



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 \geq 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 \geq 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

| | |
|------------------|----------------------|
| 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 \geq 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 |

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 |

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|---|--------------------|--|--|
| 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 occurrences (all) | 1 / 98 (1.02%) 1 | 0 / 22 (0.00%) 0 | 1 / 109 (0.92%) 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 occurrences (all) | 6 / 98 (6.12%) 6 | 0 / 22 (0.00%) 0 | 1 / 109 (0.92%) 1 |
| Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) | 1 / 98 (1.02%) 1 | 0 / 22 (0.00%) 0 | 0 / 109 (0.00%) 0 |
| Nausea subjects affected / exposed occurrences (all) | 10 / 98 (10.20%) 11 | 3 / 22 (13.64%) 3 | 2 / 109 (1.83%) 2 |
| Toothache subjects affected / exposed occurrences (all) | 1 / 98 (1.02%) 1 | 0 / 22 (0.00%) 0 | 1 / 109 (0.92%) 1 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia subjects affected / exposed occurrences (all) | 1 / 98 (1.02%) 1 | 0 / 22 (0.00%) 0 | 1 / 109 (0.92%) 1 |
| Rash subjects affected / exposed occurrences (all) | 2 / 98 (2.04%) 2 | 0 / 22 (0.00%) 0 | 0 / 109 (0.00%) 0 |
| Seborrhoeic dermatitis subjects affected / exposed occurrences (all) | 0 / 98 (0.00%) 0 | 0 / 22 (0.00%) 0 | 1 / 109 (0.92%) 1 |
| Renal and urinary disorders | | | |
| Crystalluria subjects affected / exposed occurrences (all) | 0 / 98 (0.00%) 0 | 0 / 22 (0.00%) 0 | 1 / 109 (0.92%) 1 |
| Haematuria subjects affected / exposed occurrences (all) | 1 / 98 (1.02%) 1 | 5 / 22 (22.73%) 6 | 1 / 109 (0.92%) 1 |
| Nephroptosis subjects affected / exposed occurrences (all) | 0 / 98 (0.00%) 0 | 0 / 22 (0.00%) 0 | 0 / 109 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain subjects affected / exposed occurrences (all) | 3 / 98 (3.06%) 5 | 3 / 22 (13.64%) 4 | 8 / 109 (7.34%) 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 occurrences (all) | 5 / 98 (5.10%) 5 | 2 / 22 (9.09%) 2 | 0 / 109 (0.00%) 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 occurrences (all) Depression subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 2 / 11 (18.18%) 2 1 / 11 (9.09%) 1 | | |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) Amylase increased subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all) Blood creatine phosphokinase increased subjects affected / exposed occurrences (all) Blood phosphorus increased subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0 2 / 11 (18.18%) 7 1 / 11 (9.09%) 1 | | |
| Injury, poisoning and procedural complications Epicondylitis subjects affected / exposed occurrences (all) Laceration subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 1 / 11 (9.09%) 1 | | |
| Nervous system disorders | | | |

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

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

| | | | |
|--------------------------------|-----------------|--|--|
| 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