



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 Positive, Chronic Hepatitis B

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2013-000636-10 |
| Trial protocol | IT GB DE ES PL BG |
| Global end of trial date | |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 |
| This version publication date | 02 August 2019 |
| First version publication date | 02 August 2019 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | GS-US-320-0110 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|--|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01940471 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | CTRI/2014/01/004329: CTRI, NCT02836249: 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 | 23 March 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 15 December 2016 |
| Global end of trial reached? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is 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)-positive chronic hepatitis B virus (HBV) infection. Results presented include Week 48 interim data for the main study (non-China) and 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: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 25 August 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 | Poland: 12 |
| Country: Number of subjects enrolled | Spain: 4 |
| Country: Number of subjects enrolled | United Kingdom: 8 |
| Country: Number of subjects enrolled | Bulgaria: 6 |
| Country: Number of subjects enrolled | France: 5 |
| Country: Number of subjects enrolled | Italy: 14 |
| Country: Number of subjects enrolled | China: 181 |
| Country: Number of subjects enrolled | Korea, Republic of: 173 |
| Country: Number of subjects enrolled | Hong Kong: 121 |
| Country: Number of subjects enrolled | India: 110 |
| Country: Number of subjects enrolled | Canada: 83 |
| Country: Number of subjects enrolled | Taiwan: 83 |
| Country: Number of subjects enrolled | Australia: 22 |
| Country: Number of subjects enrolled | New Zealand: 17 |
| Country: Number of subjects enrolled | Singapore: 9 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | United States: 54 |
| Country: Number of subjects enrolled | Russian Federation: 49 |
| Country: Number of subjects enrolled | Japan: 46 |
| Country: Number of subjects enrolled | Romania: 33 |
| Country: Number of subjects enrolled | Turkey: 26 |
| Worldwide total number of subjects | 1056 |
| EEA total number of subjects | 82 |

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) | 1048 |
| From 65 to 84 years | 8 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in East Asia, Europe, North America, Australia, India, New Zealand, and China. The first participant was screened on 25 August 2013 (non-China) and 19 June 2015 (China). The last Week 48 study visit occurred on 06 November 2015 (non-China) and 15 December 2016 (China).

Pre-assignment

Screening details:

1473 participants were screened in non-China and 227 participants were screened in China.

Period 1

| | |
|------------------------------|-------------------------------------|
| Period 1 title | Double-Blind Phase (overall period) |
| 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 (non-China) |

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 (non-China) |
|------------------|------------------------|

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 (non-China) | TDF 300 mg (non-China) | TAF 25 mg (China) |
|---|-----------------------|------------------------|-------------------|
| Started | 581 | 292 | 123 |
| Completed | 14 | 8 | 0 |
| Not completed | 567 | 284 | 123 |
| Withdrew Consent | 13 | 7 | - |
| Adverse Event | 1 | 2 | - |
| Protocol specified criteria for withdrawal | 1 | - | - |
| Death | 1 | - | - |
| Investigator's Discretion | 5 | - | - |
| Pregnancy | 2 | 1 | 2 |
| Non-compliance with study drug | 1 | 1 | - |
| Protocol Violation | - | 1 | - |
| Still on Study | 539 | 270 | 121 |
| Lost to follow-up | 3 | 2 | - |
| Lack of efficacy | 1 | - | - |

| Number of subjects in period 1^[1] | TDF 300 mg (China) |
|---|--------------------|
| Started | 57 |
| Completed | 0 |
| Not completed | 57 |
| Withdrew Consent | 1 |
| Adverse Event | - |
| Protocol specified criteria for withdrawal | - |
| Death | - |
| Investigator's Discretion | - |
| Pregnancy | - |
| Non-compliance with study drug | - |
| Protocol Violation | - |
| Still on Study | 55 |
| Lost to follow-up | 1 |
| Lack of efficacy | - |

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: 3 participants (1 each in non-China groups and 1 in TDF China group) who were randomized but not treated are not included in the subject disposition table.

Baseline characteristics

Reporting groups

| | |
|---|------------------------|
| Reporting group title | TAF 25 mg (non-China) |
| 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 (non-China) |
| 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 (non-China) | TDF 300 mg (non-China) | TAF 25 mg (China) |
|------------------------------------|-----------------------|------------------------|-------------------|
| Number of subjects | 581 | 292 | 123 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|--------------|--------------|-------------|
| Age continuous Units: years arithmetic mean standard deviation | 38 ± 11.0 | 38 ± 11.7 | 34 ± 9.4 |
| Gender categorical Units: Subjects | | | |
| Female | 210 | 103 | 35 |
| Male | 371 | 189 | 88 |
| Race Units: Subjects | | | |
| Asian | 482 | 232 | 123 |
| Black or African American | 2 | 3 | 0 |
| Native Hawaiian or Pacific Islander | 1 | 3 | 0 |
| White | 96 | 53 | 0 |
| Other | 0 | 1 | 0 |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 4 | 2 | 0 |
| Not Hispanic or Latino | 573 | 289 | 123 |
| Not Permitted | 4 | 1 | 0 |
| Plasma HBV DNA Level Units: Subjects | | | |
| < 8 log10 IU/mL | 309 | 150 | 74 |
| ≥ 8 log10 IU/mL | 272 | 142 | 49 |
| Oral antiviral (OAV) Treatment Status Units: Subjects | | | |

| | | | |
|--|--------|--------|--------|
| Treatment Experienced | 151 | 77 | 45 |
| Treatment Naive | 430 | 215 | 78 |
| Proteinuria by Urinalysis (dipstick) | | | |
| Urine protein was measured using the dipstick method. Grade 0 = Absent; Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe | | | |
| Units: Subjects | | | |
| Grade 0 | 538 | 259 | 117 |
| Grade 1 | 40 | 31 | 6 |
| Grade 2 | 3 | 2 | 0 |
| Grade 3 | 0 | 0 | 0 |
| IL28b Status | | | |
| The CC, CT, and TT alleles are different forms of the IL28b gene. | | | |
| Units: Subjects | | | |
| CC | 442 | 210 | 109 |
| CT | 112 | 69 | 12 |
| TT | 23 | 10 | 2 |
| Missing | 4 | 3 | 0 |
| HBV DNA | | | |
| Units: log10 IU/mL | | | |
| arithmetic mean | 7.6 | 7.6 | 7.2 |
| standard deviation | ± 1.34 | ± 1.41 | ± 1.65 |

| | | | |
|-------------------------------|--------------------|-------|--|
| Reporting group values | TDF 300 mg (China) | Total | |
| Number of subjects | 57 | 1053 | |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|-------------------------------------|-------|------|--|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 36 | | |
| standard deviation | ± 9.5 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 13 | 361 | |
| Male | 44 | 692 | |
| Race | | | |
| Units: Subjects | | | |
| Asian | 57 | 894 | |
| Black or African American | 0 | 5 | |
| Native Hawaiian or Pacific Islander | 0 | 4 | |
| White | 0 | 149 | |
| Other | 0 | 1 | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 0 | 6 | |
| Not Hispanic or Latino | 57 | 1042 | |
| Not Permitted | 0 | 5 | |
| Plasma HBV DNA Level | | | |
| Units: Subjects | | | |
| < 8 log10 IU/mL | 36 | 569 | |
| ≥ 8 log10 IU/mL | 21 | 484 | |

| | | | |
|--|--------|-----|--|
| Oral antiviral (OAV) Treatment Status | | | |
| Units: Subjects | | | |
| Treatment Experienced | 18 | 291 | |
| Treatment Naive | 39 | 762 | |
| Proteinuria by Urinalysis (dipstick) | | | |
| Urine protein was measured using the dipstick method. Grade 0 = Absent; Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe | | | |
| Units: Subjects | | | |
| Grade 0 | 54 | 968 | |
| Grade 1 | 2 | 79 | |
| Grade 2 | 1 | 6 | |
| Grade 3 | 0 | 0 | |
| IL28b Status | | | |
| The CC, CT, and TT alleles are different forms of the IL28b gene. | | | |
| Units: Subjects | | | |
| CC | 52 | 813 | |
| CT | 5 | 198 | |
| TT | 0 | 35 | |
| Missing | 0 | 7 | |
| HBV DNA | | | |
| Units: log ₁₀ IU/mL | | | |
| arithmetic mean | 7.2 | | |
| standard deviation | ± 1.48 | - | |

End points

End points reporting groups

| | |
|---|------------------------|
| Reporting group title | TAF 25 mg (non-China) |
| 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 (non-China) |
| 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 | |

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 (non-China) | TDF 300 mg (non-China) | TAF 25 mg (China) | TDF 300 mg (China) |
|-----------------------------------|-----------------------|------------------------|-------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 581 | 292 | 123 | 57 |
| Units: percentage of participants | | | | |
| number (not applicable) | 63.9 | 66.8 | 61.0 | 68.4 |

Statistical analyses

| | |
|--|---------------------------------------|
| Statistical analysis title | Statistical Analysis (non-China only) |
| 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% confidence interval (CI) approach, with a noninferiority margin of 10%. | |

| | |
|---|--|
| Comparison groups | TAF 25 mg (non-China) v TDF 300 mg (non-China) |
| Number of subjects included in analysis | 873 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[1] |
| Parameter estimate | Difference in proportions |
| Point estimate | -3.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.8 |
| upper limit | 2.6 |

Notes:

[1] - Sample sizes of 288 and 576 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 the expected difference (TAF – TDF) in the proportion of participants with HBV DNA < 29 IU/mL was 0 and the proportion of participants with HBV DNA < 29 IU/mL in the TDF group was 69%. Missing data were treated as not achieving the primary endpoint.

Secondary: Percentage of Participants With Hepatitis B e Antigen (HBeAg) Seroconversion to Antibody Against Hepatitis B e Antigen (Anti-HBe) at Week 48

| | |
|-----------------|--|
| End point title | Percentage of Participants With Hepatitis B e Antigen (HBeAg) Seroconversion to Antibody Against Hepatitis B e Antigen (Anti-HBe) at Week 48 |
|-----------------|--|

End point description:

Serologically Evaluable Full Analysis Set included participants who were randomized, had received at least 1 dose of study drug, and were HBeAg positive and anti-HBe negative or had a value missing value at baseline. Participants were analyzed according to their randomized treatment group. For the Missing = Failure approach, all missing data were treated as no HBeAg seroconversion.

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

End point timeframe:

Week 48

| End point values | TAF 25 mg (non-China) | TDF 300 mg (non-China) | TAF 25 mg (China) | TDF 300 mg (China) |
|-----------------------------------|-----------------------|------------------------|-------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 565 | 285 | 118 | 57 |
| Units: percentage of participants | | | | |
| number (not applicable) | 10.3 | 8.1 | 11.0 | 8.8 |

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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 (non-China) | TDF 300 mg (non-China) | TAF 25 mg (China) | TDF 300 mg (China) |
|--------------------------------------|---------------------------|---------------------------|--------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 537 | 271 | 53 | 31 |
| Units: percentage change | | | | |
| arithmetic mean (standard deviation) | -0.100 (\pm 2.2912) | -1.715 (\pm 2.5723) | 0.624 (\pm 2.2731) | -1.507 (\pm 2.4193) |

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 (non-China) | TDF 300 mg (non-China) | TAF 25 mg (China) | TDF 300 mg (China) |
|--------------------------------------|---------------------------|---------------------------|--------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 543 | 274 | 54 | 31 |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | -0.417 (\pm 2.9343) | -2.294 (\pm 3.1331) | 0.683 (\pm 3.3281) | -2.169 (\pm 3.4503) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 48 in Serum Creatinine

| | |
|-----------------|---|
| End point title | Change From Baseline at Week 48 in Serum Creatinine |
|-----------------|---|

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 (non-China) | TDF 300 mg (non-China) | TAF 25 mg (China) | TDF 300 mg (China) |
|--------------------------------------|--------------------------|---------------------------|----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 553 | 283 | 121 | 55 |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | 0.009 (± 0.1238) | 0.026 (± 0.0948) | -0.003 (± 0.0701) | 0.016 (± 0.0920) |

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 (non-China) | TDF 300 mg (non-China) | TAF 25 mg (China) | TDF 300 mg (China) |
|-----------------------------------|--------------------------|---------------------------|----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 577 | 286 | 123 | 57 |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Grade 1 | 23.9 | 17.8 | 24.4 | 22.8 |
| Grade 2 | 3.5 | 4.5 | 0.8 | 3.5 |
| Grade 3 | 0 | 0.3 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to the Week 48 Data Cut

Adverse event reporting additional description:

Safety Analysis Set included participants who were randomized into the study and received at least 1 dose of study drug. Participants were analyzed according to the treatment they actually received during the double-blinded phase. MedDRA version 18.0 was used for non-China participants and MedDRA version 19.1 was used for China participants.

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

Dictionary used

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

| | |
|--------------------|------------|
| Dictionary version | 18.0, 19.1 |
|--------------------|------------|

Reporting groups

| | |
|-----------------------|-----------------------|
| Reporting group title | TAF 25 mg (non-China) |
|-----------------------|-----------------------|

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 (non-China) |
|-----------------------|------------------------|

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

| Serious adverse events | TAF 25 mg (non-China) | TDF 300 mg (non-China) | TAF 25 mg (China) |
|---|-----------------------|------------------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 22 / 581 (3.79%) | 12 / 292 (4.11%) | 5 / 123 (4.07%) |
| number of deaths (all causes) | 1 | 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 / 581 (0.00%) | 2 / 292 (0.68%) | 0 / 123 (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 |
| Gastrointestinal submucosal tumour | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 581 (0.17%) | 0 / 292 (0.00%) | 0 / 123 (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 |
| Thymoma | | | |
| subjects affected / exposed | 0 / 581 (0.00%) | 1 / 292 (0.34%) | 0 / 123 (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 |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 581 (0.00%) | 1 / 292 (0.34%) | 0 / 123 (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 |
| Surgical and medical procedures | | | |
| Abortion induced | | | |
| subjects affected / exposed | 0 / 581 (0.00%) | 0 / 292 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 581 (0.17%) | 0 / 292 (0.00%) | 0 / 123 (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 |
| Reproductive system and breast disorders | | | |
| Dysfunctional uterine bleeding | | | |
| subjects affected / exposed | 0 / 581 (0.00%) | 0 / 292 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 581 (0.00%) | 1 / 292 (0.34%) | 0 / 123 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchitis chronic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 581 (0.17%) | 0 / 292 (0.00%) | 0 / 123 (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 |
| Nasal septum deviation | | | |
| subjects affected / exposed | 1 / 581 (0.17%) | 0 / 292 (0.00%) | 0 / 123 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 581 (0.00%) | 0 / 292 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Hand fracture | | | |
| subjects affected / exposed | 1 / 581 (0.17%) | 0 / 292 (0.00%) | 0 / 123 (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 |
| Ligament rupture | | | |
| subjects affected / exposed | 1 / 581 (0.17%) | 0 / 292 (0.00%) | 0 / 123 (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 |
| Limb crushing injury | | | |
| subjects affected / exposed | 1 / 581 (0.17%) | 0 / 292 (0.00%) | 0 / 123 (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 |
| Lower limb fracture | | | |
| subjects affected / exposed | 0 / 581 (0.00%) | 1 / 292 (0.34%) | 0 / 123 (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 compression fracture | | | |
| subjects affected / exposed | 1 / 581 (0.17%) | 0 / 292 (0.00%) | 0 / 123 (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 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 0 / 581 (0.00%) | 0 / 292 (0.00%) | 0 / 123 (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 | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 581 (0.17%) | 0 / 292 (0.00%) | 0 / 123 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 581 (0.34%) | 0 / 292 (0.00%) | 0 / 123 (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 |
| Basilar artery occlusion | | | |
| subjects affected / exposed | 1 / 581 (0.17%) | 0 / 292 (0.00%) | 0 / 123 (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 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 581 (0.00%) | 1 / 292 (0.34%) | 0 / 123 (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 |
| Optic neuritis | | | |
| subjects affected / exposed | 0 / 581 (0.00%) | 1 / 292 (0.34%) | 0 / 123 (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 | 1 / 581 (0.17%) | 0 / 292 (0.00%) | 0 / 123 (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 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 581 (0.17%) | 0 / 292 (0.00%) | 0 / 123 (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 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 581 (0.17%) | 0 / 292 (0.00%) | 0 / 123 (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 |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 1 / 581 (0.17%) | 0 / 292 (0.00%) | 0 / 123 (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 / 581 (0.00%) | 1 / 292 (0.34%) | 0 / 123 (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 and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 581 (0.17%) | 0 / 292 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 581 (0.17%) | 0 / 292 (0.00%) | 0 / 123 (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 |
| Intervertebral disc degeneration | | | |
| subjects affected / exposed | 1 / 581 (0.17%) | 0 / 292 (0.00%) | 0 / 123 (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 / 581 (0.00%) | 1 / 292 (0.34%) | 0 / 123 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 581 (0.17%) | 0 / 292 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal abscess | | | |
| subjects affected / exposed | 1 / 581 (0.17%) | 0 / 292 (0.00%) | 0 / 123 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 581 (0.00%) | 1 / 292 (0.34%) | 0 / 123 (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 |
| Dengue fever | | | |
| subjects affected / exposed | 0 / 581 (0.00%) | 1 / 292 (0.34%) | 0 / 123 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea infectious | | | |
| subjects affected / exposed | 1 / 581 (0.17%) | 0 / 292 (0.00%) | 0 / 123 (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 |
| Periodontitis | | | |
| subjects affected / exposed | 1 / 581 (0.17%) | 0 / 292 (0.00%) | 0 / 123 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 581 (0.17%) | 0 / 292 (0.00%) | 0 / 123 (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 |
| Scrub typhus | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 581 (0.17%) | 0 / 292 (0.00%) | 0 / 123 (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) | | |
|---|--------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 57 (3.51%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Hepatocellular carcinoma | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal submucosal tumour | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thymoma | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Abortion induced | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Dysfunctional uterine bleeding | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchitis chronic | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nasal septum deviation | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 57 (1.75%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Hand fracture | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ligament rupture | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Limb crushing injury | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lower limb fracture | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 1 / 57 (1.75%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Basilar artery occlusion | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epilepsy | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Optic neuritis | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intervertebral disc degeneration | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spondylolisthesis | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anal abscess | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dengue fever | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Diarrhoea infectious | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Periodontitis | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Scrub typhus | | | |
| subjects affected / exposed | 0 / 57 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | TAF 25 mg (non-China) | TDF 300 mg (non-China) | TAF 25 mg (China) |
|---|-----------------------|------------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 215 / 581 (37.01%) | 101 / 292 (34.59%) | 28 / 123 (22.76%) |
| Investigations | | | |
| Blood parathyroid hormone increased | | | |
| subjects affected / exposed | 1 / 581 (0.17%) | 1 / 292 (0.34%) | 6 / 123 (4.88%) |
| occurrences (all) | 3 | 1 | 8 |
| Creatinine renal clearance decreased | | | |
| subjects affected / exposed | 0 / 581 (0.00%) | 0 / 292 (0.00%) | 2 / 123 (1.63%) |
| occurrences (all) | 0 | 0 | 5 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 42 / 581 (7.23%) | 22 / 292 (7.53%) | 1 / 123 (0.81%) |
| occurrences (all) | 59 | 26 | 1 |
| General disorders and administration site conditions | | | |

| | | | |
|---|------------------------|------------------------|-------------------------|
| Fatigue subjects affected / exposed occurrences (all) | 33 / 581 (5.68%) 39 | 14 / 292 (4.79%) 19 | 1 / 123 (0.81%) 1 |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 27 / 581 (4.65%) 27 | 15 / 292 (5.14%) 17 | 3 / 123 (2.44%) 3 |
| Nausea subjects affected / exposed occurrences (all) | 28 / 581 (4.82%) 30 | 13 / 292 (4.45%) 15 | 2 / 123 (1.63%) 2 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 19 / 581 (3.27%) 22 | 15 / 292 (5.14%) 16 | 2 / 123 (1.63%) 2 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 37 / 581 (6.37%) 55 | 19 / 292 (6.51%) 19 | 1 / 123 (0.81%) 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Osteopenia subjects affected / exposed occurrences (all) | 1 / 581 (0.17%) 1 | 2 / 292 (0.68%) 2 | 0 / 123 (0.00%) 0 |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 56 / 581 (9.64%) 80 | 16 / 292 (5.48%) 27 | 27 / 123 (21.95%) 37 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 51 / 581 (8.78%) 65 | 22 / 292 (7.53%) 28 | 17 / 123 (13.82%) 19 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 9 / 581 (1.55%) 14 | 10 / 292 (3.42%) 12 | 4 / 123 (3.25%) 7 |
| Non-serious adverse events | TDF 300 mg (China) | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 28 / 57 (49.12%) | | |
| Investigations | | | |

| | | | |
|---|---|--|--|
| Blood parathyroid hormone increased subjects affected / exposed occurrences (all) | 4 / 57 (7.02%) 4 | | |
| Creatinine renal clearance decreased subjects affected / exposed occurrences (all) | 3 / 57 (5.26%) 5 | | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 1 / 57 (1.75%) 1 | | |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) | 1 / 57 (1.75%) 1 | | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) | 2 / 57 (3.51%) 3 3 / 57 (5.26%) 4 2 / 57 (3.51%) 2 | | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 2 / 57 (3.51%) 2 | | |
| Musculoskeletal and connective tissue disorders Osteopenia subjects affected / exposed occurrences (all) | 3 / 57 (5.26%) 3 | | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 7 / 57 (12.28%) 9 | | |

| | | | |
|---|---------------------|--|--|
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 5 / 57 (8.77%) 6 | | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 4 / 57 (7.02%) 5 | | |

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 | <ul style="list-style-type: none"> Lowered the entry criteria for estimated glomerular filtration rate (eGFR) from ≥ 60 mL/min to ≥ 50 mL/min 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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

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| An unplanned review of unblinded clinical trial data was performed in this study that was not prospectively specified in the protocol. There was no impact on the overall integrity or conclusions of the study. |
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Notes: