Clinical trial results:
A Randomized, Double-Blind, Controlled Evaluation of Tenofovir DF versus Adefovir Dipivoxil for the Treatment of Presumed Pre-core Mutant Chronic Hepatitis B

Summary

EudraCT number	2004-005119-27
Trial protocol	GB CZ DE ES IT
Global end of trial date	19 January 2016

Results information

Result version number	v1 (current)
This version publication date	02 February 2017
First version publication date	02 February 2017

Trial information

Trial identification

Sponsor protocol code	GS-US-174-0102

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00117676
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	19 January 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 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 pre-core mutant chronic hepatitis B.

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	07 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	Spain: 21
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Bulgaria: 72
Country: Number of subjects enrolled	Czech Republic: 12
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	Germany: 30
Country: Number of subjects enrolled	Greece: 29
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	United States: 39
Country: Number of subjects enrolled	New Zealand: 34
Country: Number of subjects enrolled	Poland: 24
Country: Number of subjects enrolled	Australia: 24
Country: Number of subjects enrolled	Turkey: 14
Country: Number of subjects enrolled	Netherlands: 2

Country: Number of subjects enrolled	Canada: 46
Worldwide total number of subjects	382
EEA total number of subjects	225

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)	376
From 65 to 84 years	6
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 07 June 2005. The last study visit occurred on 19 January 2016.

Pre-assignment

Screening details:

846 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; as part of emtricitabine/tenofovir disoproxil fumarate (200/300 mg) fixed-dose combination (FDC) tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen in the open-label period.

Arm type	Active comparator
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	250	125
Completed	244	121
Not completed	6	4
Withdrew Consent	-	1
Protocol Violation	-	1
Lost to follow-up	1	-
Safety, Tolerability, or Efficacy Reason	5	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: 7 participants who were randomized but not treated are not included in the subject disposition table.

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

Arm type	Active comparator
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	235	112
Completed	225	110
Not completed	10	2
Withdrew Consent	5	1
Lost to follow-up	2	-
Safety, Tolerability, or Efficacy Reason	3	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: 18 participants (9 TDF-TDF; 9 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen in the open-label period.

Arm type	Active comparator
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	225	110
Completed	219	109
Not completed	6	1
Withdrew Consent	1	-
Lost to follow-up	4	1
Safety, Tolerability, or Efficacy Reason	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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen in the open-label period.

Arm type	Active comparator
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	219	109
Completed	209	106
Not completed	10	3
Withdrew Consent	5	2
Investigator's Discretion	2	-
Lost to follow-up	3	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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen in the open-label period.

Arm type	Active comparator
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	209	106
Completed	202	103
Not completed	7	3
Withdrew Consent	4	1
Investigator's Discretion	1	1
Lost to follow-up	-	1
Safety, Tolerability, or Efficacy Reason	2	-

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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen in the open-label period.	
Arm type	Active comparator
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	202	103
Completed	192	100
Not completed	10	3
Withdrew Consent	5	1
Investigator's Discretion	-	1
Protocol Violation	2	-
Lost to follow-up	2	1
Safety, Tolerability, or Efficacy Reason	1	-

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

Arm type	Active comparator
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	192	100
Completed	183	93
Not completed	9	7
Withdrew Consent	-	1
Investigator's Discretion	7	4
Lost to follow-up	2	2

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

Arm type	Active comparator
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	183	93
Completed	176	90
Not completed	7	3
Withdrew Consent	2	1
Investigator's Discretion	1	1
Study Site Discontinued	1	-
Lost to follow-up	3	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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen in the open-label period.

Arm type	Active comparator
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	82	46
Completed	82	44
Not completed	0	2
Investigator's Discretion	-	1
Safety, Tolerability, or Efficacy Reason	-	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: 138 participants (94 TDF-TDF; 44 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen in the open-label period.	
Arm type	Active comparator
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	82	43
Completed	80	41
Not completed	2	2
Withdrew Consent	-	1
Lost to follow-up	1	-
Safety, Tolerability, or Efficacy Reason	1	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; as part of emtricitabine/tenofovir disoproxil fumarate (200/300 mg) fixed-dose combination (FDC) tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen in the open-label period.	

Reporting group values	TDF-TDF	ADV-TDF	Total
Number of subjects	250	125	375
Age categorical Units: Subjects			
≤ 18 years	0	1	1
Between 18 and 65 years	247	123	370
≥ 65 years	3	1	4
Age continuous Units: years			
arithmetic mean	44	43	
standard deviation	± 10.6	± 10	-
Gender categorical Units: Subjects			
Female	57	28	85
Male	193	97	290
Race Units: Subjects			
Asian	63	30	93
Native Hawaiian or Other Pacific Islander	7	2	9
Black or African American	8	4	12
White	161	81	242
Unknown or Not Reported	11	8	19
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	236	118	354
No	14	7	21
Prior Lamivudine or FTC Treatment Units: Subjects			
Yes	43	23	66
No	207	102	309

Baseline Hepatitis B Virus Deoxyribonucleic Acid (HBV DNA) Units: log10 copies/mL			
arithmetic mean	6.86	6.98	
standard deviation	± 1.308	± 1.266	-
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	7.8	7.8	
standard deviation	± 2.45	± 2.2	-

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; as part of emtricitabine/tenofovir disoproxil fumarate (200/300 mg) fixed-dose combination (FDC) tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen 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/TDF (200/300 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.

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	250	125		
Units: percentage of participants				
number (not applicable)				
Yes	70.8	48.8		
No	29.2	51.2		

Statistical analyses

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

Statistical analysis description:

A two-sided 95% confidence interval (CI), stratified by baseline ALT (≤ 2 x ULN or > 2 x ULN) was used to evaluate the difference (tenofovir DF - adefovir dipivoxil) in the proportion of complete responders between treatment groups.

Comparison groups	TDF-TDF v ADV-TDF

Number of subjects included in analysis	375
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.001 [2]
Method	Z-test
Parameter estimate	Difference in proportions
Point estimate	23.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.2
upper limit	33.8
Variability estimate	Standard error of the mean
Dispersion value	5.2

Notes:

[1] - With a sample size of 200 subjects in the tenofovir DF group and 100 subjects in the adefovir dipivoxil 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 tenofovir DF treatment was inferior to the adefovir dipivoxil treatment (difference in proportions was less than -0.100) in favor of the alternative hypothesis that the tenofovir DF treatment was not inferior.

[2] - P-value corresponds to a Z-test of the null hypothesis that the stratum-adjusted (baseline ALT ≥ 2 x ULN or > 2 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	250	125		
Units: percentage of participants				
number (not applicable)	93.2	63.2		

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	375
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [3]
Method	Z-test
Parameter estimate	Difference in proportions
Point estimate	30.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.3
upper limit	39.2
Variability estimate	Standard error of the mean
Dispersion value	4.6

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 (≤ 2 x ULN or > 2 x ULN).

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

End point title	Percentage of Participants With HBV DNA < 400 Copies/mL at Weeks 96

End point description:

Participants in the Randomized and Treated Analysis Set 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:

Week 96

End point values	TDF-TDF	ADV-TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	234	122		
Units: percentage of participants				
number (not applicable)	90.6	89.3		

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	356
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.672 [4]
Method	Z-test
Parameter estimate	Difference in proportions
Point estimate	1.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	8
Variability estimate	Standard error of the mean
Dispersion value	3.4

Notes:

[4] - P-value corresponds to a Z-test of the null hypothesis that the stratum-adjusted difference is zero. Two-sided 95% confidence intervals, stratified by baseline ALT (baseline ALT ≤ 2 x ULN, > 2 x ULN), were used to evaluate treatment arm 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	241	121		
Units: percentage of participants				
number (not applicable)				
Week 144 (TDF-TDF: N = 241; ADV-TDF: N = 121)	86.7	88.4		
Week 192 (TDF-TDF: N = 238; ADV-TDF: N = 121)	84	86.8		
Week 240 (TDF-TDF: N = 232; ADV-TDF: N = 118)	82.8	83.9		
Week 288 (TDF-TDF: N = 231; ADV-TDF: N = 117)	80.5	82.9		
Week 336 (TDF-TDF: N = 230; ADV-TDF: N = 118)	77	78		
Week 384 (TDF-TDF: N = 230; ADV-TDF: N = 118)	74.3	76.3		

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	82	44		
Units: percentage of participants				
number (not applicable)				
Week 432 (TDF-TDF: N = 82; ADV-TDF: N = 44)	97.6	97.7		
Week 480 (TDF-TDF: N = 78; ADV-TDF: N = 40)	100	100		

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	241	117		
Units: log10 copies/mL				
arithmetic mean (standard deviation)				
Week 48 (TDF-TDF: N = 241; ADV-TDF: N = 117)	-4.57 (± 1.347)	-4.07 (± 1.331)		
Week 96 (TDF-TDF: N = 220; ADV-TDF: N = 109)	-4.54 (± 1.4)	-4.74 (± 1.26)		
Week 144 (TDF-TDF: N = 215; ADV-TDF: N = 107)	-4.61 (± 1.285)	-4.77 (± 1.285)		

Week 192 (TDF-TDF: N = 205; ADV-TDF: N = 105)	-4.56 (± 1.371)	-4.75 (± 1.271)		
Week 240 (TDF-TDF: N = 195; ADV-TDF: N = 100)	-4.59 (± 1.288)	-4.77 (± 1.303)		
Week 288 (TDF-TDF: N = 189; ADV-TDF: N = 96)	-4.61 (± 1.31)	-4.81 (± 1.31)		
Week 336 (TDF-TDF: N = 180; ADV-TDF: N = 92)	-4.61 (± 1.329)	-4.81 (± 1.307)		
Week 384 (TDF-TDF: N = 174; ADV-TDF: N = 89)	-4.56 (± 1.333)	-4.79 (± 1.314)		
Week 432 (TDF-TDF: N = 82; ADV-TDF: N = 44)	-4.6 (± 1.376)	-4.69 (± 1.37)		
Week 480 (TDF-TDF: N = 78; ADV-TDF: N = 40)	-4.57 (± 1.329)	-4.75 (± 1.349)		

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	220	109		
Units: log10 copies/mL				
arithmetic mean (standard deviation)				
Week 96 (TDF-TDF: N = 220; ADV-TDF: N = 109)	0.02 (± 0.424)	-0.6 (± 1.138)		
Week 144 (TDF-TDF: N = 215; ADV-TDF: N = 107)	-0.03 (± 0.378)	-0.63 (± 1.169)		
Week 192 (TDF-TDF: N = 205; ADV-TDF: N = 105)	0.01 (± 0.61)	-0.61 (± 1.161)		
Week 240 (TDF-TDF: N = 195; ADV-TDF: N = 100)	-0.04 (± 0.299)	-0.61 (± 1.195)		
Week 288 (TDF-TDF: N = 189; ADV-TDF: N = 96)	-0.04 (± 0.353)	-0.64 (± 1.203)		
Week 336 (TDF-TDF: N = 180; ADV-TDF: N = 92)	-0.05 (± 0.38)	-0.65 (± 1.23)		
Week 384 (TDF-TDF: N = 174; ADV-TDF: N = 89)	-0.02 (± 0.241)	-0.66 (± 1.237)		

Week 432 (TDF-TDF: N = 82; ADV-TDF: N = 44)	-0.04 (± 0.393)	-0.67 (± 1.378)		
Week 480 (TDF-TDF: N = 78; ADV-TDF: N = 40)	-0.05 (± 0.366)	-0.72 (± 1.283)		

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	250	125		
Units: percentage of participants				
number (not applicable)				
Yes	72.4	68.8		
No	27.6	31.2		

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	375
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.293 [5]
Method	Z-test
Parameter estimate	Difference in proportions
Point estimate	5.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	14.9
Variability estimate	Standard error of the mean
Dispersion value	5

Notes:

[5] - P-value corresponds to a Z-test of the null hypothesis that the stratum-adjusted difference is zero. Confidence interval stratum adjusted based on baseline ALT (≤ 2 x ULN, > 2 x 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	150	74		
Units: percentage of participants				
number (not applicable)				
Yes	87.3	85.1		
No	12.7	14.9		

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	234	113		
Units: units on a scale				
arithmetic mean (standard deviation)				
Knodell Necroinflammatory Score	-3.5 (± 2.5)	-3.4 (± 2.36)		
Ishak Necroinflammatory Score	-2.6 (± 1.93)	-2.6 (± 1.9)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Baseline in Knodell and Ishak Necroinflammatory Scores at Week 240

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 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	150	74		
Units: units on a scale				
arithmetic mean (standard deviation)				
Knodell Score	-4.6 (± 2.5)	-4.9 (± 2.53)		
Ishak Score	-4 (± 2.16)	-4.2 (± 2.38)		

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	250	125		
Units: percentage of participants				
number (not applicable)				
Improvement - Necroinflammation	82	81.6		
No Change - Necroinflammation	6.8	8		
Worsening - Necroinflammation	4.8	0.8		
Missing Data - Necroinflammation	6.4	9.6		
Improvement - Fibrosis	22	25.6		
No Change - Fibrosis	63.2	54.4		
Worsening - Fibrosis	8.4	10.4		
Missing Data - Fibrosis	6.4	9.6		

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	150	74		
Units: percentage of participants				
number (not applicable)				
Improvement - Necroinflammation	96.7	94.6		
No Change - Necroinflammation	2.7	1.4		
Worsening - Necroinflammation	0.7	4.1		
Improvement - Fibrosis	62	59.5		
No Change - Fibrosis	34	33.8		
Worsening - Fibrosis	4	6.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With ALT Normalization at Week 48

End point title	Percentage of Participants With 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	236	118		
Units: percentage of participants				
number (not applicable)	76.3	77.1		

Statistical analyses

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

Statistical analysis description:

Statistical tests were not adjusted for baseline ALT stratum. Analysis set included only randomized and treated participants with baseline ALT > ULN (biochemically evaluable analysis set).

Comparison groups	TDF-TDF v ADV-TDF
Number of subjects included in analysis	354
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.859 [6]
Method	Z-test
Parameter estimate	Difference in proportions
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.2
upper limit	8.5
Variability estimate	Standard error of the mean
Dispersion value	4.8

Notes:

[6] - P-value corresponds to a Z-test of the null hypothesis that the ALT stratum-adjusted difference is zero.

Secondary: Percentage of Participants With ALT Normalization at Weeks 96

End point title	Percentage of Participants With ALT Normalization at Weeks 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	221	111		
Units: percentage of participants				
number (not applicable)	72.4	68.5		

Statistical analyses

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

Statistical analysis description:

Difference, standard error of the difference, and confidence interval are stratum adjusted (baseline ALT ≤ 2 x ULN or > 2 x ULN).

Comparison groups	ADV-TDF v TDF-TDF
Number of subjects included in analysis	332
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.359 [7]
Method	Z-test
Parameter estimate	Difference in proportions
Point estimate	4.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	15.3
Variability estimate	Standard error of the mean
Dispersion value	5.3

Notes:

[7] - P-value corresponds to a Z-test of the null hypothesis that the ALT stratum-adjusted difference is zero.

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	226	110		
Units: percentage of participants				
number (not applicable)				
Week 144 (TDF-TDF: N = 226; ADV-TDF: N = 110)	74.3	70		
Week 192 (TDF-TDF: N = 223; ADV-TDF: N = 110)	68.2	76.4		
Week 240 (TDF-TDF: N = 219; ADV-TDF: N = 107)	70.3	75.7		
Week 288 (TDF-TDF: N = 216; ADV-TDF: N = 107)	69.9	72.9		
Week 336 (TDF-TDF: N = 217; ADV-TDF: N = 107)	65.9	65.4		
Week 384 (TDF-TDF: N = 216; ADV-TDF: N = 107)	65.3	69.2		

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	240	117		
Units: units per liter				
arithmetic mean (standard deviation)				
Week 48 (TDF-TDF: N = 240; AVD-TDF: N = 117)	-95 (± 102.31)	-124.4 (± 137.23)		
Week 96 (TDF-TDF: N = 219; AVD-TDF: N = 108)	-93.7 (± 106.66)	-138.5 (± 155.75)		
Week 144 (TDF-TDF: N = 214; AVD-TDF: N = 106)	-99.1 (± 105.67)	-140 (± 155.43)		
Week 192 (TDF-TDF: N = 204; AVD-TDF: N = 104)	-99.6 (± 109.46)	-140.3 (± 153.89)		
Week 240 (TDF-TDF: N = 196; AVD-TDF: N = 100)	-97.7 (± 104.32)	-139.5 (± 156.9)		

Week 288 (TDF-TDF: N = 187; AVD-TDF: N = 97)	-98.9 (± 104.66)	-134.7 (± 152.9)		
Week 336 (TDF-TDF: N = 180; AVD-TDF: N = 92)	-98.9 (± 106.5)	-143.1 (± 160.15)		
Week 384 (TDF-TDF: N = 172; AVD-TDF: N = 89)	-96.1 (± 105.43)	-132.6 (± 142.09)		
Week 432 (TDF-TDF: N = 82; AVD-TDF: N = 43)	-97 (± 115.09)	-131.9 (± 136.65)		
Week 480 (TDF-TDF: N = 78; AVD-TDF: N = 40)	-94.9 (± 117.6)	-129.2 (± 139.24)		

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	219	108		
Units: units per liter				
arithmetic mean (standard deviation)				
Week 96 (TDF-TDF: N = 219; ADV-TDF: N = 108)	2.4 (± 22.01)	-0.6 (± 19.87)		
Week 144 (TDF-TDF: N = 214; ADV-TDF: N = 106)	-0.6 (± 12.91)	-0.3 (± 22.48)		
Week 192 (TDF-TDF: N = 204; ADV-TDF: N = 104)	0.7 (± 23.07)	-3.6 (± 22.77)		
Week 240 (TDF-TDF: N = 196; ADV-TDF: N = 100)	-2.5 (± 14.64)	-3.9 (± 20)		
Week 288 (TDF-TDF: N = 187; ADV-TDF: N = 97)	-3.9 (± 13.35)	-4.1 (± 22.3)		
Week 336 (TDF-TDF: N = 180; ADV-TDF: N = 92)	-2.6 (± 15.69)	-2 (± 20.61)		
Week 384 (TDF-TDF: N = 172; ADV-TDF: N = 89)	-2.9 (± 14.13)	-3.9 (± 21)		
Week 432 (TDF-TDF: N = 82; ADV-TDF: N = 43)	-4.6 (± 15.65)	-8.9 (± 29.12)		
Week 480 (TDF-TDF: N = 78; ADV-TDF: N = 40)	-2.8 (± 15.92)	-5.9 (± 24.12)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Participants With Hepatitis B S-Antigen (HBsAg) Loss or Seroconversion Antibody to HBs (Anti-HBs) 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 were analyzed. The missing = failure approach was used.

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	250	125		
Units: percentage of participants				
number (not applicable)				
HBsAg Loss	0	0		
Seroconversion to anti-HBs	0	0		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

Randomized and Treated Analysis Set. 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	242	121		
Units: percentage of participants				
number (not applicable)				
HBsAg Loss	0	0		
Anti-HBs Seroconversion	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HBsAg Loss and/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 and/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.

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	250	123		
Units: percentage of participants				
number (not applicable)				
HBsAg Loss - Week 144	0	0		
Anti-HBs Seroconversion - Week 144	0	0		
HBsAg Loss - Week 192	0	0		
Anti-HBs Seroconversion - Week 192	0	0		
HBsAg Loss - Week 240	0	0.8		
Anti-HBs Seroconversion - Week 240	0	0		
HBsAg Loss - Week 288	0	0.8		
Anti-HBs Seroconversion - Week 288	0	0.8		
HBsAg Loss - Week 336	0	0.8		
Anti-HBs Seroconversion - Week 336	0	0.8		
HBsAg Loss - Week 384	0.8	0.8		

Anti-HBs Seroconversion - Week 384	0.4	0.8		
HBsAg Loss - Week 432	1.2	1.6		
Anti-HBs Seroconversion - Week 432	0.4	0.8		
HBsAg Loss - Week 480	1.2	2.4		
Anti-HBs Seroconversion - Week 480	0.8	0.8		

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 ≥ 400 copies/mL at Week 48, those with viral breakthrough, and those who discontinued after Week 24 with HBV DNA ≥ 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	250	125		
Units: participants				
Participants evaluated	8	42		
Changes at conserved sites in HBV polymerase	0	7		
Changes at polymorphic sites in HBV polymerase	3	14		
No genotypic changes (wild-type virus)	4	20		
Unable to be genotyped	1	1		

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 ≥ 400 copies/mL at Week 96 on TDF monotherapy, those with viral breakthrough, those who discontinued after Week 48 with HBV DNA ≥ 400 copies/mL, and those who added emtricitabine to the open-label TDF regimen and had HBV DNA ≥ 400 copies/mL at the time of the addition. No participants in the ADV-TDF group that added FTC to their study regimen in the open-label period met this criteria so no data is presented for this group (ADV-TDF With Addition of FTC).

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	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	235	2	112	
Units: participants				
Participants evaluated	6	1	0	
Changes at conserved sites within HBV polymerase	0	0	0	
Changes at polymorphic sites in HBV polymerase	2	1	0	
No genotypic changes (wild-type virus)	4	0	0	
Unable to be genotyped	0	0	0	

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 ≥ 400 copies/mL at Week 144 on TDF monotherapy, those with viral breakthrough, those who discontinued after Week 96 with HBV DNA ≥ 400 copies/mL, and those who added emtricitabine to the open-label TDF regimen after Week 96 and had HBV DNA ≥ 400 copies/mL at the time of the addition. No participants in the ADV-TDF group that added FTC to their study regimen in the open-label period met this criteria so no data is presented for this group (ADV-TDF With Addition of FTC).

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	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	235	2	112	
Units: participants				
Participants evaluated	6	1	0	
Changes at conserved sites within HBV polymerase	0	0	0	
Changes at polymorphic sites in HBV polymerase	2	1	0	
No genotypic changes (wild-type virus)	4	0	0	
Unable to be genotyped	0	0	0	

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 ≥ 400 copies/mL at Week 192 on TDF monotherapy, those with viral breakthrough, those who discontinued after Week 144 with HBV DNA ≥ 400 copies/mL, and those who added emtricitabine to the open-label TDF regimen after Week 144 and had HBV DNA ≥ 400 copies/mL at the time of the addition. No participants in the ADV-TDF group that added FTC to their study regimen in the open-label period met this criteria so no data is presented for this group (ADV-TDF With Addition of FTC).

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	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	215	3	109	
Units: participants				
Participants evaluated	3	1	0	
Changes at conserved sites within HBV polymerase	0	0	0	
Changes at polymorphic sites in HBV polymerase	1	0	0	

No genotypic changes (wild-type virus)	1	1	0	
Unable to genotype	1	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 ≥ 400 copies/mL at Week 240 on TDF monotherapy, those with viral breakthrough, those who discontinued after Week 192 with HBV DNA ≥ 400 copies/mL, and those who added emtricitabine to the open-label TDF regimen after Week 192 and had HBV DNA ≥ 400 copies/mL at the time of the addition. No participants in the ADV-TDF group that added FTC to their study regimen in the open-label period met this criteria so no data is presented for this group (ADV-TDF With Addition of FTC).

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	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	204	3	105	
Units: participants				
Participants evaluated	1	2	2	
Changes at conserved sites within HBV polymerase	1	0	0	
Changes at polymorphic sites in HBV polymerase	0	2	0	
No genotypic changes (wild-type virus)	0	0	0	
Unable to genotype	0	0	2	

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 ≥ 400 copies/mL at Week 288 on TDF monotherapy, those with viral breakthrough, those who discontinued after Week 240 with HBV DNA ≥ 400 copies/mL, and those who added emtricitabine to the open-label TDF regimen after Week 240 and had HBV DNA ≥ 400 copies/mL at the time of the addition. No participants in the ADV-TDF group that added FTC to their study regimen in the open-label period met this criteria so no data is presented for this group (ADV-TDF With Addition of FTC).

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	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	195	3	102	
Units: participants				
Participants evaluated	3	1	1	
Changes at conserved sites within HBV polymerase	0	0	0	
Changes at polymorphic sites in HBV polymerase	2	1	1	
No genotypic changes (wild-type virus)	1	0	0	
Unable to genotype	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 ≥ 400 copies/mL at Week 336 on TDF monotherapy, those with viral breakthrough, those who discontinued after Week 288 with HBV DNA ≥ 400 copies/mL, and those who added emtricitabine to the open-label TDF regimen after Week 288 and had HBV DNA ≥ 400 copies/mL at the time of the addition. No participants in the ADV-TDF group that added FTC to their study regimen in the open-label period met this criteria so no data is presented for this group (ADV-TDF With Addition of FTC).

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	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	189	3	97	
Units: participants				
Participants evaluated	0	1	1	
Changes at conserved sites within HBV polymerase	0	0	0	
Changes at polymorphic sites in HBV polymerase	0	0	0	
No genotypic changes (wild-type virus)	0	1	0	
Unable to genotype	0	0	1	

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 ≥ 400 copies/mL at Week 384 on TDF monotherapy, those with viral breakthrough, those who discontinued after Week 336 with HBV DNA ≥ 400 copies/mL, and those who added emtricitabine to the open-label TDF regimen after Week 336 and had HBV DNA ≥ 400 copies/mL at the time of the addition. No participants in the ADV-TDF group that added FTC to their study regimen in the open-label period met this criteria so no data is presented for this group (ADV-TDF With Addition of FTC).

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	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	177	3	92	
Units: participants				
Participants evaluated	1	0	0	
Changes at conserved sites within HBV polymerase	0	0	0	
Changes at polymorphic sites in HBV polymerase	0	0	0	

No genotypic changes (wild-type virus)	0	0	0	
Unable to genotype	1	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 ≥ 400 copies/mL at Week 432 on TDF monotherapy, those with viral breakthrough, those who discontinued after Week 384 with HBV DNA ≥ 400 copies/mL, and those who added emtricitabine to the open-label TDF regimen after Week 384 and had HBV DNA ≥ 400 copies/mL at the time of the addition. No participants in the ADV-TDF group that added FTC to their study regimen in the open-label period met this criteria so no data is presented for this group (ADV-TDF With Addition of FTC).

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	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	81	1	46	
Units: participants				
Participants evaluated	2	0	1	
Changes at conserved sites within HBV polymerase	0	0	0	
Changes at polymorphic sites in HBV polymerase	0	0	1	
No genotypic changes (wild-type virus)	2	0	0	
Unable to genotype	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 ≥ 400 copies/mL at Week 480 on TDF monotherapy, those with viral breakthrough, those who discontinued after Week 432 with HBV DNA ≥ 400 copies/mL, and those who added emtricitabine to the open-label TDF regimen after Week 432 and had HBV DNA ≥ 400 copies/mL at the time of the addition. No participants in the ADV-TDF group that added FTC to their study regimen in the open-label period met this criteria so no data is presented for this group (ADV-TDF With Addition of FTC).

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	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	81	1	43	
Units: participants				
Participants evaluated	0	0	0	
Changes at conserved sites within HBV polymerase	0	0	0	
Changes at polymorphic sites in HBV polymerase	0	0	0	
No genotypic changes (wild-type virus)	0	0	0	
Unable to genotype	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	74	39		
Units: percentage of participants				
number (not applicable)				
Week 432 (TDF-TDF: N = 74; ADV-TDF: N = 39)	86.5	87.2		
Week 480 (TDF-TDF: N = 70; ADV-TDF: N = 36)	80	88.9		

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 medication.

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 384), 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 (as part of FTC/TDF (200/300 mg) FDC tablet) to their treatment regimen 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	12 / 250 (4.80%)	7 / 125 (5.60%)	90 / 347 (25.94%)
number of deaths (all causes)	0	0	15
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder neoplasm			

subjects affected / exposed	1 / 250 (0.40%)	0 / 125 (0.00%)	0 / 347 (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
Cervix carcinoma			
subjects affected / exposed	1 / 250 (0.40%)	1 / 125 (0.80%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangiocarcinoma			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Colon cancer			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
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 neoplasm			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Craniopharyngioma			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric cancer			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal carcinoma			

subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatocellular carcinoma			
subjects affected / exposed	2 / 250 (0.80%)	0 / 125 (0.00%)	8 / 347 (2.31%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Leiomyoma			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukaemia			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liposarcoma			
subjects affected / exposed	0 / 250 (0.00%)	1 / 125 (0.80%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung cancer metastatic			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lung neoplasm malignant			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metastases to peritoneum			

subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic gastric cancer			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mixed hepatocellular cholangiocarcinoma			
subjects affected / exposed	1 / 250 (0.40%)	0 / 125 (0.00%)	0 / 347 (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
Nasopharyngeal cancer			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	2 / 347 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Prostate cancer			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salivary gland adenoma			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
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			
Arteritis			

subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	0 / 250 (0.00%)	1 / 125 (0.80%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
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 / 250 (0.00%)	0 / 125 (0.00%)	4 / 347 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Condition aggravated			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Granuloma			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 250 (0.40%)	0 / 125 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Fibrocystic breast disease			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst ruptured			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchiectasis			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lung disorder			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bipolar disorder			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delusional disorder, unspecified type			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 250 (0.00%)	1 / 125 (0.80%)	2 / 347 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dissociative disorder			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	2 / 347 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia, paranoid type			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 250 (1.20%)	0 / 125 (0.00%)	2 / 347 (0.58%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase			

increased			
subjects affected / exposed	1 / 250 (0.40%)	0 / 125 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis B DNA increased			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Arterial injury			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	2 / 347 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Head injury			
subjects affected / exposed	1 / 250 (0.40%)	0 / 125 (0.00%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Limb injury			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	2 / 347 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	2 / 347 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
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 hypotension			
subjects affected / exposed	0 / 250 (0.00%)	1 / 125 (0.80%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			

subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Tibia fracture			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
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			
Angina pectoris			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	2 / 347 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	2 / 347 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			

subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	2 / 347 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic neuropathy			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
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 neuralgia			
subjects affected / exposed	0 / 250 (0.00%)	1 / 125 (0.80%)	0 / 347 (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
Loss of consciousness			

subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
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 / 250 (0.00%)	0 / 125 (0.00%)	2 / 347 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Eye disorders			
Lens disorder			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal hernia			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	2 / 347 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 250 (0.40%)	0 / 125 (0.00%)	0 / 347 (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
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	2 / 347 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			

subjects affected / exposed	1 / 250 (0.40%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	2 / 347 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	2 / 347 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cirrhosis			

subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatitis			
subjects affected / exposed	0 / 250 (0.00%)	1 / 125 (0.80%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver disorder			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urogenital fistula			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
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			
Back pain			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bone cyst			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	3 / 347 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myopathy toxic			
subjects affected / exposed	0 / 250 (0.00%)	1 / 125 (0.80%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteitis			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteopenia			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporosis			

subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tenosynovitis stenosans			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
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 limb			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	3 / 347 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 250 (0.40%)	0 / 125 (0.00%)	0 / 347 (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
Liver abscess			

subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	5 / 347 (1.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pneumococcal			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
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 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			

subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
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			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 250 (0.00%)	1 / 125 (0.80%)	0 / 347 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 250 (0.00%)	0 / 125 (0.00%)	1 / 347 (0.29%)
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	121 / 250 (48.40%)	61 / 125 (48.80%)	256 / 347 (73.78%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 250 (0.80%)	5 / 125 (4.00%)	20 / 347 (5.76%)
occurrences (all)	2	5	23
Creatinine renal clearance decreased			
subjects affected / exposed	0 / 250 (0.00%)	1 / 125 (0.80%)	30 / 347 (8.65%)
occurrences (all)	0	2	33
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	11 / 250 (4.40%)	9 / 125 (7.20%)	11 / 347 (3.17%)
occurrences (all)	11	10	11
Vascular disorders			

Hypertension			
subjects affected / exposed	9 / 250 (3.60%)	5 / 125 (4.00%)	53 / 347 (15.27%)
occurrences (all)	10	5	60
Nervous system disorders			
Dizziness			
subjects affected / exposed	11 / 250 (4.40%)	4 / 125 (3.20%)	18 / 347 (5.19%)
occurrences (all)	11	4	19
Headache			
subjects affected / exposed	26 / 250 (10.40%)	17 / 125 (13.60%)	49 / 347 (14.12%)
occurrences (all)	33	26	66
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	13 / 250 (5.20%)	9 / 125 (7.20%)	20 / 347 (5.76%)
occurrences (all)	13	9	22
Influenza like illness			
subjects affected / exposed	6 / 250 (2.40%)	2 / 125 (1.60%)	23 / 347 (6.63%)
occurrences (all)	9	2	40
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	5 / 250 (2.00%)	1 / 125 (0.80%)	18 / 347 (5.19%)
occurrences (all)	5	1	19
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	11 / 250 (4.40%)	6 / 125 (4.80%)	25 / 347 (7.20%)
occurrences (all)	12	7	33
Abdominal pain upper			
subjects affected / exposed	22 / 250 (8.80%)	10 / 125 (8.00%)	36 / 347 (10.37%)
occurrences (all)	25	11	45
Diarrhoea			
subjects affected / exposed	16 / 250 (6.40%)	8 / 125 (6.40%)	31 / 347 (8.93%)
occurrences (all)	17	9	39
Dyspepsia			
subjects affected / exposed	6 / 250 (2.40%)	6 / 125 (4.80%)	23 / 347 (6.63%)
occurrences (all)	7	7	28
Nausea			

subjects affected / exposed	15 / 250 (6.00%)	6 / 125 (4.80%)	14 / 347 (4.03%)
occurrences (all)	19	6	14
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 250 (4.40%)	4 / 125 (3.20%)	30 / 347 (8.65%)
occurrences (all)	13	5	36
Oropharyngeal pain			
subjects affected / exposed	7 / 250 (2.80%)	6 / 125 (4.80%)	23 / 347 (6.63%)
occurrences (all)	8	6	28
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	16 / 250 (6.40%)	0 / 125 (0.00%)	38 / 347 (10.95%)
occurrences (all)	17	0	49
Back pain			
subjects affected / exposed	18 / 250 (7.20%)	7 / 125 (5.60%)	54 / 347 (15.56%)
occurrences (all)	19	7	69
Osteopenia			
subjects affected / exposed	1 / 250 (0.40%)	0 / 125 (0.00%)	30 / 347 (8.65%)
occurrences (all)	1	0	31
Infections and infestations			
Influenza			
subjects affected / exposed	10 / 250 (4.00%)	3 / 125 (2.40%)	38 / 347 (10.95%)
occurrences (all)	12	3	55
Nasopharyngitis			
subjects affected / exposed	22 / 250 (8.80%)	12 / 125 (9.60%)	62 / 347 (17.87%)
occurrences (all)	29	13	106
Upper respiratory tract infection			
subjects affected / exposed	6 / 250 (2.40%)	5 / 125 (4.00%)	24 / 347 (6.92%)
occurrences (all)	7	5	38

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 September 2005	— 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 for 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.
23 December 2005	— Allowed up to 120 subjects to enroll who had previous exposure to emtricitabine or lamivudine — The ALT entry criterion was decreased from ≥ 1.5 times the upper limit of normal (ULN) to simply ≥ ULN — A provision for 10% variance for ALT and in time windows for study eligibility criteria (with approval of the medical monitor) was added. — 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	— 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.
09 September 2011	— For subjects who provided a separate informed consent form, the collection of a blood sample for biomarker analysis (including pharmacogenomics) was added. These samples may be used for exploration of appropriate markers that may be predictive of virologic response and/or the tolerability of HBV therapies. Provision of samples for these analyses will not necessarily benefit subjects participating in this study; however, results may prove beneficial in the design and/or analyses of future HBV studies, and may improve our understanding of biological factors influencing patient health and disease. — Instructions were added for subjects to have a dose modification to every 48 hour dosing if creatinine clearance (Clcr) decreased to between 30 to 49 mL/min. If creatinine clearance values were confirmed to be below 30 mL/min, the medical monitor was to be contacted. — The management of subjects who seroconvert was clarified. — Visit windows for protocol-specific visits were clarified.
17 January 2013	— The study was extended to 480 weeks for subjects who complete 384 weeks of study treatment under the original protocol. — Text was added providing instructions on Special Situations Reports. — Statements were added indicating that DEXA scans will not be performed beyond Week 384 due to unavailability of baseline values and the lack of decline in BMD from results available for Years 4 through 6. — The medical monitor for the study was changed.

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/25788199

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

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

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

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