Clinical trial results:
OPTIMA: A randomized, open-label, 156-week treatment study to evaluate the efficacy and safety of telbivudine or tenofovir treatment in HBeAg-negative chronic hepatitis B patients based on the Roadmap concept

Summary

EudraCT number	2007-000180-13
Trial protocol	AT ES DE GR BG IT
Global end of trial date	10 December 2015

Results information

Result version number	v1 (current)
This version publication date	27 December 2016
First version publication date	27 December 2016

Trial information

Trial identification

Sponsor protocol code	CLDT600A2409

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01379508
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharmaceuticals
Sponsor organisation address	CH - 4002,, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharmaceuticals, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharmaceuticals, 41 613241111,

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	10 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 December 2015
Global end of trial reached?	Yes
Global end of trial date	10 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to compare the efficacy of Roadmap-Concept-based telbivudine treatment versus Roadmap-Concept-based tenofovir treatment in hepatitis B e antigen (HBeAg)-negative chronic hepatitis B (CHB) patients. The rate of patients achieving hepatitis B virus (HBV) deoxyribonucleic acid (DNA) < 300 copies/mL (51 IU/mL) at Week 52 was used for comparison of efficacy; the hypothesis being that the rate of patients achieving HBV DNA < 300 copies/mL (51 IU/mL) at Week 52 in the telbivudine arm (Arm 1) was non-inferior to that achieved in the tenofovir arm (Arm 2).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 March 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	Austria: 7
Country: Number of subjects enrolled	Bulgaria: 125
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Greece: 10
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Russian Federation: 41
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Turkey: 35
Worldwide total number of subjects	241
EEA total number of subjects	165

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)	234
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

There was a screening period of 6 weeks to assess eligibility and to taper disallowed medications. At the Baseline visit, eligible patients were randomly assigned according to a 1:1 ratio to either treatment arms (telbivudine 600 mg once daily or tenofovir disoproxil fumarate 300 mg once daily).

Period 1

Period 1 title	Treatment to Week 104
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	LdT Mono at Week 24

Arm description:

Patients who were initially treated with telbivudine and had hepatitis B virus deoxyribonucleic acid < 300 copies/mL in their blood at Week 24 and continued to receive 600 mg telbivudine daily after Week 24. Patients who developed VB while on monotherapy received add-on therapy of tenofovir.

Arm type	Experimental
Investigational medicinal product name	Telbivudine
Investigational medicinal product code	LDT600
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

600 mg tablet orally (p.o.) taken once daily for up to 156 weeks. Dose adjustments were to be considered if CrCl decreased to 50 mL/min

Arm title	LdT+TDF at Week 24

Arm description:

Patients who were initially treated with telbivudine and had hepatitis B virus deoxyribonucleic acid > 300 copies/mL in their blood at Week 24 and continued to receive 600 mg telbivudine daily and additional 300 mg tenofovir after Week 24. If patients developed VB after Week 24 while on combination therapy already, study treatment was handled under the investigator's discretion and the patient might have been discontinued.

Arm type	experimental plus active comparator
Investigational medicinal product name	tenofovir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

300 mg tablets taken as 300 mg once daily up to 156 weeks. Tenofovir dose adjustments were to be considered if estimated calculated serum CrCl by either Cockcroft-Gault or MDRD method < 50 mL/min, confirmed by 2 estimated calculations or laboratory serum phosphate < 1.5 mg/dL confirmed on retesting at the central laboratory

Investigational medicinal product name	telbivudine
Investigational medicinal product code	LDT600
Other name	
Pharmaceutical forms	Film-coated tablet

Routes of administration	Oral use

Dosage and administration details:

600 mg tablet orally (p.o.) taken once daily for up to 156 weeks. Dose adjustments were to be considered if CrCl decreased to 50 mL/min

Arm title	TDF Mono at Week 24

Arm description:

Patients who were initially treated with tenofovir and had hepatitis B virus deoxyribonucleic acid < 300 copies/mL in their blood at Week 24 and continued to receive 300 mg tenofovir daily after Week 24. Patients who developed VB while on monotherapy received add-on therapy with telbivudine.

Arm type	Active comparator
Investigational medicinal product name	tenofovir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

300 mg tablets taken as 300 mg once daily up to 156 weeks. Tenofovir dose adjustments were to be considered if estimated calculated serum CrCl by either Cockcroft-Gault or MDRD method < 50 mL/min, confirmed by 2 estimated calculations or laboratory serum phosphate < 1.5 mg/dL confirmed on retesting at the central laboratory

Arm title	TDF + LdT at Week 24

Arm description:

Patients who were initially treated with tenofovir and had hepatitis B virus deoxyribonucleic acid > 300 copies/mL in their blood at Week 24 and continued to receive 300 mg tenofovir and additional 600 mg telbivudine after Week 24. If patients developed VB after Week 24 while on combination therapy already, study treatment was handled under the investigator's discretion and the patient might have been discontinued.

Arm type	active comparator plus experimental add-on
Investigational medicinal product name	tenofovir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

300 mg tablets taken as 300 mg once daily up to 156 weeks. Tenofovir dose adjustments were to be considered if estimated calculated serum CrCl by either Cockcroft-Gault or MDRD method < 50 mL/min, confirmed by 2 estimated calculations or laboratory serum phosphate < 1.5 mg/dL confirmed on retesting at the central laboratory

Investigational medicinal product name	telbivudine
Investigational medicinal product code	LDT600
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

600 mg tablet orally (p.o.) taken once daily for up to 156 weeks. Dose adjustments were to be considered if CrCl decreased to 50 mL/min

Number of subjects in period 1	LdT Mono at Week 24	LdT+TDF at Week 24	TDF Mono at Week 24
Started	99	22	109
Completed Wk 24	93	22	107
Treatment exposure ≥ 52 weeks	91	21	105
Completed	80	19	96
Not completed	19	3	13
Consent withdrawn by subject	6	1	4
Abnormal lab value	1	-	-
Adverse event, non-fatal	2	-	5
Administrative problems	3	1	-
Lost to follow-up	5	-	3
Abnormal test procedure result(s)	1	-	-
Protocol deviation	1	1	1

Number of subjects in period 1	TDF + LdT at Week 24
Started	11
Completed Wk 24	11
Treatment exposure ≥ 52 weeks	11
Completed	11
Not completed	0
Consent withdrawn by subject	-
Abnormal lab value	-
Adverse event, non-fatal	-
Administrative problems	-
Lost to follow-up	-
Abnormal test procedure result(s)	-
Protocol deviation	-

Period 2

Period 2 title	Extension Period Weeks 109-156
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes

Arm title	LdT Mono at Week 24

Arm description:

Patients who were initially treated with telbivudine and had hepatitis B virus deoxyribonucleic acid < 300 copies/mL in their blood at Week 24 and continued to receive 600 mg telbivudine daily after Week 24. Patients who developed VB while on monotherapy received add-on therapy of tenofovir

Arm type	Experimental
Investigational medicinal product name	Telbivudine
Investigational medicinal product code	LDT600
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

600 mg tablet orally (p.o.) taken once daily for up to 156 weeks. Dose adjustments were to be considered if CrCl decreased to 50 mL/min

Arm title	LdT+TDF at Week 24

Arm description:

Patients who were initially treated with telbivudine and had hepatitis B virus deoxyribonucleic acid > 300 copies/mL in their blood at Week 24 and continued to receive 600 mg telbivudine daily and additional 300 mg tenofovir after Week 24. If patients developed VB after Week 24 while on combination therapy already, study treatment was handled under the investigator's discretion and the patient might have been discontinued.

Arm type	telbivudine plus tenofovir add-on
Investigational medicinal product name	Telbivudine
Investigational medicinal product code	LDT600
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

600 mg tablet orally (p.o.) taken once daily for up to 156 weeks. Dose adjustments were to be considered if CrCl decreased to 50 mL/min

Investigational medicinal product name	tenofovir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

300 mg tablets taken as 300 mg once daily up to 156 weeks. Tenofovir dose adjustments were to be considered if estimated calculated serum CrCl by either Cockcroft-Gault or MDRD method < 50 mL/min, confirmed by 2 estimated calculations or laboratory serum phosphate < 1.5 mg/dL confirmed on retesting at the central laboratory

Arm title	TDF Mono at Week 24

Arm description:

Patients who were initially treated with tenofovir and had hepatitis B virus deoxyribonucleic acid < 300 copies/mL in their blood at Week 24 and continued to receive 300 mg tenofovir daily after Week 24. Patients who developed VB while on monotherapy received add-on therapy with telbivudine.

Arm type	Active comparator
Investigational medicinal product name	tenofovir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

300 mg tablets taken as 300 mg once daily up to 156 weeks. Tenofovir dose adjustments were to be considered if estimated calculated serum CrCl by either Cockcroft-Gault or MDRD method < 50 mL/min, confirmed by 2 estimated calculations or laboratory serum phosphate < 1.5 mg/dL confirmed on

retesting at the central laboratory

Arm title	TDF + LdT at Week 24

Arm description:

Patients who were initially treated with tenofovir and had hepatitis B virus deoxyribonucleic acid > 300 copies/mL in their blood at Week 24 and continued to receive 300 mg tenofovir and additional 600 mg telbivudine after Week 24. If patients developed VB after Week 24 while on combination therapy already, study treatment was handled under the investigator's discretion and the patient might have been discontinued.

Arm type	tenofovir plus telbivudine add-on
Investigational medicinal product name	tenofovir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

300 mg tablets taken as 300 mg once daily up to 156 weeks. Tenofovir dose adjustments were to be considered if estimated calculated serum CrCl by either Cockcroft-Gault or MDRD method < 50 mL/min, confirmed by 2 estimated calculations or laboratory serum phosphate < 1.5 mg/dL confirmed on retesting at the central laboratory

Investigational medicinal product name	telbivudine
Investigational medicinal product code	LDT600
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

600 mg tablet orally (p.o.) taken once daily for up to 156 weeks. Dose adjustments were to be considered if CrCl decreased to 50 mL/min

Number of subjects in period 2[1]	LdT Mono at Week 24	LdT+TDF at Week 24	TDF Mono at Week 24
Started	64	17	79
Completed	45	14	65
Not completed	19	3	14
Consent withdrawn by subject	8	1	8
Administrative problems	3	-	1
Lost to follow-up	6	1	5
Protocol deviation	2	1	-

Number of subjects in period 2[1]	TDF + LdT at Week 24
Started	10
Completed	10
Not completed	0
Consent withdrawn by subject	-

Administrative problems	-
Lost to follow-up	-
Protocol deviation	-

Notes:

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

Justification: Based on the following eligibility criteria for enrollment into the extension period, eligible patients were to be treated for 1 additional year up to Week 156: HBV DNA < 300 copies/mL at Weeks 92 and 104, and estimated serum CrCl ≥ 50 mL/min by Cockcroft-Gault, MDRD, or CKD-EPI at Weeks 92 and 104.

Baseline characteristics

Reporting groups	
Reporting group title	LdT Mono at Week 24
Reporting group description:	
Patients who were initially treated with telbivudine and had hepatitis B virus deoxyribonucleic acid < 300 copies/mL in their blood at Week 24 and continued to receive 600 mg telbivudine daily after Week 24. Patients who developed VB while on monotherapy received add-on therapy of tenofovir.	
Reporting group title	LdT+TDF at Week 24
Reporting group description:	
Patients who were initially treated with telbivudine and had hepatitis B virus deoxyribonucleic acid > 300 copies/mL in their blood at Week 24 and continued to receive 600 mg telbivudine daily and additional 300 mg tenofovir after Week 24. If patients developed VB after Week 24 while on combination therapy already, study treatment was handled under the investigator's discretion and the patient might have been discontinued.	
Reporting group title	TDF Mono at Week 24
Reporting group description:	
Patients who were initially treated with tenofovir and had hepatitis B virus deoxyribonucleic acid < 300 copies/mL in their blood at Week 24 and continued to receive 300 mg tenofovir daily after Week 24. Patients who developed VB while on monotherapy received add-on therapy with telbivudine.	
Reporting group title	TDF + LdT at Week 24
Reporting group description:	
Patients who were initially treated with tenofovir and had hepatitis B virus deoxyribonucleic acid > 300 copies/mL in their blood at Week 24 and continued to receive 300 mg tenofovir and additional 600 mg telbivudine after Week 24. If patients developed VB after Week 24 while on combination therapy already, study treatment was handled under the investigator's discretion and the patient might have been discontinued.	

Reporting group values	LdT Mono at Week 24	LdT+TDF at Week 24	TDF Mono at Week 24
Number of subjects	99	22	109
Age Categorical Units: Subjects			
< 30 years	17	4	18
Between 30 and 50 years	56	13	59
> 50 years	26	5	32
Age continuous Units: years			
arithmetic mean	42.3	41.3	43.2
standard deviation	± 11.73	± 10.77	± 12.66
Gender Categorical Units: Subjects			
Male	71	15	75
Female	28	7	34
Genotype Units: Subjects			
Genotype A	5	1	2
Genotype B	1	0	0
Genotype C	0	0	1
Genotype D	84	20	99
Genotype E	0	0	0
Genotype F	0	0	0

Genotype G	1	0	0
Other	1	0	0
Unknown	7	1	7
HBV DNA Units: Subjects			
< 7 log	81	4	83
≥ 7 log	18	18	26
ALT - Multiples of ULN Units: Subjects			
≤ 1 ×	46	3	52
> 1 × - < 2 ×	35	7	27
2 × - < 5 ×	13	11	26
5 × or more	5	1	4
AST - Multiples of ULN Units: Subjects			
≤ 1 ×	70	10	69
> 1 × - < 2 ×	14	7	23
2 × - < 5 ×	12	4	16
5 × or more	3	1	1
Study Specific Characteristic HBV DNA Units: log10 copies/mL)			
arithmetic mean	5.887	7.769	5.838
standard deviation	± 1.2862	± 1.2502	± 1.2464

Reporting group values	TDF + LdT at Week 24	Total	
Number of subjects	11	241	
Age Categorical Units: Subjects			
< 30 years	0	39	
Between 30 and 50 years	7	135	
> 50 years	4	67	
Age continuous Units: years			
arithmetic mean	44.9		
standard deviation	± 12.11	-	
Gender Categorical Units: Subjects			
Male	7	168	
Female	4	73	
Genotype Units: Subjects			
Genotype A	0	8	
Genotype B	0	1	
Genotype C	0	1	
Genotype D	11	214	
Genotype E	0	0	
Genotype F	0	0	
Genotype G	0	1	
Other	0	1	
Unknown	0	15	
HBV DNA			

Units: Subjects			
< 7 log	3	171	
≥ 7 log	8	70	
ALT - Multiples of ULN Units: Subjects			
≤ 1 ×	4	105	
> 1 × - < 2 ×	5	74	
2 × - < 5 ×	1	51	
5 × or more	1	11	
AST - Multiples of ULN Units: Subjects			
≤ 1 ×	2	151	
> 1 × - < 2 ×	7	51	
2 × - < 5 ×	1	33	
5 × or more	1	6	
Study Specific Characteristic HBV DNA Units: log10 copies/mL)			
arithmetic mean	7.938		
standard deviation	± 1.0709	-	

End points

End points reporting groups

Reporting group title	LdT Mono at Week 24
Reporting group description:	
Patients who were initially treated with telbivudine and had hepatitis B virus deoxyribonucleic acid < 300 copies/mL in their blood at Week 24 and continued to receive 600 mg telbivudine daily after Week 24. Patients who developed VB while on monotherapy received add-on therapy of tenofovir.	
Reporting group title	LdT+TDF at Week 24
Reporting group description:	
Patients who were initially treated with telbivudine and had hepatitis B virus deoxyribonucleic acid > 300 copies/mL in their blood at Week 24 and continued to receive 600 mg telbivudine daily and additional 300 mg tenofovir after Week 24. If patients developed VB after Week 24 while on combination therapy already, study treatment was handled under the investigator's discretion and the patient might have been discontinued.	
Reporting group title	TDF Mono at Week 24
Reporting group description:	
Patients who were initially treated with tenofovir and had hepatitis B virus deoxyribonucleic acid < 300 copies/mL in their blood at Week 24 and continued to receive 300 mg tenofovir daily after Week 24. Patients who developed VB while on monotherapy received add-on therapy with telbivudine.	
Reporting group title	TDF + LdT at Week 24
Reporting group description:	
Patients who were initially treated with tenofovir and had hepatitis B virus deoxyribonucleic acid > 300 copies/mL in their blood at Week 24 and continued to receive 300 mg tenofovir and additional 600 mg telbivudine after Week 24. If patients developed VB after Week 24 while on combination therapy already, study treatment was handled under the investigator's discretion and the patient might have been discontinued.	
Reporting group title	LdT Mono at Week 24
Reporting group description:	
Patients who were initially treated with telbivudine and had hepatitis B virus deoxyribonucleic acid < 300 copies/mL in their blood at Week 24 and continued to receive 600 mg telbivudine daily after Week 24. Patients who developed VB while on monotherapy received add-on therapy of tenofovir	
Reporting group title	LdT+TDF at Week 24
Reporting group description:	
Patients who were initially treated with telbivudine and had hepatitis B virus deoxyribonucleic acid > 300 copies/mL in their blood at Week 24 and continued to receive 600 mg telbivudine daily and additional 300 mg tenofovir after Week 24. If patients developed VB after Week 24 while on combination therapy already, study treatment was handled under the investigator's discretion and the patient might have been discontinued.	
Reporting group title	TDF Mono at Week 24
Reporting group description:	
Patients who were initially treated with tenofovir and had hepatitis B virus deoxyribonucleic acid < 300 copies/mL in their blood at Week 24 and continued to receive 300 mg tenofovir daily after Week 24. Patients who developed VB while on monotherapy received add-on therapy with telbivudine.	
Reporting group title	TDF + LdT at Week 24
Reporting group description:	
Patients who were initially treated with tenofovir and had hepatitis B virus deoxyribonucleic acid > 300 copies/mL in their blood at Week 24 and continued to receive 300 mg tenofovir and additional 600 mg telbivudine after Week 24. If patients developed VB after Week 24 while on combination therapy already, study treatment was handled under the investigator's discretion and the patient might have been discontinued.	
Subject analysis set title	LdT Overall
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Total of LdT Mono and LdT + TDF	
Subject analysis set title	TDF Overall
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Total of TDF and TDF = LdT

Primary: Percentage of patients achieving HBV DNA < 300 copies/mL (51 IU/mL) at Week 52 (rITT population) -

End point title	Percentage of patients achieving HBV DNA < 300 copies/mL (51 IU/mL) at Week 52 (rITT population) -

End point description:

The primary objective was to compare the efficacy of Roadmap-Concept-based telbivudine vs tenofovir treatment in HBeAg-negative CHB patients.The Roadmap intent-to-treat (rITT) population consisted of ITT population who did not discontinue before Wk 24 and did not violate the protocol-defined rules of receiving add-on. rITT was used for all of the primary endpoint analysis. Mantel-Haenszel weighted estimates (stratified by HBV DNA level (< 7 log10 copies/mL or ≥7 log10 copies/mL) and ALT(< 3×ULN or ≥ 3×ULN) at baseline) was employed to assess the % of patients (response rate)who achieve HBV DNA < 300 copies/mL after 52 wks treatment in each treatment arm, as well as the difference in % (telbivudine – tenofovir arm) and the 95% CI of the difference. The hypothesis is that the aggregated rate of HBV DNA <300 copies/mL (51 IU/mL) at wk 52 of telbivudine is non-inferior to tenofovir (non-inferiority margin of 10%). All 4 analyses with different imputing methods utilize the above.

End point type	Primary

End point timeframe:

week 52

End point values	LdT Overall	TDF Overall		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	113	117		
Units: Participants				
number (not applicable)				
Missing DNA data at Wk 52=failure (n=103,111)	91	95		
Imputing +/- 7 days DNA for Wk 52 (n=104,111)	91.9	95		
Imputing LOCF DNA for Wk 52(n=108,116)	95.4	99.2		
Imputing within +28d DNA for Wk 52 (n=105,111)	92.7	95		

Statistical analyses

Statistical analysis title	Primary - Missing DNA data at Wk 52=failure

Statistical analysis description:

For the Primary “treating missing as failure" analysis, patients who came for their primary endpoint Week 52 visit within the ± 7-day window but not on the exact designated day of the visit were treated as "missing data

Comparison groups	LdT Overall v TDF Overall

Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Difference in percentage
Point estimate	-4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.5
upper limit	2.5

Notes:

[1] - Noninferiority
was derived if the lower limit of two-sided 95% CI for the difference lied above the pre-determined non-inferiority margin (-10%).

Statistical analysis title	Imputing +/- 7 days DNA for Wk 52

Statistical analysis description:

Imputing +/- 7 days DNA for Wk 52

Comparison groups	TDF Overall v LdT Overall
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Difference in percentage
Point estimate	-3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.4
upper limit	3.1

Notes:

[2] - Noninferiority
was derived if the lower limit of two-sided 95% CI for the difference lied above the pre-determined non-inferiority margin (-10%).

Statistical analysis title	Imputing LOCF DNA for wk 52

Statistical analysis description:

Imputing LOCF DNA for wk 52: d/c for non response prior to Wk 52: Treating missing as failure for patients who discontinued prior to Week 52 due to unsatisfactory therapeutic effect and imputing missing with LOCF for other patients.

Comparison groups	LdT Overall v TDF Overall
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Difference in percentage
Point estimate	-3.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.9
upper limit	0.4

Notes:

[3] - Noninferiority
was derived if the lower limit of two-sided 95% CI for the difference lied above the pre-determined non-inferiority margin (-10%).

Statistical analysis title	Imputing within +28d DNA for wk52

Statistical analysis description:

Imputing within +28d DNA for wk52: d/c for non response <28 days from Wk 52:Treating missing as failure for patients who discontinued prior to Week 52 due to unsatisfactory therapeutic effect and imputing missing with the earliest available assessment within the 28-day window starting from the scheduled Week 52 date for other patients (if no such assessment is available, treated as failure)

Comparison groups	LdT Overall v TDF Overall
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	Difference in percentage
Point estimate	-2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.3
upper limit	3.8

Notes:

[4] - Noninferiority
was derived if the lower limit of two-sided 95% CI for the difference lied above the pre-determined non-inferiority margin (-10%).

Secondary: Percentage of patients achieving secondary efficacy endpoints (rITT)

End point title	Percentage of patients achieving secondary efficacy endpoints (rITT)

End point description:

To assess the antiviral efficacy, as evaluated by the percentage of patients achieving HBV DNA <300 copies/mL (51 IU/mL), ALT normalization, HBsAg loss, HBsAg conversion, virologic breakthrough (VB) at study visit, cumulative VB by study defined study period, cumulative treatment-emergent resistance

End point type	Secondary

End point timeframe:

week 24, 52, 104

End point values	LdT Mono at Week 24	LdT+TDF at Week 24	TDF Mono at Week 24	TDF + LdT at Week 24
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	92	21	106	11
Units: Participants				
number (confidence interval 95%)				
HBV DNA<300 Week 24 (91,0,105,0,91,105)	98.9 (94.1 to 100)	0 (0 to 0)	99.1 (94.9 to 100)	0 (0 to 28.5)
HBV DNA <300 Week 104 (n=64,16,79,9,80,88)	69.6 (59.1 to 78.7)	76.2 (52.8 to 91.8)	74.5 (65.1 to 82.5)	81.8 (48.2 to 97.7)
HBV DNA <300 Week 24(n=92,0,106,0,,92,106) LOCF	100 (96.1 to 100)	0 (0 to 16.1)	100 (96.6 to 100)	0 (0 to 28.5)
HBV DNA <300 Wk104(n=85,21,,105,11,106,116) LOCF	92.4 (84.9 to 96.9)	100 (83.9 to 100)	99.1 (94.9 to 100)	100 (71.5 to 100)
ALT Normalization Week 52 (42,15,,47,6,57,53)	84 (70.9 to 92.8)	83.3 (58.6 to 96.4)	82.5 (70.1 to 91.3)	85.7 (42.1 to 99.6)
ALT Normalization Week 104(35,13,,35,6,48,41)	70 (55.4 to 82.1)	72.2 (46.5 to 90.3)	61.4 (47.6 to 74)	85.7 (42.1 to 99.6)
ALT Normalization Week 52 (44,15,,50,6,59,56) LOCF	88 (75.7 to 95.5)	83.3 (58.6 to 96.4)	87.7 (76.3 to 94.9)	85.7 (42.1 to 99.6)

ALT Normalization Wk 104 (46,15,61,49,6,61,55)LOCF	92 (80.8 to 97.8)	83.3 (58.6 to 96.4)	86 (74.2 to 93.7)	85.7 (42.1 to 99.6)
HBsAg loss Week 52 (0,0,0,0,0,0)	0 (0 to 3.9)	0 (0 to 16.1)	0 (0 to 3.4)	0 (0 to 28.5)
HBsAg loss Week 104 (0,0,0,0,0,0)	0 (0 to 3.9)	0 (0 to 16.1)	0 (0 to 3.4)	0 (0 to 28.5)
HBsAg conversion Week 52 (0,0,0,0,0,0)	0 (0 to 3.9)	0 (0 to 16.1)	0 (0 to 3.4)	0 (0 to 28.5)
HBsAg conversion Week 104 (0,0,0,0,0,0)	0 (0 to 3.9)	0 (0 to 16.1)	0 (0 to 3.4)	0 (0 to 28.5)
Cum virol break BaseL to Wk 24 (n=0,1,0,0,1,0)	0 (0 to 0)	4.8 (0.1 to 23.8)	0 (0 to 3.4)	0 (0 to 28.5)
Cum virol break Wk 24 to Wk 52 (n=3,0,,0,0,3,0)	3.3 (0.7 to 9.2)	0 (0 to 16.1)	0 (0 to 3.4)	0 (0 to 28.5)
Cum virol break Wk 52 to Wk 104 (n=11,0,2,0,11,2)	12 (6.1 to 20.4)	0 (0 to 16.1)	1.9 (0.2 to 6.6)	0 (0 to 28.5)
Cum virol break BaseLto Wk 104 (n=13,1,2,0,14,2)	14.1 (7.7 to 23)	4.8 (0.1 to 23.8)	1.9 (0.2 to 6.6)	0 (0 to 28.5)
Cum vir break BL to Wk24 (n=0,1,0,0,1,0) LOCF	0 (0 to 3.9)	4.8 (0.1 to 23.8)	0 (0 to 3.4)	0 (0 to 28.5)
Cum virol break Wk 24 to Wk 52(n=3,0,0,0,3,0) LOCF	3.3 (0.7 to 9.2)	0 (0 to 16.1)	0 (0 to 3.4)	0 (0 to 28.5)
Cum virol break Wk52-Wk104(n=11,0,2,0,11,2) LOCF	12 (6.1 to 20.4)	0 (0 to 16.1)	1.9 (0.2 to 6.6)	0 (0 to 28.5)
Cum virol break BLto Wk 104(n=13,1,,2,0,14,2) LOCF	14.1 (7.7 to 23)	4.8 (0.1 to 23.8)	1.9 (0.2 to 6.6)	0 (0 to 28.5)
Cum tx emergent resistance Wk 52 (n=3,0,0,0,3,0)	3.3 (0.7 to 9.2)	0 (0 to 16.1)	0 (0 to 3.4)	0 (0 to 28.5)
Ccum tx emergent resistance Wk 104 (n=8,0,0,0,8,0)	9.2 (4.1 to 17.3)	0 (0 to 16.1)	0 (0 to 3.5)	0 (0 to 28.5)
Cum tx emergent resist Wk52 (n=3,0,0,0,3,0)LOCF	3.3 (0.7 to 9.2)	0 (0 to 16.1)	0 (0 to 3.4)	0 (0 to 28.5)
Cum tx emergent resist Wk 104 (n=8,0,0,0,8,0) LOCF	9.2 (4.1 to 17.3)	0 (0 to 16.1)	0 (0 to 3.5)	0 (0 to 28.5)
<7 log at BL HBV DNA <300 Wk52(n=71,3,,76,3,74,79)	93.4 (85.3 to 97.8)	75 (19.4 to 99.4)	95 (87.7 to 98.6)	100 (29.2 to 100)
<7 log HBV DNA <300 Wk104 (n=52,2,61,2,54,63)	68.4 (56.7 to 78.6)	50 (6.8 to 93.2)	76.3 (65.4 to 85.1)	66.7 (9.4 to 99.2)
<7 log HBV DNA <300 Wk52 (n=74,4,80,3,78,83)LOCF	97.4 (90.8 to 99.7)	100 (39.8 to 100)	100 (95.5 to 100)	100 (29.2 to 100)
<7 log HBV DNA <300 Wk104 (n=70,4,79,3,74,82)LOCF	92.1 (83.6 to 97)	100 (39.8 to 100)	98.8 (93.2 to 100)	100 (29.2 to 100)

End point values	LdT Overall	TDF Overall		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	113	117		
Units: Participants				
number (confidence interval 95%)				
HBV DNA<300 Week 24 (91,0,105,0,91,105)	80.5 (72 to 87.4)	89.7 (82.8 to 94.6)		
HBV DNA <300 Week 104 (n=64,16,79,9,80,88)	70.8 (61.5 to 79)	75.2 (66.4 to 82.7)		
HBV DNA <300 Week 24(n=92,0,106,0,,92,106) LOCF	81.4 (73 to 88.1)	90.6 (83.8 to 95.2)		
HBV DNA <300 Wk104(n=85,21,,105,11,106,116) LOCF	93.8 (87.7 to 97.5)	99.1 (95.3 to 100)		
ALT Normalization Week 52 (42,15,,47,6,57,53)	83.8 (72.9 to 91.6)	82.8 (71.3 to 91.1)		

ALT Normalization Week 104(35,13,,35,6,48,41)	70.6 (58.3 to 81)	64.1 (51.1 to 75.7)		
ALT Normalization Week 52 (44,15,,50,6,59,56) LOCF	86.8 (76.4 to 93.8)	87.5 (76.8 to 94.4)		
ALT Normalization Wk 104 (46,15,61,49,6,61,55)LOCF	89.7 (79.9 to 95.8)	85.9 (75 to 93.4)		
HBsAg loss Week 52 (0,0,0,0,0,0)	0 (0 to 3.2)	0 (0 to 3.1)		
HBsAg loss Week 104 (0,0,0,0,0,0)	0 (0 to 3.2)	0 (0 to 3.1)		
HBsAg conversion Week 52 (0,0,0,0,0,0)	0 (0 to 3.2)	0 (0 to 3.1)		
HBsAg conversion Week 104 (0,0,0,0,0,0)	0 (0 to 3.2)	0 (0 to 3.1)		
Cum virol break BaseL to Wk 24 (n=0,1,0,0,1,0)	0.9 (0 to 4.8)	0 (0 to 3.1)		
Cum virol break Wk 24 to Wk 52 (n=3,0,,0,0,3,0)	2.7 (0.6 to 7.6)	0 (0 to 3.1)		
Cum virol break Wk 52 to Wk 104 (n=11,0,2,0,11,2)	9.7 (5 to 16.8)	1.7 (0.2 to 6)		
Cum virol break BaseLto Wk 104 (n=13,1,2,0,14,2)	12.4 (6.9 to 19.9)	1.7 (0.2 to 6)		
Cum vir break BL to Wk24 (n=0,1,0,0,1,0) LOCF	0.9 (0 to 4.8)	0 (0 to 3.1)		
Cum virol break Wk 24 to Wk 52(n=3,0,0,0,3,0) LOCF	2.7 (0.6 to 7.6)	0 (0 to 3.1)		
Cum virol break Wk52-Wk104(n=11,0,2,0,11,2) LOCF	9.7 (5 to 16.8)	1.7 (0.2 to 6)		
Cum virol break BLto Wk 104(n=13,1,,2,0,14,2) LOCF	12.4 (6.6 to 19.9)	1.7 (0.2 to 6)		
Cum tx emergent resistance Wk 52 (n=3,0,0,0,3,0)	2.7 (0.6 to 7.6)	0 (0 to 3.1)		
Ccum tx emergent resistance Wk 104 (n=8,0,0,0,8,0)	7.4 (3.3 to 14.1)	0 (0 to 3.1)		
Cum tx emergent resist Wk52 (n=3,0,0,0,3,0)LOCF	2.7 (0.6 to 7.6)	0 (0 to 3.1)		
Cum tx emergent resist Wk 104 (n=8,0,0,0,8,0) LOCF	7.4 (3.3 to 14.1)	0 (0 to 3.1)		
<7 log at BL HBV DNA <300 Wk52(n=71,3,,76,3,74,79)	92.5 (84.4 to 97.2)	95.2 (88.1 to 98.7)		
<7 log HBV DNA <300 Wk104 (n=52,2,61,2,54,63)	67.5 (56.1 to 77.6)	75.9 (65.3 to 84.6)		
<7 log HBV DNA <300 Wk52 (n=74,4,80,3,78,83)LOCF	97.5 (91.3 to 99.7)	100 (95.7 to 100)		
<7 log HBV DNA <300 Wk104 (n=70,4,79,3,74,82)LOCF	92.5 (84.4 to 97.2)	98.8 (93.5 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients achieving secondary efficacy endpoints at Week 156 (mITT)

End point title	Percentage of patients achieving secondary efficacy endpoints at Week 156 (mITT)

End point description:

The modified intent-to-treat (mITT) population consisted of all patients in the ITT population who were eligible and enrolled into the extension period beyond Week 104. Objectives were to assess the antiviral efficacy and present the percentage of patients achieving HBV DNA <300 copies/mL (51 IU/mL) at

Week156, ALT normalization, HBsAg loss, development of HBsAg conversion , cumulative tx emergent resistance, HBV DNA <300 copies/mL with HBV DNA <7 log at Baseline.

End point type	Secondary
End point timeframe:	
156 weeks	

End point values	LdT Mono at Week 24	LdT+TDF at Week 24	TDF Mono at Week 24	TDF + LdT at Week 24
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62	17	79	10
Units: Participants				
number (confidence interval 95%)				
HBV DNA < 300 Week 156 (n=11,2,11,2,13,13)	17.7 (9.2 to 29.5)	11.8 (1.5 to 36.4)	13.9 (7.2 to 23.5)	20 (2.5 to 55.6)
HBV DNA < 300 Wk156 (n=55,17,79,10,72,89) LOCF	88.7 (78.1 to 95.3)	100 (80.5 to 100)	100 (95.4 to 100)	100 (69.2 to 100)
ALT normalization Wk 156 (n=5,1,4,2,6,6)	14.3 (4.8 to 30.3)	6.7 (0.2 to 31.9)	10.5 (2.9 to 24.8)	28.6 (3.7 to 71)
ALT normalization Wk 156 (n=30,14,33,6,44,39) LOCF	85.7 (69.7 to 95.2)	93.3 (68.1 to 99.8)	86.8 (71.9 to 95.6)	85.7 (42.1 to 99.6)
HBSAg loss/ seroconversion (n=0)	0 (0 to 7)	0 (0 to 70.8)	0 (0 to 6.6)	0 (0 to 70.8)
Cum VB Wk104-156 LOCF (n=10,0,1,0,10,1)	16.1 (8 to 27.7)	0 (0 to 19.5)	1.3 (0 to 6.9)	0 (0 to 30.8)
Cum VB BL to Wk 156 LOCF (13,0,1,0,13,1)	21 (11.7 to 33.2)	0 (0 to 19.5)	1.3 (0 to 6.9)	0 (0 to 30.8)
Cum tx emerg resist Week 156 LOCF (n=8,0,0,0,8,0)	14 (6.3 to 25.8)	0 (0 to 19.5)	0 (0 to 4.6)	0 (0 to 30.8)
HBV DNA < 300 Wk156 <7 log at BL(n=9,0,7,1,9,8)	17.6 (8.4 to 30.9)	0 (0 to 70.8)	11.7 (4.8 to 22.6)	50 (1.3 to 98.7)
HBV DNA <300 Wk156 <7 log (n=45,3,60,2,48,62) LOCF	88.2 (76.1 to 95.6)	100 (29.2 to 100)	100 (94 to 100)	100 (15.8 to 100)
Cumtx-emerg resist Wk156 <7log(n=4,0,0,0,4,0) LOCF	8.7 (2.4 to 20.8)	0 (0 to 70.8)	0 (0 to 6)	0 (0 to 84.2)

End point values	LdT Overall	TDF Overall		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	79	89		
Units: Participants				
number (confidence interval 95%)				
HBV DNA < 300 Week 156 (n=11,2,11,2,13,13)	16.5 (9.1 to 26.5)	14.6 (8 to 23.7)		
HBV DNA < 300 Wk156 (n=55,17,79,10,72,89) LOCF	91.1 (82.6 to 96.4)	100 (95.9 to 100)		
ALT normalization Wk 156 (n=5,1,4,2,6,6)	12 (4.5 to 24.3)	13.3 (5.1 to 26.8)		
ALT normalization Wk 156 (n=30,14,33,6,44,39) LOCF	88 (75.7 to 95.5)	86.7 (73.2 to 94.9)		
HBSAg loss/ seroconversion (n=0)	0 (0 to 6.6)	0 (0 to 6.6)		
Cum VB Wk104-156 LOCF (n=10,0,1,0,10,1)	12.7 (6.2 to 22)	1.1 (0 to 6.1)		
Cum VB BL to Wk 156 LOCF (13,0,1,0,13,1)	16.5 (9.1 to 26.5)	1.1 (0 to 6.1)		

Cum tx emerg resist Week 156 LOCF (n=8,0,0,0,8,0)	10.8 (4.8 to 20.2)	0 (0 to 4.1)		
HBV DNA < 300 Wk156 <7 log at BL(n=9,0,7,1,9,8)	16.7 (7.9 to 29.3)	12.9 (5.7 to 23.9)		
HBV DNA <300 Wk156 <7 log (n=45,3,60,2,48,62) LOCF	88.9 (77.4 to 95.8)	100 (94.2 to 100)		
Cumtx-emerg resist Wk156 <7log(n=4,0,0,0,4,0) LOCF	8.2 (2.3 to 19.6)	0 (0 to 5.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: eGFR change from baseline in telbivudine arm vs tenofovir arm over the course of the study

End point title	eGFR change from baseline in telbivudine arm vs tenofovir arm over the course of the study

End point description:

eGFR changes from baseline to Week52, Week104 and Week156 for the overall population.

End point type	Secondary

End point timeframe:

52 weeks, 104 weeks, 156 weeks

End point values	LdT Mono at Week 24	LdT+TDF at Week 24	TDF Mono at Week 24	TDF + LdT at Week 24
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	98	22	109	11
Units: mL/min/1.73 m2				
arithmetic mean (standard deviation)				
Week 24 Change (n=97,22,108,11,119,119)	1.43 (± 12.815)	-12.06 (± 14.394)	-2.41 (± 14.885)	-7.17 (± 15.368)
Week 52 change(n=97,22,108,11,119,119)	5.18 (± 18.842)	-6.8 (± 17.229)	-2.7 (± 18.636)	-8.39 (± 10.479)
Week 104 change(n=97,22,108,11,119,119)	5.19 (± 16.583)	-5.77 (± 15.943)	-3.83 (± 15.157)	-8.69 (± 15.632)
Week 156 change(n=62,17,79,10,79,89)	8.07 (± 16.777)	-10.89 (± 14.993)	-5.34 (± 13.393)	-6.67 (± 11.905)
Baseline actual (98,22,109,11,120,120)	94.71 (± 16.422)	109.79 (± 19.56)	95.91 (± 16.396)	94.5 (± 17.558)
Week 24 actual (n=97,22,108,11,119,119)	96.43 (± 16.434)	97.73 (± 17.69)	93.61 (± 18.5)	87.33 (± 16.854)
Week 52 actual (n=97,22,108,11,119,119)	100.18 (± 20.257)	102.99 (± 19.425)	93.32 (± 18.88)	86.12 (± 14.233)
Week 104 actual (n=97,22,108,11,119,119)	100.2 (± 16.287)	104.02 (± 18.201)	92.19 (± 18.24)	85.81 (± 13.099)
Week 156 actual (n=62,17,79,10,79,89)	101.33 (± 18.505)	100.7 (± 20.029)	88.83 (± 13.28)	87.93 (± 13.28)

End point values	LdT Overall	TDF Overall		

Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	120	120		
Units: mL/min/1.73 m2				
arithmetic mean (standard deviation)				
Week 24 Change (n=97,22,108,11,119,119)	-1.07 (± 14.076)	-2.85 (± 14.928)		
Week 52 change(n=97,22,108,11,119,119)	2.96 (± 19.064)	-3.22 (± 18.082)		
Week 104 change(n=97,22,108,11,119,119)	3.16 (± 16.947)	-4.28 (± 15.2)		
Week 156 change(n=62,17,79,10,79,89)	3.99 (± 18.104)	-5.49 (± 13.178)		
Baseline actual (98,22,109,11,120,120)	97.47 (± 17.936)	95.78 (± 16.433)		
Week 24 actual (n=97,22,108,11,119,119)	96.67 (± 16.603)	93.03 (± 18.378)		
Week 52 actual (n=97,22,108,11,119,119)	100.7 (± 20.054)	92.66 (± 18.569)		
Week 104 actual (n=97,22,108,11,119,119)	100.7 (± 20.054)	92.66 (± 18.569)		
Week 156 actual (n=62,17,79,10,79,89)	100.9 (± 16.643)	91.6 (± 17.879)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse Events are reported in this record from First Patient First Treatment until Last Patient Last Visit.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	LdT Mono at Week 24
Reporting group description: LdT Mono at Week 24	
Reporting group title	LdT+TDF at Week 24
Reporting group description: LdT+TDF at Week 24	
Reporting group title	TDF Mono at Week 24
Reporting group description: TDF Mono at Week 24	
Reporting group title	TDF+LdT at Week 24
Reporting group description: TDF+LdT at Week 24	

Serious adverse events	LdT Mono at Week 24	LdT+TDF at Week 24	TDF Mono at Week 24
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 98 (6.12%)	5 / 22 (22.73%)	11 / 109 (10.09%)
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)			
Bladder cancer			
subjects affected / exposed	1 / 98 (1.02%)	0 / 22 (0.00%)	0 / 109 (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
Breast cancer			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma			

subjects affected / exposed	2 / 98 (2.04%)	0 / 22 (0.00%)	3 / 109 (2.75%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to abdominal wall			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastasis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Arterial occlusive disease			
subjects affected / exposed	0 / 98 (0.00%)	1 / 22 (4.55%)	0 / 109 (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
Thrombophlebitis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 22 (0.00%)	0 / 109 (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
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	0 / 109 (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			
Pneumothorax spontaneous			
subjects affected / exposed	0 / 98 (0.00%)	1 / 22 (4.55%)	0 / 109 (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
Psychiatric disorders			
Psychogenic pain disorder			

subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	0 / 109 (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			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 98 (0.00%)	1 / 22 (4.55%)	0 / 109 (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
Diabetic neuropathy			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroduodenitis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Haemorrhoids			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	1 / 109 (0.92%)
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			
Bile duct stone			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 98 (1.02%)	0 / 22 (0.00%)	0 / 109 (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
Hepatic cirrhosis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	3 / 109 (2.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus ureteric			
subjects affected / exposed	0 / 98 (0.00%)	1 / 22 (4.55%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 98 (0.00%)	1 / 22 (4.55%)	0 / 109 (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
Osteonecrosis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 22 (0.00%)	0 / 109 (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
Spinal column stenosis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	0 / 109 (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			
Abdominal abscess			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	1 / 98 (1.02%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 22 (4.55%)	0 / 109 (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
Metabolism and nutrition disorders			
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	TDF+LdT at Week 24		
Total subjects affected by serious adverse events			

subjects affected / exposed	2 / 11 (18.18%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatocellular carcinoma			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastases to abdominal wall			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastasis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Arterial occlusive disease			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombophlebitis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumothorax spontaneous			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Psychogenic pain disorder			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diabetic neuropathy			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroduodenitis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrooesophageal reflux disease				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhoids				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Bile duct stone				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis acute				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic cirrhosis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Jaundice cholestatic				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				

Acute kidney injury				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Calculus ureteric				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hydronephrosis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Arthralgia				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Osteonecrosis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal column stenosis				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abdominal abscess				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anal abscess				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Appendicitis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	LdT Mono at Week 24	LdT+TDF at Week 24	TDF Mono at Week 24
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 98 (61.22%)	15 / 22 (68.18%)	56 / 109 (51.38%)
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 98 (7.14%)	4 / 22 (18.18%)	5 / 109 (4.59%)
occurrences (all)	7	4	5
Hypotension			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 98 (5.10%)	1 / 22 (4.55%)	0 / 109 (0.00%)
occurrences (all)	5	2	0
Fatigue			
subjects affected / exposed	5 / 98 (5.10%)	1 / 22 (4.55%)	8 / 109 (7.34%)
occurrences (all)	6	1	8
Influenza like illness			
subjects affected / exposed	1 / 98 (1.02%)	0 / 22 (0.00%)	0 / 109 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			
subjects affected / exposed	1 / 98 (1.02%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences (all)	2	0	1
Pyrexia			

subjects affected / exposed	1 / 98 (1.02%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences (all)	1	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 98 (1.02%)	0 / 22 (0.00%)	0 / 109 (0.00%)
occurrences (all)	1	0	0
Depression			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 98 (5.10%)	0 / 22 (0.00%)	5 / 109 (4.59%)
occurrences (all)	5	0	5
Amylase increased			
subjects affected / exposed	1 / 98 (1.02%)	2 / 22 (9.09%)	0 / 109 (0.00%)
occurrences (all)	1	2	0
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 98 (7.14%)	1 / 22 (4.55%)	4 / 109 (3.67%)
occurrences (all)	7	1	5
Blood creatine phosphokinase increased			
subjects affected / exposed	24 / 98 (24.49%)	10 / 22 (45.45%)	17 / 109 (15.60%)
occurrences (all)	48	15	42
Blood phosphorus increased			
subjects affected / exposed	1 / 98 (1.02%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences (all)	2	0	1
Injury, poisoning and procedural complications			
Epicondylitis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	0 / 109 (0.00%)
occurrences (all)	0	0	0
Laceration			
subjects affected / exposed	2 / 98 (2.04%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences (all)	2	0	1

Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	0 / 109 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	17 / 98 (17.35%)	3 / 22 (13.64%)	16 / 109 (14.68%)
occurrences (all)	29	15	35
Paraesthesia			
subjects affected / exposed	1 / 98 (1.02%)	0 / 22 (0.00%)	0 / 109 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 98 (1.02%)	0 / 22 (0.00%)	0 / 109 (0.00%)
occurrences (all)	1	0	0
Leukopenia			
subjects affected / exposed	2 / 98 (2.04%)	0 / 22 (0.00%)	6 / 109 (5.50%)
occurrences (all)	2	0	6
Thrombocytopenia			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	0 / 109 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Visual impairment			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	0 / 109 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 98 (0.00%)	1 / 22 (4.55%)	2 / 109 (1.83%)
occurrences (all)	0	1	2
Abdominal pain upper			
subjects affected / exposed	6 / 98 (6.12%)	0 / 22 (0.00%)	5 / 109 (4.59%)
occurrences (all)	6	0	7
Diarrhoea			
subjects affected / exposed	8 / 98 (8.16%)	0 / 22 (0.00%)	5 / 109 (4.59%)
occurrences (all)	9	0	5
Dyspepsia			
subjects affected / exposed	3 / 98 (3.06%)	0 / 22 (0.00%)	5 / 109 (4.59%)
occurrences (all)	3	0	5

Gastritis			
subjects affected / exposed	6 / 98 (6.12%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences (all)	6	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 98 (1.02%)	0 / 22 (0.00%)	0 / 109 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	10 / 98 (10.20%)	3 / 22 (13.64%)	2 / 109 (1.83%)
occurrences (all)	11	3	2
Toothache			
subjects affected / exposed	1 / 98 (1.02%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 98 (1.02%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences (all)	1	0	1
Rash			
subjects affected / exposed	2 / 98 (2.04%)	0 / 22 (0.00%)	0 / 109 (0.00%)
occurrences (all)	2	0	0
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Crystalluria			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences (all)	0	0	1
Haematuria			
subjects affected / exposed	1 / 98 (1.02%)	5 / 22 (22.73%)	1 / 109 (0.92%)
occurrences (all)	1	6	1
Nephroptosis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	0 / 109 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 98 (3.06%)	3 / 22 (13.64%)	8 / 109 (7.34%)
occurrences (all)	5	4	9

Groin pain			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences (all)	0	0	1
Intervertebral disc protrusion			
subjects affected / exposed	1 / 98 (1.02%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences (all)	1	0	1
Myalgia			
subjects affected / exposed	10 / 98 (10.20%)	2 / 22 (9.09%)	2 / 109 (1.83%)
occurrences (all)	14	6	4
Neck pain			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	0 / 109 (0.00%)
occurrences (all)	0	0	0
Osteoarthritis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 22 (0.00%)	0 / 109 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	4 / 98 (4.08%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences (all)	4	0	2
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences (all)	1	0	1
Ear infection			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	0 / 109 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	8 / 98 (8.16%)	2 / 22 (9.09%)	8 / 109 (7.34%)
occurrences (all)	12	2	11
Nasopharyngitis			
subjects affected / exposed	7 / 98 (7.14%)	2 / 22 (9.09%)	8 / 109 (7.34%)
occurrences (all)	14	5	9
Respiratory tract infection			
subjects affected / exposed	3 / 98 (3.06%)	0 / 22 (0.00%)	1 / 109 (0.92%)
occurrences (all)	5	0	1
Rhinitis			

subjects affected / exposed	5 / 98 (5.10%)	2 / 22 (9.09%)	0 / 109 (0.00%)
occurrences (all)	5	2	0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	0 / 109 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 98 (0.00%)	0 / 22 (0.00%)	0 / 109 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	TDF+LdT at Week 24		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 11 (72.73%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	4		
Fatigue			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Influenza like illness			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Oedema peripheral			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		

Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Amylase increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	7		
Blood phosphorus increased			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Epicondylitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Laceration			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Nervous system disorders			

Ataxia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	10		
Paraesthesia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Leukopenia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Thrombocytopenia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Eye disorders			
Visual impairment			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Gastritis			

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	3		
Toothache			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Seborrhoeic dermatitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Renal and urinary disorders			
Crystalluria			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Haematuria			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Nephroptosis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Groin pain			

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Intervertebral disc protrusion			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Osteoarthritis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Ear infection			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	11		
Nasopharyngitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		

Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	3		
Hypoalbuminaemia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 October 2011	The main purposes of this amendment were to: -align inclusion criteria to current guidelines and update to clinical practice - introduce the following key exploratory objectives to evaluate liver fibrosis and further -investigate renal function under nucleos(t)ide analogues: -- Explore changes of exploratory liver fibrosis biomarkers over the course of the study --Explore renal function using urine-kidney biomarkers -Provide further clarification for patient management in case of VB
08 April 2013	The rationale of this amendment was to extend the prospective 2-year study for an additional 1 year of treatment/follow-up (a total of 156 weeks), to assess the long-term benefits of telbivudine treatment on renal function (as assessed by eGFR), and to assess the long-term cumulative resistance rate in CHB patients. Also included in Amendment 2 was the introduction of the secondary objectives presented in the endpoints.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported