Randomized Clinical Trial

Telbivudine vs tenofovir in hepatitis B e antigen-negative chronic hepatitis B patients: OPTIMA roadmap study

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Abstract

AIM
To make efficacy and safety comparison of telbivudine-roadmap and tenofovir-roadmap in hepatitis B e antigen (HBeAg)-negative chronic hepatitis B (CHB) patients.

METHODS
This was the first prospective, randomised, two-arm, open-label, non-inferiority study in HBeAg-negative CHB patients that compared telbivudine and tenofovir administered as per roadmap concept. Patients were treated up to 24 wk and, depending on virologic response, continued the same therapy or received add-on therapy up to 104 wk. Eligible patients received an additional 52 wk of treatment in the extension period (i.e., up to 156 wk). Patients who developed virologic breakthrough (VB) while on monotherapy also received add-on therapy. The primary efficacy endpoint was the rate of patients achieving hepatitis B virus (HBV) DNA < 300 copies/mL at week 52. Secondary efficacy endpoints included the rates of HBV DNA < 300 and < 169 copies/mL, HBV DNA change from baseline, alanine aminotransferase normalisation, hepatitis B surface antigen (HBsAg) loss, HBsAg seroconversion, VB, and emergence of resistance at various timepoints throughout the study. Safety and estimated glomerular filtration rate (eGFR) were also analysed.

RESULTS
A total of 241 patients were randomised. Non-inferiority of telbivudine arm to tenofovir arm was demonstrated at week 52 (=7 d window), with over 91% of patients in each treatment arm achieving HBV DNA level < 300 copies/mL. Both arms were similar in terms of key secondary efficacy variables at weeks 104 and 156. The percentage of patients achieving HBV DNA < 300 copies/mL remained high and was similar in the telbivudine and tenofovir arms at both weeks 104 and 156. Over 82% of patients in both arms achieved alanine aminotransferase normalisation at week 52, and this percentage remained high at weeks 104 and 156. Tenofovir treatment progressively reduced serum HBsAg levels from baseline while no change was reported in quantitative HBsAg during therapy with tenofovir. Both treatments showed acceptable safety profiles. The telbivudine arm showed eGFR improvement unlike the tenofovir arm.

CONCLUSION
Efficacy was shown for both telbivudine-roadmap and tenofovir-roadmap regimens in HBeAg-negative CHB patients over 156 wk. Tenofovir arm was associated with renal improvement.

Key words: Chronic hepatitis B; Glomerular filtration rate; Telbivudine; Tenofovir; Roadmap concept

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Core tip: This was the first prospective, randomised, non-inferiority study in hepatitis B e antigen-negative chronic hepatitis B patients that compared telbivudine and tenofovir administered as per roadmap concept. Both treatments based on the roadmap approach were effective over a 156 wk treatment period. Non-inferiority of telbivudine arm to tenofovir arm was demonstrated at week 52, with over 91% of patients in each treatment arm achieving hepatitis B virus DNA level < 300 copies/mL. Both treatments showed acceptable safety profiles. Moreover, telbivudine showed an improvement in estimated glomerular filtration rate from baseline.

INTRODUCTION
Approximately 240–400 million people worldwide are chronically infected with hepatitis B virus (HBV), with a wide variation of prevalence among countries, and more than 780000 people die every year due to acute or chronic hepatitis B (CHB)[1-3]. Although CHB may be treated with interferon or nucleos(t)ide analogue (NA) antivirals, emergence of resistance due to prolonged NA therapy or incomplete suppression of HBV still remains an important concern[4]. Several studies have suggested that the use of response-guided add-on therapy is associated with a higher rate of virologic response and reduced antiviral resistance as compared to sequential monotherapy[5,6].

Early virologic response has been used as a guide to predict better outcomes and to reduce the risk of antiviral resistance[7,8]. As previously reported[9,10], the roadmap concept uses early virologic response at week 24 to individualize ongoing management of CHB patients. Patients with a complete response at week 24 can remain on their initial therapy, whereas treatment modification that may include the addition of a second drug is done for those with an inadequate virologic response. This strategy is relevant mainly in patients receiving NA with a low genetic barrier to resistance (clevudine, emtricitabine, lamivudine, telbivudine)[10]. In hepatitis B e antigen (HBeAg)-positive CHB patients treated with telbivudine, a response-guided treatment optimization strategy with telbivudine based on the roadmap concept has been demonstrated to improve the clinical outcomes of patients with a suboptimal antiviral response[11,12].

The aim of this study, OPTIMA, was to assess the efficacy and safety of telbivudine and tenofovir regimens,
Figure 1  Study design. HBV: Hepatitis B virus.

when administered using the roadmap concept, in HBeAg-negative patients with CHB. This was the first study that compared efficacy of the 2 regimens in a prospective manner. The safety of the combination of telbivudine and tenofovir, for which limited data are currently available, was also evaluated.

MATERIALS AND METHODS

Study design and conduct
OPTIMA was a prospective, randomised, 2-arm, open-label study (ClinicalTrials.gov ID: NCT01379508) that enrolled patients between February 2011 and October 2012 in 8 countries (Austria, Bulgaria, Germany, Greece, Italy, Russia, Spain and Turkey). This study was approved by the Institutional Review Board at each participating centre, and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from each patient before enrolment.

Eligible patients were randomised via an interactive voice response system in a 1:1 ratio to either telbivudine arm (600 mg/d) or tenofovir arm (300 mg/d) (Figure 1). Randomisation was stratified by the screening HBV DNA level (< 7 log_{10} copies/mL or ≥ 7 log_{10} copies/mL) and alanine aminotransferase (ALT) level [< 3 × upper limit of normal (ULN) or ≥ 3 × ULN]).

This study used the response-guided add-on strategy (roadmap concept). For patients with HBV DNA ≥ 300 copies/mL (≥ 51 IU/mL) at week 24, tenofovir was added to telbivudine by week 26 in the telbivudine arm, and telbivudine was added to tenofovir by week 26 in the tenofovir arm. For patients with HBV DNA < 300 copies/mL at week 24, telbivudine and tenofovir monotherapies in the respective arms were continued. Patients who developed virologic breakthrough (VB) while on monotherapy received add-on therapy. However, patients who developed VB after week 24 while on combination therapy were discontinued from the study.

Patients
Eligible patients were male or female ≥ 18 years of age, with detectable hepatitis B surface antigen (HBsAg) for ≥ 6 mo, HBeAg-negative with positive hepatitis B e antibody, available liver histology report within 12 mo before screening compatible with CHB (patients without evaluable liver histology were eligible if they had clinical evidence of compensated liver cirrhosis or non-invasive methods that support the diagnosis of moderate to severe liver inflammation and/or fibrosis), serum HBV DNA > 2000 IU/mL, and serum ALT level > 1 × ULN and < 10 × ULN at the screening visit. Patients with ALT ≤ 1 × ULN at screening were eligible if they had at least moderate liver inflammation or fibrosis, clinical evidence of compensated cirrhosis, or ALT level > 1 × ULN within the last 6 mo.

Main exclusion criteria included co-infection with hepatitis C virus, hepatitis D virus or human immunodeficiency virus; hepatic decompensation; liver disease other than CHB; any nucleos(t)ide or interferon/immunomodulator treatment in the previous 6 mo; chronic renal insufficiency or serum creatinine clearance < 50 mL/min; history of myopathy, myositis, or persistent muscle weakness; pregnant or nursing (lactating) women; or history of malignancy of any organ system (other than localized basal cell carcinoma of the skin).

Patients were allowed to receive an additional 52 wk of treatment in the extension period (i.e., up to 156 wk) if they had HBV DNA < 300 copies/mL at both weeks 92 and 104, and serum creatinine clearance ≥ 50 mL/min at two consecutive visits including week 104.

Efficacy and safety analyses
The primary efficacy endpoint was the rate of patients achieving HBV DNA < 300 copies/mL (51 IU/mL) at week 52. Secondary efficacy endpoints included the rates of patients with HBV DNA < 300 copies/mL at weeks 104 and 156, and HBV DNA < 169 copies/mL (29 IU/mL) (lower limit of detection) at weeks 24, 52, 104 and 156; change from baseline in HBV DNA; ALT normalisation at weeks 52, 104 and 156; HBsAg loss and HBsAg seroconversion; VB; and emergence of resistance. In addition, subgroup analyses were performed for secondary efficacy endpoints by baseline HBV DNA (i.e., < 7 log_{10} copies/mL or ≥ 7 log_{10} copies/mL).

VB was defined as an increase of HBV DNA by at least 1 log_{10} copies/mL (or 1 log_{10} IU/mL) above nadir on 2 consecutive visits, or at the last on-treatment visit in patients who did not have a primary non-response. Emergence of resistance was assessed as the rate of confirmed treatment-emergent genotypic resistance and was assessed at the time of confirmed VB and at week 24 in patients with viral load ≥ 300 copies/mL, it was calculated cumulatively at weeks 52, 104 and 156.

HBV DNA detection and quantification were performed at a central laboratory using the COBAS TaqMan real-time polymerase chain reaction assay (Roche Molecular Systems, Branchburg, NJ, United States).
Safety assessments included monitoring of adverse events (AEs), vital signs, and graded laboratory abnormalities. Estimated glomerular filtration rate (eGFR), calculated by the modification of diet in renal disease formula was recorded. AEs of special interest (muscle and renal function related events) were also reported.

**Statistical analysis**

For the primary efficacy analysis, study treatments were compared for non-inferiority.

Based on the assumptions of 96% and 97% HBV DNA < 300 copies/mL at week 52 in the telbivudine arm and the tenofovir arm, respectively, and an approximately 10% dropout rate, it was estimated that 120 randomised patients per arm would provide 87% power for the non-inferiority testing on the primary analysis. Non-inferiority in efficacy of telbivudine arm to tenofovir arm was to be claimed if the lower limit of the 2-sided confidence interval (CI) for the difference was above the pre-determined non-inferiority margin (-10%).

A weighted Cochran-Mantel-Haenszel method, adjusting for randomisation strata [HBV DNA (< or ≥ 7 log10 copies/mL) and ALT (< or ≥ 3 x ULN) levels], was used to assess comparative therapeutic response rates.

For continuous variables, summary statistics of absolute value and of change from baseline, including mean, standard deviation (SD), median, minimum, and maximum were used. For dichotomous endpoints, statistical summaries included count and percentage of patients with a positive response (response rate) and also 95%CI for the response rate.

The intent-to-treat (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. The roadmap ITT (rITT) population consisted of all patients who did not discontinue before week 24 and did not deviate from the protocol defined rules of receiving add-on at week 24 (i.e., patients who received the add-on therapy at week 24 if they had HBV DNA ≥ 300 copies/mL, or did not receive the add-on at week 24 if they had HBV DNA < 300 copies/mL). The modified ITT (mITT) population consisted of all patients in the ITT population who were eligible and enrolled in the extension period beyond week 104. The per-protocol population consisted of all patients in the ITT population who had no major protocol deviations.

All efficacy observations on or after censoring date were treated as missing. A patient’s censoring date was the date of the first occurrence of: One day after the last dose of the study drug, the start of first prohibited CHB-related medication, pregnancy, or a specific major protocol deviation. To assess the robustness of the results due to missing data, the analysis of primary and all secondary efficacy endpoints were performed based on the rITT and ITT analysis populations. The mITT population was used only for the week 156 analysis.

The primary efficacy endpoint (week 52) analysis was performed on the rITT population. The analyses presented include: (1) assessments within the ± 7 d protocol-pre-specified visit window around the scheduled week 52 date; (2) missing data at week 52 treated as failure; (3) missing data imputed using the earliest available assessment within the 28 d window starting from the scheduled week 52 date; and (4) missing data imputed using the last observation carried forward (LOCF).

Secondary efficacy parameters including HBV DNA, ALT normalisation, HBsAg loss, and HBsAg seroconversion were analysed using two imputation methods for missing data: (1) missing data treated as failure; and (2) missing data imputed using the earliest available assessment within the 28 d window starting from the scheduled visit for weeks 52 (except HBV DNA < 300 copies/mL), 104 and 156. VB and eGFR were analysed using the LOCF imputation method for missing data. Treatment-emergent genotypic resistance was analysed using cumulative imputation method for missing data. Missing eGFR assessments were imputed using the LOCF method.

Analyses of endpoints using LOCF imputation at weeks 104 and 156 are presented for the rITT and mITT populations, respectively.

**RESULTS**

**Study patients**

A total of 241 patients (121 in the telbivudine arm and 120 in the tenofovir arm) were randomised in this study. A total of 22 (18.2%) patients in the telbivudine arm and 13 (10.8%) patients in the tenofovir arm discontinued prematurely from the study. The most common reasons for discontinuation in the telbivudine arm were consent withdrawal (n = 7), lost to follow-up (n = 5), and administrative reasons (n = 4). In the tenofovir arm, the most common reasons for discontinuation were AEs (n = 5), consent withdrawal (n = 4), and lost to follow-up (n = 3).

Major protocol deviations were reported in 11 (9.1%) patients in the telbivudine arm and 8 (6.7%) patients in the tenofovir arm. The most commonly reported major deviations were patients on monotherapy with confirmed VB not starting add-on therapy within 2 wk of laboratory confirmation of VB (n = 9), patients with a positive HBeAg result (n = 6), and patients not completing 3 wk of treatment before the third visit (n = 4).

The safety population comprised 120 patients in each of the 2 treatment arms. One patient in the telbivudine arm was excluded from the safety population as this patient did not receive any study treatment. Of the 241 randomized patients, 235 patients were included in the ITT population, with 117 (96.7%) in the telbivudine arm and 118 (98.3%) in the tenofovir arm. Six patients were excluded from the ITT population (4 patients in the telbivudine arm due to no post-baseline HBV DNA assessments, non-compliance with the study conduct, or no study treatment received; and 2 patients in the tenofovir arm because of no post-baseline HBV DNA assessments and viral resistance at baseline). A total of 113 (93.4%) patients in the telbivudine arm and 117 (97.5%) patients in the tenofovir arm comprised the
ITT population. Five patients (4 in the telbivudine arm and 1 in the tenofovir arm) that were included in the ITT population were excluded from the rITT population because they discontinued before week 24 and were not eligible for or enrolled into the roadmap concept period (weeks 24 to 104).

The per-protocol population consisted of 107 (88.4%) patients in the telbivudine arm and 111 (92.5%) patients in the tenofovir arm. A total of 17 patients (10 in the telbivudine arm and 7 in the tenofovir arm) were included in the ITT and rITT populations but were excluded from the per-protocol population because of major protocol deviations. The mITT population consisted of 79 (65.3%) patients in the telbivudine arm and 89 (74.2%) patients in the tenofovir arm.

Treatment arms were balanced with respect to demographics and baseline characteristics, with no clinically meaningful differences between the telbivudine and tenofovir arms (Table 1). Most (86.0% telbivudine, 91.7% tenofovir) patients were infected with HBV genotype D, and the mean HBV DNA at baseline was 6.2 log_{10} copies/mL in the telbivudine arm and 6.0 log_{10} copies/mL in the tenofovir arm, with 70.2% and 71.7% of patients, respectively, having a baseline HBV DNA < 7 log_{10} copies/mL.

Primary efficacy endpoint

Virologic response (HBV DNA < 300 copies/mL) at week 52 was achieved in more than 91% of patients in each treatment arm (Figure 2A). The primary endpoint analysis showed that the antiviral efficacy of telbivudine-roadmap was non-inferior to that of tenofovir-roadmap application at week 52 in the rITT population; the lower bound of the 95%CI for the difference between the 2 treatment arms was above the non-inferiority margin of -10%: -9.4% (utilizing assessments within the ±7 d protocol-prespecified visit window); -8.3% for the 28 d window imputation; and -7.9% for the LOCF imputation. Using missing data as treatment failure, non-inferiority was not demonstrated (lower bound of the 95%CI: -10.5%, just below the protocol defined non-inferiority margin) (Table 2). In this analysis, HBV DNA samples from 6 patients (4 in the telbivudine arm and 2 in the tenofovir arm), although resulted in < 300 copies/mL, were considered as missing because they were not obtained at the week 52 visit date itself (i.e., patients were counted as treatment failures).

The primary endpoint analysis at week 52 in the per-protocol population supported the non-inferiority of the telbivudine arm to the tenofovir arm (98.0% in the telbivudine arm and 99.0% in the tenofovir arm, lower bound of the 95%CI: -4.3%).

Secondary efficacy endpoints

Virologic responses: Percentage of patients achieving HBV DNA < 300 copies/mL (51 IU/mL) at weeks 24 and 104, and by baseline viral load at weeks 24, 52 and 104 in the rITT population: The percentage of patients achieving HBV DNA < 300 copies/mL in the telbivudine and tenofovir arms at week 24 was 80.5% and 89.7%.

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**Table 1 Demographic and baseline characteristics, randomised population**

| Patients characteristics | Telbivudine (n = 121) | Tenofovir (n = 120) |
|--------------------------|------------------------|---------------------|
| Age, mean (SD), yr       | 42.1 (11.5)            | 43.3 (12.6)         |
| Median (min-max)         | 42.0 (19.70)           | 44.0 (18.73)        |
| Male gender, n (%)       | 86 (71.1)              | 82 (68.3)           |
| Race, Caucasian, n (%)   | 117 (96.7)             | 118 (98.3)          |
| Body mass index, mean (SD), kg/m² | 25.8 (4.1)           | 25.7 (4.0)          |
| Median (min-max)         | 25.6 (16.5-40.4)       | 25.2 (18.4-39.8)    |
| Genotype, n (%)          |                        |                     |
| A                        | 6 (5.0)                | 2 (1.7)             |
| B                        | 1 (0.8)                | 0 (0.0)             |
| C                        | 0 (0.0)                | 1 (0.8)             |
| D                        | 104 (86.0)             | 110 (91.7)          |
| G                        | 1 (0.8)                | 0 (0.0)             |
| Other                    | 1 (0.8)                | 0 (0.0)             |
| Unknown                  | 8 (6.6)                | 7 (5.8)             |
| HBV DNA, mean (SD), log₁₀ copies/mL | 6.2 (1.5)               | 6.0 (1.4)          |
| Median (min-max)         | 6.1 (3.2-9.5)          | 5.9 (2.5-9.9)       |
| < 7 log₁₀, n (%)         | 85 (70.2)              | 86 (71.7)           |
| ≥ 7 log₁₀, n (%)         | 36 (29.8)              | 34 (28.3)           |
| Serum alanine aminotransferase, mean (SD), IU/L | 79.8 (84.1)       | 78.2 (86.1)         |
| Median (min-max)         | 53.0 (13-494)          | 49.0 (5-568)        |
| Serum aspartate aminotransferase, mean (SD), IU/L | 54.0 (52.8)            | 52.5 (47.1)         |
| Median (min-max)         | 35.0 (13-347)          | 35.0 (13-322)       |
| Creatine phosphokinase, mean (SD), IU/L | 118.6 (64.4)            | 160.1 (299.3)       |
| Median (min-max)         | 104.0 (35-430)         | 111.0 (36-2976)     |
| eGFR, mean (SD), (mL/min per 1.73 m²) | 97.4 (17.9)          | 95.8 (16.4)         |
| Median (min-max)         | 96.6 (60.9-147.1)      | 94.2 (60.5-138.4)   |

*Note: eGFR: Estimated glomerular filtration rate (modification of diet in renal disease formula). HBV: Hepatitis B virus; SD: Standard deviation.*
and at week 104, 93.8% and 99.1%, respectively (Figure 2A).

In patients with lower baseline viral load (HBV DNA level < 7 log_{10} copies/mL) at week 24, telbivudine and tenofovir regimens were similar in terms of viral load reduction with 93.8% and 95.2% of patients achieving HBV DNA levels < 300 copies/mL in the telbivudine and tenofovir arms, respectively. At weeks 52 and 104, these values were 92.5% and 92.5%, respectively, for telbivudine, and 97.0% and 97.0%, respectively, for tenofovir (Figure 2A).

### Table 2  Virologic response, roadmap intent-to-treat population

| Parameters                                                                 | Telbivudine (n = 113) | Tenofovir (n = 117) | Difference between arms and 95%CI |
|---------------------------------------------------------------------------|-----------------------|---------------------|----------------------------------|
| Patients achieving HBV DNA < 300 copies/mL (51 IU/mL) at week 52, n (%)  | 104 (91.9)            | 111 (95.0)          | -3.1% (-9.4%, 3.1%)              |
| ± 7 d protocol-prespecified visit window                                  | 103 (91.0)            | 111 (95.0)          | -4.0% (-10.5%, 2.5%)             |
| Treating missing as failure                                               | 105 (92.7)            | 111 (95.0)          | -2.3% (-8.3%, 3.8%)              |
| Last observation carried forward                                          | 108 (95.4)            | 116 (99.2)          | -3.8% (-7.9%, 0.4%)              |
| Change from baseline in HBV DNA levels (log_{10} copies/mL) by visit, mean (SD) |                       |                     |                                  |
| Week 24                                                                   | -4.201 (1.256)        | -4.122 (1.165)      | P < 0.0001                       |
| Week 52                                                                   | -4.356 (1.473)        | -4.305 (1.343)      | P < 0.0001                       |
| Week 104                                                                  | -4.281 (1.753)        | -4.349 (1.382)      | P < 0.0001                       |

1Percentages and 95% CIs were calculated using Mantel-Haenszel weighted estimates stratified by baseline HBV DNA and alanine aminotransferase levels; 2P-values were calculated using paired t-test comparing post-baseline timepoints to baseline timepoints. CI: Confidence interval; HBV: Hepatitis B virus; SD: Standard deviation.

Figure 2  Proportions of patients achieving hepatitis B virus DNA < 300 (A) or < 169 copies/mL (B), by visit and by baseline hepatitis B virus DNA levels (< 7 or ≥ 7 log_{10} copies/mL), roadmap intent-to-treat population. HBV: Hepatitis B virus.
Tenofovir + telbivudine were in the telbivudine monotherapy group following the week 24 visit (92.4%, 85/92 patients) (Figure 3A).

The proportion of patients in the tenofovir arm achieving HBV DNA < 300 copies/mL at week 104 was similar in those who required telbivudine add-on therapy at week 24 (100%, 11/11 patients) to those who were in the tenofovir monotherapy group following the week 24 visit (99.1%, 105/106 patients) (Figure 3B).

Percentage of patients achieving HBV DNA < 169 copies/mL (29 IU/mL) at weeks 24, 52 and 104 in the rITT population: The rate of patients achieving HBV DNA < 169 copies/mL at weeks 24, 52 and 104 was consistent with that observed for the endpoint of HBV DNA < 300 copies/mL (Figure 2B).

Percentage of patients achieving HBV DNA < 169 copies/mL at week 104 in the rITT population according to the requirement for add-on therapy at week 24: The proportion of patients in the telbivudine and tenofovir arms achieving HBV DNA < 169 copies/mL at week 104 and receiving add-on therapy were 7.6 and 0.9 percentage points greater, respectively, than patients who received monotherapy (Figure 3).

Maintained virologic responses at week 156 in the mITT population: The percentage of patients who maintained HBV DNA < 300 copies/mL at week 156 was similar in the telbivudine and tenofovir arms: 91.1% (72/79 patients) and 100% (89/89 patients), respectively, using LOCF imputation. Similar results were found in patients maintaining HBV DNA < 169 copies/mL (91.1% (72/79 patients) and 96.6% (86/89 patients), respectively).

**HBsAg loss and HBsAg seroconversion:** HBsAg loss and HBsAg seroconversion were not observed in any patient from either treatment arm at weeks 52, 104 or 156. Telbivudine treatment progressively reduced serum HBsAg levels (mean ± SD) from baseline in the mITT population [-0.116 ± 0.581 log_{10} IU/mL at week 52 (P = 0.0368) and -0.179 ± 0.633 log_{10} IU/mL at week 104 (P = 0.0032)]. In contrast, no change was reported in quantitative HBsAg during therapy with tenofovir [-0.038 ± 0.349 log_{10} IU/mL at week 52 (P = 0.2399) and -0.030 ± 0.385 log_{10} IU/mL at week 104 (P = 0.4066)]. At week 156, change from baseline in HBsAg levels in the mITT population was -0.204 ± 0.759 log_{10} IU/mL (P = 0.0193) in the telbivudine arm and -0.031 ± 0.412 log_{10} IU/mL (P = 0.4760) in the tenofovir arm.

**Biochemical response:** ALT normalisation at weeks 52 and 104 in the rITT population: ALT levels significantly improved vs baseline in both treatment arms, with over 82% of patients in both arms achieving ALT normalisation at week 52 that was sustained up until week 104 (89.7% and 85.9% in the telbivudine and tenofovir arms, respectively) (Figure 4).

The results at week 104 by baseline viral load are presented in Figure 4.

ALT normalisation at week 104 in the rITT population according to the requirement for add-on therapy at week 24: The proportion of patients who achieved ALT
ALT normalisation at week 24 was higher (telbivudine arm) or similar (tenofovir arm) in patients who received add-on therapy (Figure 3).

Maintained biochemical response at week 156 in the mITT population: ALT normalisation was maintained in 92.0% of patients in the telbivudine arm and 91.1% of patients in the tenofovir arm.

Patients experiencing VB and emergence of resistance in the rITT and mITT populations: At weeks 52 and 104, respectively, in the rITT population, cumulative rates of VB were reported in 2.7% (3/113) and 9.7% (11/113) of patients in the telbivudine arm (3.3% and 12.4% in the monotherapy group, none in the add-on treatment group). In the tenofovir arm, no patients developed VB cumulatively at week 104 and 10.8% (8/74) in the tenofovir arm (14.0% in the monotherapy group, none in the add-on treatment group). In the telbivudine arm, 10 patients experienced VB and 5 had emergence of resistance between weeks 52 and 156 in the mITT population. In the tenofovir arm, only 1 patient had VB and none developed viral resistance. The cumulative rate of VB at week 156 was 16.5% (13/79) in the telbivudine arm, and 1.1% (1/89) in the tenofovir arm. Cumulative rates of resistance were 10.8% (8/74) in the telbivudine arm (14.0% in the monotherapy group, none in the add-on treatment group) and none in the tenofovir arm.

Safety
No patients died or experienced ALT flare during the study. The overall incidence of serious AEs (SAEs) was similar in the telbivudine arm and in the tenofovir arm [11 (9.2%) patients and 13 (10.8%) patients, respectively]. One patient in the tenofovir arm reported drug-related SAEs [moderately increased blood creatine phosphokinase (CPK), mild arthralgia, and moderate fatigue], which led to temporary interruption of the study drug (Table 3). There were no cases of myositis or myopathy.

Two patients in the telbivudine arm and 5 patients in the tenofovir arm discontinued due to AEs [myalgia and hepatocellular carcinoma (HCC) for telbivudine; headache, HCC, hepatic cirrhosis, cholestatic jaundice, and breast cancer for tenofovir], which were assessed by the investigator as unrelated to the study drugs. Most AEs were mild to moderate in severity. The proportion of patients reporting at least 1 AE, regardless of study drug relationship, was similar for telbivudine and tenofovir arms. The overall incidence of AEs suspected to be related to study drug was somewhat higher in the telbivudine arm compared with the tenofovir arm. The most frequent (≥ 2%) drug-related AEs reported in both arms are described in Table 3. Increased blood CPK levels [31 (25.8%) patients], myalgia [8 (6.7%) patients], and nausea 8 (6.7%) patients] were the drug-related AEs that were observed more frequently in the telbivudine arm compared with the tenofovir arm [16 (13.3%), 0, and 2 (1.7%) patients, respectively]. AEs of special interest were observed in 46 (38.3%) patients in the telbivudine arm and 27 (22.5%) patients in the tenofovir arm. These included elevated blood CPK and myalgia as the most commonly reported AEs in the telbivudine arm, and elevated blood CPK and ALT as the most commonly reported AEs in the tenofovir arm. Myalgia suspected to be drug related was reported in the telbivudine arm. The number of patients experiencing at least 1 muscle event along with 1 new-onset abnormal CPK episode during the study was greater in the telbivudine arm (Table 3).

The telbivudine arm showed a higher incidence of Grade 3/4 CPK elevations during the study than the tenofovir arm [19 (15.8%) patients vs 5 (4.2%) patients, respectively]. All Grade 3/4 CPK elevations were resolved (Table 3).

Tenofovir monotherapy (as of week 24) was associated with a significant improvement in eGFR as compared with tenofovir monotherapy (as of week 24). At week 24, the telbivudine monotherapy showed a statistically significant (P = 0.0798) improvement from baseline in eGFR compared to worsening with tenofovir monotherapy, with least squares mean percentage changes from baseline of 2.46% vs -1.17%, respectively. Further improvement in eGFR in the telbivudine monotherapy group (as of week 24) was observed at weeks 52 (4.90% vs -2.68% with tenofovir, P = 0.0098), 104 (5.54% vs -5.36%, P < 0.0001, respectively), and 156 (9.55% vs -6.23%, P < 0.0001, respectively) (Figure 5).

There was no significant change in vital signs from baseline for either treatment arm.

Figure 4 Proportions of patients achieving aminotransferase normalisation, by visit and by baseline hepatitis B virus DNA levels (≤ 7 or ≥ 7 log10 copies/mL), roadmap intent-to-treat population. ALT: Alanine aminotransferase; HBV: Hepatitis B virus.
**DISCUSSION**

NAs given as a single daily oral dose are considered the mainstay of CHB treatment\(^{[13]}\). In clinical practice, attaining optimal efficacy with a low emergence of drug resistance remains an important goal\(^{[4]}\). The roadmap concept utilizing add-on therapy for patients who do not achieve HBV DNA < 300 copies/mL at week 24 (in particular for agents with lower barriers to resistance) has been identified as a strategy to achieve this goal. This study was the first prospective, randomised clinical trial using the roadmap concept in HBeAg-negative CHB patients comparing efficacy and safety of telbivudine with tenofovir. As previously reported\(^{[15]}\), early detection of virologic response may be a useful guide to individualize CHB treatment. This study confirmed that monitoring virologic response at week 24 is a strong predictor of the treatment response by week 104\(^{[16]}\). These data were consistent with an earlier study comparing telbivudine with lamivudine\(^{[15]}\).

In the real-world setting, use of the roadmap concept may offer several advantages such as early identification of patients with suboptimal responses to initiate an appropriate change in therapy\(^{[10,11]}\) and to provide clinicians with options for individualized treatment decisions\(^{[5]}\). Although emergence of resistance had been identified as an issue for HBeAg-negative CHB patients treated with telbivudine monotherapy\(^{[15,17]}\), the data from our study suggest that the risk for resistance is lower if telbivudine is administered using the roadmap concept, as compared to the GLOBE trial showing higher rates of resistance\(^{[15]}\). Moreover, despite a somewhat higher percentage of patients requiring add-on therapy in the telbivudine arm, the overall efficacy profile of the 2 roadmap approach arms was comparable, as assessed by the percentages of patients achieving HBV DNA levels < 300 or < 169 copies/mL, and ALT normalisation at weeks 52, 104 and 156. Moreover, telbivudine treatment resulted in a statistically significant reduction in serum HBsAg levels from baseline while no change was reported in quantitative HBsAg during therapy with tenofovir.

Overall, both treatments based on the roadmap concept were well tolerated over the 156 wk treatment period in HBeAg-negative patients. Although myalgia and elevated blood CPK levels were reported in a higher number of patients in the telbivudine arm, the rates were consistent with the findings reported earlier in the literature\(^{[12,15,18,19]}\). It is recommended that serum CPK levels should be monitored closely during treatment with telbivudine\(^{[20]}\).

Renal safety issues with oral NAs have been well-documented\(^{[21-23]}\). Particularly, adefovir is considered to

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have high potential for nephrotoxicity and tenofovir has been associated with this risk. In our study, telbivudine was associated with improvement in eGFR from baseline to week 156 compared to the increasing deterioration over time with tenofovir. The finding of improvement in eGFR with telbivudine treatment was consistent with that reported in previous studies where telbivudine significantly improved while adeovir and lamivudine worsened renal function. CHB patients with impaired renal function at baseline have also shown an eGFR improvement after 1 year and 2 years of treatment with telbivudine. Similar results for telbivudine have also been reported in patients with cirrhosis, patients with compensated cirrhosis, or patients with no cirrhosis. These findings imply that telbivudine may offer benefit in patients known or at risk of renal impairment. Although telbivudine improves renal function, the mechanism of this renal protective effect remains to be determined.

The main limitations of the study are related to its design (open-label) and the relatively small sample size.

In conclusion, this study was the first prospective, randomised, 2-arm, open-label, non-inferiority study in hepatitis B e antigen (HBeAg)-negative chronic hepatitis B (CHB) patients that compared telbivudine and tenofovir administered as per the roadmap concept. The safety of the combination of telbivudine and tenofovir, for which limited data are currently available, was also evaluated.

**APPLICATIONS**

Efficacy was shown for both telbivudine-roadmap and tenofovir-roadmap regimens in HBeAg-negative CHB patients over 156 wk. Both treatments showed acceptable safety profiles. In addition, the telbivudine arm was associated with renal improvement.

**PEER-REVIEW**

This is an extensive randomised study to compare the roadmap treatment strategy between telbivudine and tenofovir in patients with HBeAg-negative CHB patients. As antiviral treatment may be life-long, renal protection becomes an important consideration. The current manuscript should be of benefit to the hepatologists and liver transplantation specialists worldwide.

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