**Name of Journal: *World Journal of Hepatology***

**ESPS Manuscript NO: 25600**

**Manuscript Type: ORIGINAL ARTICLE**

***Randomized Clinical Trial***

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

Krastev Z *et al*. Telbivudine roadmap approach in CHB patients

**Zahari Krastev, Diana Petrova, Iskren Kotzev, Mustafa Kemal Celen, Kamal Hamed, Richa Chandra**

**Zahari Krastev,** Clinic of Gastroenterology, St. Ivan Rilsky University Hospital, Medical University, Sofia 1606, Bulgaria

**Diana Petrova,** Department of Gastroenterology, University Hospital Alexandrovska, Sofia 1431, Bulgaria

**Iskren Kotzev,**Clinic of Hepatogastroenterology, University Hospital St Marina, Varna 9010, Bulgaria

**Celen Mustafa Kemal,**Dicle University Infectious Disease Clinic, 21280 Diyarbakir, Turkey

**Kamal Hamed, Richa Chandra,** Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936, United States

**Author contributions:** All authors were involved in study conduct, data interpretation, and defining the content for the manuscript; all authors had full access to data in the study, discussed the results, critically reviewed the draft manuscript and agreed on the final version.

**Institutional review board statement:** The study received approval from the Ethik-Kommission der Medizinischen Universität Wien und des Allgemeinen Krankenhauses der Stadt in Austria; Ethics Committee for Multicentre Trials in Bulgaria; RF MoHSD, Department of State Regulation of Circulation of Medicines, Ethics Council in Russia; National Ethics Committee for Clinical Trials in Greece; Comitato Etico Azienda Ospedaliera Universitaria Policlinico P. Giaccone in Italy; Institut Municipal D’Investigació mèdica in Spain; Ethik-Kommission der Albert-Ludwigs-Universität Freiburg in Germany; and Ege University Medical Faculty Clinical Researches Ethical Committee in Turkey.

**Informed consent statement:** This study was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines. Written informed consent was obtained from each patient before enrolment.

**Conflict-of-interest statement:** Krastev Z received fees for serving as a member of advisory board of Gilead, as well as research funding from Receptos, Centocor, Millennium Pharmaceuticals, Gilead, Abbvie, MSD, GSK, Roche, Novartis, Johnson and Johnson, Idenix, Norgine, Applied Clinical Pharmacology Services, Comac Medical, and Schwabe; Petrova D received research funding from Centocor, Gilead, GSK, Roche, Novartis, Johnson and Johnson, Idenix, Norgine, and Aventis; Kotzev I received lecture fees from Novartis; Kemal CM has nothing to declare; Hamed K and Chandra R are employees of Novartis Pharmaceuticals Corporation.

**Data sharing statement:** No data were created so no data are available.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Unsolicited manuscript

**Correspondence to: Richa Chandra, MD,** Global Program Medical **Director**, Novartis Pharmaceuticals Corporation, 1 Health Plaza, East Hanover, NJ 07936, United States. [richa.chandra@novartis.com](mailto:richa.chandra@novartis.com)

**Telephone:** +1-862-7781371

**Fax:** +1-973-7817153

**Received:** March 16, 2016

**Peer-review started:** March 18, 2016

**First decision:** April 19, 2016

**Revised:** May 6, 2016

**Accepted:** July 14, 2016

**Article in press:**

**Published online:**

**Abstract**

**AIM:** To make efficacy and safety comparison of telbivudine-raodmap 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. The primary efficacy endpoint was the rate of patients achieving 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, and alanine aminotransferase normalization 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, with over 92% of patients in each treatment arm achieving HBV DNA level < 300 copies/mL at week 52. Both arms were similar in terms of key secondary efficacy variables. The percentage of patients achieving HBV DNA < 300 copies/mL was similar in the telbivudine and tenofovir arms at week 104 (72.6% and 74.4%, respectively). Over 82% of patients in both arms achieved ALT normalization at week 52, and this percentage remained high at week 104 in the telbivudine arm (73.5%) as compared to the tenofovir arm (64.1%). Both treaments showed a good safety profile. 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 104 wk. Telbivudine arm was associated with renal improvement.

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

**© The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** This was the first prospective, randomised, non-inferiority study in HBeAg-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 104-wk treatment period. Non-inferiority of telbivudine arm to tenofovir arm was demonstrated at week 52, with over 92% of patients in each treatment arm achieving hepatitis B virus DNA level < 300 copies/mL. Both treaments showed a good safety profile. Moreover, telbivudine showed an improvement in estimated glomerular filtration rate from baseline.

Krastev Z, Petrova D, Kotzev I, Kemal CM, Hamed K, Richa Chandra. Telbivudine *vs* tenofovir in hepatitis B e antigen-negative chronic hepatitis B patients: Optima roadmap study. *World J Hepatol* 2016; In press

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](#_ENREF_1)]. 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](#_ENREF_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](#_ENREF_5),[6](#_ENREF_6)].

Early virologic response has been used as a strategy to predict better outcomes and to reduce the risk of antiviral resistance[[7](#_ENREF_7),[8](#_ENREF_8)]. As previously reported[[9-11](#_ENREF_9)], the roadmap concept uses early virologic responses at week 24 to individualize ongoing management in CHB patients. Patients with a complete response at week 24 can remain on their initial therapy and a second drug is added for those with an inadequate virologic response. This strategy is applicable mainly in patients receiving NA with low genetic barrier to resistance (clevudine, emtricitabine, lamivudine, telbivudine)[[11](#_ENREF_11)]. As such, response-guided treatment optimization strategy with telbivudine based on the roadmap concept can improve the clinical outcomes of patients with suboptimal antiviral response[[10](#_ENREF_10),[12-14](#_ENREF_12)].

The aim of this study, OPTIMA, was to assess the efficacy and safety of telbivudine and tenofovir regimens, when administered using the roadmap concept, in hepatitis B e antigen (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 daily) or tenofovir arm (300 mg daily) (Figure 1). Randomisation was stratified by the screening HBV DNA level (< 7 log10 copies/mL or ≥ 7 log10 copies/mL) and alanine aminotransferase (ALT) level (< 3 × ULN or ≥ 3 × upper limit of normal (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*

Eligible patients were male or female ≥ 18 years of age, with detectable hepatitis B surface antigen (HBsAg) ≥ 6 mo, HBeAg-negative at the screening visit with positive hepatitis B e antibody, available liver histology report within 12 mo before screening compatible with CHB, 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).

*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 week 104 and HBV DNA < 169 copies/mL (29 IU/mL) (low limit of detection) at weeks 24, 52, and 104; change from baseline in HBV DNA; ALT normalization at weeks 52 and 104; HBsAg loss and HBsAg seroconversion; virologic breakthrough (VB); and emergence of resistance. VB was defined as an increase of HBV DNA by at least 1 log10 copies/mL (or 1 log10 IU/mL) above nadir on 2 consecutive visits within a 4-wk interval, or at the last on-treatment visit. 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 and 104.

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, graded laboratory abnormalities, and standard 12-lead electrocardiogram (ECG). Estimated glomerular filtration rate (eGFR), calculated by the modification of diet in renal disease (MDRD) formula was recorded. AEs of special interest (muscle events and creatine phosphokinase (CPK) elevations) 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, 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 have at least one post-baseline assessment of serum HBV DNA. The roadmap intent-to-treat (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 per-protocol population consisted of all patients in the ITT population who had no major protocol deviations. The primary analysis population for efficacy was the rITT population.

RESULTS

*Patient demographics and clinical characteristics*

A total of 241 patients (121 in the telbivudine arm and 120 in the tenofovir arm) were randomised in this study. A total of 20 (16.5%) patients in the telbivudine arm and 11 (9.2%) patients in the tenofovir arm discontinued prematurely from the study. The most common reasons for discontinuation in the telbivudine arm were consent withdrawal (*n* = 6), lost to follow-up (*n* = 5) and administrative reasons (*n* = 4). In the tenofovir arm, the most common reasons for discontinuation were AEs (*n* = 4) and lost to follow-up (*n* = 4).

Major protocol deviations were reported in 16 (13.2%) patients in the telbivudine arm and 9 (7.5%) 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, patients with a positive HBeAg result, and patients not completing 3 wk of treatment before the third visit.

The safety population comprised 120 patients in each of the telbivudine and tenofovir 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 rITT 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 103 (85.1%) patients in the telbivudine arm and 113 (94.2%) patients in the tenofovir arm. A total of 19 patients (14 in the telbivudine arm and 5 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.

Treatment arms were balanced with respect to demographics and baseline characteristics, with no clinically meaningful differences between the telbivudine and tenofovir arms (Table 1).

***Primary efficacy endpoint***

Virologic response (HBV DNA < 300 copies/mL) at week 52 was achieved in 92.0% and 94.2% of patients in the telbivudine and tenofovir arms, respectively (Figure 2A). The primary analysis (using missing data as failure) 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 -8.7% (above the non-inferiority margin of -10%) (Table 2).

Similar results were found in the per-protocol population (96.8% and 99.0% of patients in the telbivudine and tenofovir arms, respectively, lower bound of the 95% CI being -6.2% for the difference between the 2 treatment arms).

***Secondary efficacy endpoints***

**Virologic responses:** Percentage of patients achieving HBV DNA < 300 copies/mL (51 IU/mL) at week 104, and by baseline viral load at weeks 52 and 104 in the rITT population: The percentage of patients achieving HBV DNA < 300 copies/mL was similar in the telbivudine and tenofovir arms at week 104 (72.6% and 74.4%, respectively) (Figure 2A).

In patients with lower baseline viral load (HBV DNA level < 7 log10 copies/mL), telbivudine and tenofovir regimens were similar in terms of viral load reduction, with over 93% of patients achieving HBV DNA levels < 300 copies/mL at week 52 and over 70% at week 104 (Figure 2). The proportion of patients in each arm with higher baseline viral load (≥ 7 log10 copies/mL) was relatively small to make any meaningful comparison.

Change from baseline in HBV DNA levels from week 24 to Week 104 in the rITT population: A statistically significant (*P* < 0.0001) reduction in HBV DNA levels *vs* baseline was achieved in both treatment arms at week 24 and was sustained through week 104 (Table 2).

Intensification with tenofovir or telbivudine for HBV DNA < 300 copies/mL at week 104 in the rITT population: A greater number of patients in the telbivudine arm required add-on therapy compared to the tenofovir arm (34 patients in the telbivudine arm including 22 patients requiring add on therapy at week 24 and 12 requiring add-on therapy post week 24, *vs* 11 patients in the tenofovir arm, all requiring add-on therapy at week 24).

The proportion of patients in the telbivudine arm achieving HBV DNA < 300 copies/mL at week 104 was greater in those who received tenofovir add-on therapy (81%, 17/21 patients) than patients who received telbivudine alone (70.7%, 65/92 patients) (Figure 3A).

The proportion of patients in the tenofovir arm achieving HBV DNA < 300 copies/mL at week 104 was greater in those who received telbivudine add-on therapy (81.8%, 9/11 patients) than patients who received tenofovir alone (73.6%, 78/106 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).

Intensification with tenofovir or telbivudine for HBV DNA < 169 copies/mL at week 104 in the rITT population: 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 10.3 and 8.2 percentage points greater, respectively, than patients who received monotherapy, although the numbers of patients who received add-on therapy were small(Figure 3).

***Biochemical response***

**ALT normalization 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 normalization at week 52 that was sustained up until week 104 (73.5% and 64.1% in the telbivudine and tenofovir arms, respectively) (Figure 4).

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

**Intensification with tenofovir or telbivudine for ALT normalization at week 104 in the rITT population:** The proportion of patients who achieved ALT nornalization was higher in patients who recevived add-on therapy (Figure 3).

**HBsAg loss and HBsAg seroconversion in the rITT population:** HBsAg loss and HBsAg seroconversion were not observed in any patient from either treatment arm at weeks 52 or 104. Telbivudine treatment progressively reduced serum HBsAg levels (mean ± SD) from baseline (-0.116 ± 0.581 log10 IU/mL at week 52 and -0.180 ± 0.632 log10 IU/mL at week 104. In contrast, no change was reported in quantitative HBsAg during therapy with tenofovir (-0.038 ± 0.349 log10 IU/mL at week 52 and -0.030 ± 0.385 log10 IU/mL at week 104).

**Patients experiencing virologic breakthrough and emergence of resistance in the rITT population:** At week 104, low rates of VB (6 (5.3%) patients in the telbivudine arm and 1 (0.9%) patient in the tenofovir arm) were observed. Emergence of resistance was reported in 8 (7.1%) patients in the telbivudine arm 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 both arms [11 (9.2%) patients]. One patient in the tenofovir arm reported drug-related SAEs (moderately increased blood 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 4 patients in the tenofovir arm discontinued due to AEs, which were unrelated to the study drugs. Most adverse events 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 to the tenofovir arm. The most frequent (≥ 5%) drug-related AEs reported in both arms are described in Table 3. Increased blood CPK levels [in 27 (22.5%) patients] and nausea [in 7 (5.8%) patients] were the drug-related AEs that were observed more frequently in the telbivudine arm compared to the tenofovir arm [15 (12.5%) patients and 2 (1.7%) patients, respectively]. AEs of special interest were observed in 41 (34.2%) patients in the telbivudine arm and 27 (22.5%) patients in the tenofovir arm. Elevated blood CPK and myalgia were the most commonly reported AEs in the telbivudine arm, and elevated blood CPK and ALT were 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, except 1 case in the tenofovir arm (not resolved at week 120 and no post week 120 CPK results were available for this patient) (Table 3).

Telbivudine monotherapy was associated with a significant improvement in eGFR as compared with tenofovir monotherapy. At week 24, the telbivudine monotherapy showed a statistically significant (*P* = 0.0374) improvement from baseline in eGFR compared to worsening with tenofovir monotherapy, with least squares mean percentage changes from baseline of 2.92% *vs* -1.14%, respectively. Further improvement in eGFR with telbivudine monotherapy was observed at week 52 (5.07% *vs* -2.58% with tenofovir, *P* = 0.0056), which persisted at week 104 (5.07% *vs* -4.94%, *P* < 0.0001, respectively) (Figure 5).

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

DISCUSSION

NAs given as a single daily oral dose are considered the mainstay of CHB treatment[[15](#_ENREF_15)]. In clinical practice, achieving optimal efficacy with a low emergence of drug resistance remains a challenge[[10](#_ENREF_10)]. The roadmap concept utilizing add-on therapy 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[[16](#_ENREF_16)], early detection of virologic response may be useful 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[[17](#_ENREF_17)]. These data were consistent with an earlier study comparing telbivudine with lamivudine[[16](#_ENREF_16)].

In the real world, use of the roadmap concept may offer several advantages such as identifying patients with suboptimal responses to initiate an appropriate change in therapy[[11](#_ENREF_11),[12](#_ENREF_12)], and to provide clinicians individualized treatment decisions[[5](#_ENREF_5)]. Although emergence of resistance had been identified as an issue for HBeAg-negative CHB patients treated with telbivudine monotherapy[[16](#_ENREF_16),[18](#_ENREF_18)], the data from our study suggest that this may not be much of an issue if telbivudine is administered using the roadmap concept. Moreover, despite a somewhat higher percentage of patients requiring add-on therapy in the telbivudine arm, the overall efficacy profile of the 2 roadmap concept strategy arms was comparable, as assessed by the percentages of patients achieving HBV DNA levels < 300 or < 169 copies/mL, and ALT normalization at weeks 52 and 104.

Overall, both treatments based on the roadmap concept were well tolerated over the 104-wk treatment period in HBeAg-negative patients. Although myalgia and elevated blood CPK levels were reported in higher number of patients in the telbivudine arm, the rates were consistent with the findings reported earlier in the literature[[13](#_ENREF_13),[14](#_ENREF_14),[16](#_ENREF_16),[19](#_ENREF_19)]. It is recommended that serum CPK levels should be monitored closely during treatment with telbivudine[[20](#_ENREF_20)].

Renal safety issues with oral NAs have been well-documented[[21-23](#_ENREF_21)]. Particularly, adefovir is considered to have high potential for nephrotoxicity[[24](#_ENREF_24)]. In our study, telbivudine was associated with improvement in eGFR from baseline to week 104 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 adefovir and lamivudine worsened renal function[[25](#_ENREF_25),[26](#_ENREF_26)]. In another study, the authors showed that there was no decrease in eGFR in CHB patients after 1 year of treatment with telbivudine monotherapy or combination therapy with tenofovir[[13](#_ENREF_13)]. CHB patients with impaired renal function at baseline have also shown an eGFR improvement after 1 year[[27](#_ENREF_27)], and 2 years of treatment with telbivudine[[12](#_ENREF_12),[28](#_ENREF_28)]. Similar results for telbivudine have also been reported in liver transplant recipients for HBV cirrhosis[[29](#_ENREF_29)], patients with compensated cirrhosis[[30](#_ENREF_30)], or patients with no cirrhosis[[31](#_ENREF_31)]. These findings imply that telbivudine may offer benefit in patients with known or at risk of renal impairment. Although telbivudine improves renal function, the mechanism of this renal protective effect remains to be determined[[32](#_ENREF_32)]. One study demonstrated that independent risk factors including gender, age, and eGFR at baseline were strong predictors for ≥ 20% decrease in eGFR[[33](#_ENREF_33)].

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, comparative study of telbivudine-roadmap *vs* tenofovir-roadmap concept in HBeAg-negative patients with CHB. Both treatments based on the roadmap concept were effective over the 104-wk treatment period. Moreover, telbivudine showed an improvement in eGFR from baseline while a deterioriaton was observed with tenofovir; this could be an important consideration for long term therapy in CHB patients especially in those with a high risk for renal impairment.

ACKNOWLEDGEMENTS

The authors acknowledge the work of the OPTIMA investigators and participating institutions located in various countries. The investigators included Peter Ferenci and Wolfgang Vogel (Austria); Rozalina Balabanska, Jordan Genov, and Krum Katzarov (Bulgaria); Thomas Berg, Peter Buggisch, Heinz Hartmann, Hartwig Klinker, Jens Rasenack, Hans Wedemeyer, and Stefan Zeuzem (Germany); Evangelos Akriviadis, Alexandra Alexopoulou, Ioannis Elefsiniotis, and Konstantinos Mimidis (Greece); Evangelista Sagnelli (Italy); Djamal Abdurakhmanov, Pavel Bogomolov, Vladimir Chulanov, Marina Maevskaya, Maria Matsievich, Igor Nikitin, Olga Znoiko, and Konstantin Zhdanov (Russia); Maria Buti Ferret, Jose Luis Calleja, Albert Pardo, and Ricard Sola Lamoglia (Spain); Ulus Akarca, Iftihar Koksal, and Fehmi Tabak (Turkey). The authors would like to thank Krassimir Antonov, Deian Jelev, Lyudmila Mateva, and Dimitar Popov (Bulgaria) for their technical assistance.

Medical writing support was provided by Farid Khalfi (Novartis Ireland Ltd., Dublin, Ireland).

**COMMENTS**

***Background***

Hepatitis B virus (HBV) infection is the major cause of chronic hepatitis worldwide. Emergence of resistance due to prolonged nucleos(t)ide analogue use or incomplete suppression of HBV still remains an important concern. Therefore, early virologic response at week 24 of therapy has been used as a strategy to predict better outcomes and to reduce the risk of antiviral resistance.

***Research frontiers***

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.

***Innovations and breakthroughs***

This was the first prospective, randomised, 2-arm, open-label, non-inferiority study in 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 chronic hepatitis B patients over 104 wk. Both treaments showed a good safety profile. In addition, 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.

**REFERENCES**

1 **Schweitzer A**, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *Lancet* 2015; **386**: 1546-1555 [PMID: 26231459 DOI: 10.1016/s0140-6736(15)61412-x]

2 **Tang CM**, Yau TO, Yu J. Management of chronic hepatitis B infection: current treatment guidelines, challenges, and new developments. *World J Gastroenterol* 2014; **20**: 6262-6278 [PMID: 24876747 DOI: 10.3748/wjg.v20.i20.6262]

3 **WHO**. Hepatitis B Fact Sheet No. 204. [updated 2015 Jul]. Available from: URL: http//www.who.int/mediacentre/factsheets/fs204/en/

4 **Zoulim F**, Locarnini S. Optimal management of chronic hepatitis B patients with treatment failure and antiviral drug resistance. *Liver Int* 2013; **33** Suppl 1: 116-124 [PMID: 23286855 DOI: 10.1111/liv.12069]

5 **Gu EL**, Yu YQ, Wang JL, Ji YY, Ma XY, Xie Q, Pan HY, Wu SM, Li J, Chen CW, Xu XW, Wang YE, Yao GB, Wang H, Zhang WH. Response-guided treatment of cirrhotic chronic hepatitis B patients: multicenter prospective study. *World J Gastroenterol* 2015; **21**: 653-660 [PMID: 25605989 DOI: 10.3748/wjg.v21.i2.653]

6 **Ryu HJ**, Lee JM, Ahn SH, Kim DY, Lee MH, Han KH, Chon CY, Park JY. Efficacy of adefovir add-on lamivudine rescue therapy compared with switching to entecavir monotherapy in patients with lamivudine-resistant chronic hepatitis B. *J Med Virol* 2010; **82**: 1835-1842 [PMID: 20872709 DOI: 10.1002/jmv.21898]

7 **Yang YJ**, Shim JH, Kim KM, Lim YS, Lee HC. Assessment of current criteria for primary nonresponse in chronic hepatitis B patients receiving entecavir therapy. *Hepatology* 2014; **59**: 1303-1310 [PMID: 24170683 DOI: 10.1002/hep.26910]

8 **Shin JW**, Jung SW, Park BR, Kim CJ, Eum JB, Kim BG, Du Jeong I, Bang SJ, Park NH. HBV DNA level at 24 weeks is the best predictor of virological response to adefovir add-on therapy in patients with lamivudine resistance. *Antivir Ther* 2012; **17**: 387-394 [PMID: 22293395 DOI: 10.3851/imp1945]

9 **Lo AO**, Wong GL. Current developments in nucleoside/nucleotide analogues for hepatitis B. *Expert Rev Gastroenterol Hepatol* 2014; **8**: 607-622 [PMID: 24787673 DOI: 10.1586/17474124.2014.909724]

10 **Yu HC**, Lin KH, Hsu PI, Tsay FW, Wang HM, Tsai TJ, Lai KH. Real-world application of the roadmap model in chronic hepatitis B patients with telbivudine therapy. *Clin Ther* 2013; **35**: 1386-1399 [PMID: 24054706 DOI: 10.1016/j.clinthera.2013.07.329]

11 **Gane EJ**. The Roadmap concept: using early on-treatment virologic responses to optimize long-term outcomes for patients with chronic hepatitis B. *Hepatol Int* 2008; **2**: 304-307 [PMID: 19669258 DOI: 10.1007/s12072-008-9083-0]

12 **Sun J**, Xie Q, Tan D, Ning Q, Niu J, Bai X, Fan R, Chen S, Cheng J, Yu Y, Wang H, Xu M, Shi G, Wan M, Chen X, Tang H, Sheng J, Dou X, Shi J, Ren H, Wang M, Zhang H, Gao Z, Chen C, Ma H, Jia J, Hou J. The 104-week efficacy and safety of telbivudine-based optimization strategy in chronic hepatitis B patients: a randomized, controlled study. *Hepatology* 2014; **59**: 1283-1292 [PMID: 24382690 DOI: 10.1002/hep.26885]

13 **Piratvisuth T**, Komolmit P, Tanwandee T, Sukeepaisarnjaroen W, Chan HL, Pessôa MG, Fassio E, Ono SK, Bessone F, Daruich J, Zeuzem S, Cheinquer H, Pathan R, Dong Y, Trylesinski A. 52-week efficacy and safety of telbivudine with conditional tenofovir intensification at week 24 in HBeAg-positive chronic hepatitis B. *PLoS One* 2013; **8**: e54279 [PMID: 23390496 DOI: 10.1371/journal.pone.0054279]

14 **Lai CL**, Gane E, Liaw YF, Hsu CW, Thongsawat S, Wang Y, Chen Y, Heathcote EJ, Rasenack J, Bzowej N, Naoumov NV, Di Bisceglie AM, Zeuzem S, Moon YM, Goodman Z, Chao G, Constance BF, Brown NA. Telbivudine versus lamivudine in patients with chronic hepatitis B. *N Engl J Med* 2007; **357**: 2576-2588 [PMID: 18094378 DOI: 10.1056/NEJMoa066422]

15 **Liu F**, Wang X, Wei F, Hu H, Zhang D, Hu P, Ren H. Efficacy and resistance in de novo combination lamivudine and adefovir dipivoxil therapy versus entecavir monotherapy for the treatment-naive patients with chronic hepatitis B: a meta-analysis. *Virol J* 2014; **11**: 59 [PMID: 24673792 DOI: 10.1186/1743-422x-11-59]

16 **Liaw YF**, Gane E, Leung N, Zeuzem S, Wang Y, Lai CL, Heathcote EJ, Manns M, Bzowej N, Niu J, Han SH, Hwang SG, Cakaloglu Y, Tong MJ, Papatheodoridis G, Chen Y, Brown NA, Albanis E, Galil K, Naoumov NV. 2-Year GLOBE trial results: telbivudine Is superior to lamivudine in patients with chronic hepatitis B. *Gastroenterology* 2009; **136**: 486-495 [PMID: 19027013 DOI: 10.1053/j.gastro.2008.10.026]

17 **Zeuzem S**, Gane E, Liaw YF, Lim SG, DiBisceglie A, Buti M, Chutaputti A, Rasenack J, Hou J, O'Brien C, Nguyen TT, Jia J, Poynard T, Belanger B, Bao W, Naoumov NV. Baseline characteristics and early on-treatment response predict the outcomes of 2 years of telbivudine treatment of chronic hepatitis B. *J Hepatol* 2009; **51**: 11-20 [PMID: 19345439 DOI: 10.1016/j.jhep.2008.12.019]

18 **Wang Y**, Thongsawat S, Gane EJ, Liaw YF, Jia J, Hou J, Chan HL, Papatheodoridis G, Wan M, Niu J, Bao W, Trylesinski A, Naoumov NV. Efficacy and safety of continuous 4-year telbivudine treatment in patients with chronic hepatitis B. *J Viral Hepat* 2013; **20**: e37-e46 [PMID: 23490388 DOI: 10.1111/jvh.12025]

19 **Seto WK**, Lai CL, Fung J, Wong DK, Yuen JC, Hung IF, Yuen MF. Significance of HBV DNA levels at 12 weeks of telbivudine treatment and the 3 years treatment outcome. *J Hepatol* 2011; **55**: 522-528 [PMID: 21147187 DOI: 10.1016/j.jhep.2010.11.018]

20 **Wang YH**, Wu BQ, Liu H. Continuous venovenous hemodiafiltration for hyperlactatemia caused by telbivudine in a patient with chronic hepatitis B: a case report and update review. *J Dig Dis* 2015; **16**: 164-167 [PMID: 25043654 DOI: 10.1111/1751-2980.12173]

21 **Chan HL**, Chen YC, Gane EJ, Sarin SK, Suh DJ, Piratvisuth T, Prabhakar B, Hwang SG, Choudhuri G, Safadi R, Tanwandee T, Chutaputti A, Yurdaydin C, Bao W, Avila C, Trylesinski A. Randomized clinical trial: efficacy and safety of telbivudine and lamivudine in treatment-naïve patients with HBV-related decompensated cirrhosis. *J Viral Hepat* 2012; **19**: 732-743 [PMID: 22967105 DOI: 10.1111/j.1365-2893.2012.01600.x]

22 **Liaw YF**, Raptopoulou-Gigi M, Cheinquer H, Sarin SK, Tanwandee T, Leung N, Peng CY, Myers RP, Brown RS, Jeffers L, Tsai N, Bialkowska J, Tang S, Beebe S, Cooney E. Efficacy and safety of entecavir versus adefovir in chronic hepatitis B patients with hepatic decompensation: a randomized, open-label study. *Hepatology* 2011; **54**: 91-100 [PMID: 21503940 DOI: 10.1002/hep.24361]

23 **Mallet V**, Schwarzinger M, Vallet-Pichard A, Fontaine H, Corouge M, Sogni P, Pol S. Effect of nucleoside and nucleotide analogues on renal function in patients with chronic hepatitis B virus monoinfection. *Clin Gastroenterol Hepatol* 2015; **13**: 1181-8.e1 [PMID: 25460550 DOI: 10.1016/j.cgh.2014.11.021]

24 **European Association For The Study Of The Liver**. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. *J Hepatol* 2012; **57**: 167-185 [PMID: 22436845 DOI: 10.1016/j.jhep.2012.02.010]

25 **Qi X**, Wang JY, Mao RC, Zhang JM. Impact of nucleos(t)ide analogues on the estimated glomerular filtration rate in patients with chronic hepatitis B: a prospective cohort study in China. *J Viral Hepat* 2015; **22**: 46-54 [PMID: 25402626 DOI: 10.1111/jvh.12229]

26 **Gane EJ**, Deray G, Liaw YF, Lim SG, Lai CL, Rasenack J, Wang Y, Papatheodoridis G, Di Bisceglie A, Buti M, Samuel D, Uddin A, Bosset S, Trylesinski A. Telbivudine improves renal function in patients with chronic hepatitis B. *Gastroenterology* 2014; **146**: 138-146.e5 [PMID: 24067879 DOI: 10.1053/j.gastro.2013.09.031]

27 **Tsai MC**, Chen CH, Hung CH, Lee CM, Chiu KW, Wang JH, Lu SN, Tseng PL, Chang KC, Yen YH, Hu TH. A comparison of efficacy and safety of 2-year telbivudine and entecavir treatment in patients with chronic hepatitis B: a match-control study. *Clin Microbiol Infect* 2014; **20**: O90-O100 [PMID: 23659493 DOI: 10.1111/1469-0691.12220]

28 **Lee M**, Oh S, Lee HJ, Yeum TS, Lee JH, Yu SJ, Kim HY, Yoon JH, Lee HS, Kim YJ. Telbivudine protects renal function in patients with chronic hepatitis B infection in conjunction with adefovir-based combination therapy. *J Viral Hepat* 2014; **21**: 873-881 [PMID: 24351112 DOI: 10.1111/jvh.12217]

29 **Cholongitas E**, Vasiliadis T, Goulis I, Fouzas I, Antoniadis N, Papanikolaou V, Akriviadis E. Telbivudine is associated with improvement of renal function in patients transplanted for HBV liver disease. *J Viral Hepat* 2015; **22**: 574-580 [PMID: 25385239 DOI: 10.1111/jvh.12362]

30 **Tsai MC**, Yu HC, Hung CH, Lee CM, Chiu KW, Lin MT, Tseng PL, Chang KC, Yen YH, Chen CH, Hu TH. Comparing the efficacy and clinical outcome of telbivudine and entecavir naïve patients with hepatitis B virus-related compensated cirrhosis. *J Gastroenterol Hepatol* 2014; **29**: 568-575 [PMID: 24716215]

31 **Amarapurkar DN**, Patel N. Increased eGFR with telbivudine in combination therapy of chronic hepatitis B infection. *Indian J Gastroenterol* 2014; **33**: 89-91 [PMID: 23512213 DOI: 10.1007/s12664-013-0325-2]

32 **Liang KH**, Chen YC, Hsu CW, Chang ML, Yeh CT. Decrease of serum Angiotensin converting enzyme levels upon telbivudine treatment for chronic hepatitis B virus infection and negative correlations between the enzyme levels and estimated glumerular filtration rates. *Hepat Mon* 2014; **14**: e15074 [PMID: 24596580 DOI: 10.5812/hepatmon.15074]

33 **Qi X**, Wang J, Chen L, Huang Y, Qin Y, Mao R, Zhang J. Impact of nucleos(t)ide analogue combination therapy on the estimated glomerular filtration rate in patients with chronic hepatitis B. *Medicine (Baltimore)* 2015; **94**: e646 [PMID: 25881837 DOI: 10.1097/md.0000000000000646]

**P-Reviewer:** Balaban YH, Chiu KW, Cholongitas EC, Chuang QL, Gong ZJ, Montasser MF, Romero MR, Wong GLH, Zhu Z **S-Editor:** Qiu S **L-Editor: E-Editor:**



**Figure 1 Study design.**

\\Phiedu-s2202.eu.novartis.net\khalffa1$\data\ALL FRANCHISES\EM brands\Kelly Rose\Figures\Final figures\Figure 2a Final.tif

A

\\Phiedu-s2202.eu.novartis.net\khalffa1$\data\ALL FRANCHISES\EM brands\Kelly Rose\Figures\Final figures\Figure 2b Final.tif

B

**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 log10 copies/mL), roadmap intent-to-treat population.**

\\Phiedu-s2202.eu.novartis.net\khalffa1$\data\ALL FRANCHISES\EM brands\Kelly Rose\Figures\Final figures\Figure 3a Final.tif

A

\\Phiedu-s2202.eu.novartis.net\khalffa1$\data\ALL FRANCHISES\EM brands\Kelly Rose\Figures\Final figures\Figure 3b Final.tif

B

**Figure 3 Intensification with tenofovir (A) or telbivudine (B), virologic response and aminotransferase normalization at week 104, roadmap intent-to-treat population.**

\\Phiedu-s2202.eu.novartis.net\khalffa1$\data\ALL FRANCHISES\EM brands\Kelly Rose\Figures\Final figures\Figure 4 Final.tif

**Figure 4 Proportions of patients achieving aminotransferase normalization, by visit and by baseline hepatitis B virus DNA levels (< 7 or ≥ 7 log10 copies/mL), roadmap intent-to-treat population.**

\\Phiedu-s2202.eu.novartis.net\khalffa1$\data\ALL FRANCHISES\EM brands\Kelly Rose\Figures\Final figures\Figure 5 Final.tif

**Figure 5 Changes in estimated glomerular filtration rate over time with telbivudine and tenofovir, safety population.**

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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Patients characteristics** | **Telbivudine**  **(*n* = 121)** | | **Tenofovir**  **(*n* = 120)** | |
| Age, mean (SD), years | 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 | (16.5-40.3 | 25.2 | (18.4-39.8) |
| Genotype, *n* (%)  A  B  C  D  G  Other  Unknown | 6  1  0  104  1  1  8 | (5.0%)  (0.8%)  (0.0%)  (86.0%)  (0.8%)  (0.8%)  (6.6%) | 2  0  1  110  0  0  7 | (1.7%)  (0.0%)  (0.8%)  (91.7%)  (0.0%)  (0.0%)  (5.8%) |
| HBV DNA, mean (SD), log10 copies/mL | 6.23 | (1.47) | 6.03 | (1.37) |
| Median (min-max) | 6.0 | (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) | 97.5 | (17.9) | 95.8 | (16.4) |
| Median (min-max) | 96.6 | (60.9-147.1) | 94.2 | (60.5-138.4) |

eGFR: Estimated glomerular filtration rate (MDRD formula).

**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), n (%) | | | | | | | | | -2.1% (-8.7%, 4.4%) |
| Week 52 (treating missing as failure1) | 104 | (92.0%) | | | 110 | | (94.2%) | |
| Change from baseline in HBV DNA levels (log10 copies/mL) by visit, mean (SD) | | | | | | | | | P-value |
| Week 24 | -4.001 | | (1.256) | -4.122 | | | | (1.165) | *P* < 0.00012 |
| Week 52 | -4.378 | | (1.461) | -4.299 | | | | (1.348) | *P* < 0.00012 |
| Week 104 | -4.303 | | (1.744) | -4.349 | | | | (1.382) | *P* < 0.00012 |

1For the “treating missing as failure” analysis, patients who came for their primary endpoint week 52 visit within the ± 7 d window but not on the exact designated day of the visit were treated as “missing data”; 2For both arms: Note: percentages and CI calculated using Mantel-Haenszel weighted estimates stratified by baseline HBV DNA and aminotransferase levels. HBV: Hepatitis B virus.

**Table 3 Summary of safety results, safety population**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Safety parameters** | **Telbivudine** | | | | | | **Tenofovir** | | | | | |
| **Monotherapy**  **(*n* = 98)**  **n (%)** | | **Intensification with tenofovir**  **(*n* = 22)**  **n (%)** | | **Overall**  **(*n* = 120)**  **n (%)** | | **Monotherapy**  **(*n* = 109)**  **n (%)** | | **Intensification with telbivudine**  **(*n* = 11)**  **n (%)** | | **Overall**  **(*n* = 120)**  **n (%)** | |
| Any AE | 65 | (66.3) | 16 | (72.7) | 81 | (67.5) | 75 | (68.8) | 8 | (72.7) | 83 | (69.2) |
| AE related to drug | 31 | (31.6) | 9 | (40.9) | 40 | (33.3) | 21 | (19.3) | 5 | (45.5) | 26 | (21.7) |
| AE leading to drug discontinuation | 2 | (2.0) | 0 | (0.0) | 2 | (1.7) | 4 | (3.7) | 0 | (0.0) | 4 | (3.3) |
| Any SAE | 6 | (6.1) | 5 | (22.7) | 11 | (9.2) | 9 | (8.3) | 2 | (18.2) | 11 | (9.2) |
| SAE related to drug | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (9.1) | 1 | (0.8) |
| AEs related to drug and occurring in ≥5% patients |  |  |  |  |  |  |  |  |  |  |  |  |
| Blood CPK increased | 21 | (21.4) | 6 | (27.3) | 27 | (22.5) | 13 | (11.9) | 2 | (18.2) | 15 | (12.5) |
| Nausea | 5 | (5.1) | 2 | (9.1) | 7 | (5.8) | 0 | (0.0) | 2 | (18.2) | 2 | (1.7) |
| Alanine aminotransferase increased | 1 | (1.0) | 0 | (0.0) | 1 | (0.8) | 3 | (2.8) | 1 | (9.1) | 4 | (3.3) |
| Death | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Any AE of special interest | 32 | (32.7) | 9 | (40.9) | 41 | (34.2) | 24 | (22.0) | 3 | (27.3) | 27 | (22.5) |
| AEs of special interest occurring in ≥ 1% patients |  |  |  |  |  |  |  |  |  |  |  |  |
| Blood CPK increased | 22 | (0.0) | 8 | (36.4) | 30 | (25.0) | 17 | (15.6) | 2 | (18.2) | 19 | (15.8) |
| Myalgia | 7 | (7.1) | 2 | (9.1) | 9 | (7.5) | 2 | (1.8) | 1 | (9.1) | 3 | (2.5) |
| Alanine aminotransferase increased | 4 | (4.1) | 0 | (0.0) | 4 | (3.3) | 5 | (4.6) | 1 | (9.1) | 6 | (5.0) |
| Proteinuria | 3 | (3.1) | 0 | (0.0) | 3 | (2.5) | 4 | (3.7) | 0 | (0.0) | 4 | (3.3) |
| Any patient with muscle event | 9 | (9.2) | 2 | (9.1) | 11 | (9.2) | 2 | (1.8) | 1 | (9.1) | 3 | (2.5) |
| Experiencing new-onset Grade 3/4 abnormal CPK within the study | 3 | (33.3) | 1 | (50.0) | 4 | (36.4) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| Experiencing new-onset Grade 1/2 abnormal CPK within the study | 4 | (44.4) | 1 | (50.0) | 5 | (45.5) | 1 | (50.0) | 1 | (100.0) | 2 | (66.7) |
| Any patient with new-onset Grade 3/4 CPK episode within the study | 17 | (17.3) | 2 | (9.1) | 19 | (15.8) | 3 | (2.8) | 2 | (18.2) | 5 | (4.2) |
| Episode not resolved | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (50.0) | 1 | (20.0) |

AE: Adverse event; CPK: Creatine phosphokinase; SAE: Serious adverse event.