

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

End point timeframe:

Hip BMD was assessed by DXA scan. Participants in the Hip DXA Analysis Set with available data were analyzed.

| End point values | FTC/RPV/TAF | EFV/FTC/TDF | | |
|--------------------------------------|------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 322 | 345 | | |
| Units: percentage change | | | | |
| arithmetic mean (standard deviation) | 1.831 (± 3.2925) | -0.617 (± 3.3046) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Spine BMD at Week 48

| | |
|---|--|
| End point title | Percent Change From Baseline in Spine BMD at Week 48 |
| End point description: | |
| Spine BMD was assessed by DXA scan. Participants in the Spine DXA Analysis Set (all randomized participants, received at least 1 dose of study drug, and had nonmissing baseline spine BMD values) with available data were analyzed. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline; Week 48 | |

| End point values | FTC/RPV/TAF | EFV/FTC/TDF | | |
|--------------------------------------|------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 351 | 369 | | |
| Units: percentage change | | | | |
| arithmetic mean (standard deviation) | 1.645 (± 3.3198) | -0.045 (± 2.9087) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Spine BMD at Week 96

| | |
|---|--|
| End point title | Percent Change From Baseline in Spine BMD at Week 96 |
| End point description: | |
| | |
| End point type | Secondary |
| End point timeframe: | |
| Spine BMD was assessed by DXA scan. Participants in the Spine DXA Analysis Set with available data were analyzed. | |

| End point values | FTC/RPV/TAF | EFV/FTC/TDF | | |
|--------------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 327 | 344 | | |
| Units: percentage change | | | | |
| arithmetic mean (standard deviation) | 1.701 (\pm 3.6185) | 0.126 (\pm 3.2400) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HIV Symptoms Index Score (HIVSI) at Week 48

| | |
|-----------------|---|
| End point title | Change From Baseline in HIV Symptoms Index Score (HIVSI) at Week 48 |
|-----------------|---|

End point description:

The HIV Symptoms Index was a 20-item, self-reported measure that addressed presence and perceived distress linked to symptoms commonly associated with HIV or its treatment. Twenty HIV symptoms including Fatigue, Fever, Dizziness, Hand/Foot Pain, Memory Loss, Nausea, Diarrhea, Sadness, Nervous/anxious, Sleep Trouble, Skin Problems, Cough, Headache, Appetite Loss, Stomach Pain, Muscle/Joint Pain, Sex Problems, Change in Fat Deposits, Weight Loss, and Hair Loss were assessed. There were 5 possible responses (0 = I don't have this symptom; 1 = It doesn't bother me; 2 = It bothers me a little; 3 = It bothers me; and 4 = It bothers me a lot) for each HIV symptom. Total HIV Symptoms Index Score was derived from all 20 HIV symptoms by counting the number of bothersome symptoms. Total score would be missing if any of the individual items were missing. Participants in the Safety Analysis Set with available data were analyzed.

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

End point timeframe:

Baseline; Week 48

| End point values | FTC/RPV/TAF | EFV/FTC/TDF | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 368 | 383 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 0 (\pm 3.4) | -1 (\pm 3.4) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HIVSI Score at Week 96

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|-----------------|--|
| End point title | Change From Baseline in HIVSI Score at Week 96 |
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End point description:

The HIV Symptoms Index was a 20-item, self-reported measure that addressed presence and perceived distress linked to symptoms commonly associated with HIV or its treatment. Twenty HIV symptoms including Fatigue, Fever, Dizziness, Hand/Foot Pain, Memory Loss, Nausea, Diarrhea, Sadness, Nervous/anxious, Sleep Trouble, Skin Problems, Cough, Headache, Appetite Loss, Stomach Pain,

Muscle/Joint Pain, Sex Problems, Change in Fat Deposits, Weight Loss, and Hair Loss were assessed. There were 5 possible responses (0 = I don't have this symptom; 1 = It doesn't bother me; 2 = It bothers me a little; 3 = It bothers me; and 4 = It bothers me a lot) for each HIV symptom. Total HIV Symptoms Index Score was derived from all 20 HIV symptoms by counting the number of bothersome symptoms. Total score would be missing if any of the individual items were missing. Participants in the Safety Analysis Set with available data were analyzed.

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|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline; Week 96 | |

| End point values | FTC/RPV/TAF | EFV/FTC/TDF | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 347 | 347 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 0 (\pm 4.1) | -1 (\pm 3.3) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose date to last dose date (maximum duration: 172.4 weeks) plus 30 days

Adverse event reporting additional description:

The Safety Analysis Set included participants who were randomized and received at least 1 dose of study drug.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 21.1 |
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Reporting groups

| | |
|-----------------------|----------------------------------|
| Reporting group title | FTC/RPV/TAF (Double-Blind Phase) |
|-----------------------|----------------------------------|

Reporting group description:

Adverse events reported occurred during the Double-Blind Phase in participants from the FTC/RPV/TAF group, who received FTC/RPV/TAF (200/25/25 mg) FDC tablet plus EFV/FTC/TDF placebo tablet administered orally once daily.

| | |
|-----------------------|----------------------------------|
| Reporting group title | EFV/FTC/TDF (Double-Blind Phase) |
|-----------------------|----------------------------------|

Reporting group description:

Adverse events reported occurred during the Double-Blind Phase in participants from the EFV/FTC/TDF group, who received EFV/FTC/TDF (600/200/300 mg) FDC tablet plus FTC/RPV/TAF placebo tablet administered orally once daily.

| | |
|-----------------------|---|
| Reporting group title | Open-Label FTC/RPV/TAF From FTC/RPV/TAF |
|-----------------------|---|

Reporting group description:

Adverse events reported occurred during the Open-Label Extension Phase in participants who enrolled into the Open-Label Extension Phase from the FTC/RPV/TAF group and received FTC/RPV/TAF (200/25/25 mg) FDC tablet once daily.

| | |
|-----------------------|---|
| Reporting group title | Open-Label FTC/RPV/TAF From EFV/FTC/TDF |
|-----------------------|---|

Reporting group description:

Adverse events reported occurred during the Open-Label Extension Phase in participants who enrolled into the Open-Label Extension Phase from the EFV/FTC/TDF group and received FTC/RPV/TAF (200/25/25 mg) FDC tablet once daily.

| Serious adverse events | FTC/RPV/TAF (Double-Blind Phase) | EFV/FTC/TDF (Double-Blind Phase) | Open-Label FTC/RPV/TAF From FTC/RPV/TAF |
|---|--|-------------------------------------|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 54 / 438 (12.33%) | 45 / 437 (10.30%) | 0 / 25 (0.00%) |
| number of deaths (all causes) | 3 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Prostate cancer | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 2 / 438 (0.46%) | 3 / 437 (0.69%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adenosquamous cell lung cancer | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Bronchial carcinoma | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Laryngeal papilloma | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Laryngeal squamous cell carcinoma | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Lymphoma | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Metastases to bone | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Non-small cell lung cancer stage IV | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of the tongue | | | |

| | | | |
|--|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 | | | |
| Aortic dissection | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Peripheral artery aneurysm | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Surgical and medical procedures | | | |
| Ileostomy closure | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Knee arthroplasty | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |

| | | | |
|---|-----------------|-----------------|----------------|
| Chest pain | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Reproductive system and breast disorders | | | |
| Prostatitis | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 | 1 / 438 (0.23%) | 3 / 437 (0.69%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 4 / 438 (0.91%) | 0 / 437 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthma | | | |
| subjects affected / exposed | 2 / 438 (0.46%) | 1 / 437 (0.23%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Pleuritic pain | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Pulmonary infarction | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 failure | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Psychiatric disorders | | | |
| Suicide attempt | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 2 / 437 (0.46%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicidal ideation | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Alcohol abuse | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Alcohol withdrawal syndrome | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Bipolar II disorder | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Delirium | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Drug abuse | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Mental status changes | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Injury, poisoning and procedural complications | | | |
| Overdose | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 2 / 437 (0.46%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Animal bite | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Clavicle fracture | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Fibula fracture | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |

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|---|-----------------|-----------------|----------------|
| Foot fracture | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Limb fracture | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Limb injury | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Multiple fractures | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Post procedural complication | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Road traffic accident | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Tibia fracture | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 2 / 437 (0.46%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 2 / 438 (0.46%) | 0 / 437 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 2 / 438 (0.46%) | 0 / 437 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Pericarditis | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 2 / 437 (0.46%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 438 (0.23%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Aphasia | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Ataxia | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Haemorrhagic anaemia | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 438 (0.46%) | 3 / 437 (0.69%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 2 / 437 (0.46%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine perforation | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 2 / 438 (0.46%) | 0 / 437 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal stenosis | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Incarcerated inguinal hernia | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Nausea | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Oesophageal ulcer | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Rectal perforation | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 2 / 438 (0.46%) | 0 / 437 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Skin and subcutaneous tissue disorders | | | |
| Angioedema | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 3 / 437 (0.69%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fanconi syndrome acquired | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Ureterolithiasis | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |

| | | | |
|---|-----------------|-----------------|----------------|
| Pathological fracture | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 5 / 438 (1.14%) | 3 / 437 (0.69%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Necrotising fasciitis | | | |
| subjects affected / exposed | 3 / 438 (0.68%) | 0 / 437 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 2 / 437 (0.46%) | 0 / 25 (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 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 2 / 437 (0.46%) | 0 / 25 (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 |
| Diarrhoea infectious | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Diverticulitis | | | |
| subjects affected / exposed | 2 / 438 (0.46%) | 0 / 437 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Localised infection | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Osteomyelitis | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 438 (0.00%) | 2 / 437 (0.46%) | 0 / 25 (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 |
| Sepsis | | | |
| subjects affected / exposed | 2 / 438 (0.46%) | 0 / 437 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Abdominal abscess | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Abscess | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Bacterial parotitis | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Cellulitis orbital | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Cellulitis staphylococcal | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Escherichia bacteraemia | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Gastroenteritis salmonella | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Gastroenteritis shigella | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Infectious colitis | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Orchitis | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Perineal abscess | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Scrotal infection | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (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 |
| Stoma site abscess | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 438 (0.23%) | 0 / 437 (0.00%) | 0 / 25 (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 |
| Metabolic acidosis | | | |
| subjects affected / exposed | 0 / 438 (0.00%) | 1 / 437 (0.23%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Open-Label FTC/RPV/TAF From EFV/FTC/TDF | | |
|---|---|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Prostate cancer | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed | 0 / 21 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Adenosquamous cell lung cancer | | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bronchial carcinoma | | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Laryngeal papilloma | | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Laryngeal squamous cell carcinoma | | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lymphoma | | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Metastases to bone | | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Non-small cell lung cancer stage IV | | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Squamous cell carcinoma of the tongue | | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Aortic dissection | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral artery aneurysm | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Ileostomy closure | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Knee arthroplasty | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Chest pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Prostatitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleuritic pain | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary infarction | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Alcohol abuse | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Alcohol withdrawal syndrome | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bipolar II disorder | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Delirium | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug abuse | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mental status changes | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Overdose | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Animal bite | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Clavicle fracture | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fibula fracture | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|----------------|--|--|--|
| Foot fracture | | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Limb fracture | | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Limb injury | | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Multiple fractures | | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Post procedural complication | | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Road traffic accident | | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tibia fracture | | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac disorders | | | | |
| Atrial fibrillation | | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Coronary artery disease | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient ischaemic attack | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aphasia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ataxia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Haemorrhagic anaemia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Large intestine perforation | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anal stenosis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Incarcerated inguinal hernia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oesophageal ulcer | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal perforation | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Angioedema | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fanconi syndrome acquired | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ureterolithiasis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Pathological fracture | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Necrotising fasciitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea infectious | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Localised infection | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteomyelitis | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abscess | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bacterial parotitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cellulitis orbital | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cellulitis staphylococcal | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Escherichia bacteraemia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis salmonella | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis shigella | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infectious colitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Orchitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Perineal abscess | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Scrotal infection | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Stoma site abscess | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | FTC/RPV/TAF (Double-Blind Phase) | EFV/FTC/TDF (Double-Blind Phase) | Open-Label FTC/RPV/TAF From FTC/RPV/TAF |
|---|--|-------------------------------------|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 277 / 438 (63.24%) | 270 / 437 (61.78%) | 13 / 25 (52.00%) |
| Vascular disorders | | | |
| Hypertension | | | |

| | | | |
|---|--|---|---|
| subjects affected / exposed occurrences (all) | 25 / 438 (5.71%) 25 | 16 / 437 (3.66%) 16 | 1 / 25 (4.00%) 1 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 35 / 438 (7.99%) 41 | 31 / 437 (7.09%) 38 | 1 / 25 (4.00%) 1 |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) | 41 / 438 (9.36%) 44 23 / 438 (5.25%) 25 22 / 438 (5.02%) 22 | 47 / 437 (10.76%) 54 16 / 437 (3.66%) 17 13 / 437 (2.97%) 13 | 1 / 25 (4.00%) 1 0 / 25 (0.00%) 0 0 / 25 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 45 / 438 (10.27%) 52 | 30 / 437 (6.86%) 32 | 2 / 25 (8.00%) 2 |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Eczema subjects affected / exposed occurrences (all) | 24 / 438 (5.48%) 25 4 / 438 (0.91%) 4 | 16 / 437 (3.66%) 16 2 / 437 (0.46%) 2 | 0 / 25 (0.00%) 0 0 / 25 (0.00%) 0 |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 26 / 438 (5.94%) 26 | 23 / 437 (5.26%) 23 | 0 / 25 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain | 34 / 438 (7.76%) 36 | 42 / 437 (9.61%) 43 | 0 / 25 (0.00%) 0 |

| | | | |
|---|--------------------------|-------------------------|----------------------|
| subjects affected / exposed occurrences (all) | 35 / 438 (7.99%) 37 | 37 / 437 (8.47%) 41 | 1 / 25 (4.00%) 1 |
| Pain in extremity subjects affected / exposed occurrences (all) | 28 / 438 (6.39%) 29 | 15 / 437 (3.43%) 18 | 0 / 25 (0.00%) 0 |
| Infections and infestations | | | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 74 / 438 (16.89%) 107 | 70 / 437 (16.02%) 96 | 1 / 25 (4.00%) 1 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 51 / 438 (11.64%) 67 | 39 / 437 (8.92%) 58 | 3 / 25 (12.00%) 3 |
| Syphilis subjects affected / exposed occurrences (all) | 39 / 438 (8.90%) 45 | 31 / 437 (7.09%) 39 | 0 / 25 (0.00%) 0 |
| Sinusitis subjects affected / exposed occurrences (all) | 23 / 438 (5.25%) 30 | 32 / 437 (7.32%) 38 | 1 / 25 (4.00%) 1 |
| Bronchitis subjects affected / exposed occurrences (all) | 24 / 438 (5.48%) 29 | 28 / 437 (6.41%) 34 | 2 / 25 (8.00%) 2 |
| Pharyngitis subjects affected / exposed occurrences (all) | 12 / 438 (2.74%) 12 | 19 / 437 (4.35%) 20 | 2 / 25 (8.00%) 2 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 22 / 438 (5.02%) 27 | 7 / 437 (1.60%) 9 | 0 / 25 (0.00%) 0 |
| Rhinitis subjects affected / exposed occurrences (all) | 5 / 438 (1.14%) 11 | 7 / 437 (1.60%) 8 | 4 / 25 (16.00%) 4 |

| | | | |
|---|---|--|--|
| Non-serious adverse events | Open-Label FTC/RPV/TAF From EFV/FTC/TDF | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 9 / 21 (42.86%) | | |
| Vascular disorders | | | |

| | | | |
|---|---|--|--|
| Hypertension subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 0 / 21 (0.00%) 0 0 / 21 (0.00%) 0 | | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 | | |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Eczema subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 2 / 21 (9.52%) 2 | | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain | 1 / 21 (4.76%) 3 | | |

| | | | |
|-----------------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | | |
| occurrences (all) | 1 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | | |
| occurrences (all) | 1 | | |
| Syphilis | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | | |
| occurrences (all) | 2 | | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences (all) | 0 | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | | |
| occurrences (all) | 1 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| occurrences (all) | 0 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 15 January 2015 | <ul style="list-style-type: none">• The inclusion criterion relating to documented resistance was expanded to include thymidine analog-associated mutations (TAMs).• The assessment window for a repeat HIV-1 RNA test if viral load was ≥ 50 copies/mL was changed to 2 to 4 weeks. |
| 09 September 2015 | <ul style="list-style-type: none">• The study design was changed to allow subjects in the UK to participate in the open-label phase.• It was specified that pharmacokinetic (PK) blood samples did not have to be collected in a fasted state.• The inclusion criterion relating to women of nonchildbearing potential was corrected.• It was clarified that if initial DXA scans were not collected before study drug administration at baseline/Day 1 or if the scan was not acceptable, subsequent scans were not required. Also, if either the hip or spine DXA scan was not collected at baseline/Day 1, subsequent scans were expected to contain only the region (ie, hip and/or spine) that was scanned successfully at the baseline/Day 1 visit.• The management of changes in BMD by investigators was clarified. |
| 13 April 2016 | <ul style="list-style-type: none">• The blinded phase of the study was extended from 48 weeks to 96 weeks, with corresponding changes to the study assessments.• A secondary objective was added to evaluate the efficacy, safety, and tolerability of the 2 treatment groups through Week 96, and other secondary objectives were revised to include assessment at Week 96 (as well as at Week 48).• Secondary efficacy endpoints were added to calculate the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Weeks 48 and 96, and the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 96, as determined by the US FDA-defined snapshot algorithm. The secondary efficacy endpoint for change from baseline in CD4 cell count was revised to include assessment at Week 96 (as well as at Week 48).• The definitions of the Full Analysis Set (FAS) and Per Protocol (PP) Analysis Set were expanded to include subjects who were receiving ATR prior to the screening visit. Further details were included on the exclusion criteria for the Week 48 PP Analysis Set.• It was specified that, on an ongoing basis, adverse events (AEs) would be reviewed for events that might meet the definition of a Stage 3 opportunistic illness of an AIDS-defining diagnosis. |
| 19 March 2018 | <ul style="list-style-type: none">• Updated Study Design, Study Procedures/Frequency, and Duration of Treatment to include extension of open-label FTC/RPV/TAF FDC availability post Open-Label Week 48 for countries where FTC/RPV/TAF FDC is not yet commercially available.• Safety of TAF for bone mineral density is well established. Continuing DXA exams in open-label phase would not provide a significant safety benefit so Bone evaluation was updated to clarify that DXA scans are not required after Open-Label Week 24 visit. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30101539>

<http://www.ncbi.nlm.nih.gov/pubmed/28259776>