



Clinical trial results:

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

Summary

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

Results information

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

Trial information

Trial identification

Sponsor protocol code	GS-US-174-0103
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Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

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

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements. This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 June 2005
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

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

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

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	271
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

603 participants were screened.

Period 1

Period 1 title	Double-blind Period Through Week 48
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
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Arm title	TDF-TDF
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Arm description:

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

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

Dosage and administration details:

300 mg administered once daily

Investigational medicinal product name	Adefovir dipivoxil placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered once daily

Arm title	ADV-TDF
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Arm description:

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

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

Dosage and administration details: 10 mg administered once daily	
Investigational medicinal product name	Tenofovir disoproxil fumarate placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Administered once daily	

Number of subjects in period 1^[1]	TDF-TDF	ADV-TDF
Started	176	90
Completed	165	85
Not completed	11	5
Withdrew Consent	4	2
Protocol Violation	1	1
Lost to follow-up	6	2

Notes:

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

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

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	TDF-TDF

Arm description:

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

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

Dosage and administration details:

300 mg administered once daily

Investigational medicinal product name	Adefovir dipivoxil placebo
Investigational medicinal product code	
Other name	

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

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

Notes:

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

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

Period 3

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

Arms

Are arms mutually exclusive?	Yes
Arm title	TDF-TDF

Arm description:

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

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

Dosage and administration details:

300 mg administered once daily

Investigational medicinal product name	Adefovir dipivoxil placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered once daily

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

Routes of administration	Oral use
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Dosage and administration details:

200/300 mg FDC tablet administered once daily

Arm title	ADV-TDF
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Arm description:

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

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

Dosage and administration details:

10 mg administered once daily

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

Dosage and administration details:

Administered once daily

Investigational medicinal product name	Tenofovir disoproxil fumarate
Investigational medicinal product code	
Other name	TDF, Viread®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

300 mg administered once daily

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

Dosage and administration details:

200/300 mg FDC tablet administered once daily

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

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

Period 4

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

Arms

Are arms mutually exclusive?	Yes
Arm title	TDF-TDF

Arm description:

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

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

Dosage and administration details:

300 mg administered once daily

Investigational medicinal product name	Adefovir dipivoxil placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered once daily

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

Dosage and administration details:

200/300 mg FDC tablet administered once daily

Arm title	ADV-TDF
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Arm description:

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

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

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

Period 5

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

Arms

Are arms mutually exclusive?	Yes
Arm title	TDF-TDF

Arm description:

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

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

Dosage and administration details:

300 mg administered once daily

Investigational medicinal product name	Adefovir dipivoxil placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered once daily

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

Dosage and administration details:

200/300 mg FDC tablet administered once daily

Arm title	ADV-TDF
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Arm description:

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

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

Dosage and administration details:

10 mg administered once daily

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

Dosage and administration details:

Administered once daily

Investigational medicinal product name	Tenofovir disoproxil fumarate
Investigational medicinal product code	
Other name	TDF, Viread®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

300 mg administered once daily

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

Dosage and administration details:

200/300 mg FDC tablet administered once daily

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

Period 6

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

Arms

Are arms mutually exclusive?	Yes
Arm title	TDF-TDF

Arm description:

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

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

Routes of administration	Oral use
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Dosage and administration details:

200/300 mg FDC tablet administered once daily

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

Period 7

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

Arms

Are arms mutually exclusive?	Yes
Arm title	TDF-TDF

Arm description:

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

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

Dosage and administration details:

300 mg administered once daily

Investigational medicinal product name	Adefovir dipivoxil placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered once daily

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

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

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

Period 8

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

Arms

Are arms mutually exclusive?	Yes
Arm title	TDF-TDF

Arm description:

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

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

Dosage and administration details:

300 mg administered once daily

Investigational medicinal product name	Adefovir dipivoxil placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered once daily

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

Dosage and administration details:

200/300 mg FDC tablet administered once daily

Arm title	ADV-TDF
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Arm description:

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

mg FDC tablet) in the open-label period.

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

Dosage and administration details:

10 mg administered once daily

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

Dosage and administration details:

Administered once daily

Investigational medicinal product name	Tenofovir disoproxil fumarate
Investigational medicinal product code	
Other name	TDF, Viread®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

300 mg administered once daily

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

Dosage and administration details:

200/300 mg FDC tablet administered once daily

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

Period 9

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

Arms

Are arms mutually exclusive?	Yes
Arm title	TDF-TDF

Arm description:

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

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

Dosage and administration details:

300 mg administered once daily

Investigational medicinal product name	Adefovir dipivoxil placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered once daily

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

Dosage and administration details:

200/300 mg FDC tablet administered once daily

Arm title	ADV-TDF
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Arm description:

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

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

Dosage and administration details:

10 mg administered once daily

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

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

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

Notes:

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

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

Period 10	
Period 10 title	Open-label Period Weeks 433 - 480
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes
Arm title	TDF-TDF

Arm description:

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

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

Routes of administration	Oral use
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Dosage and administration details:

200/300 mg FDC tablet administered once daily

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

Notes:

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

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

Baseline characteristics

Reporting groups

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

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

arithmetic mean	8.3	8.5	
standard deviation	± 2.11	± 2.07	-

End points

End points reporting groups

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

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

Reporting group title	ADV-TDF
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Reporting group description:

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

Reporting group title	TDF-TDF
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Reporting group description:

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

Reporting group title	ADV-TDF
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Reporting group description:

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

Reporting group title	TDF-TDF
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Reporting group description:

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

Reporting group title	ADV-TDF
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Reporting group description:

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

Reporting group title	TDF-TDF
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Reporting group description:

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

Reporting group title	ADV-TDF
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Reporting group description:

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

Reporting group title	TDF-TDF
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Reporting group description:

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

Reporting group title	ADV-TDF
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Reporting group description:

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

Subject analysis set title	TDF-TDF With No Addition of FTC
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Subject analysis set type	Sub-group analysis
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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
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

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

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

study regimen in the open-label period.

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

Subject analysis set description:

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

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

Subject analysis set description:

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

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

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

Baseline; Week 48

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

Statistical analyses

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

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

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

Notes:

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

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

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

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

Week 48

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

Statistical analyses

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

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

Notes:

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

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

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

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

Statistical analyses

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

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

Notes:

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

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

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

Weeks 432 and 480

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

Statistical analyses

No statistical analyses for this end point

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

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

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

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

End point values	TDF-TDF	ADV-TDF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	80		
Units: log ₁₀ IU/mL				
arithmetic mean (standard deviation)				
Week 96 (TDF-TDF: N = 144; ADV-TDF: N = 80)	-0.1 ($\pm$ 0.422)	-2.43 ($\pm$ 1.724)		
Week 144 (TDF-TDF: N = 131; ADV-TDF: N = 72)	-0.19 ($\pm$ 0.475)	-2.27 ($\pm$ 1.866)		
Week 192 (TDF-TDF: N = 117; ADV-TDF: N = 67)	-0.2 ($\pm$ 0.565)	-2.41 ($\pm$ 1.662)		
Week 240 (TDF-TDF: N = 105; ADV-TDF: N = 60)	-0.14 ($\pm$ 0.706)	-2.49 ($\pm$ 1.599)		
Week 288 (TDF-TDF: N = 101; ADV-TDF: N = 62)	-0.18 ($\pm$ 0.762)	-2.62 ($\pm$ 1.679)		
Week 336 (TDF-TDF: N = 94; ADV-TDF: N = 57)	-0.25 ($\pm$ 0.618)	-2.59 ($\pm$ 1.622)		
Week 384 (TDF-TDF: N = 83; ADV-TDF: N = 55)	-0.29 ($\pm$ 0.643)	-2.34 ($\pm$ 1.821)		

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

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Histological Response at Week 48

End point title	Percentage of Participants With Histological Response at Week 48
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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
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End point timeframe:

Baseline; Week 48

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

Statistical analyses

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

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

Notes:

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

Secondary: Percentage of Participants With Histological Response at Week 240

End point title	Percentage of Participants With Histological Response at Week 240
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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
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End point timeframe:

Baseline; Week 240

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

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Baseline in Knodell and Ishak Necroinflammatory Scores at Week 48
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End point description:

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

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

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

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

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Baseline in Knodel and Ishak Necroinflammatory Scores at Week 240
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End point description:

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

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Ranked Assessment of Necroinflammation and Fibrosis at Week 48

End point title	Ranked Assessment of Necroinflammation and Fibrosis at Week 48
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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
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End point timeframe:

Baseline; Week 48

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

Statistical analyses

No statistical analyses for this end point

Secondary: Ranked Assessment of Necroinflammation and Fibrosis at Week 240

End point title	Ranked Assessment of Necroinflammation and Fibrosis at Week 240
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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
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End point timeframe:

Baseline; Week 240

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

Statistical analyses

No statistical analyses for this end point

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

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

Baseline; Week 48

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

Statistical analyses

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

Notes:

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

Secondary: Percentage of Participants With ALT Normalization at Week 96

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

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

Statistical analyses

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

Notes:

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

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

End point title	Percentage of Participants With ALT Normalization at Weeks 144, 192, 240, 288, 336, and 384
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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 $\geq$ 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
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End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

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

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

End point type	Secondary
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End point timeframe:

Baseline; Week 48

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

Statistical analyses

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

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

Notes:

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

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

Notes:

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

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

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

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

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

End point type	Secondary
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End point timeframe:

Baseline; Week 96

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

Statistical analyses

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

Notes:

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

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

Notes:

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

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

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

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

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

End point type	Secondary
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End point timeframe:

Baseline; Week 48

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

Statistical analyses

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

Notes:

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

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

Notes:

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

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

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

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

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

End point type	Secondary
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End point timeframe:

Baseline; Week 96

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

Statistical analyses

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

Notes:

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

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

Notes:

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

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

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

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

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

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

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

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

End point type	Secondary
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End point timeframe:

Baseline; Week 48

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

Statistical analyses

No statistical analyses for this end point

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

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

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

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

End point type	Secondary
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End point timeframe:

Baseline; Weeks 49 to 96

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

Statistical analyses

No statistical analyses for this end point

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

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

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

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

End point type	Secondary
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End point timeframe:

Baseline; Weeks 97 to 144

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

Statistical analyses

No statistical analyses for this end point

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

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

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

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

End point type	Secondary
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End point timeframe:

Baseline; Weeks 145 to 192

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

Statistical analyses

No statistical analyses for this end point

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

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

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

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

End point type	Secondary
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End point timeframe:

Baseline; Weeks 193 to 240

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

Statistical analyses

No statistical analyses for this end point

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

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

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

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

End point type	Secondary
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End point timeframe:

Baseline; Weeks 241 to 288

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

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

Statistical analyses

No statistical analyses for this end point

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

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

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

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

End point type	Secondary
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End point timeframe:

Baseline; Weeks 289 to 336

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

Statistical analyses

No statistical analyses for this end point

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

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

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

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

End point type	Secondary
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End point timeframe:

Baseline; Weeks 337 to 384

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

Statistical analyses

No statistical analyses for this end point

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

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

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

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

End point type	Secondary
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End point timeframe:

Baseline; Weeks 385 to 432

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

Statistical analyses

No statistical analyses for this end point

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

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

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

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

End point type	Secondary
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End point timeframe:

Baseline; Weeks 433 to 480

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

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Participants With ALT Normalization at Weeks 432 and 480
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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
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End point timeframe:

Baseline; Weeks 432 and 480

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to Week 480

Adverse event reporting additional description:

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

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Double-Blind TDF
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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
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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
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Reporting group description:

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

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

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

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

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

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

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

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

Cholelithiasis			
subjects affected / exposed	1 / 176 (0.57%)	0 / 90 (0.00%)	0 / 238 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	1 / 176 (0.57%)	0 / 90 (0.00%)	1 / 238 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	0 / 176 (0.00%)	0 / 90 (0.00%)	3 / 238 (1.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 176 (0.00%)	0 / 90 (0.00%)	1 / 238 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 176 (0.00%)	1 / 90 (1.11%)	0 / 238 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 176 (0.00%)	0 / 90 (0.00%)	1 / 238 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporosis			
subjects affected / exposed	0 / 176 (0.00%)	0 / 90 (0.00%)	1 / 238 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovial cyst			
subjects affected / exposed	0 / 176 (0.00%)	0 / 90 (0.00%)	1 / 238 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations Abscess soft tissue subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 176 (0.57%) 0 / 1 0 / 0	 0 / 90 (0.00%) 0 / 0 0 / 0	 0 / 238 (0.00%) 0 / 0 0 / 0
Diverticulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 176 (0.00%) 0 / 0 0 / 0	 0 / 90 (0.00%) 0 / 0 0 / 0	 1 / 238 (0.42%) 0 / 1 0 / 0
Epididymitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 176 (0.00%) 0 / 0 0 / 0	 0 / 90 (0.00%) 0 / 0 0 / 0	 1 / 238 (0.42%) 0 / 1 0 / 0
Gastroenteritis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 176 (0.00%) 0 / 0 0 / 0	 0 / 90 (0.00%) 0 / 0 0 / 0	 1 / 238 (0.42%) 0 / 1 0 / 0
Groin abscess subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 176 (0.00%) 0 / 0 0 / 0	 0 / 90 (0.00%) 0 / 0 0 / 0	 1 / 238 (0.42%) 0 / 1 0 / 0
Hepatitis B subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 176 (0.57%) 1 / 1 0 / 0	 0 / 90 (0.00%) 0 / 0 0 / 0	 0 / 238 (0.00%) 0 / 0 0 / 0
Orchitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 176 (0.00%) 0 / 0 0 / 0	 0 / 90 (0.00%) 0 / 0 0 / 0	 1 / 238 (0.42%) 0 / 1 0 / 0
Respiratory tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 176 (0.00%) 0 / 0 0 / 0	 0 / 90 (0.00%) 0 / 0 0 / 0	 1 / 238 (0.42%) 0 / 1 0 / 0
Sepsis			

subjects affected / exposed	0 / 176 (0.00%)	0 / 90 (0.00%)	1 / 238 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 176 (0.00%)	0 / 90 (0.00%)	1 / 238 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 176 (0.00%)	0 / 90 (0.00%)	1 / 238 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 176 (0.00%)	0 / 90 (0.00%)	1 / 238 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Double-Blind TDF	Double-Blind ADV	Open-Label TDF
Total subjects affected by non-serious adverse events			
subjects affected / exposed	97 / 176 (55.11%)	49 / 90 (54.44%)	165 / 238 (69.33%)
Investigations			
Creatinine renal clearance decreased			
subjects affected / exposed	1 / 176 (0.57%)	1 / 90 (1.11%)	12 / 238 (5.04%)
occurrences (all)	1	1	13
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 176 (1.70%)	1 / 90 (1.11%)	24 / 238 (10.08%)
occurrences (all)	3	1	27
Nervous system disorders			
Dizziness			
subjects affected / exposed	12 / 176 (6.82%)	2 / 90 (2.22%)	11 / 238 (4.62%)
occurrences (all)	13	2	11
Headache			

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 September 2005	— The treatment phase of the study was extended to 240 weeks to evaluate long-term virological, serological, and biochemical response, as well as the safety profile observed among subjects initiating double-blind treatment with tenofovir DF and maintained on tenofovir DF (early) versus subjects initiating double-blind treatment with adefovir dipivoxil and switching to tenofovir DF at the end of the first year (deferred). — Statistical analysis of the antiviral and safety parameters at Week 96 (and every 48 weeks thereafter) was added to evaluate continuous (early) tenofovir DF treatment versus secondary (deferred) tenofovir DF treatment based on randomization to double-blind tenofovir DF or adefovir dipivoxil, respectively, at study entry in the first year. The original treatment assignment is to remain blinded to the subject and the investigator for the entire 240 weeks of the study. — A final required liver biopsy was added at Week 240. — To help characterize a role for combination therapy in subjects with persistent viral replication or incomplete virologic response, a provision was added allowing subjects with HBV DNA ≥ 400 copies/mL at or after Week 72, confirmed on two consecutive visits, to be eligible to remain on tenofovir DF, switch to emtricitabine 200 mg/tenofovir DF 300 mg combination tablet taken QD, or initiate commercially available HBV therapy.
14 September 2005	— A substudy was planned for sites in France, Germany, and the Netherlands to measure hepatic covalently closed circular DNA (cccDNA) in approximately 45 subjects (approximately 15 adefovir dipivoxil subjects and 30 tenofovir DF subjects) at baseline, Week 144, and Week 240. The substudy required an additional liver biopsy at Year 3, during which additional tissue samples would be collected for analysis of intrahepatic HBV DNA levels and for immunostaining. a. Post-amendment note: No subjects enrolled in the substudy; thus, the substudy was not conducted.
22 December 2005	— Subjects were allowed to enroll with up to 10% variance from the stated eligibility criterion for ALT ($> 2 \times \text{ULN}$ and no more than $10 \times \text{ULN}$) and/or in time windows for study eligibility criteria, with approval of the medical monitor. — The primary efficacy and safety analysis sets were redefined as all randomized subjects who received at least one dose of study medication.
27 June 2008	— The study duration was extended to 384 weeks (8 years). — Annual dual energy x-ray absorptiometry (DEXA) scans of the hip and spine from Week 192 to Week 384 were added to monitor for changes in bone mineral density (BMD). — Added recommendation that subjects remain on study treatment until HBsAg loss or seroconversion to anti-HBs since seroconversion to anti-HBe does not preclude the development of precore mutations. — Strengthened the protocol language recommending intensification of TDF therapy with emtricitabine 200 mg after Week 72 in order to help minimize the risk of developing resistance mutations associated with persistent viremia and continued monotherapy treatment.

13 September 2011	— Instructions were added for the collection of an optional blood sample from subjects who provided a separate informed consent form for biomarker analysis (including pharmacogenomics). These samples may be used for exploration of appropriate markers that may be predictive of virologic response and/or the tolerability of HBV therapies. — Instructions were added for subjects with creatinine clearance (CLcr) between 30 to 49 mL/min to have a dose modification to every 48 hours dosing. — Clarification was added about management of subjects who HBsAg seroconvert. — Clarification was added about visit windows for protocol-specific visits.
24 January 2013	— Study was extended to 480 weeks for subjects who completed 384 weeks of study treatment under the original protocol. — Instructions were added for reporting events categorized as special situations. — Clarification was added that dual energy x-ray absorptiometry (DEXA) scans will not be performed beyond Week 384 due to unavailability of baseline values and the lack of decline in bone mineral density from results available for Year 4 through Year 6.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

There were no limitations affecting the analysis or results.

Notes:

Online references

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

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

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

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