



Clinical trial results:

A Phase 4, Randomized, Open-label, Active-Controlled, Superiority Study to Evaluate the Efficacy and Safety of Tenofovir Disoproxil Fumarate (TDF) in Combination With Peginterferon -2a (Pegasys®) Versus Standard of Care Tenofovir Disoproxil Fumarate Monotherapy or Peginterferon -2a Monotherapy for 48 Weeks in Non-Cirrhotic Subjects With HBeAg-Positive or HBeAg-Negative Chronic Hepatitis B (CHB)

Summary

EudraCT number	2010-024586-45
Trial protocol	FR GB NL PL PT GR DE ES IT
Global end of trial date	17 July 2015

Results information

Result version number	v1 (current)
This version publication date	31 July 2016
First version publication date	31 July 2016

Trial information

Trial identification

Sponsor protocol code	GS-US-174-0149
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01277601
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	17 July 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	17 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the efficacy of tenofovir disoproxil fumarate (TDF) plus peginterferon α -2a (Peg-IFN) combination therapy for 48 weeks versus standard of care TDF monotherapy or Peg-IFN monotherapy for 48 weeks in non-cirrhotic adults with chronic hepatitis B virus (HBV) as determined by loss of hepatitis B surface antigen (HBsAg).

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	12 April 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Poland: 22
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 20
Country: Number of subjects enrolled	Greece: 9
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Korea, Republic of: 146
Country: Number of subjects enrolled	Hong Kong: 99
Country: Number of subjects enrolled	United States: 89
Country: Number of subjects enrolled	Taiwan: 67
Country: Number of subjects enrolled	Canada: 59

Country: Number of subjects enrolled	Australia: 53
Country: Number of subjects enrolled	Romania: 49
Country: Number of subjects enrolled	India: 30
Country: Number of subjects enrolled	Singapore: 27
Country: Number of subjects enrolled	Turkey: 24
Worldwide total number of subjects	751
EEA total number of subjects	157

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)	748
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, Asia, and Australia. The first participant was screened on 12 April 2011. The last study visit occurred on 17 July 2015.

Pre-assignment

Screening details:

1597 participants were screened.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	TDF+Peg-IFN 48 Weeks

Arm description:

TDF plus Peg-IFN for 48 weeks

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

Dosage and administration details:

300 mg once daily

Investigational medicinal product name	Peginterferon α-2a
Investigational medicinal product code	
Other name	Pegasys®
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

180 µg once weekly

Arm title	TDF 48 Weeks + Peg-IFN 16 Weeks
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Arm description:

TDF plus Peg-IFN for 16 weeks followed by TDF for an additional 32 weeks

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

Dosage and administration details:

300 mg once daily

Investigational medicinal product name	Peginterferon α-2a
Investigational medicinal product code	
Other name	Pegasys®

Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

180 µg once weekly

Arm title	TDF 120 Weeks
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Arm description:

TDF for 120 weeks

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

Dosage and administration details:

300 mg once daily

Arm title	Peg-IFN 48 Weeks
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Arm description:

Peg-IFN for 48 weeks

Arm type	Experimental
Investigational medicinal product name	Peginterferon α-2a
Investigational medicinal product code	
Other name	Pegasys®
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

180 µg once weekly

Number of subjects in period 1^[1]	TDF+Peg-IFN 48 Weeks	TDF 48 Weeks + Peg-IFN 16 Weeks	TDF 120 Weeks
Started	186	184	185
Completed	151	139	163
Not completed	35	45	22
Subject Withdrew Consent	17	20	6
Non-Compliance with Study Drug	1	3	2
Adverse event, non-fatal	5	3	-
Investigator's Discretion	3	5	1
Study Discontinued by Sponsor	-	1	-
Pregnancy	2	2	4
Lost to follow-up	7	9	4
Protocol deviation	-	2	5

Number of subjects in period 1	Peg-IFN 48 Weeks
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[1]	
Started	185
Completed	150
Not completed	35
Subject Withdrew Consent	17
Non-Compliance with Study Drug	-
Adverse event, non-fatal	7
Investigator's Discretion	6
Study Discontinued by Sponsor	2
Pregnancy	1
Lost to follow-up	2
Protocol deviation	-

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: 11 participants (7 subjects were never dosed with study drug and 4 withdrew consent) who were enrolled but not treated are not included in the subject disposition table.

Baseline characteristics

Reporting groups

Reporting group title	TDF+Peg-IFN 48 Weeks
Reporting group description: TDF plus Peg-IFN for 48 weeks	
Reporting group title	TDF 48 Weeks + Peg-IFN 16 Weeks
Reporting group description: TDF plus Peg-IFN for 16 weeks followed by TDF for an additional 32 weeks	
Reporting group title	TDF 120 Weeks
Reporting group description: TDF for 120 weeks	
Reporting group title	Peg-IFN 48 Weeks
Reporting group description: Peg-IFN for 48 weeks	

Reporting group values	TDF+Peg-IFN 48 Weeks	TDF 48 Weeks + Peg-IFN 16 Weeks	TDF 120 Weeks
Number of subjects	186	184	185
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	38 ± 10.7	37 ± 9.9	36 ± 10.8
Gender categorical Units: Subjects			
Female	59	65	64
Male	127	119	121
Ethnicity Units: Subjects			
Hispanic or Latino	4	4	3
Not Hispanic or Latino	182	179	181
Unknown or Not Reported	0	1	1
Race Units: Subjects			
Asian	142	134	141
Black or African American	5	3	4
Native Hawaiian or Other Pacific Islander	2	0	0
White	36	45	39
Other	1	2	1
Hepatitis B e Antigen (HBeAg) Status Units: Subjects			
Reactive	108	105	109
Nonreactive	78	79	76

HBV Genotype			
Units: Subjects			
Genotype A	17	16	14
Genotype B	50	51	49
Genotype C	78	79	78
Genotype D	39	36	41
Genotype E-H	2	2	3
Hepatitis B Surface Antigen (HBsAg)			
Units: log 10 IU/mL			
arithmetic mean	3.88	3.84	3.89
standard deviation	± 0.84	± 0.849	± 0.812
Hepatitis B Virus (HBV) DNA			
Units: log 10 IU/mL			
arithmetic mean	7.06	7.13	7.02
standard deviation	± 1.542	± 1.505	± 1.55
Alanine Aminotransferase (ALT)			
Units: U/L			
arithmetic mean	121.2	112.2	100.9
standard deviation	± 180.82	± 94.44	± 67.65

Reporting group values	Peg-IFN 48 Weeks	Total	
Number of subjects	185	740	
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	38	-	
standard deviation	± 10.5		
Gender categorical			
Units: Subjects			
Female	66	254	
Male	119	486	
Ethnicity			
Units: Subjects			
Hispanic or Latino	7	18	
Not Hispanic or Latino	177	719	
Unknown or Not Reported	1	3	
Race			
Units: Subjects			
Asian	137	554	
Black or African American	6	18	
Native Hawaiian or Other Pacific Islander	1	3	
White	41	161	
Other	0	4	
Hepatitis B e Antigen (HBeAg) Status			
Units: Subjects			
Reactive	106	428	
Nonreactive	79	312	
HBV Genotype			

Units: Subjects			
Genotype A	14	61	
Genotype B	53	203	
Genotype C	79	314	
Genotype D	38	154	
Genotype E-H	1	8	
Hepatitis B Surface Antigen (HBsAg)			
Units: log 10 IU/mL			
arithmetic mean	3.76		
standard deviation	± 0.844	-	
Hepatitis B Virus (HBV) DNA			
Units: log 10 IU/mL			
arithmetic mean	6.94		
standard deviation	± 1.619	-	
Alanine Aminotransferase (ALT)			
Units: U/L			
arithmetic mean	106.6		
standard deviation	± 91.51	-	

End points

End points reporting groups

Reporting group title	TDF+Peg-IFN 48 Weeks
Reporting group description: TDF plus Peg-IFN for 48 weeks	
Reporting group title	TDF 48 Weeks + Peg-IFN 16 Weeks
Reporting group description: TDF plus Peg-IFN for 16 weeks followed by TDF for an additional 32 weeks	
Reporting group title	TDF 120 Weeks
Reporting group description: TDF for 120 weeks	
Reporting group title	Peg-IFN 48 Weeks
Reporting group description: Peg-IFN for 48 weeks	
Subject analysis set title	TDF+Peg-IFN 48 Week (Not Retreated)
Subject analysis set type	Sub-group analysis
Subject analysis set description: TDF 300 mg tablet once daily plus Peg-IFN 180 µg s.c. injection once weekly for 48 weeks in the initial treatment phase	
Subject analysis set title	TDF+Peg-IFN 48 Weeks (Retreated)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Following the randomized treatment, participants who met protocol-specified criteria were retreated with TDF 300 mg tablet once daily up to Week 120 in the retreatment phase.	
Subject analysis set title	TDF 48 Weeks + Peg-IFN 16 Week (Not Retreated)
Subject analysis set type	Sub-group analysis
Subject analysis set description: TDF 300 mg tablet once daily plus Peg-IFN 180 µg s.c. injection once weekly for 16 weeks followed by TDF 300 mg tablet once daily for an additional 32 weeks in the initial treatment phase	
Subject analysis set title	TDF 48 Weeks + Peg-IFN 16 Weeks (Retreated)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Following the randomized treatment, participants who met protocol-specified criteria were retreated with TDF 300 mg tablet once daily up to Week 120 in the retreatment phase.	
Subject analysis set title	TDF 120 Weeks
Subject analysis set type	Sub-group analysis
Subject analysis set description: TDF 300 mg tablet once daily for 120 weeks. Participants in this group were not eligible to enter the retreatment phase.	
Subject analysis set title	Peg-IFN 48 Weeks (Not Retreated)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Peg-IFN 180 µg s.c. injection once weekly for 48 weeks in the initial treatment phase	
Subject analysis set title	Peg-IFN 48 Weeks (Retreated)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Following the randomized treatment, participants who met protocol-specified criteria were retreated with TDF 300 mg tablet once daily up to Week 120 in the retreatment phase.	

Primary: Percentage of Participants With HBsAg Loss at Week 72 Following Treatment With 48 Weeks of TDF Plus Peg-IFN Combination Versus Peg-IFN Alone for 48 Weeks or TDF Alone

End point title	Percentage of Participants With HBsAg Loss at Week 72 Following Treatment With 48 Weeks of TDF Plus Peg-IFN Combination Versus Peg-IFN Alone for 48 Weeks or TDF Alone ^[1]
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End point description:

Loss of HBsAg was defined as change of detectable HBsAg from positive to negative. Proportions are based on a Kaplan-Meier estimate.

The analysis visit window for Week 72 comprised Week 70 through Week 78, so results up to Week 78 are included in this analysis.

Full Analysis Set: participants who were randomized and received at least 1 dose of study drug. Participants in the TDF+Peg-IFN 48 Weeks, TDF 120 Weeks, and Peg-IFN 48 Weeks groups were analyzed by randomized treatment.

End point type	Primary
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End point timeframe:

Baseline; Week 72

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is specific to only certain arms of the study.

End point values	TDF+Peg-IFN 48 Weeks	TDF 120 Weeks	Peg-IFN 48 Weeks	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	186	185	185	
Units: percentage of participants				
number (not applicable)	9.05	0	2.84	

Statistical analyses

Statistical analysis title	TDF+Peg-IFN 48 Weeks vs TDF 120 Weeks
Comparison groups	TDF+Peg-IFN 48 Weeks v TDF 120 Weeks
Number of subjects included in analysis	371
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[2]
Method	Logrank

Notes:

[2] - Raw p-values comparing treatments were based on a log-rank test stratified by HBeAg status and viral genotype.

Statistical analysis title	TDF+Peg-IFN 48 Weeks vs Peg-IFN 48 Weeks
Comparison groups	TDF+Peg-IFN 48 Weeks v Peg-IFN 48 Weeks
Number of subjects included in analysis	371
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 ^[3]
Method	Logrank

Notes:

[3] - Raw p-values comparing treatments were based on a log-rank test stratified by HBeAg status and viral genotype.

Secondary: Percentage of Participants With HBsAg Loss at Week 72 Following Treatment With TDF (48 Weeks) Plus Peg-IFN (16 Weeks) Combination Versus Peg-IFN Alone for 48 Weeks or TDF Alone

End point title	Percentage of Participants With HBsAg Loss at Week 72 Following Treatment With TDF (48 Weeks) Plus Peg-IFN (16 Weeks) Combination Versus Peg-IFN Alone for 48 Weeks or TDF Alone ^[4]
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End point description:

Loss of HBsAg was defined as change of detectable HBsAg from positive to negative. Proportions are based on a Kaplan-Meier estimate.

The analysis visit window for Week 72 comprised Week 70 through Week 78, so results up to Week 78 are included in this analysis.

Full Analysis Set: participants who were randomized and received at least 1 dose of study drug. Participants in the TDF 48 week + Peg-IFN 16 Weeks, TDF 120 Weeks, and Peg-IFN 48 Weeks groups were analyzed.

End point type	Secondary
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End point timeframe:

Baseline; Week 72

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is specific to only certain arms of the study.

End point values	TDF 48 Weeks + Peg-IFN 16 Weeks	TDF 120 Weeks	Peg-IFN 48 Weeks	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	184	185	185	
Units: percentage of participants				
number (not applicable)	2.83	0	2.84	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HBsAg Loss at Weeks 96 and 120

End point title	Percentage of Participants With HBsAg Loss at Weeks 96 and 120
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End point description:

Loss of HBsAg was defined as change of detectable HBsAg from positive to negative. Proportions are based on a Kaplan-Meier estimate.

The analysis visit window for Week 96 comprised study Week 90 through Week 102, so results up to Week 102 are included in this analysis. The analysis visit window for Week 120 comprised study Week 114 through Week 126, so results up to Week 126 are included in this analysis.

Full Analysis Set: participants who were randomized and received at least 1 dose of study drug.

End point type	Secondary
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End point timeframe:

Baseline; Weeks 96 and 120

End point values	TDF+Peg-IFN 48 Weeks	TDF 48 Weeks + Peg-IFN 16 Weeks	TDF 120 Weeks	Peg-IFN 48 Weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	186	184	185	185
Units: percentage of participants				
number (not applicable)				
Week 96	9.69	3.49	0	2.84
Week 120	10.36	3.49	0	3.51

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HBsAg Seroconversion at Weeks 72, 96, and 120

End point title	Percentage of Participants With HBsAg Seroconversion at Weeks 72, 96, and 120
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End point description:

HBsAg seroconversion was defined as change of detectable antibody to HBsAg from negative to positive. Proportions are based on a Kaplan-Meier estimate.

The analysis visit window for Week 72 comprised Week 70 through Week 78, so results up to Week 78 are included in this analysis. The analysis visit window for Week 96 comprised Week 90 through Week 102, so results up to Week 102 are included in this analysis. The analysis visit window for Week 120 comprised Week 114 through Week 120.

Full Analysis Set: participants who were randomized and received at least 1 dose of study drug.

End point type	Secondary
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End point timeframe:

Baseline; Weeks 72, 96, and 120

End point values	TDF+Peg-IFN 48 Weeks	TDF 48 Weeks + Peg-IFN 16 Weeks	TDF 120 Weeks	Peg-IFN 48 Weeks
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	186	184	185	185
Units: percentage of participants				
number (not applicable)				
Week 72	8.05	0.56	0	2.87
Week 96	8.05	0.56	0	2.87
Week 120	10.08	0.56	0	2.87

Statistical analyses

Secondary: Percentage of Participants With HBeAg Loss and Seroconversion at Week 72

End point title	Percentage of Participants With HBeAg Loss and Seroconversion at Week 72
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End point description:

Loss of HBeAg was defined as change of detectable HBeAg from positive to negative. HBeAg seroconversion was defined as change of detectable antibody to HBeAg from negative to positive. Percentages were based on the number of subjects with non-missing HBeAg results or missing HBeAg results imputed as failures at each visit.

For the TDF+Peg-IFN 48 Weeks, TDF 48 Weeks + Peg-IFN 16 Weeks, and Peg-IFN 48 Weeks groups, data are presented in the "Not Retreated" column for participants who had not entered the retreatment phase by Week 72, and in the "Retreated" column for participants who did enter the retreatment phase by Week 72.

Participants in the Full Analysis Set who were HBeAg reactive or indeterminate at baseline were analyzed. The missing = failure method was used in which participants on study with missing data were considered to have failed to achieve the outcome.

End point type	Secondary
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End point timeframe:

Baseline; Week 72

End point values	TDF+Peg-IFN 48 Week (Not Retreated)	TDF+Peg-IFN 48 Weeks (Retreated)	TDF 48 Weeks + Peg-IFN 16 Week (Not Retreated)	TDF 48 Weeks + Peg-IFN 16 Weeks (Retreated)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	76	32	61	44
Units: percentage of participants				
number (not applicable)				
HBeAg Loss	35.5	15.6	32.8	15.9
HBeAg Seroconversion	28.9	15.6	31.1	13.6

End point values	TDF 120 Weeks	Peg-IFN 48 Weeks (Not Retreated)	Peg-IFN 48 Weeks (Retreated)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	109	64	42	
Units: percentage of participants				
number (not applicable)				
HBeAg Loss	14.7	32.8	14.3	
HBeAg Seroconversion	12.8	31.3	14.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HBeAg Loss and Seroconversion at Week 96

End point title	Percentage of Participants With HBeAg Loss and Seroconversion at Week 96
End point description: Loss of HBeAg was defined as change of detectable HBeAg from positive to negative. HBeAg seroconversion was defined as change of detectable antibody to HBeAg from negative to positive. Percentages were based on the number of subjects with non-missing HBeAg results or missing HBeAg results imputed as failures at each visit. For the TDF+Peg-IFN 48 Weeks, TDF 48 Weeks + Peg-IFN 16 Weeks, and Peg-IFN 48 Weeks groups, data are presented in the "Not Retreated" column for participants who had not entered the retreatment phase by Week 96, and in the "Retreated" column for participants who did enter the retreatment phase by Week 96.	
Participants in the Full Analysis Set who were HBeAg reactive or indeterminate at baseline were analyzed. The missing = failure method was used in which participants on study with missing data were considered to have failed to achieve the outcome.	
End point type	Secondary
End point timeframe: Baseline; Week 96	

End point values	TDF+Peg-IFN 48 Week (Not Retreated)	TDF+Peg-IFN 48 Weeks (Retreated)	TDF 48 Weeks + Peg-IFN 16 Week (Not Retreated)	TDF 48 Weeks + Peg-IFN 16 Weeks (Retreated)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	44	64	44	61
Units: percentage of participants				
number (not applicable)				
HBeAg Loss	43.2	20.3	45.5	14.8
HBeAg Seroconversion	36.4	18.8	43.2	13.1

End point values	TDF 120 Weeks	Peg-IFN 48 Weeks (Not Retreated)	Peg-IFN 48 Weeks (Retreated)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	109	37	69	
Units: percentage of participants				
number (not applicable)				
HBeAg Loss	18.3	37.8	14.5	
HBeAg Seroconversion	16.5	29.7	13	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With HBeAg Loss and Seroconversion at Week 120

End point title	Percentage of Participants With HBeAg Loss and
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End point description:

Loss of HBeAg was defined as change of detectable HBeAg from positive to negative. HBeAg seroconversion was defined as change of detectable antibody to HBeAg from negative to positive. Percentages were based on the number of subjects with non-missing HBeAg results or missing HBeAg results imputed as failures at each visit.

For the TDF+Peg-IFN 48 Weeks, TDF 48 Weeks + Peg-IFN 16 Weeks, and Peg-IFN 48 Weeks groups, data are presented in the "Not Retreated" column for participants who had not entered the retreatment phase by Week 120, and in the "Retreated" column for participants who did enter the retreatment phase by Week 120.

Participants in the Full Analysis Set who were HBeAg reactive or indeterminate at baseline were analyzed. The missing = failure method was used in which participants on study with missing data were considered to have failed to achieve the outcome.

End point type	Secondary
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End point timeframe:

Baseline; Week 120

End point values	TDF+Peg-IFN 48 Week (Not Retreated)	TDF+Peg-IFN 48 Weeks (Retreated)	TDF 48 Weeks + Peg-IFN 16 Week (Not Retreated)	TDF 48 Weeks + Peg-IFN 16 Weeks (Retreated)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	44	64	40	65
Units: percentage of participants				
number (not applicable)				
HBeAg Loss	38.6	25	37.5	23.1
HBeAg Seroconversion	29.5	21.9	35	15.4

End point values	TDF 120 Weeks	Peg-IFN 48 Weeks (Not Retreated)	Peg-IFN 48 Weeks (Retreated)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	109	36	70	
Units: percentage of participants				
number (not applicable)				
HBeAg Loss	20.2	33.3	18.6	
HBeAg Seroconversion	15.6	25	17.1	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Virological Response (HBV DNA < 117 IU/mL) at Week 72

End point title	Percentage of Participants With Virological Response (HBV DNA < 117 IU/mL) at Week 72
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End point description:

For the TDF+Peg-IFN 48 Weeks, TDF 48 Weeks + Peg-IFN 16 Weeks, and Peg-IFN 48 Weeks groups,

data are presented in the "Not Retreated" column for participants who had not entered the retreatment phase by Week 72, and in the "Retreated" column for participants who did enter the retreatment phase by Week 72.

Full Analysis Set: participants who were randomized and received at least 1 dose of study drug. The missing = failure method was used in which participants on study with missing data were considered to have failed to achieve the endpoint.

End point type	Secondary
End point timeframe:	
Week 72	

End point values	TDF+Peg-IFN 48 Week (Not Retreated)	TDF+Peg-IFN 48 Weeks (Retreated)	TDF 48 Weeks + Peg-IFN 16 Week (Not Retreated)	TDF 48 Weeks + Peg-IFN 16 Weeks (Retreated)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	144	42	131	53
Units: percentage of participants				
number (not applicable)	15.3	26.2	14.5	15.1

End point values	TDF 120 Weeks	Peg-IFN 48 Weeks (Not Retreated)	Peg-IFN 48 Weeks (Retreated)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	185	128	57	
Units: percentage of participants				
number (not applicable)	84.9	11.7	40.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Virological Response (HBV DNA < 117 IU/mL) at Week 96

End point title	Percentage of Participants With Virological Response (HBV DNA < 117 IU/mL) at Week 96
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End point description:

For the TDF+Peg-IFN 48 Weeks, TDF 48 Weeks + Peg-IFN 16 Weeks, and Peg-IFN 48 Weeks groups, data are presented in the "Not Retreated" column for participants who had not entered the retreatment phase by Week 96, and in the "Retreated" column for participants who did enter the retreatment phase by Week 96.

Full Analysis Set: participants who were randomized and received at least 1 dose of study drug. The missing = failure method was used in which participants on study with missing data were considered to have failed to achieve the endpoint.

End point type	Secondary
End point timeframe:	
Week 96	

End point values	TDF+Peg-IFN 48 Week (Not Retreated)	TDF+Peg-IFN 48 Weeks (Retreated)	TDF 48 Weeks + Peg-IFN 16 Week (Not Retreated)	TDF 48 Weeks + Peg-IFN 16 Weeks (Retreated)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	83	103	83	101
Units: percentage of participants				
number (not applicable)	21.7	68	15.7	80.2

End point values	TDF 120 Weeks	Peg-IFN 48 Weeks (Not Retreated)	Peg-IFN 48 Weeks (Retreated)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	185	72	113	
Units: percentage of participants				
number (not applicable)	83.8	13.9	70.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Virological Response (HBV DNA < 117 IU/mL) at Week 120

End point title	Percentage of Participants With Virological Response (HBV DNA < 117 IU/mL) at Week 120
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End point description:

For the TDF+Peg-IFN 48 Weeks, TDF 48 Weeks + Peg-IFN 16 Weeks, and Peg-IFN 48 Weeks groups, data are presented in the "Not Retreated" column for participants who had not entered the retreatment phase by Week 120, and in the "Retreated" column for participants who did enter the retreatment phase by Week 120.

Full Analysis Set: participants who were randomized and received at least 1 dose of study drug. The missing = failure method was used in which participants on study with missing data were considered to have failed to achieve the endpoint.

End point type	Secondary
End point timeframe:	
Week 120	

End point values	TDF+Peg-IFN 48 Week (Not Retreated)	TDF+Peg-IFN 48 Weeks (Retreated)	TDF 48 Weeks + Peg-IFN 16 Week (Not Retreated)	TDF 48 Weeks + Peg-IFN 16 Weeks (Retreated)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	74	112	69	115
Units: percentage of participants				
number (not applicable)	32.4	81.3	18.8	83.5

End point values	TDF 120 Weeks	Peg-IFN 48 Weeks (Not Retreated)	Peg-IFN 48 Weeks (Retreated)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	185	68	117	
Units: percentage of participants				
number (not applicable)	82.2	13.2	82.1	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Normal ALT at Week 72

End point title	Percentage of Participants With Normal ALT at Week 72
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End point description:

Normal ALT was ≤ 30 U/L for males and ≤ 19 U/L for females (based on the American Association for the Study of Liver Diseases (AASLD) 2008 guidelines), and ≤ 41 U/L for males and ≤ 31 U/L for females (based on central laboratory upper limit of the normal range (ULN) for ALT).

For the TDF+Peg-IFN 48 Weeks, TDF 48 Weeks + Peg-IFN 16 Weeks, and Peg-IFN 48 Weeks groups, data are presented in the "Not Retreated" column for participants who had not entered the retreatment phase by Week 72, and in the "Retreated" column for participants who did enter the retreatment phase by Week 72.

Full Analysis Set: participants who were randomized and received at least 1 dose of study drug. The missing = failure method was used in which participants on study with missing data were considered to have failed to achieve the endpoint.

End point type	Secondary
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End point timeframe:

Week 72

End point values	TDF+Peg-IFN 48 Week (Not Retreated)	TDF+Peg-IFN 48 Weeks (Retreated)	TDF 48 Weeks + Peg-IFN 16 Week (Not Retreated)	TDF 48 Weeks + Peg-IFN 16 Weeks (Retreated)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	126	60	118	66
Units: percentage of participants				
number (not applicable)				
AASLD Criteria	42.1	18.3	40.7	18.2

Central Laboratory Criteria	59.5	40	57.6	34.8
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End point values	TDF 120 Weeks	Peg-IFN 48 Weeks (Not Retreated)	Peg-IFN 48 Weeks (Retreated)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	185	120	65	
Units: percentage of participants				
number (not applicable)				
AASLD Criteria	47.6	35	9.2	
Central Laboratory Criteria	72.4	57.5	33.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Normal ALT at Week 96

End point title	Percentage of Participants With Normal ALT at Week 96
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End point description:

Normal ALT was ≤ 30 U/L for males and ≤ 19 U/L for females (based on the American Association for the Study of Liver Diseases (AASLD) 2008 guidelines), and ≤ 41 U/L for males and ≤ 31 U/L for females (based on central laboratory upper limit of the normal range (ULN) for ALT).

For the TDF+Peg-IFN 48 Weeks, TDF 48 Weeks + Peg-IFN 16 Weeks, and Peg-IFN 48 Weeks groups, data are presented in the "Not Retreated" column for participants who had not entered the retreatment phase by Week 96, and in the "Retreated" column for participants who did enter the retreatment phase by Week 96.

Full Analysis Set: participants who were randomized and received at least 1 dose of study drug. The missing = failure method was used in which participants on study with missing data were considered to have failed to achieve the endpoint.

End point type	Secondary
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End point timeframe:

Week 96

End point values	TDF+Peg-IFN 48 Week (Not Retreated)	TDF+Peg-IFN 48 Weeks (Retreated)	TDF 48 Weeks + Peg-IFN 16 Week (Not Retreated)	TDF 48 Weeks + Peg-IFN 16 Weeks (Retreated)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	81	105	82	102
Units: percentage of participants				
number (not applicable)				
AASLD Criteria	43.2	42.9	34.1	46.1
Central Laboratory Criteria	55.6	71.4	52.4	73.5

End point values	TDF 120 Weeks	Peg-IFN 48 Weeks (Not Retreated)	Peg-IFN 48 Weeks (Retreated)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	185	72	113	
Units: percentage of participants				
number (not applicable)				
AASLD Criteria	48.1	34.7	39.8	
Central Laboratory Criteria	73	47.2	68.1	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Normal ALT at Week 120

End point title	Percentage of Participants With Normal ALT at Week 120
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End point description:

Normal ALT was ≤ 30 U/L for males and ≤ 19 U/L for females (based on the American Association for the Study of Liver Diseases (AASLD) 2008 guidelines), and ≤ 41 U/L for males and ≤ 31 U/L for females (based on central laboratory upper limit of the normal range (ULN) for ALT).

For the TDF+Peg-IFN 48 Weeks, TDF 48 Weeks + Peg-IFN 16 Weeks, and Peg-IFN 48 Weeks groups, data are presented in the "Not Retreated" column for participants who had not entered the retreatment phase by Week 120, and in the "Retreated" column for participants who did enter the retreatment phase by Week 120.

Full Analysis Set: participants who were randomized and received at least 1 dose of study drug. The missing = failure method was used in which participants on study with missing data were considered to have failed to achieve the endpoint.

End point type	Secondary
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End point timeframe:

Week 120

End point values	TDF+Peg-IFN 48 Week (Not Retreated)	TDF+Peg-IFN 48 Weeks (Retreated)	TDF 48 Weeks + Peg-IFN 16 Week (Not Retreated)	TDF 48 Weeks + Peg-IFN 16 Weeks (Retreated)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	74	112	69	115
Units: percentage of participants				
number (not applicable)				
AASLD Criteria	39.2	54.5	30.4	48.7
Central Laboratory Criteria	44.6	72.3	40.6	78.3

End point values	TDF 120 Weeks	Peg-IFN 48 Weeks (Not Retreated)	Peg-IFN 48 Weeks (Retreated)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	185	68	117	

Units: percentage of participants				
number (not applicable)				
AASLD Criteria	48.6	30.9	47	
Central Laboratory Criteria	73	41.2	73.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Required Retreatment

End point title	Percentage of Participants Who Required Retreatment ^[5]
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End point description:

Participants in the TDF 120 week group were not eligible to enter the retreatment phase and are not presented.

Safety Analysis Set: participants who were randomized and received at least 1 dose of study drug. Participants in the TDF+Peg-IFN 48 Weeks, TDF 48 Weeks + Peg-IFN 16 Weeks, and Peg-IFN 48 Weeks groups were analyzed.

End point type	Secondary
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End point timeframe:

Up to 120 weeks

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Participants in the TDF 120 week group were not eligible to enter the retreatment phase and are not presented.

End point values	TDF+Peg-IFN 48 Weeks	TDF 48 Weeks + Peg-IFN 16 Weeks	Peg-IFN 48 Weeks	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	186	184	185	
Units: percentage of participants				
number (not applicable)	60.2	62.5	63.2	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 120 weeks plus 30 days

Adverse event reporting additional description:

Safety Analysis Set: participants who were randomized and received at least 1 dose of study drug. Participants were analyzed by actual treatment received.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18
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Reporting groups

Reporting group title	TDF+Peg-IFN 48 Weeks (Not Retreated)
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Reporting group description:

Adverse events in this reporting group are those occurring in participants who were not retreated or before retreatment through last non-retreatment dose plus 30 days.

TDF 300 mg tablet once daily plus Peg-IFN 180 µg s.c. injection once weekly for 48 weeks

Reporting group title	TDF+Peg-IFN 48 Weeks (Retreated)
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Reporting group description:

Adverse events in this reporting group are those occurring after TDF retreatment through last TDF retreatment dose plus 30 days.

TDF 300 mg tablet once daily up to Week 120

Reporting group title	TDF 48 Week + Peg-IFN 16 Weeks (Not Retreated)
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Reporting group description:

Adverse events in this reporting group are those occurring in participants who were not retreated or before retreatment through last non-retreatment dose plus 30 days.

TDF 300 mg tablet once daily plus Peg-IFN 180 µg s.c. injection once weekly for 16 weeks followed by TDF 300 mg tablet once daily for an additional 32 weeks

Reporting group title	TDF 48 Weeks + Peg-IFN 16 Weeks (Retreated)
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Reporting group description:

Adverse events in this reporting group are those occurring after TDF retreatment through last TDF retreatment dose plus 30 days.

TDF 300 mg tablet once daily up to Week 120

Reporting group title	TDF 120 Weeks
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Reporting group description:

Adverse events in this reporting group are those occurring during the initial treatment phase (up to 120 weeks plus 30 days).

TDF 300 mg tablet once daily for up to 120 weeks.

Reporting group title	Peg-IFN 48 Weeks (Not Retreated)
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Reporting group description:

Adverse events in this reporting group are those occurring in participants who were not retreated or before retreatment through last non-retreatment dose plus 30 days.

Peg-IFN 180 µg s.c. injection once weekly for 48 weeks

Reporting group title	Peg-IFN 48 Weeks (Retreated)
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Reporting group description:

Adverse events in this reporting group are those occurring after TDF retreatment through last TDF retreatment dose plus 30 days.

TDF 300 mg tablet once daily up to Week 120

Serious adverse events	TDF+Peg-IFN 48 Weeks (Not Retreated)	TDF+Peg-IFN 48 Weeks (Retreated)	TDF 48 Week + Peg-IFN 16 Weeks (Not Retreated)
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 186 (11.29%)	7 / 112 (6.25%)	18 / 184 (9.78%)
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)			
Hepatocellular carcinoma			
subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of the cervix			
subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	0 / 184 (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
B-cell lymphoma			
subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	0 / 184 (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
Benign neoplasm of bladder			
subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	0 / 184 (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
Brain cancer metastatic			
subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	0 / 184 (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
Cholangiocarcinoma			

subjects affected / exposed	0 / 186 (0.00%)	1 / 112 (0.89%)	0 / 184 (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
Gallbladder neoplasm			
subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemangioma			
subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	0 / 184 (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
Lung neoplasm malignant			
subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mixed hepatocellular cholangiocarcinoma			
subjects affected / exposed	0 / 186 (0.00%)	1 / 112 (0.89%)	0 / 184 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 186 (0.54%)	0 / 112 (0.00%)	0 / 184 (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			
Prostatitis			
subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	0 / 184 (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
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			

subjects affected / exposed	1 / 186 (0.54%)	0 / 112 (0.00%)	0 / 184 (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			
Anxiety			
subjects affected / exposed	1 / 186 (0.54%)	0 / 112 (0.00%)	0 / 184 (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
Depression			
subjects affected / exposed	1 / 186 (0.54%)	0 / 112 (0.00%)	0 / 184 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 186 (3.23%)	3 / 112 (2.68%)	8 / 184 (4.35%)
occurrences causally related to treatment / all	5 / 6	0 / 3	6 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 186 (0.54%)	2 / 112 (1.79%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase abnormal			
subjects affected / exposed	1 / 186 (0.54%)	0 / 112 (0.00%)	0 / 184 (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
Amylase increased			
subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	0 / 184 (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

Lipase increased			
subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	0 / 184 (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			
Contusion			
subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	0 / 184 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial septal defect acquired			
subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	1 / 184 (0.54%)
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			
Hepatic encephalopathy			
subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	0 / 184 (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
Myelopathy			
subjects affected / exposed	1 / 186 (0.54%)	0 / 112 (0.00%)	0 / 184 (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
Neuropathy peripheral			
subjects affected / exposed	1 / 186 (0.54%)	0 / 112 (0.00%)	0 / 184 (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
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 186 (0.54%)	0 / 112 (0.00%)	0 / 184 (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			
Haemorrhoids			

subjects affected / exposed	1 / 186 (0.54%)	0 / 112 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 186 (0.54%)	0 / 112 (0.00%)	0 / 184 (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
Haematemesis			
subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	0 / 184 (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
Pancreatitis acute			
subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	0 / 184 (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
Rectal haemorrhage			
subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	1 / 184 (0.54%)
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			
Hepatitis			
subjects affected / exposed	3 / 186 (1.61%)	2 / 112 (1.79%)	4 / 184 (2.17%)
occurrences causally related to treatment / all	3 / 3	0 / 2	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis chronic			
subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	0 / 184 (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
Cholangitis			

subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	0 / 184 (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
Cholangitis acute			
subjects affected / exposed	1 / 186 (0.54%)	0 / 112 (0.00%)	0 / 184 (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
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	0 / 184 (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
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	0 / 184 (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
Musculoskeletal and connective tissue disorders			
Exostosis			
subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	0 / 184 (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
Rotator cuff syndrome			
subjects affected / exposed	0 / 186 (0.00%)	1 / 112 (0.89%)	0 / 184 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 186 (0.54%)	0 / 112 (0.00%)	0 / 184 (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
Anal abscess			

subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	0 / 184 (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
Cellulitis			
subjects affected / exposed	1 / 186 (0.54%)	0 / 112 (0.00%)	0 / 184 (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
Gastroenteritis			
subjects affected / exposed	1 / 186 (0.54%)	0 / 112 (0.00%)	0 / 184 (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
Gastroenteritis viral			
subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	0 / 184 (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
Psoas abscess			
subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	0 / 184 (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
Sinusitis			
subjects affected / exposed	1 / 186 (0.54%)	0 / 112 (0.00%)	0 / 184 (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
Metabolism and nutrition disorders			
Cholesterosis			
subjects affected / exposed	0 / 186 (0.00%)	0 / 112 (0.00%)	0 / 184 (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

Serious adverse events	TDF 48 Weeks + Peg-IFN 16 Weeks (Retreated)	TDF 120 Weeks	Peg-IFN 48 Weeks (Not Retreated)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 115 (2.61%)	13 / 185 (7.03%)	18 / 185 (9.73%)
number of deaths (all causes)	0	0	0
number of deaths resulting from	0	0	0

adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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
Adenocarcinoma of the cervix			
subjects affected / exposed	0 / 115 (0.00%)	1 / 185 (0.54%)	0 / 185 (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
B-cell lymphoma			
subjects affected / exposed	0 / 115 (0.00%)	1 / 185 (0.54%)	0 / 185 (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
Benign neoplasm of bladder			
subjects affected / exposed	0 / 115 (0.00%)	1 / 185 (0.54%)	0 / 185 (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
Brain cancer metastatic			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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
Breast cancer			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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
Cholangiocarcinoma			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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
Gallbladder neoplasm			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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

Haemangioma			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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
Lung neoplasm malignant			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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
Mixed hepatocellular cholangiocarcinoma			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	1 / 185 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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
Depression			

subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 115 (1.74%)	1 / 185 (0.54%)	7 / 185 (3.78%)
occurrences causally related to treatment / all	0 / 2	0 / 1	6 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	2 / 185 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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
Alanine aminotransferase abnormal			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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
Amylase increased			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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
Lipase increased			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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			
Contusion			
subjects affected / exposed	0 / 115 (0.00%)	1 / 185 (0.54%)	0 / 185 (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

Cardiac disorders			
Atrial septal defect acquired			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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
Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	1 / 115 (0.87%)	0 / 185 (0.00%)	0 / 185 (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
Myelopathy			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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
Neuropathy peripheral			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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
Gastrointestinal disorders			
Haemorrhoids			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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
Abdominal pain			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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
Haematemesis			

subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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
Intestinal obstruction			
subjects affected / exposed	0 / 115 (0.00%)	1 / 185 (0.54%)	0 / 185 (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
Pancreatitis acute			
subjects affected / exposed	0 / 115 (0.00%)	1 / 185 (0.54%)	0 / 185 (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
Rectal haemorrhage			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 115 (0.00%)	1 / 185 (0.54%)	7 / 185 (3.78%)
occurrences causally related to treatment / all	0 / 0	1 / 1	6 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis chronic			
subjects affected / exposed	0 / 115 (0.00%)	2 / 185 (1.08%)	0 / 185 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	0 / 115 (0.00%)	1 / 185 (0.54%)	0 / 185 (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
Cholangitis acute			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	1 / 185 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 115 (0.00%)	1 / 185 (0.54%)	0 / 185 (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
Musculoskeletal and connective tissue disorders			
Exostosis			
subjects affected / exposed	0 / 115 (0.00%)	1 / 185 (0.54%)	0 / 185 (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
Rotator cuff syndrome			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 115 (0.00%)	1 / 185 (0.54%)	1 / 185 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	1 / 185 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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
Gastroenteritis			

subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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
Gastroenteritis viral			
subjects affected / exposed	0 / 115 (0.00%)	1 / 185 (0.54%)	0 / 185 (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
Psoas abscess			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	1 / 185 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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
Metabolism and nutrition disorders			
Cholesterosis			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	0 / 185 (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

Serious adverse events	Peg-IFN 48 Weeks (Retreated)		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 117 (5.13%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Adenocarcinoma of the cervix			

subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
B-cell lymphoma			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Benign neoplasm of bladder			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Brain cancer metastatic			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholangiocarcinoma			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gallbladder neoplasm			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemangioma			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant			

subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mixed hepatocellular cholangiocarcinoma			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	2 / 117 (1.71%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transaminases increased			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Alanine aminotransferase abnormal			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Amylase increased			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lipase increased			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial septal defect acquired			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myelopathy			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neuropathy peripheral			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Haemorrhoids			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haematemesis			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			

subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis chronic			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholangitis			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholangitis acute			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			

Hyperthyroidism			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Exostosis			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rotator cuff syndrome			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anal abscess			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Psoas abscess			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Cholesterosis			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	TDF+Peg-IFN 48 Weeks (Not Retreated)	TDF+Peg-IFN 48 Weeks (Retreated)	TDF 48 Week + Peg-IFN 16 Weeks (Not Retreated)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	147 / 186 (79.03%)	26 / 112 (23.21%)	142 / 184 (77.17%)
Nervous system disorders			
Headache			
subjects affected / exposed	54 / 186 (29.03%)	3 / 112 (2.68%)	37 / 184 (20.11%)
occurrences (all)	70	4	44
Dizziness			
subjects affected / exposed	20 / 186 (10.75%)	0 / 112 (0.00%)	18 / 184 (9.78%)
occurrences (all)	20	0	18
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	15 / 186 (8.06%)	0 / 112 (0.00%)	11 / 184 (5.98%)
occurrences (all)	17	0	11
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	40 / 186 (21.51%)	2 / 112 (1.79%)	33 / 184 (17.93%)
occurrences (all)	44	2	36
Pyrexia			

subjects affected / exposed	39 / 186 (20.97%)	1 / 112 (0.89%)	36 / 184 (19.57%)
occurrences (all)	60	2	39
Influenza like illness			
subjects affected / exposed	19 / 186 (10.22%)	0 / 112 (0.00%)	17 / 184 (9.24%)
occurrences (all)	21	0	23
Asthenia			
subjects affected / exposed	20 / 186 (10.75%)	0 / 112 (0.00%)	9 / 184 (4.89%)
occurrences (all)	20	0	9
Malaise			
subjects affected / exposed	20 / 186 (10.75%)	0 / 112 (0.00%)	12 / 184 (6.52%)
occurrences (all)	27	0	12
Chills			
subjects affected / exposed	5 / 186 (2.69%)	0 / 112 (0.00%)	13 / 184 (7.07%)
occurrences (all)	5	0	13
Injection site erythema			
subjects affected / exposed	12 / 186 (6.45%)	0 / 112 (0.00%)	11 / 184 (5.98%)
occurrences (all)	13	0	11
Pain			
subjects affected / exposed	8 / 186 (4.30%)	0 / 112 (0.00%)	5 / 184 (2.72%)
occurrences (all)	13	0	5
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	26 / 186 (13.98%)	0 / 112 (0.00%)	24 / 184 (13.04%)
occurrences (all)	27	0	25
Diarrhoea			
subjects affected / exposed	13 / 186 (6.99%)	2 / 112 (1.79%)	10 / 184 (5.43%)
occurrences (all)	16	2	12
Dyspepsia			
subjects affected / exposed	9 / 186 (4.84%)	1 / 112 (0.89%)	6 / 184 (3.26%)
occurrences (all)	9	1	6
Abdominal pain upper			
subjects affected / exposed	11 / 186 (5.91%)	2 / 112 (1.79%)	7 / 184 (3.80%)
occurrences (all)	12	2	9
Abdominal pain			
subjects affected / exposed	7 / 186 (3.76%)	1 / 112 (0.89%)	6 / 184 (3.26%)
occurrences (all)	7	2	6

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 186 (5.91%)	3 / 112 (2.68%)	9 / 184 (4.89%)
occurrences (all)	13	4	11
Oropharyngeal pain			
subjects affected / exposed	10 / 186 (5.38%)	3 / 112 (2.68%)	5 / 184 (2.72%)
occurrences (all)	12	3	6
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	46 / 186 (24.73%)	0 / 112 (0.00%)	32 / 184 (17.39%)
occurrences (all)	46	0	33
Pruritus			
subjects affected / exposed	14 / 186 (7.53%)	0 / 112 (0.00%)	14 / 184 (7.61%)
occurrences (all)	16	0	16
Rash			
subjects affected / exposed	20 / 186 (10.75%)	1 / 112 (0.89%)	17 / 184 (9.24%)
occurrences (all)	25	1	21
Psychiatric disorders			
Insomnia			
subjects affected / exposed	19 / 186 (10.22%)	3 / 112 (2.68%)	14 / 184 (7.61%)
occurrences (all)	19	3	14
Irritability			
subjects affected / exposed	11 / 186 (5.91%)	1 / 112 (0.89%)	2 / 184 (1.09%)
occurrences (all)	11	1	2
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	29 / 186 (15.59%)	0 / 112 (0.00%)	36 / 184 (19.57%)
occurrences (all)	34	0	40
Back pain			
subjects affected / exposed	16 / 186 (8.60%)	3 / 112 (2.68%)	11 / 184 (5.98%)
occurrences (all)	22	3	12
Arthralgia			
subjects affected / exposed	9 / 186 (4.84%)	3 / 112 (2.68%)	11 / 184 (5.98%)
occurrences (all)	9	4	14
Musculoskeletal pain			

subjects affected / exposed occurrences (all)	5 / 186 (2.69%) 6	2 / 112 (1.79%) 2	2 / 184 (1.09%) 3
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	10 / 186 (5.38%) 11	3 / 112 (2.68%) 4	9 / 184 (4.89%) 12
Nasopharyngitis subjects affected / exposed occurrences (all)	5 / 186 (2.69%) 7	3 / 112 (2.68%) 6	16 / 184 (8.70%) 19
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	23 / 186 (12.37%) 23	0 / 112 (0.00%) 0	36 / 184 (19.57%) 36

Non-serious adverse events	TDF 48 Weeks + Peg-IFN 16 Weeks (Retreated)	TDF 120 Weeks	Peg-IFN 48 Weeks (Not Retreated)
Total subjects affected by non-serious adverse events subjects affected / exposed	31 / 115 (26.96%)	89 / 185 (48.11%)	152 / 185 (82.16%)
Nervous system disorders Headache subjects affected / exposed occurrences (all)	3 / 115 (2.61%) 3	16 / 185 (8.65%) 34	52 / 185 (28.11%) 87
Dizziness subjects affected / exposed occurrences (all)	1 / 115 (0.87%) 1	9 / 185 (4.86%) 10	17 / 185 (9.19%) 21
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)	1 / 115 (0.87%) 1	0 / 185 (0.00%) 0	15 / 185 (8.11%) 16
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	4 / 115 (3.48%) 5	21 / 185 (11.35%) 22	41 / 185 (22.16%) 47
Pyrexia subjects affected / exposed occurrences (all)	1 / 115 (0.87%) 1	8 / 185 (4.32%) 11	43 / 185 (23.24%) 54
Influenza like illness			

subjects affected / exposed	0 / 115 (0.00%)	10 / 185 (5.41%)	17 / 185 (9.19%)
occurrences (all)	0	20	23
Asthenia			
subjects affected / exposed	1 / 115 (0.87%)	4 / 185 (2.16%)	12 / 185 (6.49%)
occurrences (all)	1	4	12
Malaise			
subjects affected / exposed	1 / 115 (0.87%)	2 / 185 (1.08%)	7 / 185 (3.78%)
occurrences (all)	1	2	8
Chills			
subjects affected / exposed	0 / 115 (0.00%)	3 / 185 (1.62%)	11 / 185 (5.95%)
occurrences (all)	0	3	11
Injection site erythema			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	10 / 185 (5.41%)
occurrences (all)	0	0	11
Pain			
subjects affected / exposed	0 / 115 (0.00%)	0 / 185 (0.00%)	11 / 185 (5.95%)
occurrences (all)	0	0	12
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 115 (2.61%)	11 / 185 (5.95%)	13 / 185 (7.03%)
occurrences (all)	3	11	16
Diarrhoea			
subjects affected / exposed	0 / 115 (0.00%)	11 / 185 (5.95%)	19 / 185 (10.27%)
occurrences (all)	0	14	30
Dyspepsia			
subjects affected / exposed	1 / 115 (0.87%)	15 / 185 (8.11%)	9 / 185 (4.86%)
occurrences (all)	1	17	10
Abdominal pain upper			
subjects affected / exposed	0 / 115 (0.00%)	7 / 185 (3.78%)	6 / 185 (3.24%)
occurrences (all)	0	7	6
Abdominal pain			
subjects affected / exposed	1 / 115 (0.87%)	6 / 185 (3.24%)	10 / 185 (5.41%)
occurrences (all)	2	7	13
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	3 / 115 (2.61%) 3	12 / 185 (6.49%) 14	16 / 185 (8.65%) 17
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 115 (0.00%) 0	9 / 185 (4.86%) 9	11 / 185 (5.95%) 11
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	1 / 115 (0.87%) 1	2 / 185 (1.08%) 2	45 / 185 (24.32%) 45
Pruritus subjects affected / exposed occurrences (all)	2 / 115 (1.74%) 2	4 / 185 (2.16%) 4	21 / 185 (11.35%) 23
Rash subjects affected / exposed occurrences (all)	1 / 115 (0.87%) 1	1 / 185 (0.54%) 1	9 / 185 (4.86%) 10
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	1 / 115 (0.87%) 1	6 / 185 (3.24%) 6	18 / 185 (9.73%) 20
Irritability subjects affected / exposed occurrences (all)	0 / 115 (0.00%) 0	0 / 185 (0.00%) 0	11 / 185 (5.95%) 11
Musculoskeletal and connective tissue disorders			
Myalgia subjects affected / exposed occurrences (all)	1 / 115 (0.87%) 1	2 / 185 (1.08%) 2	35 / 185 (18.92%) 42
Back pain subjects affected / exposed occurrences (all)	3 / 115 (2.61%) 3	11 / 185 (5.95%) 11	10 / 185 (5.41%) 13
Arthralgia subjects affected / exposed occurrences (all)	3 / 115 (2.61%) 3	4 / 185 (2.16%) 4	9 / 185 (4.86%) 9
Musculoskeletal pain subjects affected / exposed occurrences (all)	1 / 115 (0.87%) 1	10 / 185 (5.41%) 11	8 / 185 (4.32%) 9

Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	9 / 115 (7.83%) 10	16 / 185 (8.65%) 24	10 / 185 (5.41%) 13
Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 115 (2.61%) 4	20 / 185 (10.81%) 32	6 / 185 (3.24%) 6
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	2 / 115 (1.74%) 2	2 / 185 (1.08%) 2	18 / 185 (9.73%) 20

Non-serious adverse events	Peg-IFN 48 Weeks (Retreated)		
Total subjects affected by non-serious adverse events subjects affected / exposed	33 / 117 (28.21%)		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	4 / 117 (3.42%) 7		
Dizziness subjects affected / exposed occurrences (all)	4 / 117 (3.42%) 4		
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)	0 / 117 (0.00%) 0		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	6 / 117 (5.13%) 8		
Pyrexia subjects affected / exposed occurrences (all)	2 / 117 (1.71%) 2		
Influenza like illness subjects affected / exposed occurrences (all)	2 / 117 (1.71%) 2		
Asthenia			

subjects affected / exposed	1 / 117 (0.85%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	3 / 117 (2.56%)		
occurrences (all)	3		
Chills			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences (all)	1		
Injection site erythema			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	2 / 117 (1.71%)		
occurrences (all)	3		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	6 / 117 (5.13%)		
occurrences (all)	6		
Diarrhoea			
subjects affected / exposed	4 / 117 (3.42%)		
occurrences (all)	4		
Dyspepsia			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	6 / 117 (5.13%)		
occurrences (all)	6		
Abdominal pain			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 117 (2.56%)		
occurrences (all)	3		
Oropharyngeal pain			

subjects affected / exposed occurrences (all)	2 / 117 (1.71%) 2		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	2 / 117 (1.71%)		
occurrences (all)	2		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 117 (1.71%)		
occurrences (all)	2		
Irritability			
subjects affected / exposed	0 / 117 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	3 / 117 (2.56%)		
occurrences (all)	3		
Arthralgia			
subjects affected / exposed	2 / 117 (1.71%)		
occurrences (all)	2		
Musculoskeletal pain			
subjects affected / exposed	1 / 117 (0.85%)		
occurrences (all)	1		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	5 / 117 (4.27%)		
occurrences (all)	9		

Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 117 (2.56%) 3		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	0 / 117 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 January 2011	<p>1) Modified the TDF 48 Week + Peg-IFN 16 Week group from a response-guided design to a fixed-duration treatment of TDF and Peg-IFN concomitantly for 16 weeks, followed by TDF alone for another 32 weeks; updated the secondary objective and endpoint accordingly.</p> <p>2) Increased study sample size to 720 (180 in each of the 4 treatment groups).</p> <p>3) Added clarity to exclude cirrhotic subjects.</p> <p>4) Removed the allowed 10% variance for eligibility criteria in eligibility time windows.</p> <p>5) Added the EudraCT number 2010-024586-45 and clinicaltrials.gov identifier NCT01277601 to the protocol.</p>
15 April 2011	<p>1) A secondary objective to evaluate virological response (HBV DNA < 400 copies/mL [< 69 IU/mL]) was added.</p> <p>2) Subjects on statins were allowed in the study if they had no evidence of hepatic toxicity on statins.</p> <p>3) ALT levels in the inclusion criteria were changed from $> 2 \times \text{ULN} \leq 10 \times \text{ULN}$ to numeric cut-off levels of > 60 U/L and ≤ 400 U/L for men and > 40 U/L and ≤ 300 U/L for women.</p> <p>4) The study entry requirement of CLcr was changed from ≥ 70 mL/min to ≥ 80 mL/min to exclude subjects who may have beginning renal impairment.</p> <p>5) Fibroscan (< 8 kPa) may have been used to verify absence of bridging fibrosis or cirrhosis in order to meet entry criteria, but was limited to countries where Fibroscan was approved for clinical use. For all other subjects and subjects with a Fibroscan ≥ 8 kPa who wished to enroll in the study, a screening liver biopsy or documentation of prior results within 12 months of the first study visit was required.</p> <p>6) α-fetoprotein (AFP) was performed at screening to rule out hepatocellular carcinoma and follow-up AFP was to be repeated at Weeks 24, 48, 72, 96, and 120.</p> <p>7) Subjects who discontinued study drug(s) prior to the protocol-specified duration should have been followed up to 120 weeks or minimally 72 weeks. Follow-up for subjects who discontinued study drug(s) early was previously required every 4 weeks for 24 weeks, but was extended to minimally Week 72. The visit schedule/study procedures after early discontinuation of study drug(s) were changed to mirror those of the immediate off-treatment follow-up period and beyond.</p> <p>8) The amendment allowed the predose sample for the liver biopsy substudy to be taken any time after subjects consented, including at screening or between the screening and baseline visits.</p> <p>9) Flowchart for management of clinical and laboratory AEs was revised to correspond to the toxicity management guidelines described in the protocol.</p> <p>10) Grading scale for AE severity and laboratory abnormalities was updated.</p>

02 August 2011	<ol style="list-style-type: none"> 1) Use of lean body weight for calculating CLcr was changed to actual body weight. 2) Retreatment criteria #1 of increased direct bilirubin by > 1.5 mg/dL was changed to increased total bilirubin by > 1.5 mg/dL. 3) Added guidance for investigators on subjects with loss of HBsAg during study drug treatment. 4) Noted that HBV viral sequence analyses, resistance surveillance, and potential resistance testing will only be evaluated for selected subjects as clinically warranted. 5) Blood storage samples for subjects with hepatic flares and from subjects at early discontinuation visits were to be collected for exploratory analyses. 6) Representative hepatotoxic agents were added to the list of excluded medicines in exclusion criterion #13. 7) The numeric value for ALT 10 × ULN was defined as 400 U/L (males) or 300 U/L (females). 8) Frequency of prothrombin time/INR testing was modified to align with flare management guidelines. 9) The statistical considerations section was revised to include additional objectives, end points of interest, analysis conventions, analysis sets, and safety evaluation.
20 February 2012	<ol style="list-style-type: none"> 1) HBV DNA reporting units revised from copies/mL to IU/mL. 2) Documentation of CHB infection required history of either positive serum HBsAg or HBV DNA for at least 6 months prior to baseline. 3) Inclusion HBV DNA viral load for HBeAg-negative and HBeAg-positive subjects was revised to ≥ 20,000 IU/mL. 4) ALT levels in the inclusion criteria were changed from > 60 and ≤ 400 U/L for men and > 40 and ≤ 300 U/L for women to > 54 and ≤ 400 U/L for men and > 36 and ≤ 300 U/L for women. 5) Study entry requirement of creatinine clearance (CLcr) was changed from ≥ 80 to ≥ 70 mL/min (Amendment 4 only). 6) Clarified the statistical power calculation and reasoning regarding the sample size. 7) Added thyroid-stimulating hormone (TSH) monitoring at Weeks 12, 24, 32, and 48.
29 June 2012	<ol style="list-style-type: none"> 1) Inclusion HBV DNA viral load for HBeAg-negative subjects was revised to ≥ 2000 IU/mL from ≥ 20,000 IU/mL. 2) Inclusion of anti-HBV treatment-naïve subjects and subjects who had taken oral anti-HBV nucleoside therapy with the last dose ≥ 24 weeks prior to screening. 3) Exclusion criteria decompensated liver disease redefined to include subjects with isolated increase in bilirubin who were otherwise excluded as having abnormally elevated values, but otherwise normal clinical parameters of liver function. 4) Randomization strata were redefined to ensure representation of subjects across either HBeAg status and in the 4 dominant genotypes A, B, C, and D. 5) Allow for 1 rescreening of any subject who had previously screen failed twice under a previous protocol amendment. 6) Redefined ULN values for TDF retreatment and flare management after 48 weeks of treatment and management of exacerbation of hepatitis in subjects who had discontinued study drug. 7) Clarified the planned analysis of the secondary endpoint.

17 May 2013	<p>1) Local INR testing could be performed, in the opinion of the investigator, if there were safety concerns.</p> <p>2) The investigator, in conference with the medical monitor, could have provided immediate intervention based on clinical assessment or local laboratory results in the interest of subject safety.</p> <p>3) Corrected ALT range (typo).</p> <p>4) Biweekly follow-up visits were updated for consistency with retreatment criteria.</p> <p>5) Clarified when to restart retreatment or when to return for routine follow-up after Week 48.</p> <p>6) Clarified the acceptable time frame for scheduling and performing the Week 96 liver biopsy for subjects enrolled in the liver biopsy substudy.</p> <p>7) Addressed a safety concern where subjects with ALT > 400 U/L (males) or > 300 U/L (females) would not qualify for TDF retreatment based on the retreatment criteria because of their baseline ALT values.</p> <p>8) Allowed for TDF retreatment with any detectable HBV DNA for subjects with persistently elevated ALT who had been off-treatment for ≥ 12 weeks.</p> <p>9) Eliminated the requirement for confirmatory or reflex testing prior to retreatment.</p> <p>10) Clarified the management of hepatic flare by defining the abnormal laboratory values and acceptable ranges.</p> <p>11) Clarified that HLA typing and biomarker analysis would not be performed in India.</p> <p>12) Provided guidance on subject discontinuation related to noncompliance of Peg-IFN treatment.</p> <p>13) Incorporated the use of hepatitis E virus IgM for laboratory testing related to acute hepatitis exacerbation in India.</p> <p>14) Addressed the management of subjects who experienced loss of HBsAg while on TDF retreatment.</p> <p>15) Provided guidance on the frequency of laboratory monitoring and changes in Peg-IFN dose related to the occurrence of neutropenia and thrombocytopenia.</p> <p>16) Updated safety definitions and provided clarification and guidance on the reporting of safety events.</p> <p>17) Provided clarification on the frequency of retinal examinations in the study.</p>
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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/26453773>

<http://www.ncbi.nlm.nih.gov/pubmed/26143444>