



Clinical trial results:

A Phase 2, Randomized, Open-Label Study to Evaluate the Safety and Efficacy of GS-4774 in Combination With Tenofovir Disoproxil Fumarate (TDF) for the Treatment of Subjects With Chronic Hepatitis B and Who Are Currently Not on Treatment

Summary

EudraCT number	2014-001011-39
Trial protocol	IT
Global end of trial date	30 May 2018

Results information

Result version number	v1 (current)
This version publication date	31 May 2019
First version publication date	31 May 2019

Trial information

Trial identification

Sponsor protocol code	GS-US-330-1401
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02174276
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	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com
Scientific contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 February 2016
Global end of trial reached?	Yes
Global end of trial date	30 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study were as follows:

- To evaluate the safety and tolerability of GS-4774 in subjects with chronic hepatitis B infection (CHB)
- To evaluate the efficacy of GS-4774 at Week 24 as measured by mean change in serum HBsAg from Baseline (measured in log₁₀ IU/mL)

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	24 July 2014
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	Romania: 7
Country: Number of subjects enrolled	Italy: 13
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	Canada: 46
Country: Number of subjects enrolled	Korea, Republic of: 56
Country: Number of subjects enrolled	United States: 72
Worldwide total number of subjects	195
EEA total number of subjects	20

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	192
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in North America, Europe, New Zealand, and South Korea. The first participant was screened on 24 July 2014. The last study visit occurred on 30 May 2018.

Pre-assignment

Screening details:

254 participants were screened.

Period 1

Period 1 title	Study Treatment Phase (Weeks 1 to 48)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	TDF 48 Weeks

Arm description:

Participants received TDF 300 mg tablet orally once daily for 48 weeks during the main study. Participants had the option to continue receiving TDF 300 mg tablet orally once daily for up to 144 weeks (in optional treatment extension phase [OTEP]).

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

Dosage and administration details:

TDF 300 mg tablet administered orally once daily

Arm title	TDF + GS-4774 2 YU
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Arm description:

Participants received TDF 300 mg tablet orally once daily for 48 weeks + GS-4774 2 yeast units (YU) administered via subcutaneous injection every 4 weeks for 20 weeks (total of 6 doses). Participants had the option to continue receiving TDF 300 mg tablet orally once daily for up to 144 weeks (in OTEP).

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

Dosage and administration details:

TDF 300 mg tablet administered orally once daily

Investigational medicinal product name	GS-4774
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

GS-4774 subcutaneous injection administered every 4 weeks for a total of 6 doses

Arm title	TDF + GS-4774 10 YU
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Arm description:

Participants received TDF 300 mg tablet orally once daily for 48 weeks + GS-4774 10 YU administered via subcutaneous injection every 4 weeks for 20 weeks (total of 6 doses). Participants had the option to continue receiving TDF 300 mg tablet orally once daily for up to 144 weeks (in OTEP).

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

Dosage and administration details:

TDF 300 mg tablet administered orally once daily

Investigational medicinal product name	GS-4774
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

GS-4774 subcutaneous injection administered every 4 weeks for a total of 6 doses

Arm title	TDF + GS-4774 40 YU
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Arm description:

Participants received TDF 300 mg tablet orally once daily for 48 weeks + GS-4774 40 YU administered via subcutaneous injection every 4 weeks for 20 weeks (total of 6 doses). Participants had the option to continue receiving TDF 300 mg tablet orally once daily for up to 144 weeks (in OTEP).

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

Dosage and administration details:

TDF 300 mg tablet administered orally once daily

Investigational medicinal product name	GS-4774
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

GS-4774 subcutaneous injection administered every 4 weeks for a total of 6 doses

Number of subjects in period 1	TDF 48 Weeks	TDF + GS-4774 2 YU	TDF + GS-4774 10 YU
Started	27	57	56
Completed	26	56	53
Not completed	1	1	3
Pregnancy	-	-	1
Withdrawal by Subject	-	1	2
Lost to follow-up	1	-	-

Number of subjects in period 1	TDF + GS-4774 40 YU
Started	55
Completed	55
Not completed	0
Pregnancy	-
Withdrawal by Subject	-
Lost to follow-up	-

Period 2

Period 2 title	OTEP (Weeks 48 to 144)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	TDF 48 Weeks

Arm description:

Participants received TDF 300 mg tablet orally once daily for 48 weeks during the main study. Participants had the option to continue receiving TDF 300 mg tablet orally once daily for up to 144 weeks (in OTEP).

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

Dosage and administration details:

TDF 300 mg tablet administered orally once daily

Arm title	TDF + GS-4774 2 YU
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Arm description:

Participants received TDF 300 mg tablet orally once daily for 48 weeks + GS-4774 2 YU administered via subcutaneous injection every 4 weeks for 20 weeks (total of 6 doses). Participants had the option to continue receiving TDF 300 mg tablet orally once daily for up to 144 weeks (in OTEP).

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

Dosage and administration details:

TDF 300 mg tablet administered orally once daily

Investigational medicinal product name	GS-4774
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

GS-4774 subcutaneous injection administered every 4 weeks for a total of 6 doses

Arm title	TDF + GS-4774 10 YU
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Arm description:

Participants received TDF 300 mg tablet orally once daily for 48 weeks + GS-4774 10 YU administered via subcutaneous injection every 4 weeks for 20 weeks (total of 6 doses). Participants had the option to continue receiving TDF 300 mg tablet orally once daily for up to 144 weeks (in OTEP).

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

Dosage and administration details:

TDF 300 mg tablet administered orally once daily

Investigational medicinal product name	GS-4774
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

GS-4774 subcutaneous injection administered every 4 weeks for a total of 6 doses

Arm title	TDF + GS-4774 40 YU
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Arm description:

Participants received TDF 300 mg tablet orally once daily for 48 weeks + GS-4774 40 YU administered via subcutaneous injection every 4 weeks for 20 weeks (total of 6 doses). Participants had the option to continue receiving TDF 300 mg tablet orally once daily for up to 144 weeks (in OTEP).

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

Dosage and administration details:

TDF 300 mg tablet administered orally once daily

Investigational medicinal product name	GS-4774
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

GS-4774 subcutaneous injection administered every 4 weeks for a total of 6 doses

Number of subjects in period 2^[1]	TDF 48 Weeks	TDF + GS-4774 2 YU	TDF + GS-4774 10 YU
Started	26	54	51
Completed	25	54	48
Not completed	1	0	3
Withdrew Consent	1	-	1
Pregnancy	-	-	1
Lost to follow-up	-	-	1

Number of subjects in period 2^[1]	TDF + GS-4774 40 YU
Started	52
Completed	50
Not completed	2
Withdrew Consent	2
Pregnancy	-
Lost to follow-up	-

Notes:

[1] - 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: Seven participants (TDF+GS-4774 2 YU: 2; TDF+GS-4774 10 YU: 2; TDF+GS-4774 40 YU: 3) completing the study treatment phase did not continue in OTEP.

Baseline characteristics

Reporting groups

Reporting group title	TDF 48 Weeks
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Reporting group description:

Participants received TDF 300 mg tablet orally once daily for 48 weeks during the main study. Participants had the option to continue receiving TDF 300 mg tablet orally once daily for up to 144 weeks (in optional treatment extension phase [OTEP]).

Reporting group title	TDF + GS-4774 2 YU
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Reporting group description:

Participants received TDF 300 mg tablet orally once daily for 48 weeks + GS-4774 2 yeast units (YU) administered via subcutaneous injection every 4 weeks for 20 weeks (total of 6 doses). Participants had the option to continue receiving TDF 300 mg tablet orally once daily for up to 144 weeks (in OTEP).

Reporting group title	TDF + GS-4774 10 YU
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Reporting group description:

Participants received TDF 300 mg tablet orally once daily for 48 weeks + GS-4774 10 YU administered via subcutaneous injection every 4 weeks for 20 weeks (total of 6 doses). Participants had the option to continue receiving TDF 300 mg tablet orally once daily for up to 144 weeks (in OTEP).

Reporting group title	TDF + GS-4774 40 YU
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Reporting group description:

Participants received TDF 300 mg tablet orally once daily for 48 weeks + GS-4774 40 YU administered via subcutaneous injection every 4 weeks for 20 weeks (total of 6 doses). Participants had the option to continue receiving TDF 300 mg tablet orally once daily for up to 144 weeks (in OTEP).

Reporting group values	TDF 48 Weeks	TDF + GS-4774 2 YU	TDF + GS-4774 10 YU
Number of subjects	27	57	56
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	44	46	44
standard deviation	± 10.3	± 11.2	± 9.1
Gender categorical Units: Subjects			
Female	9	23	23
Male	18	34	33
Race Units: Subjects			
Asian	24	42	44
White	1	13	8
Black or African American	2	2	2
Native Hawaiian or Other Pacific Islander	0	0	2
Ethnicity Units: Subjects			
Not Hispanic or Latino	27	54	56
Not Permitted	0	3	0
Hepatitis B Envelope Antigen (HBeAg) Status at Baseline Units: Subjects			

Positive	10	22	23
Negative	17	35	33
Baseline Alanine Aminotransferase (ALT) Category			
Upper limit of normal (ULN) for ALT was defined as 19 U/L for women and 30 U/L for men.			
Units: Subjects			
≤ ULN	6	15	21
> ULN	21	42	35
Baseline Hepatitis B Surface Antigen (HBsAg)			
Units: log10 IU/mL			
arithmetic mean	3.8	3.7	3.7
standard deviation	± 0.78	± 0.82	± 0.94
Baseline Hepatitis B Virus (HBV) DNA			
Units: log10 IU/mL			
arithmetic mean	6.0	5.8	5.8
standard deviation	± 1.64	± 1.99	± 1.97

Reporting group values	TDF + GS-4774 40 YU	Total	
Number of subjects	55	195	
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	43	-	
standard deviation	± 11.6		
Gender categorical			
Units: Subjects			
Female	22	77	
Male	33	118	
Race			
Units: Subjects			
Asian	45	155	
White	6	28	
Black or African American	3	9	
Native Hawaiian or Other Pacific Islander	1	3	
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	55	192	
Not Permitted	0	3	
Hepatitis B Envelope Antigen (HBeAg) Status at Baseline			
Units: Subjects			
Positive	21	76	
Negative	34	119	
Baseline Alanine Aminotransferase (ALT) Category			
Upper limit of normal (ULN) for ALT was defined as 19 U/L for women and 30 U/L for men.			
Units: Subjects			
≤ ULN	12	54	

> ULN	43	141	
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Baseline Hepatitis B Surface Antigen (HBsAg) Units: log10 IU/mL arithmetic mean standard deviation	3.7 ± 0.80	-	
Baseline Hepatitis B Virus (HBV) DNA Units: log10 IU/mL arithmetic mean standard deviation	6.0 ± 1.80	-	

End points

End points reporting groups

Reporting group title	TDF 48 Weeks
Reporting group description:	Participants received TDF 300 mg tablet orally once daily for 48 weeks during the main study. Participants had the option to continue receiving TDF 300 mg tablet orally once daily for up to 144 weeks (in optional treatment extension phase [OTEP]).
Reporting group title	TDF + GS-4774 2 YU
Reporting group description:	Participants received TDF 300 mg tablet orally once daily for 48 weeks + GS-4774 2 yeast units (YU) administered via subcutaneous injection every 4 weeks for 20 weeks (total of 6 doses). Participants had the option to continue receiving TDF 300 mg tablet orally once daily for up to 144 weeks (in OTEP).
Reporting group title	TDF + GS-4774 10 YU
Reporting group description:	Participants received TDF 300 mg tablet orally once daily for 48 weeks + GS-4774 10 YU administered via subcutaneous injection every 4 weeks for 20 weeks (total of 6 doses). Participants had the option to continue receiving TDF 300 mg tablet orally once daily for up to 144 weeks (in OTEP).
Reporting group title	TDF + GS-4774 40 YU
Reporting group description:	Participants received TDF 300 mg tablet orally once daily for 48 weeks + GS-4774 40 YU administered via subcutaneous injection every 4 weeks for 20 weeks (total of 6 doses). Participants had the option to continue receiving TDF 300 mg tablet orally once daily for up to 144 weeks (in OTEP).
Reporting group title	TDF 48 Weeks
Reporting group description:	Participants received TDF 300 mg tablet orally once daily for 48 weeks during the main study. Participants had the option to continue receiving TDF 300 mg tablet orally once daily for up to 144 weeks (in OTEP).
Reporting group title	TDF + GS-4774 2 YU
Reporting group description:	Participants received TDF 300 mg tablet orally once daily for 48 weeks + GS-4774 2 YU administered via subcutaneous injection every 4 weeks for 20 weeks (total of 6 doses). Participants had the option to continue receiving TDF 300 mg tablet orally once daily for up to 144 weeks (in OTEP).
Reporting group title	TDF + GS-4774 10 YU
Reporting group description:	Participants received TDF 300 mg tablet orally once daily for 48 weeks + GS-4774 10 YU administered via subcutaneous injection every 4 weeks for 20 weeks (total of 6 doses). Participants had the option to continue receiving TDF 300 mg tablet orally once daily for up to 144 weeks (in OTEP).
Reporting group title	TDF + GS-4774 40 YU
Reporting group description:	Participants received TDF 300 mg tablet orally once daily for 48 weeks + GS-4774 40 YU administered via subcutaneous injection every 4 weeks for 20 weeks (total of 6 doses). Participants had the option to continue receiving TDF 300 mg tablet orally once daily for up to 144 weeks (in OTEP).

Primary: Mean Change in Serum HBsAg From Baseline to Week 24

End point title	Mean Change in Serum HBsAg From Baseline to Week 24
End point description:	The change from baseline to Week 24 in HBsAg was analyzed using a mixed effect model for repeated measures (MMRM). The model included treatment groups, ALT levels (> ULN or ≤ ULN) at baseline, HBeAg status (positive or negative) at baseline, HBsAg level at baseline, visit and treatment-by-visit interaction as fixed effects and visit as a repeated measurement. Estimated least square means of treatment effects are presented with the 95% confidence intervals (CIs). Participants in the Full Analysis Set (all participants who were randomized and received at least 1 dose of study drug) with available data were analyzed.
End point type	Primary

End point timeframe:

Baseline to Week 24

End point values	TDF 48 Weeks	TDF + GS-4774 2 YU	TDF + GS-4774 10 YU	TDF + GS-4774 40 YU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	57	54	55
Units: log ₁₀ IU/mL				
least squares mean (confidence interval 95%)	-0.079 (-0.192 to 0.035)	-0.096 (-0.174 to -0.018)	-0.016 (-0.095 to 0.064)	-0.135 (-0.215 to -0.055)

Statistical analyses

Statistical analysis title	TDF 48 Weeks Versus TDF + GS-4774 2 YU
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Statistical analysis description:

The null hypotheses was that the mean change from baseline in serum HBsAg in each of the TDF + GS-4774 groups was equal to the mean change from baseline in serum HBsAg in the TDF only group. Each null hypothesis was tested against the 2-sided alternative hypothesis that the mean change from baseline in serum HBsAg was not equal between each of the respective GS-4774 dose groups and the TDF only group.

Comparison groups	TDF 48 Weeks v TDF + GS-4774 2 YU
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.805
Method	Mixed-Effect Model for Repeated Measures
Parameter estimate	Least Square Mean Difference
Point estimate	-0.017
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.155
upper limit	0.12

Notes:

[1] - Estimated differences in treatment effects between GS-4774 treatment groups and the TDF only group at Week 24 are presented with the 95% CIs and unadjusted P-values.

Statistical analysis title	TDF 48 Weeks Versus TDF + GS-4774 10 YU
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Statistical analysis description:

The null hypotheses was that the mean change from baseline in serum HBsAg in each of the TDF + GS-4774 groups was equal to the mean change from baseline in serum HBsAg in the TDF only group. Each null hypothesis was tested against the 2-sided alternative hypothesis that the mean change from baseline in serum HBsAg was not equal between each of the respective GS-4774 dose groups and the TDF only group.

Comparison groups	TDF 48 Weeks v TDF + GS-4774 10 YU
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Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	= 0.37
Method	Mixed-Effect Model for Repeated Measures
Parameter estimate	Least Square Mean Difference
Point estimate	0.063
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.075
upper limit	0.202

Notes:

[2] - Estimated differences in treatment effects between GS-4774 treatment groups and the TDF only group at Week 24 are presented with the 95% CIs and unadjusted P-values.

Statistical analysis title	TDF 48 Weeks Versus TDF + GS-4774 40 YU
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Statistical analysis description:

The null hypotheses was that the mean change from baseline in serum HBsAg in each of the TDF + GS-4774 groups was equal to the mean change from baseline in serum HBsAg in the TDF only group. Each null hypothesis was tested against the 2-sided alternative hypothesis that the mean change from baseline in serum HBsAg was not equal between each of the respective GS-4774 dose groups and the TDF only group.

Comparison groups	TDF 48 Weeks v TDF + GS-4774 40 YU
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.426
Method	Mixed-Effect Model for Repeated Measures
Parameter estimate	Least Square Mean Difference
Point estimate	-0.056
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.194
upper limit	0.082

Notes:

[3] - Estimated differences in treatment effects between GS-4774 treatment groups and the TDF only group at Week 24 are presented with the 95% CIs and unadjusted P-values.

Secondary: Mean Change in HBsAg From Baseline to Week 12

End point title	Mean Change in HBsAg From Baseline to Week 12
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End point description:

The change from baseline to Week 12 in HBsAg was analyzed using a MMRM. The model included treatment groups, ALT levels (> ULN or ≤ ULN) at baseline, HBeAg status (positive or negative) at baseline, HBsAg level at baseline, visit and treatment-by-visit interaction as fixed effects and visit as a repeated measurement. Estimated least square means of treatment effects are presented with the 95% CIs.

Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary
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End point timeframe:

Baseline to Week 12

End point values	TDF 48 Weeks	TDF + GS-4774 2 YU	TDF + GS-4774 10 YU	TDF + GS-4774 40 YU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	55	54	54
Units: log10 IU/mL				
least squares mean (confidence interval 95%)	-0.060 (-0.165 to 0.044)	-0.061 (-0.133 to 0.011)	-0.012 (-0.086 to 0.061)	-0.095 (-0.168 to -0.021)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in HBsAg From Baseline to Week 48

End point title	Mean Change in HBsAg From Baseline to Week 48
End point description:	
<p>The change from baseline to Week 48 in HBsAg was analyzed using a MMRM. The model included treatment groups, ALT levels (> ULN or ≤ ULN) at baseline, HBeAg status (positive or negative) at baseline, HBsAg level at baseline, visit and treatment-by-visit interaction as fixed effects and visit as a repeated measurement. Estimated least square means of treatment effects are presented with the 95% CIs.</p> <p>Participants in the Full Analysis Set with available data were analyzed.</p>	
End point type	Secondary
End point timeframe:	
Baseline to Week 48	

End point values	TDF 48 Weeks	TDF + GS-4774 2 YU	TDF + GS-4774 10 YU	TDF + GS-4774 40 YU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	56	53	55
Units: log10 IU/mL				
least squares mean (confidence interval 95%)	-0.145 (-0.272 to -0.017)	-0.136 (-0.225 to -0.048)	-0.086 (-0.176 to 0.004)	-0.165 (-0.254 to -0.075)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HBsAg Loss at Week 24

End point title	Percentage of Participants With HBsAg Loss at Week 24
End point description:	
<p>HBsAg loss was defined as qualitative HBsAg test changing from positive at baseline to negative at any postbaseline visit within the targeted time window. Participants in the Full Analysis Set were analyzed. The missing equals failure approach was used.</p>	

End point type	Secondary
End point timeframe:	
Baseline to Week 24	

End point values	TDF 48 Weeks	TDF + GS-4774 2 YU	TDF + GS-4774 10 YU	TDF + GS-4774 40 YU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	57	56	55
Units: percentage of participants				
number (not applicable)	0.0	0.0	0.0	0.0

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HBsAg Loss at Week 48

End point title	Percentage of Participants With HBsAg Loss at Week 48
End point description:	
HBsAg loss was defined as qualitative HBsAg test changing from positive at baseline to negative at any postbaseline visit within the targeted time window. Participants in the Full Analysis Set were analyzed. The missing equals failure approach was used.	
End point type	Secondary
End point timeframe:	
Baseline to Week 48	

End point values	TDF 48 Weeks	TDF + GS-4774 2 YU	TDF + GS-4774 10 YU	TDF + GS-4774 40 YU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	57	56	55
Units: percentage of participants				
number (not applicable)	0.0	0.0	0.0	0.0

Statistical analyses

No statistical analyses for this end point

Secondary: Composite Endpoint Measuring the Percentage of Participants With HBsAg Loss and HBsAg Seroconversion at Week 24

End point title	Composite Endpoint Measuring the Percentage of Participants With HBsAg Loss and HBsAg Seroconversion at Week 24
End point description:	
HBsAg loss was defined as qualitative HBsAg test changing from positive at baseline to negative at any postbaseline visit within the targeted time window. HBsAg loss and seroconversion was defined as	

qualitative HBsAb result changing from negative at baseline to positive at any postbaseline visit and the participant must have achieved HBsAg loss within the targeted time window.

Participants in the Full Analysis Set were analyzed. The missing equals failure approach was used.

End point type	Secondary
End point timeframe:	
Baseline to Week 24	

End point values	TDF 48 Weeks	TDF + GS-4774 2 YU	TDF + GS-4774 10 YU	TDF + GS-4774 40 YU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	57	56	55
Units: percentage of participants				
number (not applicable)	0.0	0.0	0.0	0.0

Statistical analyses

No statistical analyses for this end point

Secondary: Composite Endpoint Measuring the Percentage of Participants With HBsAg Loss and HBsAg Seroconversion at Week 48

End point title	Composite Endpoint Measuring the Percentage of Participants With HBsAg Loss and HBsAg Seroconversion at Week 48
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End point description:

HBsAg loss was defined as qualitative HBsAg test changing from positive at baseline to negative at any postbaseline visit within the targeted time window. HBsAg loss and seroconversion was defined as qualitative HBsAb result changing from negative at baseline to positive at any postbaseline visit and the participant must have achieved HBsAg loss within the targeted time window.

Participants in the Full Analysis Set were analyzed. The missing equals failure approach was used.

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

End point values	TDF 48 Weeks	TDF + GS-4774 2 YU	TDF + GS-4774 10 YU	TDF + GS-4774 40 YU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	57	56	55
Units: percentage of participants				
number (not applicable)	0.0	0.0	0.0	0.0

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a ≥ 0.5 Log₁₀ IU/mL or a ≥ 1.0 Log₁₀

IU/mL Decline in HBsAg at Week 12

End point title	Percentage of Participants With a ≥ 0.5 Log ₁₀ IU/mL or a ≥ 1.0 Log ₁₀ IU/mL Decline in HBsAg at Week 12
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End point description:

HBsAg with a ≥ 0.5 or ≥ 1.0 log₁₀ IU/mL decline was defined as ≥ 0.5 or ≥ 1.0 decline from baseline in log₁₀ IU/mL serum HBsAg at any postbaseline visit within the targeted time window.

Participants in the Full Analysis Set were analyzed. The missing equals failure approach was used.

End point type	Secondary
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End point timeframe:

Baseline to Week 12

End point values	TDF 48 Weeks	TDF + GS-4774 2 YU	TDF + GS-4774 10 YU	TDF + GS-4774 40 YU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	57	56	55
Units: percentage of participants				
number (not applicable)				
≥ 0.5 and < 1.0 log ₁₀ IU/mL Decline	3.7	3.5	1.8	5.5
≥ 1.0 and < 2.0 log ₁₀ IU/mL Decline	0.0	3.5	0.0	0.0
≥ 2.0 log ₁₀ IU/mL Decline	0.0	0.0	0.0	1.8

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a ≥ 0.5 Log₁₀ IU/mL or a ≥ 1.0 Log₁₀ IU/mL Decline in HBsAg at Week 24

End point title	Percentage of Participants With a ≥ 0.5 Log ₁₀ IU/mL or a ≥ 1.0 Log ₁₀ IU/mL Decline in HBsAg at Week 24
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End point description:

HBsAg with a ≥ 0.5 or ≥ 1 log₁₀ IU/mL decline was defined as ≥ 0.5 or ≥ 1.0 decline from baseline in log₁₀ IU/mL serum HBsAg at any postbaseline visit within the targeted time window.

Participants in the Full Analysis Set were analyzed. The missing equals failure approach was used.

End point type	Secondary
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End point timeframe:

Baseline to Week 24

End point values	TDF 48 Weeks	TDF + GS-4774 2 YU	TDF + GS-4774 10 YU	TDF + GS-4774 40 YU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	57	56	55
Units: percentage of participants				
number (not applicable)				
≥ 0.5 and < 1.0 log ₁₀ IU/mL Decline	0.0	1.8	1.8	7.3
≥ 1.0 and < 2.0 log ₁₀ IU/mL Decline	0.0	5.3	0.0	1.8
≥ 2.0 log ₁₀ IU/mL Decline	0.0	0.0	0.0	1.8

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a ≥ 0.5 Log₁₀ IU/mL or a ≥ 1.0 Log₁₀ IU/mL Decline in HBsAg at Week 48

End point title	Percentage of Participants With a ≥ 0.5 Log ₁₀ IU/mL or a ≥ 1.0 Log ₁₀ IU/mL Decline in HBsAg at Week 48
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End point description:

HBsAg with a ≥ 0.5 or ≥ 1.0 log₁₀ IU/mL decline was defined as ≥ 0.5 or ≥ 1.0 decline from baseline in log₁₀ IU/mL serum HBsAg at any postbaseline visit within the targeted time window.

Participants in the Full Analysis Set were analyzed. The missing equals failure approach was used.

End point type	Secondary
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End point timeframe:

Baseline to Week 48

End point values	TDF 48 Weeks	TDF + GS-4774 2 YU	TDF + GS-4774 10 YU	TDF + GS-4774 40 YU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	57	56	55
Units: percentage of participants				
number (not applicable)				
≥ 0.5 and < 1.0 log ₁₀ IU/mL Decline	11.1	1.8	7.1	7.3
≥ 1.0 and < 2.0 log ₁₀ IU/mL Decline	0.0	5.3	1.8	1.8
≥ 2.0 log ₁₀ IU/mL Decline	0.0	0.0	0.0	1.8

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HBeAg Loss at Week 24

End point title	Percentage of Participants With HBeAg Loss at Week 24
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End point description:

HBeAg loss was defined as qualitative HBeAg test changing from positive at baseline to negative at any postbaseline visit within the targeted time window.

Participants in the Full Analysis Set with HBeAg positive at baseline were analyzed. The missing equals failure approach was used.

End point type	Secondary
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End point timeframe:

Baseline to Week 24

End point values	TDF 48 Weeks	TDF + GS-4774 2 YU	TDF + GS-4774 10 YU	TDF + GS-4774 40 YU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	22	23	21
Units: percentage of participants				
number (not applicable)	0.0	0.0	4.3	0.0

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HBeAg Loss at Week 48

End point title	Percentage of Participants With HBeAg Loss at Week 48
End point description:	
HBeAg loss was defined as qualitative HBeAg test changing from positive at baseline to negative at any postbaseline visit within the targeted time window. Participants in the Full Analysis Set with HBeAg positive at baseline were analyzed. The missing equals failure approach was used.	
End point type	Secondary
End point timeframe:	
Baseline to Week 48	

End point values	TDF 48 Weeks	TDF + GS-4774 2 YU	TDF + GS-4774 10 YU	TDF + GS-4774 40 YU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	22	23	21
Units: percentage of participants				
number (not applicable)	0.0	4.5	8.7	9.5

Statistical analyses

No statistical analyses for this end point

Secondary: Composite Endpoint Measuring the Percentage of Participants With HBeAg Loss and HBeAg Seroconversion at Week 24

End point title	Composite Endpoint Measuring the Percentage of Participants With HBeAg Loss and HBeAg Seroconversion at Week 24
End point description:	
HBeAg loss was defined as qualitative HBeAg test changing from positive at baseline to negative at any postbaseline visit within the targeted time window. HBeAg loss and seroconversion was defined as qualitative HBeAb result changing from negative at baseline to positive at any postbaseline visit and the participant must have achieved HBeAg loss within the targeted time window. Participants in the Full Analysis Set with HBeAg positive at baseline were analyzed. The missing equals	

failure approach was used.

End point type	Secondary
End point timeframe:	
Baseline to Week 24	

End point values	TDF 48 Weeks	TDF + GS-4774 2 YU	TDF + GS-4774 10 YU	TDF + GS-4774 40 YU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	22	23	21
Units: percentage of participants				
number (not applicable)	0.0	0.0	4.3	0.0

Statistical analyses

No statistical analyses for this end point

Secondary: Composite Endpoint Measuring the Percentage of Participants With HBeAg Loss and HBeAg Seroconversion at Week 48

End point title	Composite Endpoint Measuring the Percentage of Participants With HBeAg Loss and HBeAg Seroconversion at Week 48
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End point description:

HBeAg loss was defined as qualitative HBeAg test changing from positive at baseline to negative at any postbaseline visit within the targeted time window. HBeAg loss and seroconversion was defined as qualitative HBeAb result changing from negative at baseline to positive at any postbaseline visit and the participant must have achieved HBeAg loss within the targeted time window.

Participants in the Full Analysis Set with HBeAg positive at baseline were analyzed. The missing equals failure approach was used.

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

End point values	TDF 48 Weeks	TDF + GS-4774 2 YU	TDF + GS-4774 10 YU	TDF + GS-4774 40 YU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	22	23	21
Units: percentage of participants				
number (not applicable)	0.0	0.0	4.3	9.5

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HBV DNA < Lower Limit of Quantification (LLOQ) at Week 24

End point title	Percentage of Participants With HBV DNA < Lower Limit of Quantification (LLOQ) at Week 24
End point description:	The LLOQ was defined as 20 IU/mL. Participants in the Full Analysis Set with available data were analyzed. The missing equals excluded approach was used.
End point type	Secondary
End point timeframe:	Week 24

End point values	TDF 48 Weeks	TDF + GS-4774 2 YU	TDF + GS-4774 10 YU	TDF + GS-4774 40 YU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	56	53	55
Units: percentage of participants				
number (not applicable)	50.0	58.9	58.5	63.6

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HBV DNA < LLOQ at Week 48

End point title	Percentage of Participants With HBV DNA < LLOQ at Week 48
End point description:	The LLOQ was defined as 20 IU/mL. Participants in the Full Analysis Set with available data were analyzed. The missing equals excluded approach was used.
End point type	Secondary
End point timeframe:	Week 48

End point values	TDF 48 Weeks	TDF + GS-4774 2 YU	TDF + GS-4774 10 YU	TDF + GS-4774 40 YU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	56	54	55
Units: percentage of participants				
number (not applicable)	70.4	69.6	69.2	76.4

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Experiencing Virologic Breakthrough at Week 24

End point title	Percentage of Participants Experiencing Virologic Breakthrough
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End point description:

Virologic breakthrough was defined as HBV DNA \geq 69 IU/mL after having been $<$ 69 IU/mL, or having had \geq 1.0 log₁₀ increase in HBV DNA from nadir. Two consecutive visits that met the definition were required for a participant to be classified as having had virologic breakthrough. Participants in the Full Analysis Set were analyzed.

End point type	Secondary
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End point timeframe:

Baseline to Week 24

End point values	TDF 48 Weeks	TDF + GS-4774 2 YU	TDF + GS-4774 10 YU	TDF + GS-4774 40 YU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	57	56	55
Units: percentage of participants				
number (not applicable)	0.0	1.8	1.8	0.0

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Experiencing Virologic Breakthrough at Week 48

End point title	Percentage of Participants Experiencing Virologic Breakthrough at Week 48
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End point description:

Virologic breakthrough was defined as HBV DNA \geq 69 IU/mL after having been $<$ 69 IU/mL, or a \geq 1.0 log₁₀ increase in HBV DNA from nadir. Two consecutive visits that met the definition were required for a participant to be classified as having had virologic breakthrough. Participants in the Full Analysis Set were analyzed.

End point type	Secondary
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End point timeframe:

Baseline to Week 48

End point values	TDF 48 Weeks	TDF + GS-4774 2 YU	TDF + GS-4774 10 YU	TDF + GS-4774 40 YU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	57	56	55
Units: percentage of participants				
number (not applicable)	3.7	5.3	5.4	0.0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Drug-Resistance Mutations at Week 48 or at the Last Visit Available

End point title	Number of Participants with Drug-Resistance Mutations at Week 48 or at the Last Visit Available
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End point description:

Resistance surveillance analysis was conducted at Week 48 or Early Discontinuation (with at least 24 weeks of exposure to TDF) for any participants who met inclusion criteria (HBV DNA \geq 69 IU/mL). Drug-resistant mutation status was assessed using HBV polymerase/ reverse transcriptase (pol/RT) population sequencing.

Participants with at least 24 weeks of exposure to TDF and with HBV DNA \geq 69 IU/mL at Week 48 or Early Discontinuation were analyzed.

End point type	Secondary
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End point timeframe:

Baseline to Week 48

End point values	TDF 48 Weeks	TDF + GS-4774 2 YU	TDF + GS-4774 10 YU	TDF + GS-4774 40 YU
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	12	13	8
Units: participants	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events: First dose date up to last dose date (maximum exposure: 3 years);

All-Cause Mortality: First dose date up to 3 years

Adverse event reporting additional description:

Safety Analysis Set included all participants who received at least 1 dose of study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	TDF 48 Weeks
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Reporting group description:

Participants received TDF 300 mg tablet orally once daily for 48 weeks during the main study.

Participants had the option to continue receiving TDF 300 mg tablet orally once daily for up to 144 weeks (in optional treatment extension phase [OTEP]).

Reporting group title	TDF + GS-4774 2 YU
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Reporting group description:

Participants received TDF 300 mg tablet orally once daily for 48 weeks + GS-4774 2 yeast units (YU) administered via subcutaneous injection every 4 weeks for 20 weeks (total of 6 doses). Participants had the option to continue receiving TDF 300 mg tablet orally once daily for up to 144 weeks (in OTEP).

Reporting group title	TDF + GS-4774 10 YU
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Reporting group description:

Participants received TDF 300 mg tablet orally once daily for 48 weeks + GS-4774 10 YU administered via subcutaneous injection every 4 weeks for 20 weeks (total of 6 doses). Participants had the option to continue receiving TDF 300 mg tablet orally once daily for up to 144 weeks (in OTEP).

Reporting group title	TDF + GS-4774 40 YU
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Reporting group description:

Participants received TDF 300 mg tablet orally once daily for 48 weeks + GS-4774 40 YU administered via subcutaneous injection every 4 weeks for 20 weeks (total of 6 doses). Participants had the option to continue receiving TDF 300 mg tablet orally once daily for up to 144 weeks (in OTEP).

Serious adverse events	TDF 48 Weeks	TDF + GS-4774 2 YU	TDF + GS-4774 10 YU
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 27 (7.41%)	1 / 57 (1.75%)	1 / 56 (1.79%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	0 / 27 (0.00%)	0 / 57 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

Spinal fracture			
subjects affected / exposed	1 / 27 (3.70%)	0 / 57 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	0 / 27 (0.00%)	1 / 57 (1.75%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Meningitis tuberculous			
subjects affected / exposed	1 / 27 (3.70%)	0 / 57 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serious adverse events	TDF + GS-4774 40 YU		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 55 (1.82%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Spinal fracture			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Uterine polyp			

subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Meningitis tuberculous			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	TDF 48 Weeks	TDF + GS-4774 2 YU	TDF + GS-4774 10 YU
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 27 (44.44%)	41 / 57 (71.93%)	50 / 56 (89.29%)
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 27 (7.41%)	0 / 57 (0.00%)	0 / 56 (0.00%)
occurrences (all)	2	0	0
Alanine aminotransferase increased			
subjects affected / exposed	1 / 27 (3.70%)	0 / 57 (0.00%)	0 / 56 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	2 / 27 (7.41%)	0 / 57 (0.00%)	0 / 56 (0.00%)
occurrences (all)	2	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 27 (3.70%)	5 / 57 (8.77%)	1 / 56 (1.79%)
occurrences (all)	1	5	1
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 27 (7.41%)	9 / 57 (15.79%)	17 / 56 (30.36%)
occurrences (all)	2	15	37
General disorders and administration site conditions			

Injection site pain			
subjects affected / exposed	0 / 27 (0.00%)	16 / 57 (28.07%)	32 / 56 (57.14%)
occurrences (all)	0	39	117
Injection site erythema			
subjects affected / exposed	0 / 27 (0.00%)	14 / 57 (24.56%)	20 / 56 (35.71%)
occurrences (all)	0	27	61
Fatigue			
subjects affected / exposed	5 / 27 (18.52%)	10 / 57 (17.54%)	21 / 56 (37.50%)
occurrences (all)	8	15	50
Injection site swelling			
subjects affected / exposed	0 / 27 (0.00%)	9 / 57 (15.79%)	11 / 56 (19.64%)
occurrences (all)	0	11	28
Injection site pruritus			
subjects affected / exposed	0 / 27 (0.00%)	4 / 57 (7.02%)	18 / 56 (32.14%)
occurrences (all)	0	6	29
Injection site induration			
subjects affected / exposed	0 / 27 (0.00%)	4 / 57 (7.02%)	5 / 56 (8.93%)
occurrences (all)	0	6	16
Chills			
subjects affected / exposed	0 / 27 (0.00%)	2 / 57 (3.51%)	6 / 56 (10.71%)
occurrences (all)	0	2	18
Pyrexia			
subjects affected / exposed	1 / 27 (3.70%)	3 / 57 (5.26%)	1 / 56 (1.79%)
occurrences (all)	2	3	1
Pain			
subjects affected / exposed	0 / 27 (0.00%)	1 / 57 (1.75%)	3 / 56 (5.36%)
occurrences (all)	0	1	3
Influenza like illness			
subjects affected / exposed	0 / 27 (0.00%)	3 / 57 (5.26%)	3 / 56 (5.36%)
occurrences (all)	0	4	5
Injection site oedema			
subjects affected / exposed	0 / 27 (0.00%)	0 / 57 (0.00%)	2 / 56 (3.57%)
occurrences (all)	0	0	6
Asthenia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 57 (1.75%)	1 / 56 (1.79%)
occurrences (all)	0	1	1

Injection site reaction subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	0 / 57 (0.00%) 0	4 / 56 (7.14%) 9
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	6 / 57 (10.53%) 7	10 / 56 (17.86%) 26
Diarrhoea subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	3 / 57 (5.26%) 3	2 / 56 (3.57%) 2
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	2 / 57 (3.51%) 2	3 / 56 (5.36%) 3
Dyspepsia subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	4 / 57 (7.02%) 4	1 / 56 (1.79%) 1
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 4	7 / 57 (12.28%) 8	8 / 56 (14.29%) 12
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 2	2 / 57 (3.51%) 2	3 / 56 (5.36%) 4
Rhinorrhoea subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	2 / 57 (3.51%) 2	1 / 56 (1.79%) 1
Nasal congestion subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 4	2 / 57 (3.51%) 2	0 / 56 (0.00%) 0
Productive cough subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 3	0 / 57 (0.00%) 0	0 / 56 (0.00%) 0
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	0 / 57 (0.00%) 0	0 / 56 (0.00%) 0

Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 57 (1.75%)	1 / 56 (1.79%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	1 / 27 (3.70%)	6 / 57 (10.53%)	13 / 56 (23.21%)
occurrences (all)	1	6	38
Back pain			
subjects affected / exposed	1 / 27 (3.70%)	6 / 57 (10.53%)	0 / 56 (0.00%)
occurrences (all)	1	7	0
Arthralgia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 57 (1.75%)	3 / 56 (5.36%)
occurrences (all)	0	1	3
Musculoskeletal pain			
subjects affected / exposed	2 / 27 (7.41%)	2 / 57 (3.51%)	1 / 56 (1.79%)
occurrences (all)	2	2	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 27 (7.41%)	1 / 57 (1.75%)	2 / 56 (3.57%)
occurrences (all)	2	1	3
Upper respiratory tract infection			
subjects affected / exposed	2 / 27 (7.41%)	0 / 57 (0.00%)	2 / 56 (3.57%)
occurrences (all)	5	0	2
Influenza			
subjects affected / exposed	0 / 27 (0.00%)	0 / 57 (0.00%)	3 / 56 (5.36%)
occurrences (all)	0	0	3
Sinusitis			
subjects affected / exposed	0 / 27 (0.00%)	2 / 57 (3.51%)	2 / 56 (3.57%)
occurrences (all)	0	3	4
Folliculitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 57 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	TDF + GS-4774 40 YU		
Total subjects affected by non-serious adverse events			

subjects affected / exposed	53 / 55 (96.36%)		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Alanine aminotransferase increased			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Nervous system disorders			
Headache			
subjects affected / exposed	20 / 55 (36.36%)		
occurrences (all)	35		
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	45 / 55 (81.82%)		
occurrences (all)	189		
Injection site erythema			
subjects affected / exposed	34 / 55 (61.82%)		
occurrences (all)	117		
Fatigue			
subjects affected / exposed	22 / 55 (40.00%)		
occurrences (all)	45		
Injection site swelling			
subjects affected / exposed	22 / 55 (40.00%)		
occurrences (all)	72		
Injection site pruritus			
subjects affected / exposed	18 / 55 (32.73%)		
occurrences (all)	44		

Injection site induration			
subjects affected / exposed	18 / 55 (32.73%)		
occurrences (all)	64		
Chills			
subjects affected / exposed	9 / 55 (16.36%)		
occurrences (all)	14		
Pyrexia			
subjects affected / exposed	7 / 55 (12.73%)		
occurrences (all)	9		
Pain			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	4		
Influenza like illness			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Injection site oedema			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	12		
Asthenia			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	7		
Injection site reaction			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	11 / 55 (20.00%)		
occurrences (all)	20		
Diarrhoea			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Dyspepsia			

subjects affected / exposed occurrences (all)	0 / 55 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 55 (14.55%)		
occurrences (all)	12		
Oropharyngeal pain			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	4		
Rhinorrhoea			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	2		
Nasal congestion			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	22 / 55 (40.00%)		
occurrences (all)	56		
Back pain			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Arthralgia			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	4		

Musculoskeletal pain subjects affected / exposed occurrences (all)	2 / 55 (3.64%) 2		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	9 / 55 (16.36%) 10		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	6 / 55 (10.91%) 6		
Influenza subjects affected / exposed occurrences (all)	5 / 55 (9.09%) 5		
Sinusitis subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 3		
Folliculitis subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 June 2015	The main changes were as follows: <ul style="list-style-type: none">- An optional treatment extension phase was added: Weeks 48 through 144.- Language for participation in an optional biomarker substudy was clarified to align with the updated protocol template.- The Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities version was updated to the version dated 18 June 2012.
21 October 2016	Changes were made to clarify definition of treatment-emergent for adverse events and laboratory evaluations as well as to update Gilead Study Director and Gilead Medical Monitor contact information and to provide the updated United States (US) Investigational New Drug (IND) (application) number.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30930022>