



Clinical trial results:

A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Tenofovir Alafenamide (TAF) 25 mg QD versus Tenofovir Disoproxil Fumarate (TDF) 300 mg QD for the Treatment of HBeAg-Negative, Chronic Hepatitis B

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2013-000626-63 |
| Trial protocol | IT GB DE ES PL |
| Global end of trial date | |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 |
| This version publication date | 21 September 2023 |
| First version publication date | 21 September 2023 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | GS-US-320-0108 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01940341 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | NCT02836236: ClinicalTrials.gov identifier (NCT number) |

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, GileadClinicalTrials@gilead.com |
| Scientific contact | Gilead Clinical Study Information Center, Gilead Sciences, 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 | Interim |
| Date of interim/final analysis | 31 August 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 30 September 2015 |
| Global end of trial reached? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare the efficacy, safety, and tolerability of tenofovir alafenamide (TAF) versus tenofovir disoproxil fumarate (TDF) in treatment-naïve and treatment-experienced adults with hepatitis B e antigen (HBeAg)-negative chronic hepatitis B virus (HBV) infection. Results presented include Week 384 final data for the main study (Global cohorts) and Week 48 interim data for China study.

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:

This study was conducted globally in multiple countries including China. As enrollment began later on clinicaltrials.gov, it has separately registered. Global study has NCT identifier - NCT01940341 and China study has identifier - NCT02836236.

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 12 September 2013 |
| 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 | China: 155 |
| Country: Number of subjects enrolled | Hong Kong: 69 |
| Country: Number of subjects enrolled | Canada: 46 |
| Country: Number of subjects enrolled | Korea, Republic of: 46 |
| Country: Number of subjects enrolled | Taiwan: 37 |
| Country: Number of subjects enrolled | United States: 37 |
| Country: Number of subjects enrolled | Russian Federation: 35 |
| Country: Number of subjects enrolled | India: 33 |
| Country: Number of subjects enrolled | Japan: 27 |
| Country: Number of subjects enrolled | Romania: 21 |
| Country: Number of subjects enrolled | Poland: 18 |
| Country: Number of subjects enrolled | Turkey: 14 |
| Country: Number of subjects enrolled | New Zealand: 12 |
| Country: Number of subjects enrolled | Australia: 10 |

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Italy: 9 |
| Country: Number of subjects enrolled | United Kingdom: 6 |
| Country: Number of subjects enrolled | France: 3 |
| Country: Number of subjects enrolled | Spain: 3 |
| Worldwide total number of subjects | 581 |
| EEA total number of subjects | 54 |

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) | 564 |
| From 65 to 84 years | 17 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in East Asia, Europe, North America, Australia, India, and New Zealand.

Pre-assignment

Screening details:

877 participants were screened in global cohorts and 239 participants were screened in China cohort.

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 |

Arms

| | |
|------------------------------|--------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | TAF 25 mg (Global) |

Arm description:

TAF 25 mg tablet + TDF placebo tablet once daily for up to 96 weeks (per amendment 1 & 2) or 144 weeks (per amendment 3).

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tenofovir alafenamide |
| Investigational medicinal product code | |
| Other name | TAF, Vemlidy® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

25 mg administered once daily.

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

Dosage and administration details:

Administered once daily.

| | |
|------------------|---------------------|
| Arm title | TDF 300 mg (Global) |
|------------------|---------------------|

Arm description:

TDF 300 mg tablet + TAF placebo tablet once daily for up to 96 weeks (per amendment 1 & 2) or 144 weeks (per amendment 3).

| | |
|--|-------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Tenofovir disoproxil fumarate |
| Investigational medicinal product code | |
| Other name | TDF, Viread® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

300 mg administered once daily.

| | |
|--|-------------------------------|
| Investigational medicinal product name | TAF placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: Administered once daily. | |
| Arm title | TAF 25 mg (China) |
| Arm description: TAF 25 mg tablet + TDF placebo tablet once daily for up to 144 weeks. | |
| Arm type | Experimental |
| Investigational medicinal product name | Tenofovir alafenamide |
| Investigational medicinal product code | |
| Other name | TAF, Vemlidy® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: 25 mg administered once daily. | |
| Investigational medicinal product name | TDF placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: Administered once daily. | |
| Arm title | TDF 300 mg (China) |
| Arm description: TDF 300 mg tablet + TAF placebo tablet once daily for up to 144 weeks. | |
| Arm type | Active comparator |
| Investigational medicinal product name | Tenofovir disoproxil fumarate |
| Investigational medicinal product code | |
| Other name | TDF, Viread® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: 300 mg administered once daily. | |
| Investigational medicinal product name | TAF placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: Administered once daily. | |

| Number of subjects in period 1 ^[1] | TAF 25 mg (Global) | TDF 300 mg (Global) | TAF 25 mg (China) |
|---|--------------------|---------------------|-------------------|
| Started | 285 | 140 | 104 |
| Completed | 261 | 129 | 0 |
| Not completed | 24 | 11 | 104 |
| Withdrew Consent | 7 | 4 | 2 |
| Protocol specified criteria for withdrawal | 1 | - | - |
| Death | - | 1 | - |
| Adverse event | 4 | 2 | - |
| Non-compliance with study drug | 1 | 1 | - |
| Lost to follow-up | 8 | 1 | - |
| Investigator's discretion | 3 | 1 | 1 |
| Continuing Study | - | - | 101 |
| Pregnancy | - | 1 | - |

| Number of subjects in period 1 ^[1] | TDF 300 mg (China) |
|---|--------------------|
| Started | 50 |
| Completed | 0 |
| Not completed | 50 |
| Withdrew Consent | - |
| Protocol specified criteria for withdrawal | - |
| Death | - |
| Adverse event | 1 |
| Non-compliance with study drug | - |
| Lost to follow-up | - |
| Investigator's discretion | - |
| Continuing Study | 49 |
| Pregnancy | - |

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: Global study - One participant randomised to TDF arm did not receive treatment.

China study - One participant randomised to TAF arm did not receive treatment.

Period 2

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

Arms

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

| | |
|---|----------------------------------|
| Arm title | TAF 25 mg to TAF 25 mg (Global) |
| Arm description: | |
| After Week 96 or 144 in the Blinded Treatment Phase, participants were given the option to continue with Open-label (OL) TAF 25 mg for additional 288 or 240 weeks (Up to Week 384), respectively. | |
| After the completion of OL TAF Extension Phase treatment or when there was early discontinuation of treatment, participants either switched to commercially available anti-HBV treatments in their country or entered follow-up phase and were followed-up every 4 weeks for 24 weeks off treatment (treatment-free follow-up [TFFU]) for the assessment of safety. | |
| Arm type | Experimental |
| Investigational medicinal product name | Tenofovir alafenamide |
| Investigational medicinal product code | |
| Other name | TAF, Vemlidy® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 25 mg administered once daily. | |
| Investigational medicinal product name | TDF placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Administered once daily. | |
| Arm title | TDF 300 mg to TAF 25 mg (Global) |

Arm description:

After Week 96 or 144 in the Blinded Treatment Phase, participants were given the option to switch to OL TAF 25 mg for additional 288 or 240 weeks (Up to Week 384), respectively.

After the completion of OL TAF Extension Phase treatment or when there was early discontinuation of treatment, participants either switched to commercially available anti-HBV treatments in their country or entered follow-up phase and were followed-up every 4 weeks for 24 weeks off treatment (TFFU) for the assessment of safety.

| | |
|--|-------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Tenofovir disoproxil fumarate |
| Investigational medicinal product code | |
| Other name | TDF, Viread® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 300 mg administered once daily. | |
| Investigational medicinal product name | TAF placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Administered once daily.

| Number of subjects in period 2 | TAF 25 mg to TAF 25 mg (Global) | TDF 300 mg to TAF 25 mg (Global) |
|--|--|---|
| Started | 261 | 129 |
| Completed | 227 | 118 |
| Not completed | 34 | 11 |
| Withdrew Consent | 17 | 4 |
| Lost to follow-up | 6 | - |
| Protocol specified criteria for withdrawal | 3 | 1 |
| Death | 1 | - |
| Pregnancy | - | 1 |
| Adverse event | 2 | - |
| Non-compliance with study drug | - | 1 |
| Investigator's discretion | 3 | 4 |
| Progressive disease | 1 | - |
| Hbsag seroconversion | 1 | - |

Baseline characteristics

Reporting groups

| | |
|--|---------------------|
| Reporting group title | TAF 25 mg (Global) |
| Reporting group description: TAF 25 mg tablet + TDF placebo tablet once daily for up to 96 weeks (per amendment 1 & 2) or 144 weeks (per amendment 3). | |
| Reporting group title | TDF 300 mg (Global) |
| Reporting group description: TDF 300 mg tablet + TAF placebo tablet once daily for up to 96 weeks (per amendment 1 & 2) or 144 weeks (per amendment 3). | |
| Reporting group title | TAF 25 mg (China) |
| Reporting group description: TAF 25 mg tablet + TDF placebo tablet once daily for up to 144 weeks. | |
| Reporting group title | TDF 300 mg (China) |
| Reporting group description: TDF 300 mg tablet + TAF placebo tablet once daily for up to 144 weeks. | |

| Reporting group values | TAF 25 mg (Global) | TDF 300 mg (Global) | TAF 25 mg (China) |
|---|--------------------|---------------------|-------------------|
| Number of subjects | 285 | 140 | 104 |
| Age categorical | | | |
| Units: Subjects | | | |
| <=18 years | 0 | 0 | 0 |
| Between 18 and 65 years | 276 | 136 | 102 |
| >=65 years | 9 | 4 | 2 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 45 | 48 | 42 |
| standard deviation | ± 11.6 | ± 10.4 | ± 9.9 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 112 | 54 | 30 |
| Male | 173 | 86 | 74 |
| Race | | | |
| Units: Subjects | | | |
| Asian | 205 | 102 | 104 |
| White | 71 | 35 | 0 |
| Black or African American | 5 | 3 | 0 |
| Other or More Than One Race | 2 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 2 | 0 | 0 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Not Hispanic or Latino | 279 | 140 | 104 |
| Unknown or Not Reported | 4 | 0 | 0 |
| Hispanic or Latino | 2 | 0 | 0 |
| IL28B Genotype | | | |
| The CC, CT, and TT alleles are different forms of the IL28b gene. | | | |
| Units: Subjects | | | |
| CC | 209 | 106 | 94 |

| | | | |
|---|--------|--------|--------|
| CT | 65 | 23 | 8 |
| TT | 10 | 9 | 1 |
| Missing | 1 | 2 | 1 |
| Plasma HBV DNA Level Units: Subjects | | | |
| < 7 log10 IU/mL | 230 | 116 | 77 |
| >= 7 log10 IU/mL - < 8 log10 IU/mL | 42 | 20 | 21 |
| >= 8 log10 IU/mL | 13 | 4 | 6 |
| Oral Antiviral Treatment Status Units: Subjects | | | |
| Treatment Experienced | 60 | 31 | 41 |
| Treatment Naive | 225 | 109 | 63 |
| Proteinuria by Urinalysis (dipstick) Units: Subjects | | | |
| Grade 0 | 270 | 135 | 101 |
| Grade 1 | 13 | 5 | 3 |
| Grade 2 | 2 | 0 | 0 |
| Grade 3 | 0 | 0 | 0 |
| HBV DNA Units: log10 IU/mL | | | |
| arithmetic mean | 5.7 | 5.8 | 5.5 |
| standard deviation | ± 1.34 | ± 1.32 | ± 1.73 |

| Reporting group values | TDF 300 mg (China) | Total | |
|---|--------------------|-------|--|
| Number of subjects | 50 | 579 | |
| Age categorical Units: Subjects | | | |
| <=18 years | 0 | 0 | |
| Between 18 and 65 years | 48 | 562 | |
| >=65 years | 2 | 17 | |
| Age continuous Units: years | | | |
| arithmetic mean | 45 | - | |
| standard deviation | ± 11.2 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 12 | 208 | |
| Male | 38 | 371 | |
| Race Units: Subjects | | | |
| Asian | 50 | 461 | |
| White | 0 | 106 | |
| Black or African American | 0 | 8 | |
| Other or More Than One Race | 0 | 2 | |
| Native Hawaiian or Other Pacific Islander | 0 | 2 | |
| Ethnicity Units: Subjects | | | |
| Not Hispanic or Latino | 50 | 573 | |
| Unknown or Not Reported | 0 | 4 | |
| Hispanic or Latino | 0 | 2 | |

| | | | |
|---|--------|-----|--|
| IL28B Genotype | | | |
| The CC, CT, and TT alleles are different forms of the IL28b gene. | | | |
| Units: Subjects | | | |
| CC | 39 | 448 | |
| CT | 10 | 106 | |
| TT | 1 | 21 | |
| Missing | 0 | 4 | |
| Plasma HBV DNA Level | | | |
| Units: Subjects | | | |
| < 7 log10 IU/mL | 39 | 462 | |
| >= 7 log10 IU/mL - < 8 log10 IU/mL | 10 | 93 | |
| >= 8 log10 IU/mL | 1 | 24 | |
| Oral Antiviral Treatment Status | | | |
| Units: Subjects | | | |
| Treatment Experienced | 20 | 152 | |
| Treatment Naive | 30 | 427 | |
| Proteinuria by Urinalysis (dipstick) | | | |
| Units: Subjects | | | |
| Grade 0 | 48 | 554 | |
| Grade 1 | 2 | 23 | |
| Grade 2 | 0 | 2 | |
| Grade 3 | 0 | 0 | |
| HBV DNA | | | |
| Units: log10 IU/mL | | | |
| arithmetic mean | 5.3 | | |
| standard deviation | ± 1.63 | - | |

End points

End points reporting groups

| | |
|---|----------------------------------|
| Reporting group title | TAF 25 mg (Global) |
| Reporting group description: TAF 25 mg tablet + TDF placebo tablet once daily for up to 96 weeks (per amendment 1 & 2) or 144 weeks (per amendment 3). | |
| Reporting group title | TDF 300 mg (Global) |
| Reporting group description: TDF 300 mg tablet + TAF placebo tablet once daily for up to 96 weeks (per amendment 1 & 2) or 144 weeks (per amendment 3). | |
| Reporting group title | TAF 25 mg (China) |
| Reporting group description: TAF 25 mg tablet + TDF placebo tablet once daily for up to 144 weeks. | |
| Reporting group title | TDF 300 mg (China) |
| Reporting group description: TDF 300 mg tablet + TAF placebo tablet once daily for up to 144 weeks. | |
| Reporting group title | TAF 25 mg to TAF 25 mg (Global) |
| Reporting group description: After Week 96 or 144 in the Blinded Treatment Phase, participants were given the option to continue with Open-label (OL) TAF 25 mg for additional 288 or 240 weeks (Up to Week 384), respectively. After the completion of OL TAF Extension Phase treatment or when there was early discontinuation of treatment, participants either switched to commercially available anti-HBV treatments in their country or entered follow-up phase and were followed-up every 4 weeks for 24 weeks off treatment (treatment-free follow-up [TFFU]) for the assessment of safety. | |
| Reporting group title | TDF 300 mg to TAF 25 mg (Global) |
| Reporting group description: After Week 96 or 144 in the Blinded Treatment Phase, participants were given the option to switch to OL TAF 25 mg for additional 288 or 240 weeks (Up to Week 384), respectively. After the completion of OL TAF Extension Phase treatment or when there was early discontinuation of treatment, participants either switched to commercially available anti-HBV treatments in their country or entered follow-up phase and were followed-up every 4 weeks for 24 weeks off treatment (TFFU) for the assessment of safety. | |

Primary: Percentage of Participants with Hepatitis B Virus (HBV) DNA < 29 IU/mL (Missing = Failure)

| | |
|---|--|
| End point title | Percentage of Participants with Hepatitis B Virus (HBV) DNA < 29 IU/mL (Missing = Failure) |
| End point description: Full Analysis Set included participants who were randomized into the study and received at least 1 dose of study drugs. Participants were analyzed according to the treatment to which they were randomized. A Missing = Failure approach was employed for the efficacy endpoints, in which all missing data will be treated as not achieving the endpoint. | |
| End point type | Primary |
| End point timeframe: Week 48 | |

| End point values | TAF 25 mg (Global) | TDF 300 mg (Global) | TAF 25 mg (China) | TDF 300 mg (China) |
|-----------------------------------|--------------------|---------------------|-------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 285 | 140 | 104 | 50 |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 94.0 | 92.9 | 89.4 | 98.0 |

Statistical analyses

| Statistical analysis title | Participants with HBV DNA < 29 IU/mL at Week 48 |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

The null hypothesis was that the TAF group is at least 10% worse than the TDF group with respect to the proportion of participants with HBV DNA < 29 IU/mL at Week 48. The alternative hypothesis was that the TAF group is less than 10% worse than the TDF group with respect to the proportion of participants with HBV DNA < 29 IU/mL at Week 48. Noninferiority was assessed using a 95% CI, with a noninferiority margin of 10%. Data adjusted by baseline HBV DNA categories+oral antiviral treatment status.

| | |
|---|--|
| Comparison groups | TAF 25 mg (Global) v TDF 300 mg (Global) |
| Number of subjects included in analysis | 425 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[1] |
| Parameter estimate | Difference in percentage of participants |
| Point estimate | 1.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.6 |
| upper limit | 7.2 |

Notes:

[1] - Sample sizes of 130 and 260 participants in the TDF and TAF groups, respectively, were planned to give 84% power to rule out the noninferiority margin of 10% at a 1-sided significance level of 0.025. This sample size based on the assumption that expected difference (TAF–TDF) in proportion of participants with HBV DNA < 29 IU/mL was 0 and the proportion of participants with HBV DNA < 29 IU/mL in TDF group=69%. Missing data=not achieving the primary endpoint.

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:

Participants in the Hip Dual-Energy X-ray Absorptiometry (DXA) Analysis Set (participants who were randomized, received at least 1 dose of study drugs, and had nonmissing baseline hip BMD values) with available data were analyzed. Participants were analyzed according to the treatment they actually received. Missing data were excluded from analysis.

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

End point timeframe:

Baseline, Week 48

| End point values | TAF 25 mg (Global) | TDF 300 mg (Global) | TAF 25 mg (China) | TDF 300 mg (China) |
|--------------------------------------|--------------------|---------------------|-------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 270 | 133 | 39 | 22 |
| Units: Percentage change | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change at Week 48 | -0.288 (± 2.1448) | -2.156 (± 2.1672) | -0.718 (± 2.0131) | -1.096 (± 2.9200) |

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: | |
| Participants in the Spine DXA Analysis Set (participants who were randomized, received at least 1 dose of study drugs, and had nonmissing baseline spine BMD values) with available data were analyzed. Participants were analyzed according to the treatment they actually received. Missing data were excluded from analysis. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 48 | |

| End point values | TAF 25 mg (Global) | TDF 300 mg (Global) | TAF 25 mg (China) | TDF 300 mg (China) |
|--------------------------------------|--------------------|---------------------|-------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 271 | 133 | 39 | 22 |
| Units: Percentage change | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change at Week 48 | -0.876 (± 2.8558) | -2.514 (± 3.3558) | 0.740 (± 3.3764) | -3.456 (± 3.1071) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Serum Creatinine at Week 48

| | |
|---|---|
| End point title | Change From Baseline in Serum Creatinine at Week 48 |
| End point description: | |
| Participants in the Safety Analysis Set (participants who were randomized into the study and received at least 1 dose of study drug) with available data were analyzed. Participants were analyzed according to the treatment they actually received. Missing data were excluded from analysis. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 48 | |

| End point values | TAF 25 mg (Global) | TDF 300 mg (Global) | TAF 25 mg (China) | TDF 300 mg (China) |
|--------------------------------------|-----------------------|------------------------|----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 275 | 135 | 101 | 49 |
| Units: Percentage change | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change at Week 48 | 0.01 (± 0.092) | 0.02 (± 0.103) | 0.012 (± 0.0827) | 0.030 (± 0.0754) |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Participants With Treatment-emergent Proteinuria by Urinalysis (Dipstick) Through Week 48

| | |
|-----------------|---|
| End point title | Percentage of Participants With Treatment-emergent Proteinuria by Urinalysis (Dipstick) Through Week 48 |
|-----------------|---|

End point description:

Grades 1 (mild), 2 (moderate), and 3 (severe) were the highest treatment-emergent postbaseline grades for urine protein using the dipstick method. Participants in the Safety Analysis Set with at least 1 postbaseline urine protein value were analyzed.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Up to 48 weeks

| End point values | TAF 25 mg (Global) | TDF 300 mg (Global) | TAF 25 mg (China) | TDF 300 mg (China) |
|-----------------------------------|-----------------------|------------------------|----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 282 | 140 | 102 | 50 |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Grade 1 | 18.1 | 16.4 | 21.6 | 18.0 |
| Grade 2 | 1.1 | 2.1 | 2.9 | 4.0 |
| Grade 3 | 0 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Deaths: For Global cohorts: Randomization up to approximately 427.6 weeks. For China Cohort: Up to Week 48 Data cut; Adverse events - For Global cohorts: First dose date up to Week 384. For China Cohort: Up to Week 48 Data cut

Adverse event reporting additional description:

All-cause mortality: Randomized Analysis Set: All participants randomized into the study. Adverse events: Safety Analysis Set: Participants who received at least 1 dose of study drug in the respective period.

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

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 22 |
|--------------------|----|

Reporting groups

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| Reporting group title | TAF 25 mg (Global) |
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Reporting group description:

TAF 25 mg tablet + TDF placebo tablet once daily for up to 96 weeks (per amendment 1 & 2) or 144 weeks (per amendment 3).

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|-----------------------|---------------------|
| Reporting group title | TDF 300 mg (Global) |
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Reporting group description:

TDF 300 mg tablet + TAF placebo tablet once daily for up to 96 weeks (per amendment 1 & 2) or 144 weeks (per amendment 3).

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| Reporting group title | TAF 25 mg to TAF 25 mg (Global) |
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Reporting group description:

After Week 144 in the Blinded Treatment Phase, participants were given the option to continue with OL TAF for additional 288 or 240 weeks (Up to Week 384).

After the end of treatment in OL phase or Blinded Treatment Phase, participants either switched to commercially available anti-HBV treatments in their country or entered follow-up phase and were followed-up every 4 weeks for 24 weeks for the assessment of safety.

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| Reporting group title | TDF 300 mg (China) |
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Reporting group description:

TAF 25 mg tablet + TDF placebo tablet once daily for up to 144 weeks.

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| Reporting group title | TDF 300 mg to TAF 25 mg (Global) |
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Reporting group description:

After Week 144 in the Blinded Treatment Phase, participants were given the option to switch to Open-label (OL) TAF for additional 288 or 240 weeks (Up to Week 384).

After the end of treatment in OL phase or Blinded Treatment Phase, participants either switched to commercially available anti-HBV treatments in their country or entered follow-up phase and were followed-up every 4 weeks for 24 weeks for the assessment of safety.

| | |
|-----------------------|-------------------|
| Reporting group title | TAF 25 mg (China) |
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Reporting group description:

TAF 25 mg tablet + TAF placebo tablet once daily for up to 144 weeks

| Serious adverse events | TAF 25 mg (Global) | TDF 300 mg (Global) | TAF 25 mg to TAF 25 mg (Global) |
|---|--------------------|---------------------|---------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 26 / 285 (9.12%) | 17 / 140 (12.14%) | 17 / 129 (13.18%) |
| number of deaths (all causes) | 0 | 2 | 1 |

| | | | |
|---|-----------------|-----------------|-----------------|
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Hepatocellular carcinoma | | | |
| subjects affected / exposed | 2 / 285 (0.70%) | 4 / 140 (2.86%) | 3 / 129 (2.33%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 2 / 285 (0.70%) | 0 / 140 (0.00%) | 0 / 129 (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 |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 1 / 285 (0.35%) | 0 / 140 (0.00%) | 0 / 129 (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 |
| Breast cancer in situ | | | |
| subjects affected / exposed | 1 / 285 (0.35%) | 0 / 140 (0.00%) | 0 / 129 (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 |
| Breast cancer stage I | | | |
| subjects affected / exposed | 1 / 285 (0.35%) | 0 / 140 (0.00%) | 0 / 129 (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 |
| Chronic lymphocytic leukaemia | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung neoplasm malignant | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant melanoma | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to lung | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatic carcinoma metastatic | | | |
| subjects affected / exposed | 1 / 285 (0.35%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 285 (0.35%) | 0 / 140 (0.00%) | 0 / 129 (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 | | | |
| Chest discomfort | | | |
| subjects affected / exposed | 1 / 285 (0.35%) | 0 / 140 (0.00%) | 0 / 129 (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 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 1 / 140 (0.71%) | 0 / 129 (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 | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Product issues | | | |
| Device dislocation | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device breakage | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Lymphocyte count increased | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Head injury | | | |
| subjects affected / exposed | 1 / 285 (0.35%) | 0 / 140 (0.00%) | 0 / 129 (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 |
| Clavicle fracture | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 1 / 140 (0.71%) | 0 / 129 (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 |
| Foot fracture | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foreign body | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hand fracture | | | |
| subjects affected / exposed | 1 / 285 (0.35%) | 0 / 140 (0.00%) | 0 / 129 (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 |
| Heat exhaustion | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 1 / 140 (0.71%) | 0 / 129 (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 |
| Joint injury | | | |
| subjects affected / exposed | 1 / 285 (0.35%) | 0 / 140 (0.00%) | 0 / 129 (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 |
| Meniscus injury | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 285 (0.35%) | 0 / 140 (0.00%) | 0 / 129 (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 |
| Tendon rupture | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin laceration | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural complication | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic fracture | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 1 / 140 (0.71%) | 0 / 129 (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 |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Palpitations | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus node dysfunction | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Bell's palsy | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 285 (0.35%) | 0 / 140 (0.00%) | 0 / 129 (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 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervical radiculopathy | | | |
| subjects affected / exposed | 1 / 285 (0.35%) | 0 / 140 (0.00%) | 0 / 129 (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 |
| Cerebrospinal fluid leakage | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 1 / 140 (0.71%) | 0 / 129 (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 |
| Carpal tunnel syndrome | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 285 (0.35%) | 0 / 140 (0.00%) | 0 / 129 (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 disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 2 / 129 (1.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 1 / 140 (0.71%) | 0 / 129 (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 |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 1 / 140 (0.71%) | 0 / 129 (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 |
| Enteritis | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis ulcerative | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toothache | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal polyp | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Obstructive pancreatitis | | | |
| subjects affected / exposed | 1 / 285 (0.35%) | 0 / 140 (0.00%) | 0 / 129 (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 |
| Large intestine polyp | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 285 (0.35%) | 0 / 140 (0.00%) | 0 / 129 (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 | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 285 (0.35%) | 0 / 140 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bile duct stenosis | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic fibrosis | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 1 / 140 (0.71%) | 0 / 129 (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 |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Calculus urinary | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 2 / 140 (1.43%) | 0 / 129 (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 |
| Ureterolithiasis | | | |
| subjects affected / exposed | 2 / 285 (0.70%) | 0 / 140 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 1 / 285 (0.35%) | 0 / 140 (0.00%) | 0 / 129 (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 |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal colic | | | |
| subjects affected / exposed | 1 / 285 (0.35%) | 0 / 140 (0.00%) | 0 / 129 (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 impairment | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Back pain | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 1 / 140 (0.71%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal stenosis | | | |
| subjects affected / exposed | 1 / 285 (0.35%) | 0 / 140 (0.00%) | 0 / 129 (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 |
| Spondylolisthesis | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Pneumonia | | | |
| subjects affected / exposed | 1 / 285 (0.35%) | 1 / 140 (0.71%) | 2 / 129 (1.55%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 2 / 140 (1.43%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 1 / 140 (0.71%) | 0 / 129 (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 |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 285 (0.35%) | 0 / 140 (0.00%) | 0 / 129 (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 |
| Chronic hepatitis B | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 1 / 285 (0.35%) | 0 / 140 (0.00%) | 0 / 129 (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 | 1 / 285 (0.35%) | 0 / 140 (0.00%) | 0 / 129 (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 |
| Otitis externa | | | |
| subjects affected / exposed | 0 / 285 (0.00%) | 0 / 140 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Plasmodium vivax infection | | | |
| subjects affected / exposed | 1 / 285 (0.35%) | 0 / 140 (0.00%) | 0 / 129 (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 / 285 (0.00%) | 1 / 140 (0.71%) | 0 / 129 (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 | | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 285 (0.35%) | 1 / 140 (0.71%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gout | | | |
| subjects affected / exposed | 1 / 285 (0.35%) | 0 / 140 (0.00%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | TDF 300 mg (China) | TDF 300 mg to TAF 25 mg (Global) | TAF 25 mg (China) |
|---|--------------------|----------------------------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 50 (10.00%) | 38 / 261 (14.56%) | 5 / 104 (4.81%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Hepatocellular carcinoma | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 6 / 261 (2.30%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 7 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast cancer in situ | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast cancer stage I | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic lymphocytic leukaemia | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 261 (0.00%) | 0 / 104 (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 |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant melanoma | | | |

| | | | |
|--|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 lung | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Pancreatic carcinoma metastatic | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|-----------------|-----------------|
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Product issues | | | |
| Device dislocation | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Device breakage | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Investigations | | | |
| Lymphocyte count increased | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 261 (0.00%) | 0 / 104 (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 | | | |
| Head injury | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foot fracture | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Foreign body | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Hand fracture | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Heat exhaustion | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Joint injury | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meniscus injury | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tendon rupture | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin laceration | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural complication | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Pelvic fracture | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 2 / 261 (0.77%) | 0 / 104 (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 |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Palpitations | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus node dysfunction | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Bell's palsy | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Cervical radiculopathy | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrospinal fluid leakage | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Carpal tunnel syndrome | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Presyncope | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Syncope | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 2 / 261 (0.77%) | 0 / 104 (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 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 2 / 261 (0.77%) | 0 / 104 (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 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Inguinal hernia | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enteritis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis ulcerative | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Toothache | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Rectal polyp | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Obstructive pancreatitis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine polyp | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Bile duct stenosis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 2 / 261 (0.77%) | 0 / 104 (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 |
| Hepatic fibrosis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 1 / 104 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Calculus urinary | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ureterolithiasis | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 2 / 261 (0.77%) | 0 / 104 (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 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Renal colic | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 | | | |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Back pain | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal stenosis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spondylolisthesis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 261 (0.00%) | 0 / 104 (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 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Chronic hepatitis B | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 261 (0.00%) | 0 / 104 (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 | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia bacteraemia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Otitis externa | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Plasmodium vivax infection | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 261 (0.38%) | 0 / 104 (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 |
| Gout | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 261 (0.00%) | 0 / 104 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | TAF 25 mg (Global) | TDF 300 mg (Global) | TAF 25 mg to TAF 25 mg (Global) |
|---|--------------------|---------------------|---------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 185 / 285 (64.91%) | 92 / 140 (65.71%) | 58 / 129 (44.96%) |
| Investigations | | | |
| Blood parathyroid hormone increased | | | |
| subjects affected / exposed | 1 / 285 (0.35%) | 1 / 140 (0.71%) | 0 / 129 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 2 / 285 (0.70%) | 2 / 140 (1.43%) | 0 / 129 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Vascular disorders | | | |

| | | | |
|--|--------------------------|-------------------------|------------------------|
| Hypertension subjects affected / exposed occurrences (all) | 8 / 285 (2.81%) 10 | 9 / 140 (6.43%) 9 | 11 / 129 (8.53%) 12 |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 8 / 285 (2.81%) 9 | 7 / 140 (5.00%) 8 | 4 / 129 (3.10%) 7 |
| Headache subjects affected / exposed occurrences (all) | 53 / 285 (18.60%) 118 | 15 / 140 (10.71%) 42 | 10 / 129 (7.75%) 21 |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) | 17 / 285 (5.96%) 18 | 10 / 140 (7.14%) 12 | 4 / 129 (3.10%) 4 |
| Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) | 13 / 285 (4.56%) 18 | 3 / 140 (2.14%) 6 | 3 / 129 (2.33%) 3 |
| Diarrhoea subjects affected / exposed occurrences (all) | 17 / 285 (5.96%) 18 | 5 / 140 (3.57%) 5 | 7 / 129 (5.43%) 8 |
| Nausea subjects affected / exposed occurrences (all) | 18 / 285 (6.32%) 20 | 10 / 140 (7.14%) 10 | 1 / 129 (0.78%) 1 |
| Abdominal distension subjects affected / exposed occurrences (all) | 7 / 285 (2.46%) 7 | 1 / 140 (0.71%) 1 | 3 / 129 (2.33%) 3 |
| Toothache subjects affected / exposed occurrences (all) | 9 / 285 (3.16%) 9 | 3 / 140 (2.14%) 3 | 2 / 129 (1.55%) 2 |
| Chronic gastritis subjects affected / exposed occurrences (all) | 0 / 285 (0.00%) 0 | 0 / 140 (0.00%) 0 | 1 / 129 (0.78%) 1 |
| Dyspepsia subjects affected / exposed occurrences (all) | 11 / 285 (3.86%) 15 | 8 / 140 (5.71%) 9 | 3 / 129 (2.33%) 3 |

| | | | |
|---|-------------------------|-------------------------|------------------------|
| Abdominal pain subjects affected / exposed occurrences (all) | 15 / 285 (5.26%) 19 | 3 / 140 (2.14%) 3 | 3 / 129 (2.33%) 3 |
| Gastroesophageal reflux disease subjects affected / exposed occurrences (all) | 3 / 285 (1.05%) 3 | 3 / 140 (2.14%) 3 | 2 / 129 (1.55%) 2 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 12 / 285 (4.21%) 16 | 1 / 140 (0.71%) 1 | 4 / 129 (3.10%) 4 |
| Cough subjects affected / exposed occurrences (all) | 25 / 285 (8.77%) 34 | 12 / 140 (8.57%) 14 | 8 / 129 (6.20%) 11 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain subjects affected / exposed occurrences (all) | 19 / 285 (6.67%) 21 | 7 / 140 (5.00%) 8 | 10 / 129 (7.75%) 11 |
| Arthralgia subjects affected / exposed occurrences (all) | 30 / 285 (10.53%) 35 | 17 / 140 (12.14%) 21 | 8 / 129 (6.20%) 8 |
| Pain in extremity subjects affected / exposed occurrences (all) | 13 / 285 (4.56%) 14 | 7 / 140 (5.00%) 7 | 3 / 129 (2.33%) 3 |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 40 / 285 (14.04%) 80 | 19 / 140 (13.57%) 27 | 10 / 129 (7.75%) 15 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 38 / 285 (13.33%) 84 | 16 / 140 (11.43%) 33 | 10 / 129 (7.75%) 39 |
| Influenza subjects affected / exposed occurrences (all) | 18 / 285 (6.32%) 22 | 9 / 140 (6.43%) 10 | 1 / 129 (0.78%) 1 |
| Pharyngitis subjects affected / exposed occurrences (all) | 12 / 285 (4.21%) 13 | 4 / 140 (2.86%) 4 | 4 / 129 (3.10%) 4 |

| | | | |
|--|-----------------------|-----------------------|----------------------|
| Urinary tract infection subjects affected / exposed occurrences (all) | 9 / 285 (3.16%) 12 | 8 / 140 (5.71%) 11 | 6 / 129 (4.65%) 9 |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 1 / 285 (0.35%) 1 | 5 / 140 (3.57%) 6 | 0 / 129 (0.00%) 0 |

| Non-serious adverse events | TDF 300 mg (China) | TDF 300 mg to TAF 25 mg (Global) | TAF 25 mg (China) |
|---|---------------------|-------------------------------------|----------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 33 / 50 (66.00%) | 114 / 261 (43.68%) | 62 / 104 (59.62%) |
| Investigations Blood parathyroid hormone increased subjects affected / exposed occurrences (all) | 4 / 50 (8.00%) 7 | 0 / 261 (0.00%) 0 | 2 / 104 (1.92%) 3 |
| Weight decreased subjects affected / exposed occurrences (all) | 3 / 50 (6.00%) 3 | 0 / 261 (0.00%) 0 | 2 / 104 (1.92%) 2 |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 15 / 261 (5.75%) 15 | 2 / 104 (1.92%) 2 |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 10 / 261 (3.83%) 11 | 1 / 104 (0.96%) 1 |
| Headache subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 27 / 261 (10.34%) 56 | 5 / 104 (4.81%) 5 |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 5 / 261 (1.92%) 5 | 2 / 104 (1.92%) 2 |
| Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) | 3 / 50 (6.00%) 3 | 10 / 261 (3.83%) 10 | 7 / 104 (6.73%) 7 |

| | | | |
|---|----------------|------------------|-----------------|
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 50 (6.00%) | 11 / 261 (4.21%) | 4 / 104 (3.85%) |
| occurrences (all) | 3 | 11 | 4 |
| Nausea | | | |
| subjects affected / exposed | 3 / 50 (6.00%) | 5 / 261 (1.92%) | 1 / 104 (0.96%) |
| occurrences (all) | 3 | 5 | 1 |
| Abdominal distension | | | |
| subjects affected / exposed | 3 / 50 (6.00%) | 5 / 261 (1.92%) | 4 / 104 (3.85%) |
| occurrences (all) | 3 | 5 | 4 |
| Toothache | | | |
| subjects affected / exposed | 4 / 50 (8.00%) | 2 / 261 (0.77%) | 2 / 104 (1.92%) |
| occurrences (all) | 5 | 3 | 2 |
| Chronic gastritis | | | |
| subjects affected / exposed | 3 / 50 (6.00%) | 3 / 261 (1.15%) | 0 / 104 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 9 / 261 (3.45%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 12 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 9 / 261 (3.45%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 9 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 15 / 261 (5.75%) | 1 / 104 (0.96%) |
| occurrences (all) | 2 | 15 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 0 / 261 (0.00%) | 7 / 104 (6.73%) |
| occurrences (all) | 2 | 0 | 7 |
| Cough | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 13 / 261 (4.98%) | 9 / 104 (8.65%) |
| occurrences (all) | 1 | 14 | 11 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 13 / 261 (4.98%) | 3 / 104 (2.88%) |
| occurrences (all) | 0 | 14 | 3 |
| Arthralgia | | | |

| | | | |
|---|----------------------|------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 16 / 261 (6.13%) 19 | 3 / 104 (2.88%) 3 |
| Pain in extremity subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 9 / 261 (3.45%) 10 | 2 / 104 (1.92%) 2 |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 6 / 50 (12.00%) 7 | 19 / 261 (7.28%) 35 | 19 / 104 (18.27%) 23 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 5 / 50 (10.00%) 5 | 23 / 261 (8.81%) 68 | 17 / 104 (16.35%) 18 |
| Influenza subjects affected / exposed occurrences (all) | 4 / 50 (8.00%) 4 | 13 / 261 (4.98%) 14 | 4 / 104 (3.85%) 5 |
| Pharyngitis subjects affected / exposed occurrences (all) | 2 / 50 (4.00%) 2 | 14 / 261 (5.36%) 17 | 3 / 104 (2.88%) 3 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 9 / 261 (3.45%) 10 | 1 / 104 (0.96%) 1 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 3 / 50 (6.00%) 3 | 0 / 261 (0.00%) 0 | 1 / 104 (0.96%) 1 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 12 July 2013 | <ul style="list-style-type: none">• Extended the double-blind phase from 48 to 96 weeks and added Week 96 evaluations to other secondary objectives, as applicable• Changed the primary efficacy endpoint of proportion of subjects with HBV DNA levels at Week 48 from below 69 IU/mL to below 29 IU/mL• Replaced eGFR with serum creatinine as a key secondary safety objective• Extended duration of ophthalmologic substudy to 144 weeks, with additional ophthalmologic assessment at Weeks 72, 96, and 144• Clarified and revised study entry criteria• Updated statistical section to reflect changes in objectives and to better define analyses of key secondary efficacy and safety endpoints• Revised the number of subjects for PK substudy from 30 subjects to approximately 16 subjects• Added section for Management of Potential Posterior Uveitis Cases and section for Multiplicity Adjustments |
| 04 December 2013 | <p>Lowered the entry criteria for estimated glomerular filtration rate (eGFR) from ≥ 60 mL/min to ≥ 50 mL/min</p> <ul style="list-style-type: none">• Clarified and revised study entry criteria• Added clarification regarding subjects who elected an evening study drug dosing schedule: such individuals were no longer required to undergo in-clinic dosing and population PK blood draws at the Week 4 and 12 visits• Updated statistical analysis methods for key secondary endpoints to align with the TAF HIV Phase 3 development program• Added cystatin C to the baseline assessments to accommodate the revision to toxicity management for possible nephrotoxicity• Updated information about the drug formulation for TDF, the comparator, to include the formulation used in developing markets• Updated information on the management of potential nephrotoxicity• Added reflex testing for HEV in the event of an ALT elevation |
| 20 February 2015 | <p>This protocol change was only applicable for China:</p> <ul style="list-style-type: none">• Added the number of subjects to be enrolled in China• Specified that the dual-energy x-ray absorptiometry (DXA) scan procedure at all protocol-specified visits would be performed only at sites that have the capability• Added statement that fracture risk assessment at the baseline visit was intended for sites with DXA capability only• Added hepatitis E virus (HEV) testing as a reflex test for subjects who discontinued study drug and had confirmed ALT elevation• Updated the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities to reconcile with the scale that was employed in the global program via an administrative letter |
| 05 February 2016 | <ul style="list-style-type: none">• Extended the blinded period of the study to Week 144 (from Week 96).• Extended the open label period of the study to Week 384 (from Week 144).• Updated the last study visit date of treatment from Week 144/Early Discontinuation (ED) to Week 384/ED.• Added 10 study visits (Week 168, 192, 216, 240, 264, 288, 312, 336, 360, and 384/ED) to be conducted during the additional 5 years of the study.• Revised visit Week numbers to accommodate extension of blinded and open label periods of the study.• Clarified when open label study drug is to be dispensed to participants who rollover to open-label TAF treatment following Amendment 1 or 2, and under Amendment 3.• Clarified visit windows for analysis timepoints (Weeks 48, 96, and 144) to be in alignment with DXA windows.• Added hepatic ultrasound for surveillance of hepatocellular carcinoma every 24 weeks from visit Week 96 to Week 384/ED. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported