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Sponsor

Novartis

Generic Drug Name

Telbivudine
Tenofovir

Therapeutic Area of Trial

Compensated Chronic Hepatitis B

Approved Indication

Indicated for the treatment of chronic hepatitis B in adults with evidence of viral replication and active liver inflammation.

Study Number

CLDT600A2410

Title

A single-arm, multinational, two year study evaluating the efficacy and safety of lead-in telbivudine for 24 weeks with or without tenofovir treatment intensification in adult patients with HBeAg-positive chronic hepatitis B

Phase of Development : Phase IV

Study Start/End Dates

28-Feb-2008 to 26-Sep-2011

Study Design/Methodology

The design was a prospective, single-arm, 104 week, multicenter, multinational, phase IV study to characterize the efficacy and safety of treatment with telbivudine with or without treatment intensification by adding tenofovir disoproxil fumarate at Week 24 in adult patients with HBeAg-positive chronic hepatitis B. The study consisted of 4 periods: Screening (≤ 6 weeks prior to Baseline Visit), Baseline Visit (Day 1), Treatment Phase (104 weeks) and Post-treatment Follow-up

(up to 16 weeks). Patient eligibility was established during the Screening period. In the event that a screened patient failed to meet entry criteria based on laboratory outcomes, the patient could be retested one additional time for the analyte(s) previously failed in order to reassess eligibility. If the patient failed the retest, they should not be further evaluated, and dropped as a screen failure. Once eligible, patients began treatment with their first dose of study medication at the Baseline Visit (Day 1). Finally patients were evaluated for safety and sustained treatment effects in the Post-treatment Follow-up phase. Data analyses were planned at two points during this study. The first analysis was to be at 52 weeks (i.e. the primary efficacy analysis), and secondly a consolidated analysis was to be performed at the completion of the treatment phase at week 104 and the subsequent follow-up at week 120.

Centers: The study was conducted across 18 centers in Thailand, Hong Kong, Argentina, Brazil and Germany

Outcome measures

Primary objective(s)

The primary objective of the study was to determine if telbivudine early non-responders can achieve an antiviral response with the addition of tenofovir.

Secondary objective(s)

- To estimate the rate of virologic breakthrough up to week 48 and week 104
- To assess the rate of treatment-emergent genotypically confirmed HBV resistance associated with viral breakthrough up to weeks 48 and 104
- Other secondary objectives of the study include:
- Assessment of HBV DNA < 300 copies/mL) reduction in HBV DNA from baseline and sustained reduction in HBV DNA over the course of study
- Assessment of HBeAg loss and HBeAg seroconversion (defined as loss of HBeAg and development of HBeAb) over course of study
- To describe the ALT normalization rate at weeks 52 and 104

Test Product (s), Dose(s), and Mode(s) of Administration

- LDT 600 (telbivudine, Sebivo®) 600 mg, film-coated tablets
- Tenofovir disoproxil fumarate (Viread®) 300mg tablets

Statistical methods

Data analysis

Data was summarized with respect to background, demographic and baseline characteristics, efficacy measurements and safety observations and measurements. For continuous variables, summary statistics included were n (number of observations), mean, standard deviation, median, 25^{th} percentile, 75^{th} percentile, minimum and maximum values, and for categorical variables, frequencies and percentages were presented. When appropriate, separate summaries were generated for patients with add on tenofovir(Week 24 $\geq$ 300 copies/ml: LDT+TDF) and patients continuing on telbivudine(week 24<300 copies/mL: LDT). When appropriate, separate summaries by PCR status at every visit were presented along with treatment group.Until week 24, any analysis by treatment group was displayed by Overall at report level.

When appropriate, two-sided 95% confidence intervals (95% CI) for means and/or proportions as well as p-values were provided. The p-values were used in a non confirmatory manner, if not otherwise specified.

Analysis sets

The **Enrolled population** was defined as all patients who passed the screening in the study.

The **ITT population** consisted of all patients who received at least one dose of study drug and had at least one post-baseline assessment of serum HBV DNA. Efficacy analyses were conducted over the ITT population and following the intent-to-treatment principle.

The **modified ITT population** (a subset of ITT above) was used for all key efficacy analyses. It excluded the patients who discontinued before Week 24 or who did not take add-on medication in the prescribed manner or who did not have a baseline HBV DNA mutation that would preclude testing of LDT600A efficacy. Below is the list of baseline HBV DNA mutations; patients with any one of these were to be excluded from mITT:

1. M204I or M204V
2. N236T
3. A181V or A181T
4. A194T

The **Per-protocol population** was defined as a subset of ITT population who did not have major protocol deviations, such as patient takes prohibited Hep-B related medications during treatment period. Other criteria for major protocol deviations were established and documented based upon the review of data before clinical database lock for both the week 52 and week 104 primary data analyses. No analysis was performed on the Per-protocol population.

The **Safety Population** consisted of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment. All safety analysis was performed on the safety population.

Patient demographics and other baseline characteristics

Demographic and baseline characteristics were summarized for the ITT population by treatment groups (LDT+TDF and LDT) and overall.

Demographic variables

Continuous variables were age, height, weight, and BMI. Categorical variables were gender, race, and ethnicity.

Baseline variables

Baseline characteristics were serum HBV DNA in log copies/mL, HBV DNA level, HBV Genotype, and serum ALT level and baseline GFR.

Continuous variables were presented with summary statistics, and the number of non-missing observations.

Categorical data were displayed via absolute and relative frequencies for each category (including a category labeled as 'missing' when appropriate).

Study Population: Inclusion/Exclusion Criteria and Demographics

The study population planned to enrol at least 100 outpatients with HBeAg-positive chronic hepatitis B, and who satisfied the inclusion and exclusion criteria below.

Inclusion criteria

Patients eligible for inclusion in this study were required to fulfill all of the following criteria:

1. Male or female, at least 18 years of age.
2. Documented HBeAg positive CHB defined by all of the following:
   - Clinical history compatible with CHB
   - Detectable serum HBsAg at the Screening visit and at least 6 months prior
   - HBeAg positive at the Screening visit
   - HBeAb negative at the Screening visit
   - Serum HBV DNA level ≥ 5 $\log_{10}$ copies/mL, as determined by the COBAS Amplicor HBV PCR assay (LLOD = 300 copies / mL) at the central study laboratory at Screening visit
   - Evidence of chronic liver inflammation, documented by previous history of elevated serum ALT and /or AST levels (at least two elevated ALT or AST values spanning six months or more, documented in available records) with or without prior liver biopsy that is consistent with CHB
   - For patients with cirrhosis, clinical history compatible with compensated liver disease
   - Elevated serum ALT level (1.3 – 10 × ULN) at the Screening visit
3. Patient is willing and able to comply with the study drug regimen and all other study requirements.
4. The patient is willing and able to provide written informed consent to participate in the study.

Exclusion criteria

Patients were to be excluded from the study for any of the following:

1. History of hypersensitivity to any of the study drugs or to drugs with similar chemical structures.
2. Patient is pregnant or breastfeeding.
3. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner, and women whose partners have been sterilized by vasectomy or other means. An exception is if they meet the following definition of post-menopausal: 12 months of natural (spontaneous) amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels >40 mIU/ml (IU/L) or 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy or have been surgically sterilized (e.g. bilateral tubal ligation) or the patient must agree to use two approved methods of birth control. Women of childbearing potential must have

a negative serum beta-human chorionic gonadotropin (β-HCG) during Screening.

4. Is a male who is capable of reproduction, UNLESS the female partner meets the following definition of post-menopausal: 12 months of natural (spontaneous) amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels >40 mIU/ml (IU/L) or the patient must agree to use two approved methods of birth control.
5. Patient is co-infected with HCV, HDV, or HIV.
6. Patients who have previously been involved in a trial with telbivudine.
7. Patient has received nucleoside or nucleotide drugs whether approved or investigational at any time.
8. Patient has received IFN or other immunomodulatory treatment in the 6 months before Screening for this study.
9. Patient has a history of or clinical signs/symptoms of hepatic decompensation such as ascites, esophageal variceal bleeding, hepatic encephalopathy, hepatorenal syndrome, hepatic hydrothorax, hepatopulmonary syndrome or spontaneous bacterial peritonitis.
10. Patient has a medical condition that requires prolonged or frequent use of systemic acyclovir or famciclovir.
11. History of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin. Patients with previous findings suggestive of possible HCC, should have the disease ruled out prior to entrance into the study.
12. Patient has one or more additional known primary or secondary causes of liver disease, other than CHB, including steatohepatitis and autoimmune hepatitis among other liver diseases. Note: Gilbert's syndrome and Dubin-Johnson syndrome are not considered exclusion criteria for this study.
13. History of any other acute or chronic medical condition that in the opinion of the investigator would make the patient unsuitable for inclusion into the study.
14. Patient is currently abusing alcohol or illicit drugs, or has a history of alcohol abuse or illicit substance abuse within the preceding two years.
15. Patient has a medical condition that requires frequent or prolonged use of systemic corticosteroids, although topical and inhaled corticosteroids are allowed.
16. Patient has a history of clinical and laboratory evidence of chronic renal insufficiency defined as an estimated serum creatinine clearance < 50 mL/min using the Cockcroft-Gault method.
17. Patient has a medical condition requiring the chronic or prolonged use of potentially hepatotoxic drugs or nephrotoxic drugs.
18. Patient has any other concurrent medical or social condition likely to preclude compliance with the schedule of evaluations in the protocol, or likely to confound the efficacy or safety observations of the study.
19. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer.
20. Patient has a history of myopathy, myositis, or persistent muscle weakness.
21. Patient has any of the following laboratory values during Screening:
    - Hemoglobin <11 g/dL (110 g/L) for men or <10 g/dL (100 g/L) for women
    - Total WBC <3,500/mm^3 (3.5×10^9/Liter)
    - Absolute neutrophil count (ANC) <1,500/mm^3 (1.5×10^9/Liter)
    - Platelet count <75,000/mm^3 (75×10^9/Liter)
    - Serum amylases or lipase ≥ 1.5 × ULN
    - Serum albumin <3.3 g/dL (33g/L)
    - Total bilirubin ≥ 2.0 mg/dL (34.2 μmol/L)

- Estimated calculated serum creatinine clearance < 50 mL/min (0.48 ml/s) using the Cockcroft-Gault method with lean or ideal body weight
- AFP > 50 ng/mL or µg/L (requires further work-up per local medical standards)

Disposition of patients

Patient disposition is shown for the period up to Week 26 (when add-on tenofovir was initiated), and for the period after Week 26 up to Week 52 in the table below. Of the 105 patients in the safety population, 2 discontinued before add-on commenced at Week 26. Two further patients discontinued up to Week 52, so that 101 patients completed up to Week 52.

Completion of the treatment phase, including follow-up, is summarized in the table for week 104.. A total of 13 patients discontinued in the treatment phase after Week 52 and up to Week 104; therefore 88/105 patients completed treatment phase.

Patient disposition up to week 52 (Safety population)

Disposition Reason	LDT n (%)	LDT+TDF n (%)	Overall n (%)
	N=105	**n/a***	**N=105**
Up to Week 26			
Completed week 26	103 (98.1)	--	103 (98.1)
Discontinued up to week 26	2 (1.9)	--	2 (1.9)
Lost to follow-up	2 (1.9)	--	2 (1.9)
	N=59	**N=46**	**N=105**
Up to Week 52			
Completed week 52	56 (94.9)	45 (97.8)	101 (96.2)
Discontinued after week 26 and on or before week 52	1 (1.7)	1 (2.2)	2 (1.9)
Unsatisfactory therapeutic effect	1 (1.7)	0	1 (1.0)
Lost to follow-up	0	1 (2.2)	1 (1.0)

* Up to Week 26, all patients on the single treatment arm were on LDT monotherapy. From Week 26, treatment was intensified by the addition of TDF in 46/105 patients.

Patient overall disposition up to week 104, including follow-up (Safety population)

Disposition Reason	LDT N=59 n (%)	LDT+TDF N=46 n (%)	Overall N=105 n (%)
Completed treatment phase	49 (83.1)	39 (84.8)	88 (83.8)
Completed both treatment and follow-up phase	48 (81.4)	37 (80.4)	85 (81.0)
Discontinued treatment phase	10 (16.9)	7 (15.2)	17 (16.2)
Adverse Event(s)	4 (6.8)	2 (4.3)	6 (5.7)
Unsatisfactory therapeutic effect	2 (3.4)	2 (4.3)	4 (3.8)
Subject withdrew consent	0	1 (2.2)	1 (1.0)
Lost to follow-up	4 (6.8)	2 (4.3)	6 (5.7)

Baseline Characteristics

Summary of Demographic Details

Demographic variable		LDT N=59	LDT+TDF N=46	Overall N=105
Sex, n (%)	Male	39 (66.1)	31 (67.4)	70 (66.7)
	Female	20 (33.9)	15 (32.6)	35 (33.3)
Age (Year)	Mean (SD)	36.1 (10.36)	39.3 (14.98)	37.5 (12.62)
	Median	35.0	35.0	35.0

	25th / 75th percentile	27.0 / 46.0	28.0 / 49.0	28.0 / 46.0
	Min - Max	20.0 - 60.0	18.0 - 74.0	18.0 - 74.0
Race, n(%)	Caucasian	12 (20.3)	16 (34.8)	28 (26.7)
	Black	1 (1.7)	2 (4.3)	3 (2.9)
	Asian	43 (72.9)	28 (60.9)	71 (67.6)
	Other	3 (5.1)	0	3 (2.9)
Ethnicity, n(%)	Hispanic/Latino	10 (16.9)	13 (28.3)	23 (21.9)
	Chinese	4 (6.8)	7 (15.2)	11 (10.5)
	Japanese	0	1 (2.2)	1 (1.0)
	Other	45 (76.3)	25 (54.3)	70 (66.7)
Height (cm)	Mean (SD)	168.4 (9.38)	167.9 (9.74)	168.2 (9.50)
	Median	169.0	169.0	169.0
	25^{th} / 75th percentile	162.0 / 176.0	160.0 / 175.0	161.0 / 175.0
	Min - Max	147.0 - 188.0	148.0 - 190.0	147.0 - 190.0
Weight (kg)	Mean (SD)	69.4 (15.55)	65.7 (13.42)	67.8 (14.70)
	Median	70.0	66.9	68.0
	25th / 75th percentile	57.0 / 78.0	56.8 / 75.0	57.0 / 76.9
	Min - Max	36.6 - 127.1	40.0 - 93.0	36.6 - 127.1
BMI (kg/m^2)	Mean (SD)	24.3 (4.52)	23.1 (3.42)	23.8 (4.09)
	Median	23.6	23.3	23.5
	25th / 75th percentile	21.0 - 26.0	20.8 - 25.7	20.9 - 26.0
	Min - Max	16.8 - 46.7	14.5 - 29.7	14.5 - 46.7

Summary of Baseline characteristics

Disease variable		**LDT N=59**	**LDT+TDF N=46**	**Overall N=105**
Baseline HBV DNA level (log_{10}copies/mL)	Mean (SD)	8.3 (1.80)	9.8 (1.75)	9.0 (1.91)
	Median	8.2	9.7	9.1
	25th / 75^{th} percentile	7.1 / 9.4	8.9 / 10.8	7.8 / 9.9
	Min - Max	5.0 - 14.1	5.5 - 14.4	5.0 - 14.4
Baseline HBV DNA level (log_{10}copies/mL)	5 log_{10} - < 6 log_{10}	5 (8.5)	1 (2.2)	6 (5.7)
	6 log_{10} - < 7 log_{10}	8 (13.6)	1 (2.2)	9 (8.6)
	7 log_{10} - < 8 log_{10}	12 (20.3)	4 (8.7)	16 (15.2)
	8 log_{10} - < 9 log_{10}	13 (22.0)	6 (13.0)	19 (18.1)
	≥ 9 log_{10}	21 (35.6)	34 (73.9)	55 (52.4)
Baseline GFR (by MDRD formula)	Mean (SD)	94.1 (14.91)	92.6 (18.58)	93.5 (16.55)
	Median	93.3	94.6	93.4
	25th / 75th percentile	84.1 / 104.8	81.4 / 104.6	83.0 / 104.6
	Min - Max	56.8 - 134.1	57.4 - 133.8	56.8 - 134.1
Baseline GFR (by Cockcroft-Gault formula)	Mean (SD)	104.9 (24.60)	94.7 (22.41)	100.5 (24.09)
	Median	102.0	98.5	101.6
	25th / 75^{th} percentile	91.6 / 116.2	75.6 / 108.9	81.9 / 114.1
	Min - Max	61.1 - 216.2	56.7 - 146.6	56.7 - 216.2
Baseline ALT level(U/L)	Mean (SD)	160.0 (159.10)	97.3 (63.77)	132.6 (129.82)
	Median	118.0	79.5	95.0
	25th / 75^{th} percentile	83.0 / 163.0	63.0 / 107.0	72.0 / 143.0
	Min - Max	22.0 - 902.0	38.0 - 384.0	22.0 - 902.0
HBV Genotype	A	7 (11.9)	8 (17.4)	15 (14.3)

B	5 (8.5)	6 (13.0)	11 (10.5)
C	37 (62.7)	22 (47.8)	59 (56.2)
D	1 (1.7)	6 (13.0)	7 (6.7)
F	8 (13.6)	3 (6.5)	11 (10.5)
Indeterminate	1 (1.7)	1 (2.2)	2 (1.9)
Baseline HBV DNA and ALT level			
HBV DNA < 9 log & ALT < 2 × ULN	12 (20.3)	9 (19.6)	21 (20.0)
HBV DNA < 9 log & ALT ≥ 2 × ULN	26 (44.1)	3 (6.5)	29 (27.6)
HBV DNA ≥ 9 log & ALT < 2 × ULN	5 (8.5)	23 (50.0)	28 (26.7)
HBV DNA ≥ 9 log & ALT ≥ 2 × ULN	16 (27.1)	11 (23.9)	27 (25.7)
Baseline HBV DNA category			
HBV DNA < 9 log copies	38 (64.4)	12 (26.1)	50 (47.6)
HBV DNA ≥ 9 log copies	21 (35.6)	34 (73.9)	55 (52.4)

Outcome measures

Primary Outcome Result(s)

Proportion of patients with HBV DNA <300 copies/mL at treatment efficacy endpoints up to week 104 (mITT population, LOCF)

	HBV DNA <300 copies/ml					
Week	LDT N=55 n/m (%)	95% CI	LDT+TDF N=45 n/m (%)	95% CI	Overall N=100 n/m (%)	95% CI
Week 24	55/55 (100)	(100, 100)	0/45 (0.0)	n.a.	55/100 (55.0)	(45.3, 64.8)
Week 52	55/55 (100)	(100, 100)	38/45 (84.4)	(73.9, 95)	93/100 (93.0)	(88, 98)
Week 104	52/55 (94.5)	(88.5, 100)	42/45 (93.3)	(86.1, 100)	94/100 (94.0)	(89.4, 98.7)

-N= the number of patients in the treatment group
-m= the number of patients with non-missing observation for the respective week
-n= the number of patients with efficacy endpoint
-Binomial test is used to calculate the 95% confidence interval.

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Secondary Outcome Result(s)

Change from baseline in HBV DNA level (log_{10} copies/ml) up to week 104 by treatment group (Modified Intent-to-treat population)

Week	Treatment group	n	Baseline value	Post baseline	Change from baseline	95% CI	p-value
Week 2	LDT (N= 55)	55	8.396	5.510	-2.886	(-3.32, -2.45)	<0.0001
	LDT+TDF (N= 45)	45	9.761	7.197	-2.565	(-2.92, -2.21)	<0.0001
	Overall (N=100)	100	9.010	6.269	-2.741	(-3.02, -2.46)	<0.0001
Week 8	LDT (N= 55)	55	8.396	3.502	-4.894	(-5.29, -4.50)	<0.0001
	LDT+TDF (N= 45)	45	9.761	5.269	-4.493	(-4.92, -4.06)	<0.0001
	Overall (N=100)	100	9.010	4.297	-4.714	(-5.00, -4.43)	<0.0001
Week 24	LDT (N= 55)	54	8.388	2.176	-6.212	(-6.69, -5.73)	<0.0001
	LDT+TDF (N= 45)	45	9.761	3.780	-5.981	(-6.48, -5.48)	<0.0001
	Overall (N=100)	99	9.012	2.905	-6.107	(-6.45, -5.77)	<0.0001
Week 52	LDT (N= 55)	55	8.396	2.176	-6.220	(-6.69, -5.75)	<0.0001
	LDT+TDF (N= 45)	43	9.697	2.315	-7.383	(-7.93, -6.84)	<0.0001
	Overall (N=100)	98	8.967	2.237	-6.730	(-7.10, -6.36)	<0.0001
Week 52 LOCF	LDT (N= 55)	55	8.396	2.176	-6.220	(-6.69, -5.75)	<0.0001
	LDT+TDF (N= 45)	45	9.761	2.319	-7.442	(-7.97, -6.91)	<0.0001
	Overall (N=100)	100	9.010	2.241	-6.770	(-7.14, -6.40)	<0.0001
Week 76	LDT (N= 55)	52	8.246	2.218	-6.027	(-6.46, -5.59)	<0.0001
	LDT+TDF (N= 45)	40	9.683	2.176	-7.507	(-8.08, -6.94)	<0.0001
	Overall (N=100)	92	8.871	2.200	-6.671	(-7.05, -6.30)	<0.0001
Week 104	LDT (N= 55)	42	8.197	2.210	-5.987	(-6.49, -5.48)	<0.0001
	LDT+TDF (N= 45)	36	9.766	2.176	-7.590	(-8.20, -6.98)	<0.0001
	Overall (N=100)	78	8.921	2.194	-6.727	(-7.15, -6.30)	<0.0001
Week 104 LOCF	LDT (N= 55)	55	8.396	2.257	-6.139	(-6.60, -5.68)	<0.0001
	LDT+TDF (N= 45)	45	9.761	2.243	-7.518	(-8.03, -7.00)	<0.0001
	Overall (N=100)	100	9.010	2.251	-6.759	(-7.13, -6.39)	<0.0001

-N= the number of patients in the treatment group.
-n= the number of patients who have both baseline and post baseline observation for the respective week.
-Paired t test is used to calculate the 95% confidence interval and p-value.
-Baseline value is defined as the last non-missing measurement before the treatment start date.
All subjects received only LDT treatment up to week 24.

Proportion of patients with efficacy endpoints at treatment timepoints up to week 104 (mITT population, LOCF)

Week	LDT N=55 n/m (%)	95% CI	LDT+TDF N=45 n/m (%)	95% CI	Overall N=100 n/m (%)	95% CI
HBV DNA <300 copies/mL						
Week 24	55/55 (100)	(100, 100)	0/45 (0.0)	n.a.	55/100 (55.0)	(45.3, 64.8)
Week 52	55/55 (100)	(100, 100)	38/45 (84.4)	(73.9, 95)	93/100 (93.0)	(88, 98)
Week 104	52/55 (94.5)	(88.5, 100)	42/45 (93.3)	(86.1, 100)	94/100 (94.0)	(89.4, 98.7)
HBeAg loss						
Week 52	36/55 (65.5)	(52.9, 78)	7/44 (15.9)	(5.1, 26.7)	43/99 (43.4)	(33.7, 53.2)
Week 104	39/55 (70.9)	(58.9, 82.9)	11/44 (25.0)	(12.2, 37.8)	50/99 (50.5)	(40.7, 60.4)
HBeAg seroconversion						
Week 52	34/55 (61.8)	(49, 74.7)	5/44 (11.4)	(2, 20.7)	39/99 (39.4)	(29.8, 49)
Week 104	37/55 (67.3)	(54.9, 79.7)	7/44 (15.9)	(5.1, 26.7)	44/99 (44.4)	(34.7, 54.2)
ALT Normalization						

Week 24	47/55 (85.5)	(76.1, 94.8)	19/45 (42.2)	(27.8, 56.7)	66/100 (66.0)	(56.7, 75.3)
Week 52	48/55 (87.3)	(78.5, 96.1)	29/45 (64.4)	(50.5, 78.4)	77/100 (77.0)	(68.8, 85.3)
Week 104	48/55 (87.3)	(78.5, 96.1)	36/45 (80.0)	(68.3, 91.7)	84/100 (84.0)	(76.8, 91.2)
HBsAg loss						
Week 52	1/55 (1.8)	(0, 5.4)	5/44 (11.4)	(2, 20.7)	6/99 (6.1)	(1.4, 10.8)
Week 104	1/55 (1.8)	(0, 5.4)	6/44 (13.6)	(3.5, 23.8)	7/99 (7.1)	(2, 12.1)
HBsAg seroconversion						
Week 52	0/55 (0.0)	n.a.	3/44 (6.8)	(0, 14.3)	3/99 (3.0)	(0, 6.4)
Week 104	0/55 (0.0)	n.a.	4/44 (9.1)	(0.6, 17.6)	4/99 (4.0)	(0.2, 7.9)
1-log above nadir breakthrough						
Week 48†	0/55 (0.0)	n.a.	0/44 (0.0)	n.a.	0/99 (0.0)	n.a.
Week 52	0/55 (0.0)	n.a.	0/45 (0.0)	n.a.	0/100 (0.0)	n.a.
Week 104	2/55 (3.6)	(0, 8.6)	0/45 (0.0)	n.a.	2/100 (2.0)	(0, 4.7)
HBV resistance *						
Week 52	0/55 (0.0)	n.a.	0/43 (0.0)	n.a.	0/98 (0.0)	n.a.
Week 104	2/49 (4.1)	(0.2, 8.0)	0/39 (0.0)	n.a.	2/88 (2.3)	(0.1, 4.5)

† not LOCF, timepoint for virological breakthrough is Week 48 and Week 104 per protocol
* HBV resistance parameter used ITT population, and no LOCF employed. A patient was treatment emergent resistant at a time point if they developed resistance prior to or on that time point.
-m= the number of patients with non-missing observation for the respective week
-n= the number of patients with efficacy endpoint
-Binomial test is used to calculate the 95% confidence interval.

Proportion of patients with efficacy endpoints by baseline HBV DNA level subgroup up to week 104 (mITT population, LOCF)

	Week	LDT n/m (%)	LDT+TDF n/m (%)	Overall n/m (%)
HBV DNA <300 copies/mL*				
Subgroup: HBV DNA	Week 24	35/35 (100)	0/12 (0.0)	35/47(74.5)
< 9$\log_{10}$ copies/mL	Week 52	35/35 (100)	12/12 (100)	47/47 (100)
	Week 104	35/35 (100)	12/12 (100)	47/47 (100)
Subgroup: HBV DNA	Week 24	20/20 (100)	0/33 (0.0)	20/53 (37.7)
≥ 9$\log_{10}$ copies/mL	Week 52	20/20 (100)	26/33 (78.8)	46/53 (86.8)
	Week 104	17/20 (85.0)	30/33 (90.9)	47/53 (88.7)
HBeAg seroconversion				
Subgroup: HBV DNA	Week 52	18/35 (51.4)	0/12 (0.0)	18/47 (38.3)
< 9$\log_{10}$ copies/mL	Week 104	21/35 (60.0)	1/12(8.3)	22/47(46.8)
Subgroup: HBV DNA	Week 52	16/20 (80.0)	5/32 (15.6)	21/52 (40.4)
≥ 9$\log_{10}$ copies/mL	Week 104	16/20 (80.0)	6/32 (18.8)	22/52 (42.3)
ALT Normalization				
Subgroup: HBV DNA	Week 24	29/35 (82.9)	2/12 (16.7)	31/47 (66.0)
< 9$\log_{10}$ copies/mL	Week 52	30/35 (85.7)	4/12 (33.3)	34/47 (72.3)
	Week 104	31/35 (88.6)	9/12 (75.0)	40/47 (85.1)
Subgroup: HBV DNA	Week 24	18/20 (90.0)	17/33 (51.5)	35/53 (66.0)
≥ 9$\log_{10}$ copies/mL	Week 52	18/20 (90.0)	25/33 (75.8)	43/53 (81.1)
	Week 104	17/20 (85.0)	27/33 (81.8)	44/53 (83.0)
HBsAg loss				
Subgroup: HBV DNA	Week 52	0/35 (0.0)	0/12 (0.0)	0/47 (0.0)
< 9$\log_{10}$ copies/mL	Week 104	0/35 (0.0)	0/12 (0.0)	0/47 (0.0)
Subgroup: HBV DNA	Week 52	1/20 (5.0)	5/32 (15.6)	6/ 52 (11.5)
≥ 9$\log_{10}$ copies/mL	Week 104	1/20 (5.0)	6/ 32 (18.8)	7/ 52 (13.5)

-N= the number of patients in the treatment group
-m= the number of patients with non-missing observation for the respective week

-n= the number of patients with efficacy endpoint
-Binomial test is used to calculate the 95% confidence interval.

Change from baseline in GFR up to week 104 by treatment group (Modified Intent-to-treat population)

Week	Treatment group	n	Baseline value	Change from baseline*	95% CI	p-value
Week 12	LDT (N= 55)	54	93.619	0.269	(-2.977, 3.514)	0.8688
	LDT+TDF (N= 45)	43	92.572	0.733	(-2.486, 3.951)	0.6484
	Overall (N=100)	97	93.155	0.474	(-1.788, 2.736)	0.6783
Week 24	LDT (N= 55)	55	93.435	0.836	(-2.877, 4.550)	0.6534
	LDT+TDF (N= 45)	42	92.043	0.764	(-3.487, 5.015)	0.7184
	Overall (N=100)	97	92.832	0.805	(-1.941, 3.551)	0.5619
Week 52	LDT (N= 55)	55	93.435	6.944	(2.105, 11.783)	0.0057
	LDT+TDF (N= 45)	44	92.373	7.825	(2.725, 12.925)	0.0035
	Overall (N=100)	99	92.963	7.335	(3.880, 10.791)	<0.0001
Week 104	LDT (N= 55)	43	93.272	6.560	(1.246, 11.875)	0.0168
	LDT+TDF (N= 45)	38	91.079	7.821	(1.304, 14.338)	0.0200
	Overall (N=100)	81	92.243	7.152	(3.082, 11.222)	0.0008

-n= the number of patients who contributed data (had both baseline and respective visit values)
* change from baseline up to week 24; change from week 24 for other timepoints
-Paired t test is used to calculate the 95% confidence interval and p-value.
-Baseline value is defined as the last non-missing measurement before the treatment start date.
All subjects received only LDT monotherapy treatment up to week 24

GFR mean change and shifts in patients with abnormal baseline GFR

Visit	GFR absolute value change vs. baseline	Number (%) patients shifting to GFR>90 mL/min/1.73m^2

		LDT	LDT+TDF	LDT	LDT+TDF
Baseline GFR 60 to <90 mL/min/1.73m^2	Week 52 (p-value)*	12.6 (p=0.0007)	12.1 (p=0.0169)	11/22 (50%)	7/16 (43.8%)
	Week 104 (p-value)*	11.4 (p=0.0122)	14.1 (p=0.0463)	8/17 (47.1%)	5/14 (35.7%)
Baseline GFR 60 to ≤80 mL/min/1.73m^2	Week 52	18.1	6.9	4/8 (50%)	1/8 (12.5%)
	Week 104	19.8	3.9	4/7 (57.1%)	0/7 (0%)

* Paired t test is used to calculate p-value (only performed for 60 to <90 GFR category)

Safety Results

Adverse Events by System Organ Class

Incidence of on–treatment adverse events by primary system organ class (Safety population)

	LDT mono group (LDT)	Tenofovir add on group (LDT+TDF)			Overall
Primary system organ class	**(N=59) n (%)**	**LDT only period (N=46) n (%)**	**TDF add on period (N=46) n (%)**	**Total (N=46) n (%)**	**(N=105) n (%)**
-Total number (%) patients with an AE in any primary SOC	50 (84.7)	23 (50.0)	25 (54.3)	31 (67.4)	81 (77.1)
Musculoskeletal and connective tissue disorders	19 (32.2)	7 (15.2)	12 (26.1)	14 (30.4)	33 (31.4)
Infections and infestations	18 (30.5)	9 (19.6)	8 (17.4)	15 (32.6)	33 (31.4)
Gastrointestinal disorders	16 (27.1)	7 (15.2)	10 (21.7)	14 (30.4)	30 (28.6)
Nervous system disorders	11 (18.6)	6 (13.0)	4 (8.7)	8 (17.4)	19 (18.1)
General disorders and administration site conditions	9 (15.3)	3 (6.5)	5 (10.9)	8 (17.4)	17 (16.2)
Respiratory, thoracic and mediastinal disorders	3 (5.1)	2 (4.3)	3 (6.5)	5 (10.9)	8 (7.6)
Skin and subcutaneous tissue disorders	4 (6.8)	2 (4.3)	2 (4.3)	4 (8.7)	8 (7.6)
Injury, poisoning and procedural complications	3 (5.1)	1 (2.2)	3 (6.5)	4 (8.7)	7 (6.7)
Investigations	3 (5.1)	0	3 (6.5)	3 (6.5)	6 (5.7)
Metabolism and nutrition disorders	2 (3.4)	0	3 (6.5)	3 (6.5)	5 (4.8)
Eye disorders	1 (1.7)	0	2 (4.3)	2 (4.3)	3 (2.9)
Hepatobiliary disorders	1 (1.7)	1 (2.2)	1 (2.2)	2 (4.3)	3 (2.9)
Vascular disorders	2 (3.4)	1 (2.2)	0	1 (2.2)	3 (2.9)
Congenital, familial and genetic disorders	2 (3.4)	0	0	0	2 (1.9)
Endocrine disorders	1 (1.7)	0	1 (2.2)	1 (2.2)	2 (1.9)
Psychiatric disorders	1 (1.7)	0	1 (2.2)	1 (2.2)	2 (1.9)
Reproductive system and breast disorders	1 (1.7)	0	1 (2.2)	1 (2.2)	2 (1.9)
Cardiac disorders	0	1 (2.2)	0	1 (2.2)	1 (1.0)
Ear and labyrinth disorders	0	0	1 (2.2)	1 (2.2)	1 (1.0)

Neoplasms benign, malignant and unspecified (incl cysts and polyps	1 (1.7)	0	0	0	1 (1.0)
Pregnancy, puerperium and perinatal conditions	1 (1.7)	0	0	0	1 (1.0)
Renal and urinary disorders	0	1 (2.2)	0	1 (2.2)	1 (1.0)
Social circumstances	0	0	1 (2.2)	1 (2.2)	1 (1.0)

Preferred terms are sorted in descending frequency in the Overall group.

On–treatment adverse events (>5% in any treatment group) regardless of study drug relationship, by preferred term (Safety population)

	LDT mono group (LDT)	Tenofovir add on group (LDT+TDF)			
Preferred term	**(N=59) n (%)**	**LDT only period (N=46) n (%)**	**TDF add on period (N=46) n (%)**	**Total (N=46) n (%)**	**Overall (N=105) n (%)**
Total no. (%) patients with any AE	50 (84.7)	23 (50.0)	25 (54.3)	31 (67.4)	81 (77.1)
Myalgia	13 (22.0)	3 (6.5)	3 (6.5)	4 (8.7)	17 (16.2)
Upper respiratory tract infection	8 (13.6)	4 (8.7)	2 (4.3)	6 (13.0)	14 (13.3)
Headache	7 (11.9)	5 (10.9)	3 (6.5)	6 (13.0)	13 (12.4)
Dyspepsia	6 (10.2)	0	4 (8.7)	4 (8.7)	10 (9.5)
Arthralgia	2 (3.4)	2 (4.3)	6 (13.0)	7 (15.2)	9 (8.6)
Cough	2 (3.4)	2 (4.3)	3 (6.5)	5 (10.9)	7 (6.7)
Nasopharyngitis	6 (10.2)	0	1 (2.2)	1 (2.2)	7 (6.7)
Diarrhoea	3 (5.1)	1 (2.2)	2 (4.3)	3 (6.5)	6 (5.7)
Pyrexia	5 (8.5)	1 (2.2)	0	1 (2.2)	6 (5.7)
Dizziness	4 (6.8)	1 (2.2)	0	1 (2.2)	5 (4.8)
Fatigue	4 (6.8)	1 (2.2)	0	1 (2.2)	5 (4.8)
Nausea	2 (3.4)	0	3 (6.5)	3 (6.5)	5 (4.8)
Abdominal pain upper	0	3 (6.5)	1 (2.2)	4 (8.7)	4 (3.8)
Decreased appetite	1 (1.7)	0	3 (6.5)	3 (6.5)	4 (3.8)
Muscular weakness	1 (1.7)	0	3 (6.5)	3 (6.5)	4 (3.8)
Pain in extremity	3 (5.1)	1 (2.2)	0	1 (2.2)	4 (3.8)
Vomiting	1 (1.7)	0	3 (6.5)	3 (6.5)	4 (3.8)
Influenza	3 (5.1)	0	0	0	3 (2.9)

Preferred terms are sorted in descending frequency in the Overall group

Number of patients who died or experienced other serious or clinically significant adverse events (Safety population)

	LDT mono group (LDT)	Tenofovir add-on group (LDT+TDF)			Overall
Patients with serious or significant AEs	**(N=59) n (%)**	**LDT only period (N=46) n (%)**	**TDF add-on period (N=46) n (%)**	**Total (N=46) n (%)**	**(N=105) n (%)**
Death	0	0	0	0	0
SAEs	3 (5.1)	1 (2.2)	2 (4.3)	3 (6.5)	6 (5.7)
Discontinued due to AEs	4 (6.8)	0	2 (4.3)	2 (4.3)	6 (5.7)
AESIs	17 (28.8)	4 (8.7)	9 (19.6)	10 (21.7)	27 (25.7)

Number of patients with on-treatment serious adverse events (Safety population)

Primary system organ class Preferred term	LDT mono group (LDT) (N=59) n (%)	Tenofovir add on group (LDT+TDF) LDT only period (N=46) n (%)	 TDF add on period (N=46) n (%)	 Total (N=46) n (%)	Overall (N=105) n (%)
Any primary system organ class	3 (5.1)	1 (2.2)	2 (4.3)	3 (6.5)	6 (5.7)
Congenital, familial and genetic disorders					
Atrial Septal Defect	1 (1.7)	0	0	0	1 (1.0)
Gastrointestinal disorders					
Inguinal hernia			1 (2.2)	1 (2.2)	1 (1.0)
Hepatobiliary disorders					
Gallbladder Polyp	0	1 (2.2)	0	1 (2.2)	1 (1.0)
Injury, poisoning and procedural complications					
Foot Fracture	0	0	1 (2.2)	1 (2.2)	1 (1.0)
Vascular Injury	1 (1.7)	0	0	0	1 (1.0)
Pregnancy, puerperium and perinatal conditions					
Abortion Spontaneous*	1 (1.7)	0	0	0	1 (1.0)
Pregnancy*	1 (1.7)	0	0	0	1 (1.0)

NB. A total of 3 SAE were reported off-treatment so are not included in table:
*The pregnancy and abortion events were reported by the same patient

Number of patients who discontinued due to adverse events (Safety population)

Primary system organ class Preferred term	LDT mono group (LDT) (N=59) n (%)	Tenofovir add on group (LDT+TDF) LDT only period (N=46) n (%)	 TDF add on period (N=46) n (%)	 Total (N=46) n (%)	Overall (N=105) n (%)
Any primary system organ class	4 (6.8)	0	2 (4.3)	2 (4.3)	6 (5.7)
Investigations					
Blood CPK increased	1 (1.7)	0	0	0	1 (1.0)
Musculoskeletal and connective tissue disorders					
Muscular weakness	1 (1.7)	0	2 (4.3)	2 (4.3)	3 (2.9)
Myalgia	2 (3.4)	0	0	0	2 (1.9)

On–treatment adverse events of special interest (AESI), by preferred term – AESI defined for LDT project (Safety population)

Special AE class Preferred term	LDT mono group (LDT) (N=59) n (%)	Tenofovir add on group (LDT+TDF) LDT only period (N=46) n (%)	 TDF add on period (N=46) n (%)	 Total (N=46) n (%)	Overall (N=105) n (%)
-No. (%) patients with any AESI					
Total	17 (28.8)	4 (8.7)	9 (19.6)	10 (21.7)	27 (25.7)
ALT elevation					
Total	0	0	0	0	0
CK events					
Total	2 (3.4)	0	0	0	2 (1.9)
Blood CPK increased	2 (3.4)	0	0	0	2 (1.9)
Investigator determined possibly drug-related hypersensitivity					
Total	1 (1.7)	0	2 (4.3)	2 (4.3)	3 (2.9)
Dermatitis contact	1 (1.7)	0	0	0	1 (1.0)
Rhinitis allergic	0	0	1 (2.2)	1 (2.2)	1 (1.0)
Urticaria	0	0	1 (2.2)	1 (2.2)	1 (1.0)
Lactic acidosis					
Total	0	0	0	0	0
Muscle related events					
Total	14 (23.7)	4 (8.7)	6 (13.0)	8 (17.4)	22 (21.0)
Myalgia	13 (22.0)	3 (6.5)	3 (6.5)	4 (8.7)	17 (16.2)
Muscular Weakness	1 (1.7)	0	3 (6.5)	3 (6.5)	4 (3.8)
Muscle Fatigue	0	1 (2.2)	0	1 (2.2)	1 (1.0)
Pancreatitis					
Total	0	0	0	0	0
Peripheral neuropathy					
Total	0	0	0	0	0
Renal related events					
Total	0	0	1 (2.2)	1 (2.2)	1 (1.0)
Blood Creatinine Increased	0	0	1 (2.2)	1 (2.2)	1 (1.0)

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Date Inclusion on Novartis Clinical Trial Results Database

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Date of Latest Update :

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