



Clinical trial results:

A Randomized, Double-Blind, Controlled Evaluation of Tenofovir DF versus Adefovir Dipivoxil for the Treatment of HBeAg Positive Chronic Hepatitis B

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2004-005120-41 |
| Trial protocol | GB DE CZ ES IT |
| Global end of trial date | 28 January 2016 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 11 February 2017 |
| First version publication date | 11 February 2017 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | GS-US-174-0103 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00116805 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Gilead Sciences |
| Sponsor organisation address | 333 Lakeside Drive, Foster City, CA, United States, 94404 |
| Public contact | Clinical Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com |
| Scientific contact | Clinical Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 28 January 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 January 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

This primary objectives of this study were to compare the efficacy, safety, and tolerability of tenofovir disoproxil fumarate (TDF) versus adefovir dipivoxil (ADV) for the treatment of HBeAg-positive chronic hepatitis B. Participants will receive TDF or ADV for 48 weeks (double-blind). After 48 weeks, eligible participants switched to open-label TDF for up to 480 weeks.

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 | 09 June 2005 |
| 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 | United States: 45 |
| Country: Number of subjects enrolled | Australia: 30 |
| Country: Number of subjects enrolled | Canada: 26 |
| Country: Number of subjects enrolled | Poland: 24 |
| Country: Number of subjects enrolled | New Zealand: 19 |
| Country: Number of subjects enrolled | Turkey: 14 |
| Country: Number of subjects enrolled | Netherlands: 10 |
| Country: Number of subjects enrolled | Greece: 3 |
| Country: Number of subjects enrolled | Spain: 10 |
| Country: Number of subjects enrolled | United Kingdom: 8 |
| Country: Number of subjects enrolled | Bulgaria: 28 |
| Country: Number of subjects enrolled | Czech Republic: 8 |
| Country: Number of subjects enrolled | France: 16 |
| Country: Number of subjects enrolled | Germany: 29 |

| | |
|--------------------------------------|----------|
| Country: Number of subjects enrolled | Italy: 1 |
| Worldwide total number of subjects | 271 |
| EEA total number of subjects | 137 |

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) | 271 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in North America, Europe, and Australia/New Zealand. The first participant was screened on 09 June 2005. The last study visit occurred on 28 January 2016.

Pre-assignment

Screening details:

603 participants were screened.

Period 1

| | |
|------------------------------|-------------------------------------|
| Period 1 title | Double-blind Period Through Week 48 |
| 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 | TDF-TDF |
|------------------|---------|

Arm description:

Tenofovir disoproxil fumarate (TDF) 300 mg plus placebo to match adefovir dipivoxil (ADV) (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added emtricitabine (FTC) to their treatment regimen (as part of FTC 200 mg/TDF 300 mg fixed-dose combination (FDC) tablet) in the open-label period.

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

Dosage and administration details:

Administered once daily

| | |
|------------------|---------|
| Arm title | ADV-TDF |
|------------------|---------|

Arm description:

ADV 10 mg plus placebo to match TDF (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Adefovir dipivoxil |
| Investigational medicinal product code | |
| Other name | ADV, Hepsera® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

| | |
|--|---------------------------------------|
| Dosage and administration details: | |
| 10 mg administered once daily | |
| Investigational medicinal product name | Tenofovir disoproxil fumarate 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] | TDF-TDF | ADV-TDF |
|---|---------|---------|
| Started | 176 | 90 |
| Completed | 165 | 85 |
| Not completed | 11 | 5 |
| Withdrew Consent | 4 | 2 |
| Protocol Violation | 1 | 1 |
| Lost to follow-up | 6 | 2 |

Notes:

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

Justification: 6 participants who were randomized but not treated are not included in the subject disposition table. 1 subject who was randomized into the study but was not included in the worldwide number enrolled because that subject's country of enrollment and age was not documented.

Period 2

| | |
|------------------------------|---------------------------------|
| Period 2 title | Open-label Period Weeks 49 - 96 |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | TDF-TDF |

Arm description:

TDF 300 mg plus placebo to match ADV (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period.

| | |
|--|-------------------------------|
| Arm type | Experimental |
| 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 | Adefovir dipivoxil placebo |
| Investigational medicinal product code | |
| Other name | |

| | |
|---|---|
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Administered once daily | |
| Investigational medicinal product name | Emtricitabine/tenofovir disoproxil fumarate |
| Investigational medicinal product code | |
| Other name | FTC/TDF, Truvada® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 200/300 mg FDC tablet administered once daily | |
| Arm title | ADV-TDF |
| Arm description: | |
| ADV 10 mg plus placebo to match TDF (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period. | |
| Arm type | Experimental |
| Investigational medicinal product name | Adefovir dipivoxil |
| Investigational medicinal product code | |
| Other name | ADV, Hepsera® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 10 mg administered once daily | |
| Investigational medicinal product name | Tenofovir disoproxil fumarate placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Administered once daily | |
| 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 | Emtricitabine/tenofovir disoproxil fumarate |
| Investigational medicinal product code | |
| Other name | FTC/TDF, Truvada® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 200/300 mg FDC tablet administered once daily | |

| Number of subjects in period 2 ^[2] | TDF-TDF | ADV-TDF |
|---|---------|---------|
| Started | 154 | 84 |
| Completed | 144 | 83 |
| Not completed | 10 | 1 |
| Seroconversion | 2 | - |
| Withdrew Consent | 2 | 1 |
| Investigator's Discretion | 1 | - |
| Protocol Violation | 2 | - |
| Lost to follow-up | 2 | - |
| Safety, Tolerability, or Efficacy Reason | 1 | - |

Notes:

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

Justification: 12 participants (11 TDF-TDF; 1 ADV-TDF) completed 48 weeks but did not continue on study.

Period 3

| | |
|------------------------------|----------------------------------|
| Period 3 title | Open-label Period Weeks 97 - 144 |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | TDF-TDF |

Arm description:

TDF 300 mg plus placebo to match ADV (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period.

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

Dosage and administration details:

Administered once daily

| | |
|--|---|
| Investigational medicinal product name | Emtricitabine/tenofovir disoproxil fumarate |
| Investigational medicinal product code | |
| Other name | FTC/TDF, Truvada® |
| Pharmaceutical forms | Tablet |

| | |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

200/300 mg FDC tablet administered once daily

| | |
|------------------|---------|
| Arm title | ADV-TDF |
|------------------|---------|

Arm description:

ADV 10 mg plus placebo to match TDF (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Adefovir dipivoxil |
| Investigational medicinal product code | |
| Other name | ADV, Hepsera® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

10 mg administered once daily

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

Dosage and administration details:

Administered once daily

| | |
|--|-------------------------------|
| 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 | Emtricitabine/tenofovir disoproxil fumarate |
| Investigational medicinal product code | |
| Other name | FTC/TDF, Truvada® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

200/300 mg FDC tablet administered once daily

| Number of subjects in period 3 | TDF-TDF | ADV-TDF |
|---------------------------------------|---------|---------|
| Started | 144 | 83 |
| Completed | 133 | 74 |
| Not completed | 11 | 9 |
| Seroconversion | 2 | 3 |
| Withdrew Consent | 1 | 3 |
| Investigator's Discretion | 2 | - |

| | | |
|--------------------|---|---|
| Protocol Violation | - | 1 |
| Lost to follow-up | 5 | 2 |
| Completed Study | 1 | - |

Period 4

| | |
|------------------------------|-----------------------------------|
| Period 4 title | Open-label Period Weeks 145 - 192 |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | TDF-TDF |

Arm description:

TDF 300 mg plus placebo to match ADV (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period.

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

Dosage and administration details:

Administered once daily

| | |
|--|---|
| Investigational medicinal product name | Emtricitabine/tenofovir disoproxil fumarate |
| Investigational medicinal product code | |
| Other name | FTC/TDF, Truvada® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

200/300 mg FDC tablet administered once daily

| | |
|------------------|---------|
| Arm title | ADV-TDF |
|------------------|---------|

Arm description:

ADV 10 mg plus placebo to match TDF (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period.

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

| | |
|---|---|
| Investigational medicinal product name | Adefovir dipivoxil |
| Investigational medicinal product code | |
| Other name | ADV, Hepsera® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: 10 mg administered once daily | |
| Investigational medicinal product name | Tenofovir disoproxil fumarate placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: Administered once daily | |
| 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 | Emtricitabine/tenofovir disoproxil fumarate |
| Investigational medicinal product code | |
| Other name | FTC/TDF, Truvada® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: 200/300 mg FDC tablet administered once daily | |

| Number of subjects in period 4 | TDF-TDF | ADV-TDF |
|--|----------------|----------------|
| Started | 133 | 74 |
| Completed | 123 | 68 |
| Not completed | 10 | 6 |
| Withdrew Consent | 3 | 2 |
| Seroconversion | - | 1 |
| Investigator's Discretion | 2 | - |
| Protocol Violation | 1 | - |
| Lost to follow-up | 3 | 1 |
| Completed Study | 1 | 1 |
| Safety, Tolerability, or Efficacy Reason | - | 1 |

Period 5

| | |
|------------------------------|-----------------------------------|
| Period 5 title | Open-label Period Weeks 193 - 240 |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | TDF-TDF |

Arm description:

TDF 300 mg plus placebo to match ADV (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period.

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

Dosage and administration details:

Administered once daily

| | |
|--|---|
| Investigational medicinal product name | Emtricitabine/tenofovir disoproxil fumarate |
| Investigational medicinal product code | |
| Other name | FTC/TDF, Truvada® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

200/300 mg FDC tablet administered once daily

| | |
|------------------|---------|
| Arm title | ADV-TDF |
|------------------|---------|

Arm description:

ADV 10 mg plus placebo to match TDF (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Adefovir dipivoxil |
| Investigational medicinal product code | |
| Other name | ADV, Hepsera® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

10 mg administered once daily

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

Dosage and administration details:

Administered once daily

| | |
|--|-------------------------------|
| 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 | Emtricitabine/tenofovir disoproxil fumarate |
| Investigational medicinal product code | |
| Other name | FTC/TDF, Truvada® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

200/300 mg FDC tablet administered once daily

| Number of subjects in period 5 | TDF-TDF | ADV-TDF |
|--|---------|---------|
| Started | 123 | 68 |
| Completed | 110 | 64 |
| Not completed | 13 | 4 |
| Withdrew Consent | 7 | 1 |
| Investigator's Discretion | 1 | - |
| Lost to follow-up | 3 | - |
| Safety, Tolerability, or Efficacy Reason | 2 | 2 |
| Completed Study | - | 1 |

Period 6

| | |
|------------------------------|-----------------------------------|
| Period 6 title | Open-label Period Weeks 241 - 288 |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | TDF-TDF |

Arm description:

TDF 300 mg plus placebo to match ADV (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period.

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

| | |
|---|---|
| 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 | Adefovir dipivoxil placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Administered once daily | |
| Investigational medicinal product name | Emtricitabine/tenofovir disoproxil fumarate |
| Investigational medicinal product code | |
| Other name | FTC/TDF, Truvada® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 200/300 mg FDC tablet administered once daily | |
| Arm title | ADV-TDF |
| Arm description: | |
| ADV 10 mg plus placebo to match TDF (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period. | |
| Arm type | Experimental |
| Investigational medicinal product name | Adefovir dipivoxil |
| Investigational medicinal product code | |
| Other name | ADV, Hepsera® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 10 mg administered once daily | |
| Investigational medicinal product name | Tenofovir disoproxil fumarate placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Administered once daily | |
| 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 | Emtricitabine/tenofovir disoproxil fumarate |
| Investigational medicinal product code | |
| Other name | FTC/TDF, Truvada® |
| Pharmaceutical forms | Tablet |

| | |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

200/300 mg FDC tablet administered once daily

| Number of subjects in period 6 | TDF-TDF | ADV-TDF |
|--|---------|---------|
| Started | 110 | 64 |
| Completed | 104 | 64 |
| Not completed | 6 | 0 |
| Withdrew Consent | 4 | - |
| Safety, Tolerability, or Efficacy Reason | 2 | - |

Period 7

| | |
|------------------------------|-----------------------------------|
| Period 7 title | Open-label Period Weeks 289 - 336 |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | TDF-TDF |

Arm description:

TDF 300 mg plus placebo to match ADV (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period.

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

Dosage and administration details:

Administered once daily

| | |
|---|---|
| Investigational medicinal product name | Emtricitabine/tenofovir disoproxil fumarate |
| Investigational medicinal product code | |
| Other name | FTC/TDF, Truvada® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: 200/300 mg FDC tablet administered once daily | |
| Arm title | ADV-TDF |

Arm description:

ADV 10 mg plus placebo to match TDF (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Adefovir dipivoxil |
| Investigational medicinal product code | |
| Other name | ADV, Hepsera® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

10 mg administered once daily

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

Dosage and administration details:

Administered once daily

| | |
|--|-------------------------------|
| 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 | Emtricitabine/tenofovir disoproxil fumarate |
| Investigational medicinal product code | |
| Other name | FTC/TDF, Truvada® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

200/300 mg FDC tablet administered once daily

| Number of subjects in period 7 | TDF-TDF | ADV-TDF |
|---------------------------------------|---------|---------|
| Started | 104 | 64 |
| Completed | 98 | 57 |
| Not completed | 6 | 7 |
| Withdrew Consent | 2 | - |

| | | |
|--|---|---|
| Investigator's Discretion | 3 | 2 |
| Study Site Discontinued | - | 1 |
| Protocol Violation | - | 1 |
| Lost to follow-up | 1 | 1 |
| Completed Study | - | 1 |
| Safety, Tolerability, or Efficacy Reason | - | 1 |

Period 8

| | |
|------------------------------|-----------------------------------|
| Period 8 title | Open-label Period Weeks 337 - 384 |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | TDF-TDF |

Arm description:

TDF 300 mg plus placebo to match ADV (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period.

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

Dosage and administration details:

Administered once daily

| | |
|--|---|
| Investigational medicinal product name | Emtricitabine/tenofovir disoproxil fumarate |
| Investigational medicinal product code | |
| Other name | FTC/TDF, Truvada® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

200/300 mg FDC tablet administered once daily

| | |
|------------------|---------|
| Arm title | ADV-TDF |
|------------------|---------|

Arm description:

ADV 10 mg plus placebo to match TDF (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period.

mg FDC tablet) in the open-label period.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Adefovir dipivoxil |
| Investigational medicinal product code | |
| Other name | ADV, Hepsera® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

10 mg administered once daily

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

Dosage and administration details:

Administered once daily

| | |
|--|-------------------------------|
| 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 | Emtricitabine/tenofovir disoproxil fumarate |
| Investigational medicinal product code | |
| Other name | FTC/TDF, Truvada® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

200/300 mg FDC tablet administered once daily

| Number of subjects in period 8 | TDF-TDF | ADV-TDF |
|---------------------------------------|----------------|----------------|
| Started | 98 | 57 |
| Completed | 90 | 56 |
| Not completed | 8 | 1 |
| Withdrew Consent | 3 | 1 |
| Investigator's Discretion | 1 | - |
| Protocol Violation | 1 | - |
| Lost to follow-up | 2 | - |
| Completed Study | 1 | - |

Period 9

| | |
|------------------------------|-----------------------------------|
| Period 9 title | Open-label Period Weeks 385 - 432 |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | TDF-TDF |

Arm description:

TDF 300 mg plus placebo to match ADV (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period.

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

Dosage and administration details:

Administered once daily

| | |
|--|---|
| Investigational medicinal product name | Emtricitabine/tenofovir disoproxil fumarate |
| Investigational medicinal product code | |
| Other name | FTC/TDF, Truvada® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

200/300 mg FDC tablet administered once daily

| | |
|------------------|---------|
| Arm title | ADV-TDF |
|------------------|---------|

Arm description:

ADV 10 mg plus placebo to match TDF (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Adefovir dipivoxil |
| Investigational medicinal product code | |
| Other name | ADV, Hepsera® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

10 mg administered once daily

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

Dosage and administration details:

Administered once daily

| | |
|--|-------------------------------|
| 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 | Emtricitabine/tenofovir disoproxil fumarate |
| Investigational medicinal product code | |
| Other name | FTC/TDF, Truvada® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

200/300 mg FDC tablet administered once daily

| Number of subjects in period 9[3] | TDF-TDF | ADV-TDF |
|--------------------------------------|---------|---------|
| Started | 59 | 30 |
| Completed | 57 | 30 |
| Not completed | 2 | 0 |
| Withdrew Consent | 1 | - |
| Investigator's Discretion | 1 | - |

Notes:

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

Justification: 57 participants (31 TDF-TDF; 26 ADV-TDF) completed 384 weeks but did not continue on study.

Period 10

| | |
|------------------------------|-----------------------------------|
| Period 10 title | Open-label Period Weeks 433 - 480 |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | TDF-TDF |

Arm description:

TDF 300 mg plus placebo to match ADV (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period.

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

| | |
|---|---|
| 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 | Adefovir dipivoxil placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Administered once daily | |
| Investigational medicinal product name | Emtricitabine/tenofovir disoproxil fumarate |
| Investigational medicinal product code | |
| Other name | FTC/TDF, Truvada® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 200/300 mg FDC tablet administered once daily | |
| Arm title | ADV-TDF |
| Arm description: | |
| ADV 10 mg plus placebo to match TDF (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period. | |
| Arm type | Experimental |
| Investigational medicinal product name | Adefovir dipivoxil |
| Investigational medicinal product code | |
| Other name | ADV, Hepsera® |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 10 mg administered once daily | |
| Investigational medicinal product name | Tenofovir disoproxil fumarate placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Administered once daily | |
| 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 | Emtricitabine/tenofovir disoproxil fumarate |
| Investigational medicinal product code | |
| Other name | FTC/TDF, Truvada® |
| Pharmaceutical forms | Tablet |

| | |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

200/300 mg FDC tablet administered once daily

| Number of subjects in period 10^[4] | TDF-TDF | ADV-TDF |
|--|---------|---------|
| Started | 57 | 29 |
| Completed | 53 | 29 |
| Not completed | 4 | 0 |
| Withdrew Consent | 3 | - |
| Investigator's Discretion | 1 | - |

Notes:

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

Justification: 1 participant (ADV-TDF) completed 432 weeks but did not continue on study.

Baseline characteristics

Reporting groups

| | |
|--|---------|
| Reporting group title | TDF-TDF |
| Reporting group description: Tenofovir disoproxil fumarate (TDF) 300 mg plus placebo to match adefovir dipivoxil (ADV) (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added emtricitabine (FTC) to their treatment regimen (as part of FTC 200 mg/TDF 300 mg fixed-dose combination (FDC) tablet) in the open-label period. | |
| Reporting group title | ADV-TDF |
| Reporting group description: ADV 10 mg plus placebo to match TDF (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period. | |

| Reporting group values | TDF-TDF | ADV-TDF | Total |
|--|---------|---------|-------|
| Number of subjects | 176 | 90 | 266 |
| Age categorical Units: Subjects | | | |
| ≤ 18 years | 3 | 1 | 4 |
| Between 18 and 65 years | 173 | 89 | 262 |
| ≥ 65 years | 0 | 0 | 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 34 | 34 | - |
| standard deviation | ± 11.3 | ± 12.2 | - |
| Gender categorical Units: Subjects | | | |
| Female | 57 | 26 | 83 |
| Male | 119 | 64 | 183 |
| Baseline Alanine Aminotransferase (ALT) above the Upper Limit of the Normal (ULN) Range | | | |
| The ULN was 43 U/L for males and 34 U/L for females aged 18 to < 69, and 35 U/L for males and 32 U/L for females aged ≥ 69. | | | |
| Units: Subjects | | | |
| Yes | 169 | 90 | 259 |
| No | 7 | 0 | 7 |
| Prior Lamivudine or FTC Treatment Units: Subjects | | | |
| Yes | 8 | 1 | 9 |
| No | 168 | 89 | 257 |
| Baseline Hepatitis B Deoxyribonucleic Acid (HBV DNA) Units: log10 copies/mL | | | |
| arithmetic mean | 8.64 | 8.88 | - |
| standard deviation | ± 1.076 | ± 0.93 | - |
| Baseline Knodell Necroinflammatory Score | | | |
| Based on Knodell numerical scoring of liver biopsy specimens. The Knodell necroinflammatory score is the combined necrosis and inflammation domain scores and ranges 0 (best) to 14 (worst). | | | |
| Units: units on a scale | | | |

| | | | |
|--------------------|--------|--------|---|
| arithmetic mean | 8.3 | 8.5 | |
| standard deviation | ± 2.11 | ± 2.07 | - |

End points

End points reporting groups

| | |
|--|---------|
| Reporting group title | TDF-TDF |
| Reporting group description: Tenofovir disoproxil fumarate (TDF) 300 mg plus placebo to match adefovir dipivoxil (ADV) (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added emtricitabine (FTC) to their treatment regimen (as part of FTC 200 mg/TDF 300 mg fixed-dose combination (FDC) tablet) in the open-label period. | |
| Reporting group title | ADV-TDF |
| Reporting group description: ADV 10 mg plus placebo to match TDF (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period. | |
| Reporting group title | TDF-TDF |
| Reporting group description: TDF 300 mg plus placebo to match ADV (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period. | |
| Reporting group title | ADV-TDF |
| Reporting group description: ADV 10 mg plus placebo to match TDF (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period. | |
| Reporting group title | TDF-TDF |
| Reporting group description: TDF 300 mg plus placebo to match ADV (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period. | |
| Reporting group title | ADV-TDF |
| Reporting group description: ADV 10 mg plus placebo to match TDF (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period. | |
| Reporting group title | TDF-TDF |
| Reporting group description: TDF 300 mg plus placebo to match ADV (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period. | |
| Reporting group title | ADV-TDF |
| Reporting group description: ADV 10 mg plus placebo to match TDF (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period. | |
| Reporting group title | TDF-TDF |
| Reporting group description: TDF 300 mg plus placebo to match ADV (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period. | |
| Reporting group title | ADV-TDF |
| Reporting group description: ADV 10 mg plus placebo to match TDF (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period. | |
| Reporting group title | TDF-TDF |
| Reporting group description: TDF 300 mg plus placebo to match ADV (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period. | |
| Reporting group title | ADV-TDF |
| Reporting group description: ADV 10 mg plus placebo to match TDF (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period. | |
| Reporting group title | TDF-TDF |
| Reporting group description: TDF 300 mg plus placebo to match ADV (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period. | |
| Reporting group title | ADV-TDF |
| Reporting group description: ADV 10 mg plus placebo to match TDF (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period. | |
| Reporting group title | TDF-TDF |
| Reporting group description: TDF 300 mg plus placebo to match ADV (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period. | |

period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period.

| | |
|-----------------------|---------|
| Reporting group title | ADV-TDF |
|-----------------------|---------|

Reporting group description:

ADV 10 mg plus placebo to match TDF (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period.

| | |
|-----------------------|---------|
| Reporting group title | TDF-TDF |
|-----------------------|---------|

Reporting group description:

TDF 300 mg plus placebo to match ADV (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period.

| | |
|-----------------------|---------|
| Reporting group title | ADV-TDF |
|-----------------------|---------|

Reporting group description:

ADV 10 mg plus placebo to match TDF (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period.

| | |
|-----------------------|---------|
| Reporting group title | TDF-TDF |
|-----------------------|---------|

Reporting group description:

TDF 300 mg plus placebo to match ADV (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period.

| | |
|-----------------------|---------|
| Reporting group title | ADV-TDF |
|-----------------------|---------|

Reporting group description:

ADV 10 mg plus placebo to match TDF (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period.

| | |
|-----------------------|---------|
| Reporting group title | TDF-TDF |
|-----------------------|---------|

Reporting group description:

TDF 300 mg plus placebo to match ADV (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period.

| | |
|-----------------------|---------|
| Reporting group title | ADV-TDF |
|-----------------------|---------|

Reporting group description:

ADV 10 mg plus placebo to match TDF (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period.

| | |
|-----------------------|---------|
| Reporting group title | TDF-TDF |
|-----------------------|---------|

Reporting group description:

TDF 300 mg plus placebo to match ADV (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period.

| | |
|-----------------------|---------|
| Reporting group title | ADV-TDF |
|-----------------------|---------|

Reporting group description:

ADV 10 mg plus placebo to match TDF (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period.

| | |
|----------------------------|---------------------------------|
| Subject analysis set title | TDF-TDF With No Addition of FTC |
|----------------------------|---------------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

TDF 300 mg plus placebo to match ADV (double-blind period), followed by TDF 300 mg (open-label period).

Participants in this reporting group did not add FTC to their study regimen in the open-label period.

| | |
|----------------------------|------------------------------|
| Subject analysis set title | TDF-TDF With Addition of FTC |
|----------------------------|------------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

TDF 300 mg plus placebo to match ADV (double-blind period), followed by TDF 300 mg (open-label period).

Participants in this reporting group added FTC (as part of FTC 200 mg/TDF 300 mg FDC tablet) to their

study regimen in the open-label period.

| | |
|----------------------------|---------------------------------|
| Subject analysis set title | ADV-TDF With No Addition of FTC |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

ADV 10 mg plus placebo to match TDF (double-blind period), followed by TDF 300 mg (open-label period). Participants in this reporting group did not add FTC to their study regimen in the open-label period.

| | |
|----------------------------|------------------------------|
| Subject analysis set title | ADV-TDF With Addition of FTC |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

ADV 10 mg plus placebo to match TDF (double-blind period), followed by TDF 300 mg (open-label period). Participants in this reporting group added FTC (as part of FTC 200 mg/TDF 300 mg FDC tablet) to their study regimen in the open-label period.

Primary: Percentage of Participants With HBV DNA < 400 Copies/mL and Histological Improvement (2-point Reduction in Knodell Necroinflammatory Score Without Worsening in Knodell Fibrosis Score) at Week 48

| | |
|-----------------|--|
| End point title | Percentage of Participants With HBV DNA < 400 Copies/mL and Histological Improvement (2-point Reduction in Knodell Necroinflammatory Score Without Worsening in Knodell Fibrosis Score) at Week 48 |
|-----------------|--|

End point description:

Complete response was a composite endpoint defined as histological response and HBV DNA < 400 copies/mL. Histological response was based on the Knodell numerical scoring of liver biopsy specimens and defined as at least a 2-point reduction in Knodell necroinflammatory score without worsening in Knodell fibrosis score. The Knodell necroinflammatory score is the combined necrosis and inflammation domain scores and ranges from 0 to 14; the Knodell fibrosis domain score ranges from 0 to 4.

A participant was a nonresponder for the primary endpoint if either biopsy (baseline or end-of-treatment) was missing or if there was not an HBV DNA value available at or beyond Week 40.

Randomized and Treated Analysis Set: all participants who were randomized and received at least one dose of study medication; the missing-equals-failure approach was used where participants with missing data were considered to have failed to reach the endpoint.

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

End point timeframe:

Baseline; Week 48

| End point values | TDF-TDF | ADV-TDF | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 176 | 90 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 66.5 | 12.2 | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Statistical Analysis - TDF-TDF vs ADV-TDF |
|----------------------------|---|

Statistical analysis description:

2-sided 95% confidence interval (CI), stratified by baseline ALT was used to evaluate difference between groups in proportion of complete responders.

| | |
|-------------------|-------------------|
| Comparison groups | TDF-TDF v ADV-TDF |
|-------------------|-------------------|

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 266 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[1] |
| P-value | < 0.001 ^[2] |
| Method | Z-test |
| Parameter estimate | Difference in proportions |
| Point estimate | 54.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 44.6 |
| upper limit | 63.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.8 |

Notes:

[1] - With a sample size of 160 subjects in the TDF group and 80 subjects in the ADV group, a two group large-sample normal approximation test of proportions with a one-sided 0.025 significance level would have 95% power to reject the null hypothesis that the TDF treatment was inferior to the ADV treatment (the difference in proportions was less than -0.080) in favor of the alternative hypothesis that the TDF treatment was not inferior.

[2] - P-value corresponds to a Z-test of the null hypothesis that the stratum-adjusted (baseline ALT \leq 4 x upper limit of the normal range [ULN] or $>$ 4 x ULN) difference is 0.

Secondary: Percentage of Participants With HBV DNA < 400 Copies/mL at Week 48

| | |
|-----------------|--|
| End point title | Percentage of Participants With HBV DNA < 400 Copies/mL at Week 48 |
|-----------------|--|

End point description:

Randomized and Treated Analysis Set; the missing-equals-failure approach was used where participants with missing data were considered to have failed to reach the endpoint.

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

End point timeframe:

Week 48

| End point values | TDF-TDF | ADV-TDF | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 176 | 90 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 76.1 | 13.3 | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Statistical Analysis - TDF-TDF vs ADV-TDF |
| Comparison groups | TDF-TDF v ADV-TDF |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 266 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 ^[3] |
| Method | Z-test |
| Parameter estimate | Difference in proportions |
| Point estimate | 63.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 53.8 |
| upper limit | 72.3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.7 |

Notes:

[3] - P-value corresponds to a Z-test of the null hypothesis that the stratum-adjusted difference is zero. Difference, standard error of the difference, and the CI are stratum adjusted based on baseline ALT category ($\leq 4 \times \text{ULN}$ or $> 4 \times \text{ULN}$).

Secondary: Percentage of Participants With HBV DNA < 400 Copies/mL at Week 96

| | |
|------------------------|---|
| End point title | Percentage of Participants With HBV DNA < 400 Copies/mL at Week 96 |
| End point description: | Participants in the Randomized and Treated Analysis Set with available data were analyzed. Data included for participants who discontinued study unless the discontinuation was unrelated to protocol criteria. |
| End point type | Secondary |
| End point timeframe: | Week 96 |

| End point values | TDF-TDF | ADV-TDF | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 165 | 86 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 77.6 | 77.9 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical Analysis - TDF-TDF vs ADV-TDF |
| Comparison groups | TDF-TDF v ADV-TDF |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.801 ^[4] |
| Method | Z-test |
| Parameter estimate | Difference in proportions |
| Point estimate | -1.4 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12 |
| upper limit | 9.3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.4 |

Notes:

[4] - P-value corresponds to a Z-test of the null hypothesis that the stratum-adjusted difference is zero. Two-sided 95% CIs, stratified by baseline ALT (baseline ALT $\leq 4 \times$ ULN or $> 4 \times$ ULN), were used to evaluate treatment group differences.

Secondary: Percentage of Participants With HBV DNA < 400 Copies/mL at Weeks 144, 192, 240, 288, 336, and 384

| | |
|-----------------|---|
| End point title | Percentage of Participants With HBV DNA < 400 Copies/mL at Weeks 144, 192, 240, 288, 336, and 384 |
|-----------------|---|

End point description:

Randomized and Treated Analysis Set. Data included for participants who had discontinued unless the reason for discontinuation was unrelated to protocol criteria. Participants with missing values related to protocol criteria or who added FTC to their open-label TDF regimen were considered to have failed to reach the endpoint.

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

End point timeframe:

Weeks 144, 192, 240, 288, 336, and 384

| End point values | TDF-TDF | ADV-TDF | | |
|--|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 166 | 88 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Week 144 (TDF-TDF: N = 166; ADV-TDF: N = 88) | 71.7 | 70.5 | | |
| Week 192 (TDF-TDF: N = 165; ADV-TDF: N = 88) | 67.9 | 71.6 | | |
| Week 240 (TDF-TDF: N = 164; ADV-TDF: N = 86) | 63.4 | 66.3 | | |
| Week 288 (TDF-TDF: N = 163; ADV-TDF: N = 88) | 61.3 | 64.8 | | |
| Week 336 (TDF-TDF: N = 160; ADV-TDF: N = 87) | 59.4 | 62.1 | | |
| Week 384 (TDF-TDF: N = 155; ADV-TDF: N = 86) | 56.1 | 60.5 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HBV DNA < 400 Copies/mL at Weeks 432 and 480

| | |
|-----------------|--|
| End point title | Percentage of Participants With HBV DNA < 400 Copies/mL at Weeks 432 and 480 |
|-----------------|--|

End point description:

Participants in the Randomized and Treated Analysis Set with observed data were analyzed; the missing-equals-excluded approach was used where participants with missing data were excluded from the analysis. Data for participants who added emtricitabine to their open-label TDF regimen were included in the analysis.

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

End point timeframe:

Weeks 432 and 480

| End point values | TDF-TDF | ADV-TDF | | |
|---|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 57 | 29 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Week 432 (TDF-TDF: N = 57; ADV-TDF: N = 28) | 93 | 100 | | |
| Week 480 (TDF-TDF: N = 51; ADV-TDF: N = 29) | 98 | 96.6 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HBV DNA at Weeks 48, 96, 144, 192, 240, 288, 336, 384, 432, and 480

| | |
|-----------------|---|
| End point title | Change From Baseline in HBV DNA at Weeks 48, 96, 144, 192, 240, 288, 336, 384, 432, and 480 |
|-----------------|---|

End point description:

Participants in the Randomized and Treated Analysis Set with observed data were analyzed; the missing-equals-excluded approach was used where participants with missing data were excluded from the analysis. Data for participants who added FTC to their open-label TDF regimen were included in the analysis.

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

End point timeframe:

Baseline; Weeks 48, 96, 144, 192, 240, 288, 336, 384, 432, and 480

| End point values | TDF-TDF | ADV-TDF | | |
|--|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 160 | 85 | | |
| Units: log10 IU/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 48 (TDF-TDF: N = 160; ADV-TDF: N = 85) | -6.17 (± 1.067) | -3.93 (± 1.728) | | |
| Week 96 (TDF-TDF: N = 144; ADV-TDF: N = 80) | -6.26 (± 1.137) | -6.38 (± 1.184) | | |
| Week 144 (TDF-TDF: N = 131; ADV-TDF: N = 72) | -6.32 (± 1.098) | -6.31 (± 1.407) | | |

| | | | | |
|--|-----------------|-----------------|--|--|
| Week 192 (TDF-TDF: N = 117; ADV-TDF: N = 67) | -6.3 (± 1.203) | -6.49 (± 1.028) | | |
| Week 240 (TDF-TDF: N = 105; ADV-TDF: N = 60) | -6.22 (± 1.217) | -6.45 (± 0.986) | | |
| Week 288 (TDF-TDF: N = 101; ADV-TDF: N = 62) | -6.27 (± 1.248) | -6.49 (± 1.003) | | |
| Week 336 (TDF-TDF: N = 94; ADV-TDF: N = 57) | -6.35 (± 1.208) | -6.46 (± 1.017) | | |
| Week 384 (TDF-TDF: N = 83; ADV-TDF: N = 55) | -6.38 (± 1.167) | -6.28 (± 1.45) | | |
| Week 432 (TDF-TDF: N = 57; ADV-TDF: N = 28) | -6.13 (± 1.306) | -6.45 (± 1.008) | | |
| Week 480 (TDF-TDF: N = 51; ADV-TDF: N = 29) | -6.18 (± 1.3) | -6.37 (± 1.159) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Week 48 in HBV DNA at Weeks 96, 144, 192, 240, 288, 336, 384, 432, and 480

| | |
|-----------------|--|
| End point title | Change From Week 48 in HBV DNA at Weeks 96, 144, 192, 240, 288, 336, 384, 432, and 480 |
|-----------------|--|

End point description:

Participants in the Randomized and Treated Analysis Set with observed data were analyzed; the missing-equals-excluded approach was used where participants with missing data were excluded from the analysis. Data for participants who added FTC to their open-label TDF regimen were included in the analysis.

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

End point timeframe:

Week 48; Weeks 96, 144, 192, 240, 288, 336, 384, 432, and 480

| End point values | TDF-TDF | ADV-TDF | | |
|--|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 144 | 80 | | |
| Units: log10 IU/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 96 (TDF-TDF: N = 144; ADV-TDF: N = 80) | -0.1 (± 0.422) | -2.43 (± 1.724) | | |
| Week 144 (TDF-TDF: N = 131; ADV-TDF: N = 72) | -0.19 (± 0.475) | -2.27 (± 1.866) | | |
| Week 192 (TDF-TDF: N = 117; ADV-TDF: N = 67) | -0.2 (± 0.565) | -2.41 (± 1.662) | | |
| Week 240 (TDF-TDF: N = 105; ADV-TDF: N = 60) | -0.14 (± 0.706) | -2.49 (± 1.599) | | |
| Week 288 (TDF-TDF: N = 101; ADV-TDF: N = 62) | -0.18 (± 0.762) | -2.62 (± 1.679) | | |
| Week 336 (TDF-TDF: N = 94; ADV-TDF: N = 57) | -0.25 (± 0.618) | -2.59 (± 1.622) | | |
| Week 384 (TDF-TDF: N = 83; ADV-TDF: N = 55) | -0.29 (± 0.643) | -2.34 (± 1.821) | | |

| | | | | |
|---|-----------------|-----------------|--|--|
| Week 432 (TDF-TDF: N = 57; ADV-TDF: N = 28) | -0.13 (± 0.854) | -2.32 (± 1.694) | | |
| Week 480 (TDF-TDF: N = 51; ADV-TDF: N = 29) | -0.24 (± 0.63) | -2.16 (± 1.882) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Histological Response at Week 48

| | |
|-----------------|--|
| End point title | Percentage of Participants With Histological Response at Week 48 |
|-----------------|--|

End point description:

Histological response was based on the Knodell numerical scoring of liver biopsy specimens and defined as at least a 2-point reduction in Knodell necroinflammatory score without worsening in Knodell fibrosis score. The Knodell necroinflammatory score is the combined necrosis and inflammation domain scores and ranges from 0 to 14; the Knodell fibrosis domain score ranges from 0 to 4.

Randomized and Treated Analysis Set; the missing-equals-failure approach was used where participants with missing data were considered to have failed to reach the endpoint.

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

End point timeframe:

Baseline; Week 48

| End point values | TDF-TDF | ADV-TDF | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 176 | 90 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Yes | 74.4 | 67.8 | | |
| No | 25.6 | 32.2 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical Analysis - TDF-TDF vs ADV-TDF |
| Comparison groups | ADV-TDF v TDF-TDF |
| Number of subjects included in analysis | 266 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.32 ^[5] |
| Method | Z-test |
| Parameter estimate | Difference in proportions |
| Point estimate | 5.8 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.6 |
| upper limit | 17.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.8 |

Notes:

[5] - P-value corresponds to a Z-test of the null hypothesis that the stratum-adjusted difference is zero. Difference, standard error of the difference, and the CI are stratum adjusted based on baseline ALT category ($\leq 4 \times \text{ULN}$ or $> 4 \times \text{ULN}$).

Secondary: Percentage of Participants With Histological Response at Week 240

| | |
|-----------------|---|
| End point title | Percentage of Participants With Histological Response at Week 240 |
|-----------------|---|

End point description:

Histological response was based on the Knodell numerical scoring of liver biopsy specimens and defined as at least a 2-point reduction in Knodell necroinflammatory score without worsening in Knodell fibrosis score. The Knodell necroinflammatory score is the combined necrosis and inflammation domain scores and ranges from 0 to 14; the Knodell fibrosis domain score ranges from 0 to 4.

Participants in the Randomized and Treated Analysis Set with observed data were analyzed; the missing-equals-excluded approach was used where participants with missing data were excluded from the analysis. Data for participants who added FTC to their open-label TDF regimen were included in the analysis.

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

End point timeframe:

Baseline; Week 240

| End point values | TDF-TDF | ADV-TDF | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 76 | 48 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Yes | 88.2 | 89.6 | | |
| No | 11.8 | 10.4 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Knodell and Ishak Necroinflammatory Scores at Week 48

| | |
|-----------------|---|
| End point title | Change From Baseline in Knodell and Ishak Necroinflammatory Scores at Week 48 |
|-----------------|---|

End point description:

The Knodell necroinflammatory score is the combined score for necrosis and inflammation domains of the Knodell scoring system, and ranges from 0 (best) to 14 (worst). The Ishak score measures the degree of liver fibrosis (scarring) caused by chronic necroinflammation (inflammation leading to cell death) and ranges from 0 (best) to 6 (worst).

Participants in the Randomized and Treated Analysis Set with measurements at Baseline and Week 48 were analyzed; the missing-equals-excluded approach was used where participants with missing data were excluded from the analysis.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline; Week 48 | |

| End point values | TDF-TDF | ADV-TDF | | |
|--------------------------------------|-------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 157 | 79 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Knodel Necroinflammatory Score | -3.6 (\pm 2.3) | -3.2 (\pm 2.35) | | |
| Ishak Necroinflammatory Score | -2.7 (\pm 1.7) | -2.6 (\pm 1.94) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Knodel and Ishak Necroinflammatory Scores at Week 240

| | |
|-----------------|---|
| End point title | Change From Baseline in Knodel and Ishak Necroinflammatory Scores at Week 240 |
|-----------------|---|

End point description:

The Knodel necroinflammatory score is the combined score for necrosis and inflammation domains of the Knodel scoring system, and ranges from 0 (best) to 14 (worst). The Ishak score measures the degree of liver fibrosis (scarring) caused by chronic necroinflammation (inflammation leading to cell death) and ranges from 0 (best) to 6 (worst).

Participants in the Randomized and Treated Analysis Set with observed data were analyzed; the missing-equals-excluded approach was used where participants with missing data were excluded from the analysis. Data for participants who added FTC to their open-label TDF regimen were included in the analysis.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline; Week 240 | |

| End point values | TDF-TDF | ADV-TDF | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 76 | 48 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Knodel Necroinflammatory Score | -4.8 (\pm 2.34) | -5.1 (\pm 2.43) | | |
| Ishak Necroinflammatory Score | -4.1 (\pm 2.14) | -4.5 (\pm 2.32) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Ranked Assessment of Necroinflammation and Fibrosis at Week 48

| | |
|-----------------|--|
| End point title | Ranked Assessment of Necroinflammation and Fibrosis at Week 48 |
|-----------------|--|

End point description:

Participants were ranked as having improvement, no change, worsening, or missing data (compared to Baseline) based on the Knodell scoring system, and results are presented as the percentage of participants in each category. The Knodell necroinflammatory score is the combined score for necrosis and inflammation domains of the Knodell scoring system, which ranges from 0 (best) to 14 (worst). The Knodell fibrosis domain score ranges from 0 (best) to 4 (worst). A decrease of 1 point or more indicated improvement, and an increase of 1 point or more indicated worsening.

Randomized and Treated Analysis Set; the missing-equals-failure approach was used where participants with missing data were considered to have failed to reach the endpoint.

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

End point timeframe:

Baseline; Week 48

| End point values | TDF-TDF | ADV-TDF | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 176 | 90 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Improvement - Necroinflammation | 81.3 | 78.9 | | |
| No Change - Necroinflammation | 4.5 | 3.3 | | |
| Worsening - Necroinflammation | 3.4 | 5.6 | | |
| Missing Data - Necroinflammation | 10.8 | 12.2 | | |
| Improvement - Fibrosis | 19.9 | 20 | | |
| No Change - Fibrosis | 63.6 | 61.1 | | |
| Worsening - Fibrosis | 5.1 | 6.7 | | |
| Missing Data - Fibrosis | 11.4 | 12.2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Ranked Assessment of Necroinflammation and Fibrosis at Week 240

| | |
|-----------------|---|
| End point title | Ranked Assessment of Necroinflammation and Fibrosis at Week 240 |
|-----------------|---|

End point description:

Participants were ranked as having improvement, no change, worsening, or missing data (compared to Baseline) based on the Knodell scoring system, and results are presented as the percentage of participants in each category. The Knodell necroinflammatory score is the combined score for necrosis and inflammation domains of the Knodell scoring system, which ranges from 0 (best) to 14 (worst). The Knodell fibrosis domain score ranges from 0 (best) to 4 (worst). A decrease of 1 point or more indicated improvement, and an increase of 1 point or more indicated worsening.

Participants in the Randomized and Treated Analysis Set with observed data were analyzed; the missing-equals-excluded approach was used where participants with missing data were excluded from the analysis. Data for participants who added FTC to their open-label TDF regimen were included in the analysis.

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

End point timeframe:

Baseline; Week 240

| End point values | TDF-TDF | ADV-TDF | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 76 | 48 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Improvement - Necroinflammation | 96.1 | 97.9 | | |
| No Change - Necroinflammation | 3.9 | 2.1 | | |
| Worsening - Necroinflammation | 0 | 0 | | |
| Improvement - Fibrosis | 56.6 | 58.3 | | |
| No Change - Fibrosis | 39.5 | 39.6 | | |
| Worsening - Fibrosis | 3.9 | 2.1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Alanine Aminotransferase (ALT) Normalization at Week 48

| | |
|-----------------|---|
| End point title | Percentage of Participants With Alanine Aminotransferase (ALT) Normalization at Week 48 |
|-----------------|---|

End point description:

ALT normalization was defined as ALT > upper limit of normal (ULN) at baseline and within the normal range at the end of blinded treatment. The ULN was 43 U/L for males and 34 U/L for females aged 18 to < 69, and 35 U/L for males and 32 U/L for females aged ≥ 69.

Participants in the Randomized and Treated Analysis Set with ALT > ULN at baseline were analyzed; the missing-equals-failure approach was used where participants with missing data were considered to have failed to reach the endpoint.

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

End point timeframe:

Baseline; Week 48

| End point values | TDF-TDF | ADV-TDF | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 169 | 90 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 68 | 54.4 | | |

Statistical analyses

| Statistical analysis title | Statistical Analysis - TDF-TDF vs ADV-TDF |
|---|---|
| Comparison groups | TDF-TDF v ADV-TDF |
| Number of subjects included in analysis | 259 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.032 ^[6] |
| Method | Z-test |
| Parameter estimate | Difference in proportions |
| Point estimate | 13.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.1 |
| upper limit | 26.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 6.4 |

Notes:

[6] - P-value corresponds to a Z-test. Statistical tests were not adjusted for baseline ALT stratum. Difference, standard error of the difference, and CI are stratum adjusted (baseline ALT $\leq 4 \times$ ULN or $> 4 \times$ ULN).

Secondary: Percentage of Participants With ALT Normalization at Week 96

| End point title | Percentage of Participants With ALT Normalization at Week 96 |
|------------------------|--|
| End point description: | ALT normalization was defined as ALT $>$ ULN at baseline and within the normal range at Week 96. The ULN was 43 U/L for males and 34 U/L for females aged 18 to < 69 , and 35 U/L for males and 32 U/L for females aged ≥ 69 . |
| | Participants in the Randomized and Treated Analysis Set with ALT $>$ ULN at baseline. Data included for participants who had discontinued unless the reason for discontinuation was unrelated to protocol criteria; data for participants who added FTC to their open-label TDF regimen were included in the analysis. |
| End point type | Secondary |
| End point timeframe: | |
| Baseline; Week 96 | |

| End point values | TDF-TDF | ADV-TDF | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 158 | 86 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 65.2 | 74.4 | | |

Statistical analyses

| Statistical analysis title | Statistical Analysis - TDF-TDF vs ADV-TDF |
|---|---|
| Comparison groups | TDF-TDF v ADV-TDF |
| Number of subjects included in analysis | 244 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.1 ^[7] |
| Method | Z-test |
| Parameter estimate | Difference in proportions |
| Point estimate | -9.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -21.5 |
| upper limit | 1.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 6 |

Notes:

[7] - P-value corresponds to a Z-test of the null hypothesis that the ALT stratum-adjusted difference is zero. Difference, standard error of the difference, and CI are stratum adjusted (baseline ALT $\leq 4 \times$ ULN or $> 4 \times$ ULN).

Secondary: Percentage of Participants With ALT Normalization at Weeks 144, 192, 240, 288, 336, and 384

| | |
|-----------------|---|
| End point title | Percentage of Participants With ALT Normalization at Weeks 144, 192, 240, 288, 336, and 384 |
|-----------------|---|

End point description:

ALT normalization was defined as ALT $>$ ULN at baseline and within the normal range at the subsequent time point. The ULN was 43 U/L for males and 34 U/L for females aged 18 to < 69 , and 35 U/L for males and 32 U/L for females aged ≥ 69 .

Participants in the Randomized and Treated Analysis Set with ALT $>$ ULN at baseline and available data were analyzed. Data included for participants who had discontinued unless the reason for discontinuation was unrelated to protocol criteria; data for participants who added FTC to their open-label TDF regimen were included in the analysis.

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

End point timeframe:

Baseline; Weeks 144, 192, 240, 288, 336, and 384

| End point values | TDF-TDF | ADV-TDF | | |
|--|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 161 | 87 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Week 144 (TDF-TDF: N = 161; ADV-TDF: N = 87) | 60.2 | 67.8 | | |
| Week 192 (TDF-TDF: N = 161; ADV-TDF: N = 85) | 59.6 | 69.4 | | |
| Week 240 (TDF-TDF: N = 156; ADV-TDF: N = 85) | 50 | 65.9 | | |
| Week 288 (TDF-TDF: N = 158; ADV-TDF: N = 87) | 51.3 | 70.1 | | |
| Week 336 (TDF-TDF: N = 156; ADV-TDF: N = 84) | 46.2 | 67.9 | | |
| Week 384 (TDF-TDF: N = 154; ADV-TDF: N = 82) | 52.6 | 67.1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in ALT at Weeks 48, 96, 144, 192, 240, 288, 336, 384, 432, and 480

| | |
|-----------------|---|
| End point title | Change From Baseline in ALT at Weeks 48, 96, 144, 192, 240, 288, 336, 384, 432, and 480 |
|-----------------|---|

End point description:

Participants in the Randomized and Treated Analysis Set with observed data were analyzed; the missing-equals-excluded approach was used where participants with missing data were excluded from the analysis. Data for participants who added FTC to their open-label TDF regimen were included in the analysis.

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

End point timeframe:

Baseline; Weeks 48, 96, 144, 192, 240, 288, 336, 384, 432, and 480

| End point values | TDF-TDF | ADV-TDF | | |
|--|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 160 | 84 | | |
| Units: U/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 48 (TDF-TDF: N = 160; ADV-TDF: N = 84) | -107.2 (± 109.44) | -106.1 (± 118.9) | | |
| Week 96 (TDF-TDF: N = 141; ADV-TDF: N = 81) | -107.8 (± 108.07) | -120.4 (± 138.03) | | |
| Week 144 (TDF-TDF: N = 131; ADV-TDF: N = 72) | -100.7 (± 105.96) | -126.2 (± 150.46) | | |
| Week 192 (TDF-TDF: N = 119; ADV-TDF: N = 67) | -101.4 (± 108.63) | -139.6 (± 137.95) | | |
| Week 240 (TDF-TDF: N = 102; ADV-TDF: N = 62) | -95.9 (± 117.03) | -134.8 (± 135.59) | | |

| | | | | |
|--|-------------------|-------------------|--|--|
| Week 288 (TDF-TDF: N = 100; ADV-TDF: N = 62) | -102.3 (± 111.68) | -130.9 (± 123.08) | | |
| Week 336 (TDF-TDF: N = 95; ADV-TDF: N = 57) | -101.9 (± 112.72) | -132.3 (± 125.81) | | |
| Week 384 (TDF-TDF: N = 85; ADV-TDF: N = 54) | -108.1 (± 118.05) | -133.7 (± 128.57) | | |
| Week 432 (TDF-TDF: N = 57; ADV-TDF: N = 28) | -105 (± 139.61) | -162.1 (± 157.83) | | |
| Week 480 (TDF-TDF: N = 51; ADV-TDF: N = 29) | -92.3 (± 83.56) | -157.5 (± 159.96) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Week 48 in ALT at Weeks 96, 144, 192, 240, 288, 336, 384, 432, and 480

| | |
|--|--|
| End point title | Change From Week 48 in ALT at Weeks 96, 144, 192, 240, 288, 336, 384, 432, and 480 |
| End point description: | |
| Participants in the Randomized and Treated Analysis Set with observed data were analyzed; the missing-equals-excluded approach was used where participants with missing data were excluded from the analysis. Data for participants who added FTC to their open-label TDF regimen were included in the analysis. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 48; Weeks 96, 144, 192, 240, 288, 336, 384, 432, and 480 | |

| End point values | TDF-TDF | ADV-TDF | | |
|--|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 141 | 81 | | |
| Units: U/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 96 (TDF-TDF: N = 141; ADV-TDF: N = 81) | -2 (± 17.94) | -6.9 (± 59.64) | | |
| Week 144 (TDF-TDF: N = 131; ADV-TDF: N = 72) | -0.4 (± 21.94) | -0.7 (± 82.7) | | |
| Week 192 (TDF-TDF: N = 119; ADV-TDF: N = 67) | -1.3 (± 19.57) | -7.8 (± 27.07) | | |
| Week 240 (TDF-TDF: N = 102; ADV-TDF: N = 62) | 3.7 (± 32.48) | -8.1 (± 22.92) | | |
| Week 288 (TDF-TDF: N = 100; ADV-TDF: N = 62) | -1.6 (± 19.91) | -10.3 (± 25.26) | | |
| Week 336 (TDF-TDF: N = 95; ADV-TDF: N = 57) | -1.2 (± 19.72) | -9.3 (± 22.69) | | |
| Week 384 (TDF-TDF: N = 85; ADV-TDF: N = 54) | -4.4 (± 24.87) | -6.9 (± 31.76) | | |
| Week 432 (TDF-TDF: N = 57; ADV-TDF: N = 28) | -4.3 (± 24.27) | -11.6 (± 27.09) | | |
| Week 480 (TDF-TDF: N = 51; ADV-TDF: N = 29) | -5.5 (± 19.28) | -7.1 (± 39.76) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Hepatitis B e Antigen (HBeAg) Loss/Seroconversion at Week 48

| | |
|-----------------|--|
| End point title | Percentage of Participants With Hepatitis B e Antigen (HBeAg) Loss/Seroconversion at Week 48 |
|-----------------|--|

End point description:

HBeAg loss was defined as HBeAg positive at baseline and HBeAg negative at Week 48. Seroconversion to anti-HBe was defined as change of detectable antibody to HBeAg from negative at baseline to positive at Week 48.

Participants in the Randomized and Treated Analysis Set who were HBeAg-positive at baseline and with available data were analyzed.

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

End point timeframe:

Baseline; Week 48

| End point values | TDF-TDF | ADV-TDF | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 153 | 80 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| HBeAg Loss | 22.2 | 17.5 | | |
| HBeAg Seroconversion | 20.9 | 17.5 | | |

Statistical analyses

| | |
|---|---------------------------------|
| Statistical analysis title | HBeAg Loss - TDF-TDF vs ADV-TDF |
| Comparison groups | TDF-TDF v ADV-TDF |
| Number of subjects included in analysis | 233 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.245 ^[8] |
| Method | Z-test |
| Parameter estimate | Difference in proportions |
| Point estimate | 6.1 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.2 |
| upper limit | 16.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.3 |

Notes:

[8] - P-value above for HBeAg loss corresponds to a Z-test of the null hypothesis that stratum-adjusted difference is zero. Difference, standard error of the difference, and CI are stratum adjusted based on baseline ALT category ($\leq 4 \times \text{ULN}$ or $> 4 \times \text{ULN}$).

| | |
|---|---|
| Statistical analysis title | HBeAg Seroconversion - TDF-TDF vs ADV-TDF |
| Comparison groups | TDF-TDF v ADV-TDF |
| Number of subjects included in analysis | 233 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.363 ^[9] |
| Method | Z-test |
| Parameter estimate | Difference in proportions |
| Point estimate | 4.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.5 |
| upper limit | 14.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.2 |

Notes:

[9] - P-value for HBeAg seroconversion corresponds to Z-test of the null hypothesis that stratum-adjusted difference is zero. Difference, standard error of difference, and CI are stratum adjusted based on baseline ALT category ($\leq 4 \times \text{ULN}$ or $> 4 \times \text{ULN}$).

Secondary: Percentage of Participants With HBeAg Loss or Seroconversion to Anti-HBe at Week 96

| | |
|-----------------|---|
| End point title | Percentage of Participants With HBeAg Loss or Seroconversion to Anti-HBe at Week 96 |
|-----------------|---|

End point description:

HBeAg loss was defined as HBeAg positive at baseline and HBeAg negative at Week 96. Seroconversion to anti-HBe was defined as change of detectable antibody to HBeAg from negative at baseline to positive at Week 96.

Participants in the Randomized and Treated Analysis Set who were HBeAg-positive at baseline and with available data were analyzed. Data included for participants who had discontinued unless the reason for discontinuation was unrelated to protocol criteria.

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

End point timeframe:

Baseline; Week 96

| End point values | TDF-TDF | ADV-TDF | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 158 | 82 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| HBeAg Loss | 25.9 | 25.6 | | |
| Seroconversion to Anti-HBe | 22.8 | 22 | | |

Statistical analyses

| Statistical analysis title | HBeAg Loss - TDF-TDF vs ADV-TDF |
|---|---------------------------------|
| Comparison groups | TDF-TDF v ADV-TDF |
| Number of subjects included in analysis | 240 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.963 ^[10] |
| Method | Z-test |
| Parameter estimate | Difference in proportions |
| Point estimate | 0.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.9 |
| upper limit | 11.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.9 |

Notes:

[10] - P-value above for HBeAg loss corresponds to a Z-test of the null hypothesis that stratum-adjusted difference is zero. Difference, standard error of the difference, and CI are stratum adjusted based on baseline ALT category ($\leq 4 \times \text{ULN}$ or $> 4 \times \text{ULN}$).

| Statistical analysis title | Seroconversion to Anti-HBe - TDF-TDF vs ADV-TDF |
|---|---|
| Comparison groups | TDF-TDF v ADV-TDF |
| Number of subjects included in analysis | 240 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.904 ^[11] |
| Method | Z-test |
| Parameter estimate | Difference in proportions |
| Point estimate | 0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.4 |
| upper limit | 11.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.6 |

Notes:

[11] - P-value above for HBeAg loss corresponds to a Z-test of the null hypothesis that stratum-adjusted difference is zero. Difference, standard error of the difference, and CI are stratum adjusted based on baseline ALT category ($\leq 4 \times \text{ULN}$ or $> 4 \times \text{ULN}$).

Secondary: Percentage of Participants With Hepatitis B S-Antigen (HBsAg) Loss or Seroconversion at Week 48

| | |
|-----------------|---|
| End point title | Percentage of Participants With Hepatitis B S-Antigen (HBsAg) Loss or Seroconversion at Week 48 |
|-----------------|---|

End point description:

HBsAg loss was defined as HBsAg positive at baseline and HBsAg negative at Week 48. Seroconversion to anti-HBs was defined as change of detectable antibody to HBsAg from negative at baseline to positive at Week 48.

Participants in the Randomized and Treated Analysis Set with available data were analyzed.

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

End point timeframe:

Baseline; Week 48

| End point values | TDF-TDF | ADV-TDF | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 158 | 82 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| HBsAg Loss | 3.2 | 0 | | |
| HBsAg Seroconversion | 1.3 | 0 | | |

Statistical analyses

| | |
|---|---------------------------------|
| Statistical analysis title | HBsAg Loss - TDF-TDF vs ADV-TDF |
| Comparison groups | TDF-TDF v ADV-TDF |
| Number of subjects included in analysis | 240 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.018 ^[12] |
| Method | Z-test |
| Parameter estimate | Difference in proportions |
| Point estimate | 10.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.9 |
| upper limit | 19.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.6 |

Notes:

[12] - P-value corresponds to a Z-test of the null hypothesis that the ALT stratum-adjusted difference is zero. Difference, standard error of the difference, and confidence interval (CI) are stratum adjusted (baseline ALT $\leq 4 \times \text{ULN}$ or $> 4 \times \text{ULN}$).

| | |
|---|---|
| Statistical analysis title | HBsAg Seroconversion - TDF-TDF vs ADV-TDF |
| Comparison groups | TDF-TDF v ADV-TDF |
| Number of subjects included in analysis | 240 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.148 ^[13] |
| Method | Z-test |
| Parameter estimate | Difference in proportions |
| Point estimate | 4.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.5 |
| upper limit | 10.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3 |

Notes:

[13] - P-value corresponds to a Z-test of the null hypothesis that the ALT stratum-adjusted difference is zero. Difference, standard error of the difference, and confidence interval (CI) are stratum adjusted (baseline ALT $\leq 4 \times$ ULN or $> 4 \times$ ULN).

Secondary: Percentage of Participants With HBsAg Loss or Seroconversion to Anti-HBs at Week 96

| | |
|-----------------|---|
| End point title | Percentage of Participants With HBsAg Loss or Seroconversion to Anti-HBs at Week 96 |
|-----------------|---|

End point description:

HBsAg loss was defined as HBsAg positive at baseline and HBsAg negative at the subsequent time point. Seroconversion to anti-HBs was defined as change of detectable antibody to HBsAg from negative at baseline to positive at the subsequent time point.

Participants in the Randomized and Treated Analysis Set with available data were analyzed. Data is included for participants who had discontinued unless the reason for discontinuation was unrelated to protocol criteria.

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

End point timeframe:

Baseline; Week 96

| End point values | TDF-TDF | ADV-TDF | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 171 | 86 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| HBsAg Loss | 5.3 | 5.8 | | |
| Anti-HBs Seroconversion | 4.1 | 4.7 | | |

Statistical analyses

| | |
|---|---------------------------------|
| Statistical analysis title | HBsAg Loss - TDF-TDF vs ADV-TDF |
| Comparison groups | TDF-TDF v ADV-TDF |
| Number of subjects included in analysis | 257 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.757 ^[14] |
| Method | Z-test |
| Parameter estimate | Difference in proportions |
| Point estimate | 0.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.8 |
| upper limit | 6.5 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.9 |

Notes:

[14] - P-value above for HBsAg loss corresponds to a Z-test of the null hypothesis that stratum-adjusted difference is zero. Difference, standard error of the difference, and CI are stratum adjusted based on baseline ALT category ($\leq 4 \times \text{ULN}$ or $> 4 \times \text{ULN}$).

| | |
|---|---|
| Statistical analysis title | Seroconversion to Anti-HBs - TDF-TDF vs ADV-TDF |
| Comparison groups | TDF-TDF v ADV-TDF |
| Number of subjects included in analysis | 257 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.733 ^[15] |
| Method | Z-test |
| Parameter estimate | Difference in proportions |
| Point estimate | 0.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.2 |
| upper limit | 5.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.6 |

Notes:

[15] - P-value above corresponds to Z-test of the null hypothesis that stratum-adjusted difference is zero. Difference, standard error of the difference, and CI are stratum adjusted based on baseline ALT category ($\leq 4 \times \text{ULN}$ or $> 4 \times \text{ULN}$).

Secondary: Percentage of Participants With HBsAg Loss or Seroconversion to Anti-HBs at Weeks 144, 192, 240, 288, 336, 384, 432, and 480

| | |
|-----------------|--|
| End point title | Percentage of Participants With HBsAg Loss or Seroconversion to Anti-HBs at Weeks 144, 192, 240, 288, 336, 384, 432, and 480 |
|-----------------|--|

End point description:

HBsAg loss was defined as HBsAg positive at baseline and HBsAg negative at the subsequent time point. Seroconversion to anti-HBs was defined as change of detectable antibody to HBsAg from negative at baseline to positive at the subsequent time point.

Randomized and Treated Analysis Set. Data is included for participants who had discontinued unless the reason for discontinuation was unrelated to protocol criteria. Participants with missing values related to

protocol criteria or who added FTC to their open-label TDF regimen were considered to have failed to reach the endpoint.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline; Weeks 144, 192, 240, 288, 336, 384, 432, and 480 | |

| End point values | TDF-TDF | ADV-TDF | | |
|---|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 174 | 89 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Loss-Wk 144 (TDF: N = 173; ADV: N = 88) | 7.5 | 8 | | |
| Seroconversion-Wk 144 (TDF: N = 173; ADV: N = 88) | 5.2 | 6.8 | | |
| Loss-Wk 192 (TDF: N = 171; ADV: N = 89) | 9.4 | 7.9 | | |
| Seroconversion-Wk 192 (TDF: N = 171; ADV: N = 89) | 6.4 | 6.7 | | |
| Loss-Wk 240 (TDF: N = 174; ADV: N = 88) | 9.2 | 8 | | |
| Seroconversion-Wk 240 (TDF: N = 174; ADV: N = 88) | 6.3 | 8 | | |
| Loss-Wk 288 (TDF: N = 173; ADV: N = 88) | 9.2 | 8 | | |
| Seroconversion-Wk 288 (TDF: N = 173; ADV: N = 88) | 6.4 | 8 | | |
| Loss-Wk 336 (TDF: N = 174; ADV: N = 89) | 10.3 | 7.9 | | |
| Seroconversion-Wk 336 (TDF: N = 174; ADV: N = 89) | 7.5 | 7.9 | | |
| Loss-Wk 384 (TDF: N = 173; ADV: N = 89) | 11 | 9 | | |
| Seroconversion-Wk 384 (TDF: N = 173; ADV: N = 89) | 8.1 | 7.9 | | |
| Loss-Wk 432 (TDF: N = 174; ADV: N = 88) | 10.9 | 10.2 | | |
| Seroconversion-Wk 432 (TDF: N = 172; ADV: N = 87) | 7.6 | 8 | | |
| Loss-Wk 480 (TDF: N = 174; ADV: N = 89) | 10.9 | 10.1 | | |
| Seroconversion-Wk 480 (TDF: N = 174; ADV: N = 89) | 8 | 7.9 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With HBV Genotypic Changes From Baseline at Week 48 (Resistance Surveillance)

| | |
|-----------------|--|
| End point title | Number of Participants With HBV Genotypic Changes From Baseline at Week 48 (Resistance Surveillance) |
|-----------------|--|

End point description:

Of the total number analyzed, participants evaluated for resistance included those with HBV DNA \geq 400 copies/mL, those with viral breakthrough, and those who discontinued after Week 24 with HBV DNA \geq 400 copies/mL.

Participants in the Randomized and Treated Analysis Set were analyzed to determine if they qualified for protocol criteria for resistance surveillance, and those meeting the criteria were evaluated.

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

End point timeframe:

Baseline; Week 48

| End point values | TDF-TDF | ADV-TDF | | |
|--|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 176 | 90 | | |
| Units: participants | | | | |
| Participants evaluated | 31 | 75 | | |
| Changes at conserved sites in HBV polymerase | 2 | 8 | | |
| Changes at polymorphic sites in HBV polymerase | 13 | 17 | | |
| No genotypic changes (wild-type virus) | 7 | 43 | | |
| Unable to be genotyped | 9 | 7 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With HBV Genotypic Changes From Baseline at Week 96 (Resistance Surveillance)

| | |
|-----------------|--|
| End point title | Number of Participants With HBV Genotypic Changes From Baseline at Week 96 (Resistance Surveillance) |
|-----------------|--|

End point description:

Of the total number analyzed, participants evaluated for resistance included those with HBV DNA \geq 400 copies/mL at Week 96 on TDF monotherapy, those with viral breakthrough, those who discontinued after Week 48 with HBV DNA \geq 400 copies/mL, and those who added emtricitabine to the open-label TDF regimen and had HBV DNA \geq 400 copies/mL at the time of the addition.

Participants in the Randomized and Treated Analysis Set who continued on the study after Week 48 (ie, entered the open-label phase) were analyzed to determine if they qualified for protocol criteria for resistance surveillance, and those meeting the criteria were evaluated.

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

End point timeframe:

Baseline; Weeks 49 to 96

| End point values | TDF-TDF With No Addition of FTC | TDF-TDF With Addition of FTC | ADV-TDF With No Addition of FTC | ADV-TDF With Addition of FTC |
|--|---------------------------------|------------------------------|---------------------------------|------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 154 | 15 | 84 | 13 |
| Units: participants | | | | |
| Participants evaluated | 18 | 13 | 16 | 10 |
| Changes at conserved sites in HBV polymerase | 2 | 0 | 2 | 3 |
| Changes at polymorphic sites in HBV polymerase | 3 | 1 | 1 | 2 |
| No genotypic changes (wild-type virus) | 10 | 5 | 12 | 3 |
| Unable to be genotyped | 3 | 7 | 1 | 2 |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With HBV Genotypic Changes From Baseline at Week 144 (Resistance Surveillance)

| | |
|-----------------|---|
| End point title | Number of Participants With HBV Genotypic Changes From Baseline at Week 144 (Resistance Surveillance) |
|-----------------|---|

End point description:

Of the total number analyzed, participants evaluated for resistance included those with HBV DNA \geq 400 copies/mL at Week 144 on TDF monotherapy, those with viral breakthrough, those who discontinued after Week 96 with HBV DNA \geq 400 copies/mL, and those who added emtricitabine to the open-label TDF regimen after Week 96 and had HBV DNA \geq 400 copies/mL at the time of the addition.

Participants in the Randomized and Treated Analysis Set who continued on the study after Week 96 with available data were analyzed to determine if they qualified for protocol criteria for resistance surveillance, and those meeting the criteria were evaluated.

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

End point timeframe:

Baseline; Weeks 97 to 144

| End point values | TDF-TDF With No Addition of FTC | TDF-TDF With Addition of FTC | ADV-TDF With No Addition of FTC | ADV-TDF With Addition of FTC |
|--|---------------------------------|------------------------------|---------------------------------|------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 126 | 17 | 69 | 13 |
| Units: participants | | | | |
| Participants evaluated | 2 | 7 | 5 | 5 |
| Changes at conserved sites in HBV polymerase | 1 | 2 | 2 | 0 |
| Changes at polymorphic sites in HBV polymerase | 0 | 3 | 3 | 0 |
| No genotypic changes (wild-type virus) | 1 | 2 | 0 | 3 |
| Unable to be genotyped | 0 | 0 | 0 | 1 |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With HBV Genotypic Changes From Baseline at Week 192 (Resistance Surveillance)

| | |
|-----------------|---|
| End point title | Number of Participants With HBV Genotypic Changes From Baseline at Week 192 (Resistance Surveillance) |
|-----------------|---|

End point description:

Of the total number analyzed, participants evaluated for resistance included those with HBV DNA \geq 400 copies/mL at Week 192 on TDF monotherapy, those with viral breakthrough, those who discontinued after Week 144 with HBV DNA \geq 400 copies/mL, and those who added emtricitabine to the open-label TDF regimen after Week 144 and had HBV DNA \geq 400 copies/mL at the time of the addition.

Participants in the Randomized and Treated Analysis Set who continued on the study after Week 144 with available data were analyzed to determine if they qualified for protocol criteria for resistance surveillance, and those meeting the criteria were evaluated.

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

End point timeframe:

Baseline; Weeks 145 to 192

| End point values | TDF-TDF With No Addition of FTC | TDF-TDF With Addition of FTC | ADV-TDF With No Addition of FTC | ADV-TDF With Addition of FTC |
|--|---------------------------------|------------------------------|---------------------------------|------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 115 | 15 | 61 | 10 |
| Units: participants | | | | |
| Participants evaluated | 2 | 5 | 1 | 1 |
| Changes at conserved sites in HBV polymerase | 0 | 0 | 0 | 0 |
| Changes at polymorphic sites in HBV polymerase | 1 | 0 | 1 | 1 |
| No genotypic changes (wild-type virus) | 0 | 1 | 0 | 0 |
| Unable to be genotyped | 1 | 3 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With HBV Genotypic Changes From Baseline at Week 240 (Resistance Surveillance)

| | |
|-----------------|---|
| End point title | Number of Participants With HBV Genotypic Changes From Baseline at Week 240 (Resistance Surveillance) |
|-----------------|---|

End point description:

Of the total number analyzed, participants evaluated for resistance included those with HBV DNA \geq 400 copies/mL at Week 240 on TDF monotherapy, those with viral breakthrough, those who discontinued after Week 192 with HBV DNA \geq 400 copies/mL, and those who added emtricitabine to the open-label TDF regimen after Week 192 and had HBV DNA \geq 400 copies/mL at the time of the addition.

Participants in the Randomized and Treated Analysis Set who continued on the study after Week 192 with available data were analyzed to determine if they qualified for protocol criteria for resistance surveillance, and those meeting the criteria were evaluated.

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

End point timeframe:

Baseline; Weeks 193 to 240

| End point values | TDF-TDF With No Addition of FTC | TDF-TDF With Addition of FTC | ADV-TDF With No Addition of FTC | ADV-TDF With Addition of FTC |
|--|---------------------------------|------------------------------|---------------------------------|------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 103 | 13 | 55 | 12 |
| Units: participants | | | | |
| Participants evaluated | 3 | 3 | 0 | 1 |
| Changes at conserved sites in HBV polymerase | 0 | 0 | 0 | 1 |
| Changes at polymorphic sites in HBV polymerase | 2 | 0 | 0 | 0 |
| No genotypic changes (wild-type virus) | 1 | 2 | 0 | 0 |
| Unable to be genotyped | 0 | 1 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With HBV Genotypic Changes From Baseline at Week 288 (Resistance Surveillance)

| | |
|-----------------|---|
| End point title | Number of Participants With HBV Genotypic Changes From Baseline at Week 288 (Resistance Surveillance) |
|-----------------|---|

End point description:

Of the total number analyzed, participants evaluated for resistance included those with HBV DNA \geq 400 copies/mL at Week 288 on TDF monotherapy, those with viral breakthrough, those who discontinued after Week 240 with HBV DNA \geq 400 copies/mL, and those who added emtricitabine to the open-label TDF regimen after Week 240 and had HBV DNA \geq 400 copies/mL at the time of the addition.

Participants in the Randomized and Treated Analysis Set who continued on the study after Week 240 with available data were analyzed to determine if they qualified for protocol criteria for resistance surveillance, and those meeting the criteria were evaluated.

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

End point timeframe:

Baseline; Weeks 241 to 288

| End point values | TDF-TDF With No Addition of FTC | TDF-TDF With Addition of FTC | ADV-TDF With No Addition of FTC | ADV-TDF With Addition of FTC |
|--|---------------------------------|------------------------------|---------------------------------|------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 92 | 11 | 52 | 12 |
| Units: participants | | | | |
| Participants evaluated | 3 | 0 | 0 | 0 |
| Changes at conserved sites in HBV polymerase | 0 | 0 | 0 | 0 |

| | | | | |
|--|---|---|---|---|
| Changes at polymorphic sites in HBV polymerase | 0 | 0 | 0 | 0 |
| No genotypic changes (wild-type virus) | 2 | 0 | 0 | 0 |
| Unable to be genotyped | 1 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With HBV Genotypic Changes From Baseline at Week 336 (Resistance Surveillance)

| | |
|-----------------|---|
| End point title | Number of Participants With HBV Genotypic Changes From Baseline at Week 336 (Resistance Surveillance) |
|-----------------|---|

End point description:

Of the total number analyzed, participants evaluated for resistance included those with HBV DNA \geq 400 copies/mL at Week 336 on TDF monotherapy, those with viral breakthrough, those who discontinued after Week 288 with HBV DNA \geq 400 copies/mL, and those who added emtricitabine to the open-label TDF regimen after Week 288 and had HBV DNA \geq 400 copies/mL at the time of the addition.

Participants in the Randomized and Treated Analysis Set who continued on the study after Week 288 with available data were analyzed to determine if they qualified for protocol criteria for resistance surveillance, and those meeting the criteria were evaluated.

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

End point timeframe:

Baseline; Weeks 289 to 336

| End point values | TDF-TDF With No Addition of FTC | TDF-TDF With Addition of FTC | ADV-TDF With No Addition of FTC | ADV-TDF With Addition of FTC |
|--|---------------------------------|------------------------------|---------------------------------|------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 93 | 12 | 53 | 12 |
| Units: participants | | | | |
| Participants evaluated | 1 | 0 | 1 | 0 |
| Changes at conserved sites in HBV polymerase | 0 | 0 | 0 | 0 |
| Changes at polymorphic sites in HBV polymerase | 0 | 0 | 0 | 0 |
| No genotypic changes (wild-type virus) | 0 | 0 | 1 | 0 |
| Unable to be genotyped | 1 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With HBV Genotypic Changes From Baseline at Week 384 (Resistance Surveillance)

| | |
|-----------------|---|
| End point title | Number of Participants With HBV Genotypic Changes From Baseline at Week 384 (Resistance Surveillance) |
|-----------------|---|

End point description:

Of the total number analyzed, participants evaluated for resistance included those with HBV DNA \geq 400 copies/mL at Week 384 on TDF monotherapy, those with viral breakthrough, those who discontinued after Week 336 with HBV DNA \geq 400 copies/mL, and those who added emtricitabine to the open-label TDF regimen after Week 336 and had HBV DNA \geq 400 copies/mL at the time of the addition.

Participants in the Randomized and Treated Analysis Set who continued on the study after Week 336 with available data were analyzed to determine if they qualified for protocol criteria for resistance surveillance, and those meeting the criteria were evaluated.

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

End point timeframe:

Baseline; Weeks 337 to 384

| End point values | TDF-TDF With No Addition of FTC | TDF-TDF With Addition of FTC | ADV-TDF With No Addition of FTC | ADV-TDF With Addition of FTC |
|--|---------------------------------|------------------------------|---------------------------------|------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 87 | 12 | 50 | 10 |
| Units: participants | | | | |
| Participants evaluated | 1 | 0 | 2 | 2 |
| Changes at conserved sites in HBV polymerase | 0 | 0 | 1 | 0 |
| Changes at polymorphic sites in HBV polymerase | 0 | 0 | 1 | 1 |
| No genotypic changes (wild-type virus) | 0 | 0 | 0 | 1 |
| Unable to be genotyped | 1 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With HBV Genotypic Changes From Baseline at Week 432 (Resistance Surveillance)

| | |
|-----------------|---|
| End point title | Number of Participants With HBV Genotypic Changes From Baseline at Week 432 (Resistance Surveillance) |
|-----------------|---|

End point description:

Of the total number analyzed, participants evaluated for resistance included those with HBV DNA \geq 400 copies/mL at Week 432 on TDF monotherapy, those with viral breakthrough, those who discontinued after Week 384 with HBV DNA \geq 400 copies/mL, and those who added emtricitabine to the open-label TDF regimen after Week 384 and had HBV DNA \geq 400 copies/mL at the time of the addition.

Participants in the Randomized and Treated Analysis Set who continued on the study after Week 384 with available data were analyzed to determine if they qualified for protocol criteria for resistance surveillance, and those meeting the criteria were evaluated.

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

End point timeframe:

Baseline; Weeks 385 to 432

| End point values | TDF-TDF With No Addition of FTC | TDF-TDF With Addition of FTC | ADV-TDF With No Addition of FTC | ADV-TDF With Addition of FTC |
|--|---------------------------------|------------------------------|---------------------------------|------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 49 | 10 | 26 | 4 |
| Units: participants | | | | |
| Participants evaluated | 1 | 3 | 0 | 1 |
| Changes at conserved sites in HBV polymerase | 0 | 0 | 0 | 0 |
| Changes at polymorphic sites in HBV polymerase | 1 | 0 | 0 | 0 |
| No genotypic changes (wild-type virus) | 0 | 3 | 0 | 1 |
| Unable to be genotyped | 0 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With HBV Genotypic Changes From Baseline at Week 480 (Resistance Surveillance)

| | |
|-----------------|---|
| End point title | Number of Participants With HBV Genotypic Changes From Baseline at Week 480 (Resistance Surveillance) |
|-----------------|---|

End point description:

Of the total number analyzed, participants evaluated for resistance included those with HBV DNA \geq 400 copies/mL at Week 480 on TDF monotherapy, those with viral breakthrough, those who discontinued after Week 432 with HBV DNA \geq 400 copies/mL, and those who added emtricitabine to the open-label TDF regimen after Week 432 and had HBV DNA \geq 400 copies/mL at the time of the addition.

Participants in the Randomized and Treated Analysis Set who continued on the study after Week 432 with available data were analyzed to determine if they qualified for protocol criteria for resistance surveillance, and those meeting the criteria were evaluated.

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

End point timeframe:

Baseline; Weeks 433 to 480

| End point values | TDF-TDF With No Addition of FTC | TDF-TDF With Addition of FTC | ADV-TDF With No Addition of FTC | ADV-TDF With Addition of FTC |
|--|---------------------------------|------------------------------|---------------------------------|------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 47 | 10 | 26 | 3 |
| Units: participants | | | | |
| Participants evaluated | 0 | 3 | 1 | 0 |
| Changes at conserved sites in HBV polymerase | 0 | 0 | 0 | 0 |
| Changes at polymorphic sites in HBV polymerase | 0 | 1 | 0 | 0 |
| No genotypic changes (wild-type virus) | 0 | 2 | 1 | 0 |
| Unable to be genotyped | 0 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With ALT Normalization at Weeks 432 and 480

| | |
|-----------------|--|
| End point title | Percentage of Participants With ALT Normalization at Weeks 432 and 480 |
|-----------------|--|

End point description:

ALT normalization was defined as ALT > ULN at baseline and within the normal range at the subsequent time point. The ULN was 43 U/L for males and 34 U/L for females aged 18 to < 69, and 35 U/L for males and 32 U/L for females aged ≥ 69.

Participants in the Randomized and Treated Analysis Set with ALT > ULN at baseline and with observed data were analyzed; the missing-equals-excluded approach was used where participants with missing data were excluded from the analysis. Data for participants who added FTC to their open-label TDF regimen were included in the analysis.

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

End point timeframe:

Baseline; Weeks 432 and 480

| End point values | TDF-TDF | ADV-TDF | | |
|---|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 54 | 29 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Week 432 (TDF-TDF: N = 54; ADV-TDF: N = 28) | 79.6 | 78.6 | | |
| Week 480 (TDF-TDF: N = 48; ADV-TDF: N = 29) | 75 | 82.8 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to Week 480

Adverse event reporting additional description:

Randomized and Treated Analysis Set: all participants who were randomized and received at least one dose of study drug.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Double-Blind TDF |
|-----------------------|------------------|

Reporting group description:

Adverse events this reporting group include those occurring in the TDF-TDF group during the double-blind period only (baseline to Week 48).

TDF 300 mg plus placebo to match ADV (double-blind period).

| | |
|-----------------------|------------------|
| Reporting group title | Double-Blind ADV |
|-----------------------|------------------|

Reporting group description:

Adverse events this reporting group include those occurring in the ADV-TDF group during the double-blind period only (baseline to Week 48).

ADV 10 mg plus placebo to match TDF (double-blind period).

| | |
|-----------------------|----------------|
| Reporting group title | Open-Label TDF |
|-----------------------|----------------|

Reporting group description:

Adverse events for this reporting group include those occurring during the open-label TDF 300 mg period (Week 49 up to Week 480), regardless of which group they were randomized to in the double-blind period.

TDF 300 mg + ADV placebo or ADV 10 mg + TDF placebo (double-blind period), followed by TDF 300 mg (open-label period). Participants may have added FTC to their treatment regimen (as part of FTC 200 mg/TDF 300 mg FDC tablet) in the open-label period.

| Serious adverse events | Double-Blind TDF | Double-Blind ADV | Open-Label TDF |
|---|------------------|------------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 15 / 176 (8.52%) | 7 / 90 (7.78%) | 41 / 238 (17.23%) |
| number of deaths (all causes) | 0 | 0 | 4 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colon adenoma | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| 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 cancer | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| 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 cancer metastatic | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Hepatic neoplasm | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatocellular carcinoma | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 2 / 238 (0.84%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hodgkin's disease | | | |
| subjects affected / exposed | 1 / 176 (0.57%) | 0 / 90 (0.00%) | 0 / 238 (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 |
| Lung cancer metastatic | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Lymphoma | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer | | | |

| | | | |
|--|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 2 / 238 (0.84%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tonsillar neoplasm | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Abortion induced | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| 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 | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 1 / 90 (1.11%) | 1 / 238 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Ovarian cyst ruptured | | | |
| subjects affected / exposed | 1 / 176 (0.57%) | 0 / 90 (0.00%) | 0 / 238 (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 |
| Psychiatric disorders | | | |
| Drug dependence | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed | 6 / 176 (3.41%) | 4 / 90 (4.44%) | 6 / 238 (2.52%) |
| occurrences causally related to treatment / all | 4 / 6 | 4 / 4 | 2 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 2 / 176 (1.14%) | 1 / 90 (1.11%) | 2 / 238 (0.84%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Glucose urine present | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 2 / 238 (0.84%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 1 / 90 (1.11%) | 0 / 238 (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 |
| Lower limb fracture | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Procedural dizziness | | | |
| subjects affected / exposed | 1 / 176 (0.57%) | 0 / 90 (0.00%) | 0 / 238 (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 |
| Skull fracture | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|----------------|-----------------|
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ulna fracture | | | |
| subjects affected / exposed | 1 / 176 (0.57%) | 0 / 90 (0.00%) | 0 / 238 (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 |
| Congenital, familial and genetic disorders | | | |
| Congenital anomaly in offspring | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| 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 | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| 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 pectoris | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic cardiomyopathy | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocarditis | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| 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 | | | |
| Diabetic neuropathy | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial spasm | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| 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 | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 2 / 238 (0.84%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 176 (0.57%) | 0 / 90 (0.00%) | 0 / 238 (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 |
| Gastrointestinal disorders | | | |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 1 / 90 (1.11%) | 0 / 238 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|----------------|-----------------|
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 176 (0.57%) | 0 / 90 (0.00%) | 0 / 238 (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 |
| Hepatitis | | | |
| subjects affected / exposed | 1 / 176 (0.57%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Calculus ureteric | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 3 / 238 (1.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tubulointerstitial nephritis | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 1 / 90 (1.11%) | 0 / 238 (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 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoporosis | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Synovial cyst | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| 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 Abscess soft tissue subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 176 (0.57%) 0 / 1 0 / 0 | 0 / 90 (0.00%) 0 / 0 0 / 0 | 0 / 238 (0.00%) 0 / 0 0 / 0 |
| Diverticulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 176 (0.00%) 0 / 0 0 / 0 | 0 / 90 (0.00%) 0 / 0 0 / 0 | 1 / 238 (0.42%) 0 / 1 0 / 0 |
| Epididymitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 176 (0.00%) 0 / 0 0 / 0 | 0 / 90 (0.00%) 0 / 0 0 / 0 | 1 / 238 (0.42%) 0 / 1 0 / 0 |
| Gastroenteritis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 176 (0.00%) 0 / 0 0 / 0 | 0 / 90 (0.00%) 0 / 0 0 / 0 | 1 / 238 (0.42%) 0 / 1 0 / 0 |
| Groin abscess subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 176 (0.00%) 0 / 0 0 / 0 | 0 / 90 (0.00%) 0 / 0 0 / 0 | 1 / 238 (0.42%) 0 / 1 0 / 0 |
| Hepatitis B subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 176 (0.57%) 1 / 1 0 / 0 | 0 / 90 (0.00%) 0 / 0 0 / 0 | 0 / 238 (0.00%) 0 / 0 0 / 0 |
| Orchitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 176 (0.00%) 0 / 0 0 / 0 | 0 / 90 (0.00%) 0 / 0 0 / 0 | 1 / 238 (0.42%) 0 / 1 0 / 0 |
| Respiratory tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 176 (0.00%) 0 / 0 0 / 0 | 0 / 90 (0.00%) 0 / 0 0 / 0 | 1 / 238 (0.42%) 0 / 1 0 / 0 |
| Sepsis | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| 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 infection | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 0 / 176 (0.00%) | 0 / 90 (0.00%) | 1 / 238 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| 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 | Double-Blind TDF | Double-Blind ADV | Open-Label TDF |
|---|-------------------|------------------|--------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 97 / 176 (55.11%) | 49 / 90 (54.44%) | 165 / 238 (69.33%) |
| Investigations | | | |
| Creatinine renal clearance decreased | | | |
| subjects affected / exposed | 1 / 176 (0.57%) | 1 / 90 (1.11%) | 12 / 238 (5.04%) |
| occurrences (all) | 1 | 1 | 13 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 3 / 176 (1.70%) | 1 / 90 (1.11%) | 24 / 238 (10.08%) |
| occurrences (all) | 3 | 1 | 27 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 12 / 176 (6.82%) | 2 / 90 (2.22%) | 11 / 238 (4.62%) |
| occurrences (all) | 13 | 2 | 11 |
| Headache | | | |

| | | | |
|---|-------------------------|------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 31 / 176 (17.61%) 50 | 14 / 90 (15.56%) 27 | 30 / 238 (12.61%) 36 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 22 / 176 (12.50%) | 8 / 90 (8.89%) | 20 / 238 (8.40%) |
| occurrences (all) | 24 | 8 | 21 |
| Influenza like illness | | | |
| subjects affected / exposed | 9 / 176 (5.11%) | 3 / 90 (3.33%) | 14 / 238 (5.88%) |
| occurrences (all) | 10 | 5 | 20 |
| Immune system disorders | | | |
| Seasonal allergy | | | |
| subjects affected / exposed | 4 / 176 (2.27%) | 1 / 90 (1.11%) | 17 / 238 (7.14%) |
| occurrences (all) | 5 | 1 | 22 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 6 / 176 (3.41%) | 3 / 90 (3.33%) | 22 / 238 (9.24%) |
| occurrences (all) | 9 | 3 | 26 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 15 / 176 (8.52%) | 4 / 90 (4.44%) | 25 / 238 (10.50%) |
| occurrences (all) | 16 | 4 | 26 |
| Diarrhoea | | | |
| subjects affected / exposed | 12 / 176 (6.82%) | 3 / 90 (3.33%) | 12 / 238 (5.04%) |
| occurrences (all) | 16 | 3 | 15 |
| Nausea | | | |
| subjects affected / exposed | 26 / 176 (14.77%) | 1 / 90 (1.11%) | 9 / 238 (3.78%) |
| occurrences (all) | 30 | 1 | 9 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 10 / 176 (5.68%) | 5 / 90 (5.56%) | 30 / 238 (12.61%) |
| occurrences (all) | 10 | 5 | 45 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 8 / 176 (4.55%) | 5 / 90 (5.56%) | 18 / 238 (7.56%) |
| occurrences (all) | 10 | 6 | 28 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|-----------------------------------|-------------------|------------------|-------------------|
| Arthralgia | | | |
| subjects affected / exposed | 5 / 176 (2.84%) | 6 / 90 (6.67%) | 17 / 238 (7.14%) |
| occurrences (all) | 5 | 7 | 25 |
| Back pain | | | |
| subjects affected / exposed | 13 / 176 (7.39%) | 3 / 90 (3.33%) | 18 / 238 (7.56%) |
| occurrences (all) | 13 | 4 | 20 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 2 / 176 (1.14%) | 3 / 90 (3.33%) | 15 / 238 (6.30%) |
| occurrences (all) | 2 | 4 | 17 |
| Myalgia | | | |
| subjects affected / exposed | 8 / 176 (4.55%) | 5 / 90 (5.56%) | 11 / 238 (4.62%) |
| occurrences (all) | 11 | 5 | 12 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 176 (1.14%) | 4 / 90 (4.44%) | 13 / 238 (5.46%) |
| occurrences (all) | 2 | 4 | 17 |
| Influenza | | | |
| subjects affected / exposed | 8 / 176 (4.55%) | 5 / 90 (5.56%) | 25 / 238 (10.50%) |
| occurrences (all) | 8 | 5 | 36 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 22 / 176 (12.50%) | 13 / 90 (14.44%) | 43 / 238 (18.07%) |
| occurrences (all) | 31 | 13 | 76 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 7 / 176 (3.98%) | 6 / 90 (6.67%) | 21 / 238 (8.82%) |
| occurrences (all) | 7 | 8 | 42 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 13 September 2005 | <ul style="list-style-type: none">— The treatment phase of the study was extended to 240 weeks to evaluate long-term virological, serological, and biochemical response, as well as the safety profile observed among subjects initiating double-blind treatment with tenofovir DF and maintained on tenofovir DF (early) versus subjects initiating double-blind treatment with adefovir dipivoxil and switching to tenofovir DF at the end of the first year (deferred).— Statistical analysis of the antiviral and safety parameters at Week 96 (and every 48 weeks thereafter) was added to evaluate continuous (early) tenofovir DF treatment versus secondary (deferred) tenofovir DF treatment based on randomization to double-blind tenofovir DF or adefovir dipivoxil, respectively, at study entry in the first year. The original treatment assignment is to remain blinded to the subject and the investigator for the entire 240 weeks of the study.— A final required liver biopsy was added at Week 240.— To help characterize a role for combination therapy in subjects with persistent viral replication or incomplete virologic response, a provision was added allowing subjects with HBV DNA ≥ 400 copies/mL at or after Week 72, confirmed on two consecutive visits, to be eligible to remain on tenofovir DF, switch to emtricitabine 200 mg/tenofovir DF 300 mg combination tablet taken QD, or initiate commercially available HBV therapy. |
| 14 September 2005 | <ul style="list-style-type: none">— A substudy was planned for sites in France, Germany, and the Netherlands to measure hepatic covalently closed circular DNA (cccDNA) in approximately 45 subjects (approximately 15 adefovir dipivoxil subjects and 30 tenofovir DF subjects) at baseline, Week 144, and Week 240. The substudy required an additional liver biopsy at Year 3, during which additional tissue samples would be collected for analysis of intrahepatic HBV DNA levels and for immunostaining. <p>a. Post-amendment note: No subjects enrolled in the substudy; thus, the substudy was not conducted.</p> |
| 22 December 2005 | <ul style="list-style-type: none">— Subjects were allowed to enroll with up to 10% variance from the stated eligibility criterion for ALT ($> 2 \times \text{ULN}$ and no more than $10 \times \text{ULN}$) and/or in time windows for study eligibility criteria, with approval of the medical monitor.— The primary efficacy and safety analysis sets were redefined as all randomized subjects who received at least one dose of study medication. |
| 27 June 2008 | <ul style="list-style-type: none">— The study duration was extended to 384 weeks (8 years).— Annual dual energy x-ray absorptiometry (DEXA) scans of the hip and spine from Week 192 to Week 384 were added to monitor for changes in bone mineral density (BMD).— Added recommendation that subjects remain on study treatment until HBsAg loss or seroconversion to anti-HBs since seroconversion to anti-HBe does not preclude the development of precore mutations.— Strengthened the protocol language recommending intensification of TDF therapy with emtricitabine 200 mg after Week 72 in order to help minimize the risk of developing resistance mutations associated with persistent viremia and continued monotherapy treatment. |

| | |
|-------------------|--|
| 13 September 2011 | <ul style="list-style-type: none"> — Instructions were added for the collection of an optional blood sample from subjects who provided a separate informed consent form for biomarker analysis (including pharmacogenomics). These samples may be used for exploration of appropriate markers that may be predictive of virologic response and/or the tolerability of HBV therapies. — Instructions were added for subjects with creatinine clearance (CLcr) between 30 to 49 mL/min to have a dose modification to every 48 hours dosing. — Clarification was added about management of subjects who HBsAg seroconvert. — Clarification was added about visit windows for protocol-specific visits. |
| 24 January 2013 | <ul style="list-style-type: none"> — Study was extended to 480 weeks for subjects who completed 384 weeks of study treatment under the original protocol. — Instructions were added for reporting events categorized as special situations. — Clarification was added that dual energy x-ray absorptiometry (DEXA) scans will not be performed beyond Week 384 due to unavailability of baseline values and the lack of decline in bone mineral density from results available for Year 4 through Year 6. |

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.

There were no limitations affecting the analysis or results.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/23939953>

<http://www.ncbi.nlm.nih.gov/pubmed/23234725>

<http://www.ncbi.nlm.nih.gov/pubmed/23364953>

<http://www.ncbi.nlm.nih.gov/pubmed/25179493>

<http://www.ncbi.nlm.nih.gov/pubmed/25277773>

<http://www.ncbi.nlm.nih.gov/pubmed/25046847>

<http://www.ncbi.nlm.nih.gov/pubmed/25788199>

<http://www.ncbi.nlm.nih.gov/pubmed/25532501>

<http://www.ncbi.nlm.nih.gov/pubmed/27658343>