Outcomes of Long-term Treatment of Chronic HBV Infection With Entecavir or Other Agents From a Randomized Trial in 24 Countries

Jin-Lin Hou,[*] Wei Zhao,[‡] Changhyeong Lee,[§] Hie-Won Hann,[‖] Cheng-Yuan Peng,[¶] Tawesak Tanwandee,[#] Viacheslav Morozov,[**] Hartwig Klinker,[‡‡] Jose D. Sollano,[§§] Adrian Streinu-Cercel,[‖‖] Hugo Cheinquer,[¶¶] Qing Xie,[##] Yu-Ming Wang,[***] Lai Wei,[‡‡‡] Ji-Dong Jia,[§§§] Guozhong Gong,[‖‖‖] Kwang-Hyub Han,[¶¶¶] Wukui Cao,[###] Mingliang Cheng,[****] Xiaoping Tang,[‡‡‡‡] Deming Tan,[§§§§] Hong Ren,[‖‖‖‖] Zhongping Duan,[¶¶¶¶] Hong Tang,[####] Zhiliang Gao,[*****] Shijun Chen,[‡‡‡‡‡] Shumei Lin,[§§§§§] Jifang Sheng,[‖‖‖‖‖] Chengwei Chen,[¶¶¶¶¶] Jia Shang,[#####] Tao Han,[******] Yanyan Ji,[‡‡‡‡‡‡] Junqi Niu,[§§§§§§] Jian Sun,[*] Yongpeng Chen,[*] Elizabeth L. Cooney,[‖‖‖‖‖‖] and Seng-Gee Lim[¶¶¶¶¶¶]

[*]*Department of Infectious Diseases, Institute of Hepatology, Nanfang Hospital, Southern Medical University, Guangzhou, China;* [‡]*Department of Infectious Diseases, 2nd Hospital Nanjing, Nanjing, China;* [§]*Daegu Catholic University Hospital, Daegu, Korea;* [‖]*Division of Gastroenterology and Hepatology, Department of Medicine, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania;* [¶]*Division of Hepatogastroenterology, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan;* [#]*Division of Gastroenterology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand;* [**]*LLC Medical Company "Hepatolog," Samara, Russian Federation;* [‡‡]*Department of Medicine II, Division of Hepatology, University of Würzburg Medical Center, Würzberg, Germany;* [§§]*Department of Medicine, Cardinal Santos Medical Center, Manila, Philippines;* [‖‖]*Department of Infectious Diseases I, Carol Davila University of Medicine and Pharmacy, National Institute for Infectious Diseases, "Prof. Dr. Matei Bals," Bucharest, Romania;* [¶¶]*Gastroenterology and Hepatology Division, Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil;* [##]*Department of Infectious Diseases, Shanghai Rui Jin Hospital, Shanghai, China;* [***]*Institute for Infectious Diseases, Southwest Hospital, Chongqing, China;* [‡‡‡]*Hepatology Department, Peking University People's Hospital, Beijing, China;* [§§§]*National Clinical Research Center for Digestive Disease, Beijing Friendship Hospital, Capitol Medical University, Beijing, China;* [‖‖‖]*Department of Infectious Disease, The Second Xiangya Hospital of Central South University, Changsha, China;* [¶¶¶]*Department of Internal Medicine, Institute of Gastroenterology and Yonsei Liver Center, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea;* [###]*Department of Infectious Diseases, Tianjin Second People's Hospital, Tianjin, China;* [****]*Department of Infectious Diseases, Affiliated Hospital of Guiyang Medical College, Guiyang, China;* [‡‡‡‡]*Department of Infectious Diseases, Guangzhou No. 8 People's Hospital, Guangzhou, China;* [§§§§]*Department of Infectious Diseases, Xiangya Hospital, Central South University, Changsha, China;* [‖‖‖‖]*Department of Infectious Diseases, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China;* [¶¶¶¶]*Beijing Institute of Hepatology, Beijing YouAn Hospital, Capital Medical University, Beijing, China;* [####]*Center of Infectious Diseases, West China Hospital, Sichuan University, Chengdu, China;* [*****]*Department of Infectious Diseases, The Third Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China;* [‡‡‡‡‡]*Hepatology Department, Jinan Infectious Disease Hospital, Jinan, China;* [§§§§§]*Department of Infectious Diseases, The First Affiliated Hospital of Xi'An Jiaotong University, Xi'An, China;* [‖‖‖‖‖]*Department of Infectious Diseases, The First Affiliated Hospital, Zhejiang University, Hangzhou, China;* [¶¶¶¶¶]*Hepatology Department, 85th Hospital of People's Liberation Army, Shanghai, China;* [#####]*Department of Infectious Diseases, Henan Provincial People's hospital, Zhengzhou, China;* [******]*Department of Hepatology and Gastroenterology, Tianjin Third Central Hospital, Tianjin, China;* [‡‡‡‡‡‡]*Hepatology Department, Shanghai Jing'an District Central Hospital, Shanghai, China;* [§§§§§§]*Hepatobiliary Medical Ward, The First Hospital of Jilin University, Changchun, China;* [‖‖‖‖‖‖]*Bristol-Myers Squibb, Inc, Wallingford, Connecticut;* [¶¶¶¶¶¶]*Division of Gastroenterology and Hepatology, National University Health System, National University of Singapore, Singapore*

BACKGROUND & AIMS: **Treatment of chronic hepatitis B virus (HBV) infection with entecavir suppresses virus replication and reduces disease progression, but could require life-long therapy. To investigate clinical outcome events and safety associated with long-term treatment with entecavir, we followed up patients treated with entecavir or another standard-of-care HBV nucleos(t)ide analogue for up to 10 years. We assessed long-term outcomes and relationships with virologic response.**

Abbreviations used in this paper: CHB, chronic hepatitis B virus infection; COE, clinical outcome event; EAC, event adjudication committee; ETV, entecavir; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; nuc, nucleos(t)ide analogue; REALM, Randomized, Observational Study of Entecavir to Assess Long-term Outcomes Associated with Nucleoside/Nucleotide Monotherapy for Patients with Chronic HBV Infection; SAE, serious adverse event.

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METHODS: **Patients with chronic HBV infection at 299 centers in Asia, Europe, and North and South America were assigned randomly to groups that received entecavir (n = 6216) or an investigator-selected nonentecavir HBV nucleos(t)ide analogue (n = 6162). Study participants were followed up for up to 10 years in hospital-based or community clinics. Key end points were time to adjudicated clinical outcome events and serious adverse events. In a substudy, we examined relationships between these events and virologic response.**

RESULTS: **There were no significant differences between groups in time to event assessments for primary end points including malignant neoplasms, liver-related HBV disease progression, and death. There were no differences between groups in the secondary end points of nonhepatocellular carcinoma malignant neoplasms and hepatocellular carcinoma. In a substudy of 5305 patients in China, virologic response, regardless of treatment group, was associated with a reduced risk of liver-related HBV disease progression (hazard ratio, 0.09; 95% CI, 0.038–0.221) and hepatocellular carcinoma (hazard ratio, 0.03; 95% CI, 0.009–0.113). Twelve patients given entecavir (0.2%) and 50 patients given nonentecavir drugs (0.8%) reported treatment-related serious adverse events.**

CONCLUSIONS: **In a randomized controlled trial of patients with chronic HBV infection, we associated entecavir therapy with a low rate of adverse events over 10 years of follow-up evaluation. Patients receiving entecavir vs another nucleos(t)ide analogue had comparable rates of liver- and non–liver-related clinical outcome events. Participants in a China cohort who maintained a virologic response, regardless of treatment group, had a reduced risk of HBV-related outcome events including hepatocellular carcinoma. ClinicalTrials.gov identifier no: NCT00388674.**

Keywords: HCC; CHB; Long-Term Follow-Up Study; Complication.

Chronic hepatitis B virus (HBV) infection (CHB) remains a significant public health concern, affecting an estimated 240 to 400 million individuals worldwide.[1,2] Nucleos(t)ide (nuc) analogues approved for CHB treatment can reduce HBV disease progression, reverse liver fibrosis, and reduce the risk of acquiring hepatocellular carcinoma (HCC), but have shown differing potencies, safety profiles, and barriers to HBV resistance.[3–5]

Entecavir (ETV), a third-generation HBV nuc with a high resistance barrier, is approved for treating adults with hepatitis B e antigen (HBeAg)-positive or HBeAg-negative CHB. Genotypic resistance and virologic breakthrough are rare in nuc-naive patients after 5 years of treatment with ETV,[6] and beneficial effects on HBV disease progression, including regression of fibrosis and cirrhosis, have been shown.[7,8]

No association between ETV and the risk of specific adverse events was shown with up to 5 years of therapy in randomized studies and long-term follow-up evaluation.[9] However, in 2-year preclinical studies, benign and malignant tumors involving lung, liver, and brain were observed in ETV-exposed mice and rats.[10] With the exception of lung tumors, which were limited to male mice, rodent tumors occurred only at ETV exposures significantly higher than those achieved in human beings with standard approved doses.

No malignancy signals were identified during 2 to 3 years of monitoring in clinical development studies, suggesting that rodent carcinogenicity findings may not be relevant to human beings. However, given this relatively short duration of follow-up evaluation compared with the extended timeframe over which many malignancies develop, a large long-term study of ETV therapy was initiated to assess the human relevance of rodent carcinogenicity findings.

The REALM study (Randomized, Observational Study of Entecavir to Assess Long-term Outcomes Associated with Nucleoside/Nucleotide Monotherapy for Patients with Chronic HBV Infection) prospectively assessed long-term clinical outcome events (COEs) and treatment-related serious adverse events (SAEs) in patients receiving up to 10 years of monotherapy with ETV or other standard-of-care HBV nucs. A substudy of participants enrolled at REALM study sites located in China compared COEs with serum levels of HBV DNA during treatment. With an anticipated enrollment of approximately 12,500 patients in 299 research centers, an independent event adjudication committee (EAC) was established to review and adjudicate investigator-reported COEs.

Methods

Study Design

Enrolled patients were adults with CHB and were considered eligible for monotherapy with ETV or another standard-of-care HBV nuc, regardless of HBeAg status, prior treatment experience, liver disease stage, or hepatitis C or D co-infection. Patients were ineligible if co-infected with human immunodeficiency virus, had an expected liver transplant-free survival shorter than 1

year, a history of malignant neoplasm (except nonmelanoma skin cancers) or premalignancies including dysplastic liver nodule, prior ETV use, or intention to receive interferon-alfa monotherapy, HBV nuc combinations, or investigational HBV therapy. Historic information was collected at baseline pertaining to liver disease status (cirrhosis), HBeAg status, HBV genotype, chronic viral co-infections, and comorbidities. Because this study focused on safety outcomes, HBV DNA data were not collected during therapy except in China (see Data Collection, below).

Patients were assigned randomly (1:1) to receive ETV (0.5 or 1.0 mg once daily)[10] or another standard-of-care HBV nuc. The ETV dose was based on liver disease status and prior treatment experience, consistent with the product label. Randomization was conducted centrally by the sponsor without investigator or patient awareness, based on a block design (block size of 4, assigned within each country) and stratified by prior HBV nuc treatment experience. Comparator nucs were investigator-selected and limited to those available in the patient's country of residence. Concurrent dosing with interferon-alfa-2b or pegylated interferon-alfa-2a was allowed. After initiation of randomized therapy, HBV treatment could be modified at the investigators' discretion to add or switch nucs or terminate treatment. Follow-up evaluation was maintained regardless of therapeutic changes.

The study was conducted in accordance with Good Clinical Practice, following local regulations and ethical principles described in the Declaration of Helsinki. The study protocol received approval from an institutional review board or ethics committee at each site; oversight was provided by an independent data monitoring committee. All patients provided written informed consent. The authors had full access to the study data and reviewed and approved the final manuscript.

Data Collection

The 10-year follow-up period began after the first patient-initiated treatment. With full enrollment expected to take 3 years, 7 to 10 years of treatment and follow-up evaluation was anticipated for each patient. Follow-up visits occurred every 6 months, with 1 telephone contact between visits. Monitored COEs included non-HCC malignancies (all events per patient, excluding nonmelanoma skin cancers), HCC (first event per patient), non-HCC liver-related events of HBV disease progression (first event per patient, hereafter referenced as non-HCC HBV disease progression), and death (Supplementary Materials and Methods and Supplementary Table 1).

At each contact, patients were assessed for medical status, COEs, and treatment-related SAEs. In the China cohort, samples were collected for HBV DNA analysis at baseline, week 24, year 1, and then annually. Specific work-ups for COEs and SAEs were at the investigators' discretion; case reports were submitted to support EAC adjudication of each event. The EAC charter (Supplementary Materials and Methods and Supplementary Table 1) describes the EAC structure and the adjudication process.

What You Need to Know

Background

Treatment of chronic hepatitis B virus (HBV) infection with entecavir suppresses virus replication and reduces disease progression. However, maintaining efficacy could require life-long therapy. We investigated the long-term effects of entecavir therapy on outcomes and safety in a large, randomized, global study.

Findings

Rates of liver-related and non–liver-related outcome events were similar with entecavir vs other nucleos(t)ide analogues for up to 10 years of therapy. Maintained virologic response, regardless of treatment, was associated with a reduced risk of liver-related HBV disease progression and hepatocellular carcinoma.

Implications for patient care

These findings confirm the long-term safety of entecavir and its appropriateness for extended therapy of chronic HBV infection. Maintaining virologic response reduces the risk of adverse clinical outcome events.

Statistical Methods

The planned sample size of 12,500 patients would provide more than 85% power to detect clinically relevant relative risks of 1.4, 0.7, and 1.3 for non-HCC malignant neoplasms, HCC, and overall malignant neoplasms, respectively. The study also was powered (>85%) to detect decreased risk (≤0.7) for liver-related HBV disease progression and all-cause death. Power calculations were based on the log-rank test at an alfa level of 0.05 for each end point and assumed a 30% attrition rate.

The principal analysis population was all randomized patients who received 1 or more doses of study medication. Primary end points were as follows: (1) rates of overall malignant neoplasms (HCC plus non-HCC malignancies), (2) rates of all-cause death, and (3) rates of liver-related HBV disease progression (composite of non-HCC disease progression, HCC, and liver-related death). Secondary end points included rates of non-HCC malignant neoplasms, HCC, and liver-related death; non-HCC HBV disease progression was a post hoc exploratory end point. Treatment-related SAEs also were assessed.

The principal intention-to-treat analysis of time-to-adjudicated COEs used a Cox proportional hazards model stratified by geographic region and prior HBV nuc experience. Patients lost to follow-up evaluation were censored at their last contact date. Treatment relative risk for each primary end point was assessed using a hazard ratio, comparing treatment groups with a 2-sided 95.03% CI and nominal *P* value. The 95.03% CI was based on a 0.05 alfa level adjusted for 3 interim analyses. Primary end points were tested hierarchically as follows: (1) overall malignant neoplasm, (2) death, and (3) liver-related HBV disease progression. An end point test was considered significant if its nominal *P* value and those from all end points tested previously were less than 0.0497. Secondary and exploratory end points were assessed analogously with a hazard ratio and 95% CI, but no *P* value.

The as-treated covariate-adjusted sensitivity analysis of time-to-adjudicated COEs used a stratified Cox proportional hazards model with cumulative ETV exposure up to the time of event and additional baseline covariates (age, sex, race, historic cirrhosis status, cigarette smoking ever, alcohol drinking ever, and body mass index), providing the cumulative ETV exposure coefficient and corresponding 95% CI.

HBV DNA data in the China cohort were summarized descriptively; the study was not powered to support statistical comparison of virologic efficacy by treatment group. Virologic response was defined as a HBV DNA less than 50 IU/mL at 2 or more consecutive visits and maintained subsequently without virologic rebound. Virologic response rates were presented with Agresti–Coull 95% CIs. The relationship between HBV-related, EAC-adjudicated COEs and virologic response was assessed using a Cox proportional hazards model adjusted by time-to-virologic response and select baseline parameters. A hazard ratio (responder vs nonresponder) with a 2-sided 95% CI was used to assess relative risk separately by treatment group and for each COE. Time-to-event COE distributions were described by Kaplan–Meier plots by treatment group and virologic response status.

Results

Patients

A total of 12,522 patients were enrolled at 299 sites in 24 countries (Supplementary Materials and Methods and Supplementary Table 1) over approximately 3 years (2007–2009); 12,378 randomized patients initiated treatment with ETV (n = 6216) or a non-ETV nuc (n = 6162), with follow-up evaluation continuing until 2016. The study was completed by 72.1% and 64.8% of patients in the ETV and non-ETV groups, respectively (Supplementary Figure 1).

Overall, most patients were Asian men, naive to HBV nuc treatment, and noncirrhotic; 17% of those with cirrhosis had decompensated disease (Table 1). Cirrhosis prevalence was comparable in treatment-experienced (22.2%) and nuc-naive patients (19.3%). Most of the 566 patients with HBV genotype data had genotype B (26.5%) or C (41.7%) infection; less than 1% with available data were co-infected with hepatitis C virus (56 of 9075) or hepatitis D virus (69 of 4875). The most common therapies used in the non-ETV group were adefovir (71.7% of patients), telbivudine (10.7%), and lamivudine (7.2%) (Supplementary Table 2).

The China cohort comprised 5305 patients (ETV, n = 2659; non-ETV, n = 2646). The China cohort was slightly younger than the global cohort, with higher proportions of male, noncirrhotic, and HBeAg-positive patients (Table 1). The mean HBV DNA level was 6.48 $\log_{10}$ IU/mL. The most common therapies used in the non-ETV group of the China cohort were adefovir (91.3% of patients), lamivudine (5.1%), and telbivudine (2.0%).

Treatment

Patients remained on initial therapy for a mean of 86.1 months (ETV group) and 78.1 months (non-ETV group). Cross-over from ETV to a non-ETV regimen and vice versa was infrequent: 5.6% of ETV recipients switched to non-ETV regimens after a mean of 77.1 months, and 12.2% of non-ETV recipients switched to ETV-containing regimens after a mean of 48.0 months. Patients in the ETV group most frequently switched to tenofovir or adefovir; patients in the non-ETV group most frequently switched to ETV or ETV plus adefovir (Supplementary Figure 2).

Clinical Outcome Events and Serious Adverse Events

Rates of all types of EAC-adjudicated COEs were comparable between treatment groups (Table 2). Small differences between reported and adjudicated COEs were observed. The most common discrepancies between investigator-reported and EAC-adjudicated diagnoses related to causes of death and manifestations signifying HBV disease progression; differences primarily were owing to insufficient diagnostic data to support adjudication.

The principal time-to-adjudicated-COE analysis showed no significant differences between treatment groups for all COE end points (Table 3); nonsignificant differences between treatment groups were evident in time-to-event plots (Figure 1) and event rate tables (Supplementary Tables 3–6). In an assessment of relationships between ETV exposure and adjudicated event risk, coefficient estimates of cumulative ETV exposure were slightly negative for all COE end points, indicating that time on ETV had a modest protective effect on each end point (Supplementary Table 7).

HCC was the most common malignancy (Table 3), with a time-to-event profile similar to that of other COEs

Table 1. Demographic and Disease Characteristics

	All patients			China cohort	
	ETV (N = 6216)	Non-ETV (N = 6162)	Total (N = 12,378)	ETV (N = 2659)	Non-ETV (N = 2646)
Age, *y*					
Median	39.0	39.0	39.0	35.0	35.0
Minimum, maximum	16, 88	16, 86	16, 88	16, 70	16, 74
Sex, n (%)					
Men	4713 (75.8)	4672 (75.8)	9385 (75.8)	2148 (80.8)	2128 (80.4)
Race, n (%)					
Asian	5221 (84.0)	5201 (84.4)	10,422 (84.2)	2659 (100.0)	2646 (100.0)
White	819 (13.2)	780 (12.7)	1599 (12.9)	0	0
Black/African American	59 (0.9)	68 (1.1)	127 (1.0)	0	0
Other	117 (1.9)	113 (1.8)	230 (1.9)	0	0
Region/country, n (%)					
China	2659 (42.8)	2646 (42.9)	5305 (42.9)	2659 (100.0)	2646 (100.0)
Asia excluding China	2320 (37.3)	2304 (37.4)	4624 (37.4)	0	0
Europe	662 (10.6)	645 (10.5)	1307 (10.6)	0	0
North America	287 (4.6)	281 (4.6)	568 (4.6)	0	0
South America	288 (4.6)	286 (4.6)	574 (4.6)	0	0
HBV treatment experience, n (%)					
Naive	4016 (64.6)	3984 (64.7)	8000 (64.6)	1766 (66.4)	1760 (66.5)
Experienced	2200 (35.4)	2178 (35.3)	4378 (35.4)	893 (33.6)	886 (33.5)
Historic cirrhosis status, n (%)					
No cirrhosis	4956 (79.7)	4901 (79.5)	9857 (79.6)	2342 (88.1)	2339 (88.4)
Compensated cirrhosis	1044 (16.8)	1044 (16.9)	2088 (16.9)	256 (9.6)	252 (9.5)
Decompensated cirrhosis	216 (3.5)	217 (3.5)	433 (3.5)	61 (2.3)	55 (2.1)
Historic HBeAg status, n (%)					
Positive	3375 (54.3)	3252 (52.8)	6627 (53.5)	1752 (65.9)	1733 (65.5)
Negative	2438 (39.2)	2441 (39.6)	4879 (39.4)	862 (32.4)	846 (32.0)
Other	71 (1.1)	71 (1.2)	142 (1.1)	16 (0.6)	20 (0.8)
Unknown	332 (5.3)	397 (6.4)	729 (5.9)	29 (1.1)	47 (1.8)
Not reported	0	1 (<0.1)	1 (<0.1)	0	0
Historic HBeAb status, n (%)					
Positive	2184 (35.1)	2208 (35.8)	4392 (35.5)	712 (26.8)	712 (26.9)
Negative	3272 (52.6)	3167 (51.4)	6439 (52.0)	1875 (70.5)	1851 (70.0)
Other	75 (1.2)	77 (1.2)	152 (1.2)	16 (0.6)	21 (0.8)
Unknown	685 (11.0)	709 (11.5)	1394 (11.3)	56 (2.1)	62 (2.3)
Not reported	0	1 (<0.1)	1 (<0.1)	0	0
HBV DNA level, log_{10} *IU/mL*					
Mean (SD)	-	-	-	6.48 (1.81)	6.48 (1.78)
HBV DNA category, log_{10} *IU/mL*, n (%)					
<5	-	-	-	544 (20.5)	525 (19.8)
5 to <8	-	-	-	1531 (57.6)	1545 (58.4)
≥8	-	-	-	537 (20.2)	515 (19.5)
Not reported	-	-	-	47 (1.8)	61 (2.3)

ETV, entecavir; HBeAb, hepatitis B e antibody; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus.

(Figure 1*D*). The most common non-HCC malignancies were gastrointestinal, most often colorectal and gastric cancers (Supplementary Table 8). Adjudicated rates of non-HCC HBV disease progression, HCC, and death were approximately 5- to 11-fold higher in patients with vs without pre-existing cirrhosis (Supplementary Table 9). Rates of non-HCC malignant neoplasms were not significantly higher in patients with pre-existing cirrhosis. Treatment-related SAEs that were not protocol-defined COEs were reported in 12 ETV (0.2%) and 50 non-ETV (0.8%) recipients (Supplementary Table 10).

China Cohort Outcomes

Adjudicated COE rates were numerically lower than in the global population, likely owing to the younger median age of the China cohort, with no notable differences between treatment groups (Table 2). In both groups, the incidence of overall malignant neoplasms, HCC, liver-related HBV disease progression, and deaths were 10% higher or more in patients aged 55 years and older and in those with historic cirrhosis, compared with younger patients and those without cirrhosis, respectively (Supplementary Table 11).

Table 2. Investigator-Reported and EAC-Reviewed COEs

Patients with events, n (%)	All patients		China cohort	
	ETV (N = 6216)	Non-ETV (N = 6162)	ETV (N = 2659)	Non-ETV (N = 2646)
Reported and EAC-reviewed deaths	**240 (3.9)**	**264 (4.3)**	63 (2.4)	74 (2.8)
Adjudicated as death	238 (3.8)	264 (4.3)	62 (2.3)	74 (2.8)
Unable to adjudicate	2 (<0.1)	0		
Reported HCC events	**289 (4.6)**	**316 (5.1)**		
EAC reviewed[a]	290 (4.7)	316 (5.1)	91 (3.4)	104 (3.9)
Adjudicated as HCC	241 (3.9)	263 (4.3)	69 (2.6)	87 (3.3)
Pre-existing event	0	1 (<0.1)		
Unable to adjudicate	51 (0.8)	53 (0.9)		
Reported and EAC-reviewed non-HCC malignant neoplasm events	**109 (1.8)**	**91 (1.5)**	26 (1.0)	20 (0.8)
Adjudicated as non-HCC malignant neoplasm	95 (1.5)	81 (1.3)	22 (0.8)	18 (0.7)
Adjudicated as alternative event	1 (<0.1)[b]	0		
Unable to adjudicate	13 (0.2)	10 (0.2)		
Reported non-HCC events of HBV disease progression	**208 (3.3)**	**207 (3.4)**		
EAC reviewed	202 (3.2)[c]	202 (3.3)[d]	51 (1.9)	57 (2.2)
Adjudicated as non-HCC HBV disease progression	137 (2.2)	146 (2.4)	36 (1.4)	44 (1.7)
Adjudicated with alternate diagnosis	0	3 (<0.1)		
Pre-existing event	21 (0.3)	8 (0.1)		
Unable to adjudicate	44 (0.7)	48 (0.8)		

NOTE. Row headers in bold type identify the four major categories of COE.
COE, clinical outcome event; EAC, event adjudication committee; ETV, entecavir; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.
[a]One ETV recipient had an EAC-reviewed event that was not investigator-reported. Three patients (ETV, n = 2; non-ETV, n = 1) erroneously had the same diagnosis reported both as unable to adjudicate and as adjudicated.
[b]Adjudicated as benign endometrial hyperplasia.
[c]The 6-patient difference is the result of 7 patients with investigator-reported events that were not EAC reviewed, and 1 patient with an EAC-reviewed event that was not investigator-reported.
[d]The 5-patient difference is the result of 6 patients with investigator-reported events that were not EAC reviewed, and 1 patient with an EAC-reviewed event that was not investigator-reported.

HBV DNA levels decreased rapidly with treatment. The proportion of patients with HBV DNA levels less than 50 IU/mL was approximately 45% higher in the ETV group vs the non-ETV group at 24 weeks; subsequently, the difference favoring ETV persisted but decreased progressively (Figure 2). During the 10-year follow-up period, virologic response was confirmed and maintained in 79.7% and 60.8% of patients in the ETV and non-ETV groups, respectively; differences favoring ETV persisted regardless of prior treatment experience, HBV DNA category, or historic cirrhosis or HBeAg status. Correspondingly, rates of incomplete virologic suppression were significantly lower ($P < .001$) in the ETV group compared with the non-ETV group throughout the 10-

Table 3. Principal Analysis of Time-to-Adjudicated COEs

Patients with events, n	ETV (N = 6216)	Non-ETV (N = 6162)	Hazard ratio, ETV: non-ETV (CI)[a]	*P* value[b]
Primary end points				
Overall malignant neoplasm	331	337	0.93 (0.800–1.084)	.36
Death	238	264	0.85 (0.713–1.012)	.068
Liver-related HBV disease progression	350	375	0.89 (0.769–1.030)	.12
Secondary end points				
Non-HCC malignant neoplasm	95	81	1.10 (0.817–1.478)	–
HCC[c]	240	263	0.87 (0.727–1.032)	–
Liver-related death	46	48	0.91 (0.608–1.365)	–
Post hoc exploratory end point				
Non-HCC HBV disease progression	137	146	0.90 (0.712–1.135)	–

NOTE. Analyses were stratified by geographic region and prior HBV nucleoside/tide experience.
COE, clinical outcome event; ETV, entecavir; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.
[a]The 95.03% CI was used for primary end points, and the 95% CI was used for secondary and exploratory end points.
[b]In accordance with the statistical analysis plan, *P* values were determined only for primary end points.
[c]One patient had pretreatment HCC and therefore was excluded.

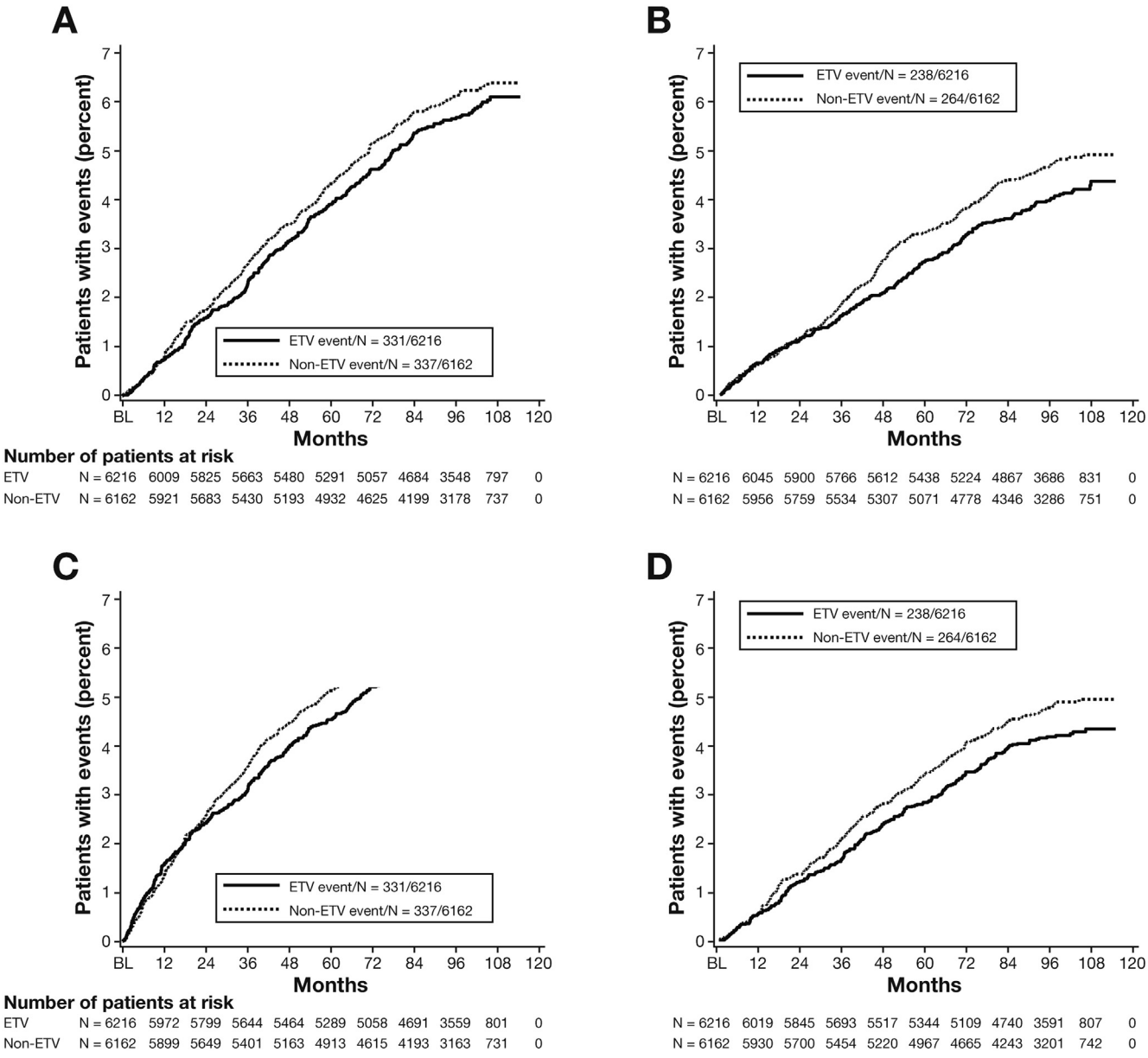

Figure 1. Time to adjudicated clinical outcome events. Kaplan–Meier plots show the proportions of patients in each treatment group who experienced the (*A*–*C*) adjudicated primary study end points or (*D*) hepatocellular carcinoma. (*A*) Overall malignant neoplasms; (*B*) all-cause death; (*C*) liver-related HBV disease progression; (*D*) hepatocellular carcinoma. ETV, entecavir; HBV, hepatitis B virus.

year follow-up period (Supplementary Table 12). However, within each treatment group, historic HBeAg-negative (vs positive) status and baseline HBV DNA level less than 5 $\log_{10}$ IU/mL (vs $\geq$8 $\log_{10}$ IU/mL) were associated with higher response rates.

When adjusted for response time and baseline covariates, virologic response was associated with a lower risk of liver-related HBV disease progression and HCC in both treatment groups (Supplementary Table 13). Similarly, Kaplan–Meier estimates of time-to-COEs showed lower estimates of COEs in virologic responders vs nonresponders in both groups (Figure 3). Overall, differences between responders and nonresponders were significant for liver-related HBV disease progression ($P = .0001$), non-HCC liver-related HBV disease progression ($P = .04$), HCC ($P < .0001$), and liver-related death ($P < .0001$).

Discussion

The efficacy and safety of ETV have been characterized in multiple studies involving different HBV disease cohorts.[7–9,11–14] To address preclinical findings of ETV-associated malignancies and to characterize the long-term risk-benefit profile of ETV, we prospectively compared monotherapy with ETV vs other standard-of-care HBV nucs to assess HBV-associated and HBV-unassociated COEs, including malignant neoplasms.

HBV nuc therapy can maintain viral suppression in most patients, with the potential to reverse liver fibrosis

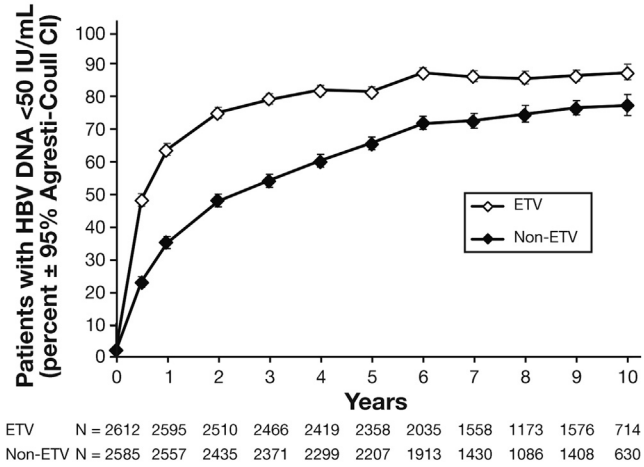

Figure 2. China cohort: hepatitis B virus (HBV) DNA level less than 50 IU/mL over time. The proportion of patients in each treatment group with a HBV DNA level less than 50 IU/mL, ± 95% Agresti-Coull CI, is shown from baseline to year 10. ETV, entecavir.

or cirrhosis and reduce the risk of HCC, but most previous studies were relatively small and/or with limited follow-up evaluation; only a few studies provided data beyond 5 years.[4,9,15,16] In contrast, the REALM study was a large prospective randomized trial to assess the long-term impact of HBV nuc monotherapy on HBV-related or HBV-unrelated clinical outcomes, applying independent event adjudication to ensure consistency and accuracy. The design provided the opportunity to assess relatively low-frequency COEs and those with long latency, such as malignant neoplasms.[17]

The principal analysis of time-to-adjudicated COEs showed that ETV treatment, compared with non-ETV, was not associated with an increased risk of malignant neoplasms, including HCC, non-HCC malignancies, and overall malignancies. Thus, ETV carcinogenicity findings in rodents were not predictive of any type of malignancy in this trial.[10] In both treatment groups, the most commonly reported malignancies aside from HCC were gastrointestinal, predominantly colorectal and gastric cancers, consistent with previous data in adults with CHB.[18,19]

COE rates were higher in patients with cirrhosis, consistent with previous findings.[20] Differences of 6- to 11-fold between patients with or without cirrhosis were observed for HCC, all-cause death, and non-HCC HBV disease progression; however, cirrhosis status had comparable effects on COE rates in both treatment groups. Because of the large cohort size and extended follow-up evaluation, this study provides an improved reference for HCC event rates in HBV nuc-treated patients with or without cirrhosis.

Malignancy rates in our study confirm the findings from a retrospective cohort study from Hong Kong that compared the relative risk of malignancies in patients treated (n = 4782) or not treated (n = 39,712) with HBV nucs.[19] After a mean 3.6 and 4.5 years in treated and untreated patients, respectively, 5.7% and 2.1% of patients experienced malignancies, 3.7% and 1.0% experienced HCC, and 2.7% and 1.3% experienced non-HCC malignancies. After propensity score weighting to control for confounding variables, treatment-related differences in event risks were insignificant. The incidences of malignancies in the ETV and non-ETV groups from our study are in line with data for nuc-treated patients in the Hong Kong study (3.9% and 4.3% vs 3.7% for HCC; 1.5% and 1.3% vs 2.7% for non-HCC). In both studies, HCC followed by gastrointestinal malignancies were the most frequent types of cancer. Our results for nononcology end points were similar to the malignancy findings. In the primary analysis of time-to-adjudicated COEs, ETV and non-ETV were associated with comparable rates of non-HCC HBV disease progression, liver-related death, or the composite end point of liver-related HBV disease progression. Treatment-related SAEs were uncommon, although numerically higher in the non-ETV group.

Our study establishes an improved standard regarding non-HCC HBV disease progression in nuc-treated patients. Relevant prior studies have been shorter and have varied regarding patient characteristics and/or definitions of HBV disease progression.[3,8,14,21] The Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer (REVEAL) long-term natural history study, conducted before the advent of HBV nucs, provides perspective for expected rates of HCC and non-HCC events of HBV disease progression in untreated patients.[22,23] However, direct comparisons of disease progression rates are limited by differences in patient populations, methodology, and evolving measures of disease progression.

The REALM China cohort afforded a unique opportunity to extend previous observations from natural history studies[22] and treatment studies[3,4,15,24] regarding relationships between virologic response and HBV-associated COEs. Although the proportion of patients with HBV DNA levels less than 50 IU/mL was 10% higher or more in the ETV group than in the non-ETV group at all time points, the study was not designed for statistical comparison between treatment groups of quantitative virologic responses and relationships with HBV disease progression. However, our results corroborate previous observations that virologic response, regardless of treatment type, correlates with an improved clinical course. In the time-to-event analysis, maintained virologic response was associated with a decreased risk of liver-related HBV disease progression and HCC in both treatment groups when adjusted by response time and baseline covariates. As predicted by previous studies, higher rates of virologic response were observed in both treatment groups in patients with lower baseline HBV DNA levels or HBeAg-negative disease and, in the ETV group, higher baseline serum alanine aminotransferase level.

However, in a recent Korean retrospective cohort study, HCC was reported in a higher proportion of

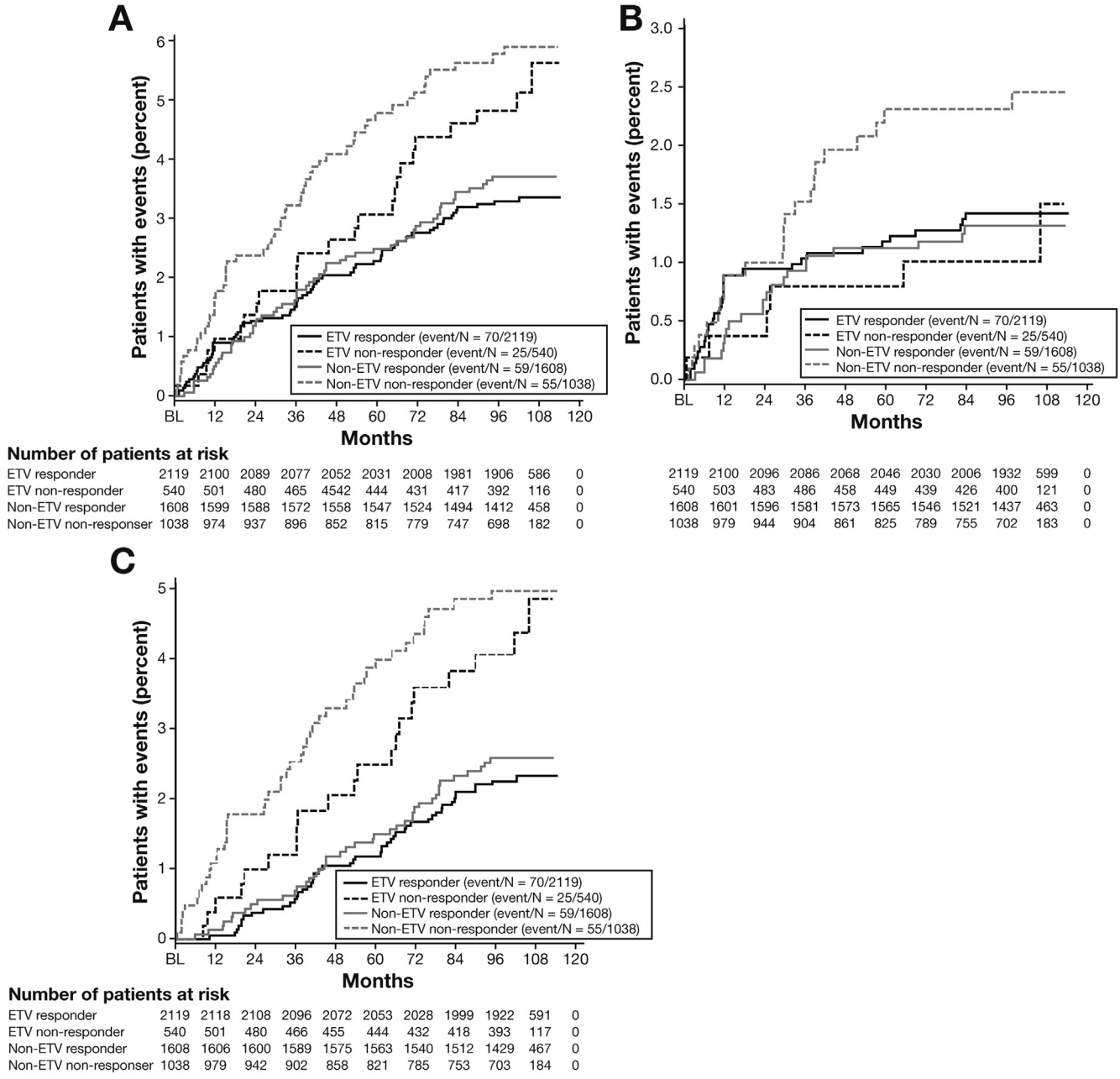

Figure 3. China cohort: time-to-adjudicated clinical outcome events (COEs). Kaplan–Meier plots of primary study end points show the proportion of patients in each treatment group, according to virologic response status, who experienced the indicated adjudicated COEs. (*A*) Liver-related disease progression; (*B*) non-hepatocellular carcinoma HBV disease progression; (*C*) hepatocellular carcinoma. ETV, entecavir.

patients receiving ETV vs tenofovir for CHB treatment. This finding suggests that treatment type influences HCC risk, rather than virologic response as shown in the REALM study.[25] Fewer than 3% of patients in the non-ETV group from REALM received tenofovir as the initial therapy, and none in the China cohort that provided virologic response data, precluding statistical comparison of outcomes with ETV vs tenofovir. Conversely, longitudinal viral load data were not available for the Korean analysis, precluding analysis of the relationship between virologic response and HCC risk over time. Furthermore, unanticipated confounding variables may have influenced outcomes because of the lack of randomized treatment assignments. A prospective randomized comparison of ETV and tenofovir may help resolve this apparent discrepancy.

Limitations of these data include the lack of serial HBV DNA data collection in sites outside China. Hence, HBV disease-related COE rates could not be compared across treatment groups with respect to whether virologic suppression was maintained and whether HBV resistance emerged. In addition, the population was relatively young, precluding a comparison of malignancies, particularly non-HCC malignancies,

according to age. Nonetheless, the age distribution is representative of most nuc-treated patients with CHB in clinical care and comparable with other studies of malignancies in CHB, including non-HCC malignant neoplasms.[19]

In conclusion, this trial showed that long-term treatment of CHB with ETV, compared with other standard-of-care HBV nucs, provided a high margin of safety and was not associated with a higher occurrence of HCC or non-HCC malignancies. Long-term ETV therapy was associated with a low rate of disease progression, comparable with other standard-of-care HBV nucs when viral suppression was maintained. ETV was associated with a low rate of treatment-related SAEs, consistent with the known ETV safety profile. These findings confirm the long-term safety of entecavir and its appropriateness for long-standing therapy of CHB as recommended by current guidelines.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2019.07.010.

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Reprint requests
Address requests for reprints to: Jin-Lin Hou, MD, Hepatology Unit, Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China. e-mail: jlhousmu@163.com; fax: (86) 20-61641941.

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The BMS policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

Conflicts of interest

These authors disclose the following: Jin-Lin Hou received grants and personal fees from Bristol-Myers Squibb during the conduct of the study, and grants and personal fees from Bristol-Myers Squibb, GlaxoSmithKline, and Novartis outside the submitted work; Hie-Won Hann received research grants from Bristol-Myers Squibb during the conduct of this study, received research grants from Gilead, Assembly Biosciences, Arbutus Biopharma, and TrioHealth, and serves on the national advisory board of Gilead; Cheng-Yuan Peng has served as an advisory committee member for AbbVie, Bristol-Myers Squibb, Gilead, and Merck; Tawesak Tanwandee received grants from Bristol-Myers Squibb and Merck during the conduct of the study; Hartwig Klinker has served as a speaker and/or an advisory board member for AbbVie, Bristol-Myers Squibb, Gilead, Hexal, Janssen, and Merck, and has received research funding from AbbVie, Arrowhead, Bristol-Myers Squibb, Gilead, Janssen, Merck, and Novartis; Adrian Streinu-Cercel received research funding from Bristol-Myers Squibb during the conduct of the study, other support from Arbutus Biopharma, and personal fees and other support from Gilead, Janssen, and Bristol-Myers Squibb outside the submitted work; Lai Wei has received research grants from AbbVie, Bristol-Myers Squibb, and Roche, and consulting fees from AbbVie, Allergan, Bristol-Myers Squibb, Gilead, and Johnson & Johnson; Ji-Dong Jia has received consulting and speaker fees from AbbVie, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, and Merck; Hong Ren has received grants and personal fees from Gilead, and personal fees from Roche and Bristol-Myers Squibb outside the submitted work; Yongpeng Chen has received speaker fees from Bristol-Myers Squibb; Elizabeth L. Cooney was a salaried employee of Bristol-Myers Squibb and worked as medical monitor during the conduct of the study, and owns stock in Bristol-Myers Squibb; and Seng-Gee Lim has received grants, personal fees, and nonfinancial support from Gilead and Abbott Diagnostics, personal fees from AbbVie, Bristol Myers Squibb, and Janssen, grants and personal fees from Merck and Biopredictive, and other support from Roche outside the submitted work. The remaining authors disclose no conflicts.

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Supplementary Materials and Methods

Clinical Event Adjudication

The objective of independent clinical event adjudication was to obtain adjudicated diagnoses in accordance with predefined event criteria. Baseline liver imaging study reports were requested for all reported events of HCC or a dysplastic liver nodule. Investigators could be queried using data request forms for additional information needed for EAC review of reported events.

The EAC was co-chaired by a hepatologist and an oncologist; each EAC member served on the hepatology or oncology subcommittee that reviewed events relevant to their expertise. Responsibility was shared for reviewing reported events of HCC and dysplastic liver nodule and non–liver-related or non–malignancy-related deaths. Each reported COE was reviewed by 2 EAC members; when assigned reviewers disagreed regarding diagnosis, the full committee reviewed the event. Treatment-related SAEs were reviewed by the sponsor; if reported SAEs had characteristics consistent with a COE per predefined criteria, the investigator was requested to submit the event as a COE. If an event meeting COE criteria was reported as both an SAE and a COE, the SAE report was deleted to prevent double reporting.

Diagnostic Criteria for Clinical Outcomes Events: Excerpted From the Randomized, Observational Study of Entecavir to Assess Long-term Outcomes Associated with Nucleoside/Nucleotide Monotherapy for Patients with Chronic HBV Infection Event Adjudication Committee Charter

Diagnostic criteria for liver-related events of hepatitis B virus disease progression. Liver-related events of HBV disease progression (including HCC and dysplastic liver nodules) requiring adjudication by the Hepatology EAC Subcommittee (and EAC Full Committee, when necessary) are broadly defined as follows:

- Diagnosis of cirrhosis;
- Decompensated cirrhosis;
  - Development of first non-neoplastic liver-related clinical manifestation;
- Progression (worsening) of pre-existing decompensated cirrhosis;
  - Development of a first additional, non-neoplastic, liver-related clinical manifestation of decompensated cirrhosis;
  - Development of a first recurrent, non-neoplastic, liver-related clinical manifestation of decompensated cirrhosis;
  - Progression of a pre-existing, non-neoplastic, liver-related clinical manifestation of decompensated cirrhosis;
- Diagnosis of HCC;
- Diagnosis of a dysplastic liver nodule;
- Liver-related death.

From an adjudication and analysis perspective, the categories of decompensated cirrhosis and progression of decompensated cirrhosis are treated separately from the other clinical outcomes of cirrhosis, HCC, dysplastic liver nodule, death, and development of a non-HCC malignant neoplasm (including carcinoma in situ but excluding nonmelanoma skin cancer).

- A patient who enters the study with known cirrhosis, staged clinically as compensated cirrhosis (ie, patient has never previously experienced a manifestation of decompensated cirrhosis) will be followed up in the study for development of the following clinical outcomes events: decompensated cirrhosis (first clinical liver-related manifestation) HCC, dysplastic liver nodule, a non-HCC malignant neoplasm (including carcinoma in situ but excluding nonmelanoma skin cancer), and death. If the patient develops a liver-related event of decompensated cirrhosis (eg, new-onset ascites), the patient will be considered to have met this clinical outcome. The investigator will be expected to report subsequent liver-related events of decompensated cirrhosis that might be experienced by that patient. However, only the first reported event for that patient will undergo adjudication by the Hepatology EAC Subcommittee; none of the subsequent non-neoplastic, liver-related events of HBV disease progression that might be experienced by the patient will require adjudication. Subsequent experienced events of HCC, dysplastic liver nodule, a non-HCC malignant neoplasm (including carcinoma in situ but excluding nonmelanoma skin cancer), and/or death, however, will require review/adjudication by the EAC.
- A patient who enters the study without a prior history of cirrhosis will be followed up for development of the following clinical outcomes events: compensated or decompensated cirrhosis, HCC, dysplastic liver nodule, non-HCC malignant neoplasm (including carcinoma in situ but excluding nonmelanoma skin cancer), and death. If the patient develops compensated or decompensated cirrhosis, as outlined earlier, although the investigator will be expected to report any subsequent non-HCC liver-related events of HBV disease progression experienced by the patient, none of these additional non-neoplastic, liver-related events of HBV disease progression will require adjudication. Subsequent experienced events of HCC,

dysplastic liver nodule, non-HCC malignant neoplasm (including carcinoma in situ but excluding non-melanoma skin cancer), and/or death, however, will require review/adjudication by the Hepatology EAC Subcommittee.

From an adjudication and analysis perspective, the categories of HCC and dysplastic liver nodule will be treated as separate entities from the other non-neoplastic categories for a liver-related event of HBV disease progression, as follows:

- Patients who experience their first event of HCC will be considered to have met this clinical outcomes event (and the clinical outcomes event of a dysplastic liver nodule). Any (per patient) subsequent (eg, second, third) reported events of HCC, as well as any subsequent reported events of dysplastic liver nodule, will be included in summary data for events of HBV disease progression but will not be adjudicated by the Hepatology EAC Subcommittee. Such patients subsequently will be monitored for the occurrence of any additional (per patient) first reported non-neoplastic liver-related events of HBV disease progression, for occurrence of any non-HCC malignant neoplasms (including carcinoma in situ but excluding nonmelanoma skin cancers), and for death. All aforementioned clinical outcomes events will be tabulated, as outlined earlier, and undergo review/adjudication by the EAC.
- Patients who experience their first dysplastic liver nodule for which histologic confirmation of diagnosis is available will have this event submitted to the EAC for review/adjudication. Only the first reported event of a dysplastic liver nodule for which histologic confirmation has been provided will be submitted for EAC review/adjudication. All subsequent reported events of dysplastic liver nodule will be included in summary data for events of HBV disease progression but will not be adjudicated by the Hepatology EAC Subcommittee.
- For submitted events of liver dysplasia for which histologic confirmation of diagnosis is absent, data will be stored electronically for subsequent submission to the EAC in the event that biopsy data eventually become available or the patient develops HCC (for which liver dysplasia is a risk factor).
- Patients with submitted events of liver dysplasia (irrespective of whether histologic confirmation of the diagnosis has been provided) will continue to be monitored for any (per patient) first reported events of HCC and other, non-HCC liver-related events of HBV disease progression, any non-HCC malignant neoplasms (including carcinoma in situ but excluding non-melanoma skin cancers), and for death. All aforementioned clinical outcomes events will be tabulated and undergo review/adjudication by the EAC.
- All liver-related deaths will be tabulated and adjudicated by the Hepatology EAC Subcommittee. All non–liver-related, non–malignancy-related deaths will be tabulated. The EAC Hepatology and Oncology Subcommittees will share responsibility for adjudication of these deaths.

Compensated cirrhosis. Compensated cirrhosis will be defined by a patient who fulfills the criteria for cirrhosis, based on liver biopsy, imaging, and/or upper endoscopy finding, and also shows normal synthetic and excretory hepatic function. The former is indicated by a normal serum albumin level and/or international normalized ratio. The latter is indicated by a normal total bilirubin level. Also, the patient with compensated cirrhosis will be free of any complication associated with decompensated cirrhosis, as defined in the section, "Development of decompensated cirrhosis."

- **Liver Biopsy**

  Definite diagnosis: The histology report from the liver biopsy performed notes the presence of cirrhosis. Because this was an observational study, in which liver biopsies are not mandated and for which there is no central review process for liver biopsy specimens obtained, criteria for cirrhosis used by pathologists will necessarily vary. Cirrhosis is a new finding, based on comparison with a prior liver biopsy performed 12 or fewer months before study randomization. A standardized scoring system for liver fibrosis (eg, Knodell fibrosis, METAVIR, Ishak, or other scoring system) may or may not have been used to make the histologic diagnosis.[1,2]

  Probable diagnosis: The histology report from the liver biopsy performed notes the presence of incipient or probable cirrhosis. Cirrhosis is a new finding, based on comparison with prior liver biopsy performed 12 or fewer months before study randomization.

- **Imaging study**
  - **Key concepts**
    - Diagnosis of cirrhosis based on imaging studies (ie, abdominal ultrasound, computed tomography scan, magnetic resonance imaging) describing an inhomogeneous hepatic texture or surface is neither sensitive nor specific when applied to the general population[3,4];
    - However, specificity of these changes as diagnostic indicators of cirrhosis is high when imaging studies are applied to a population that is at known risk for the occurrence of cirrhosis (eg, chronic hepatitis B);
    - Likewise, if imaging studies detect morphologic changes attributable to portal hypertension in such a population, a definite diagnosis of cirrhosis can be achieved;

- In areas with a high prevalence of noncirrhotic portal hypertension, including extrahepatic portal vein thrombosis, idiopathic portal hypertension, or schistosomiasis, these causes still may need to be excluded before attributing portal hypertensive changes to chronic hepatitis B disease progression.

Based on the earlier-described criteria, cirrhosis will be defined by the presence of the following:

1) 2 signs of altered liver parenchyma (combination of texture or surface irregularity and left lobe/caudate lobe hypertrophy) as described later; or
2) 1 sign of altered liver parenchyma and evidence of portal hypertension as described later.

A. Changes of altered liver parenchyma, as follows:

a. Hepatic texture or surface, heterogeneity or nodularity of the liver;

b. Atrophy of the right liver lobe with hypertrophy of the left and caudate lobes.

B. Evidence of portal hypertension (1 major or 2 minor), as follows:

c. Major criteria:

i. Esophageal or gastric varices (verified by endoscopy or imaging);

ii. Splenomegaly;

iii. Ascites;

iv. Portosystemic collaterals;

v. Portal hepatofugal flow;

vi. Hepatic venous pressure gradient greater than 6 mm Hg.

d. Minor criteria:

i. Enlarged portal vein (>14 mm);

ii. Enlarged splenic vein (>10 mm);

iii. Decreased portal vein flow (maximum flow <26 cm/s, mean flow <12 cm/s);

iv. Gallbladder wall thickening (in absence of gallbladder pathology);

v. Thrombocytopenia (<100,000/μL).

• Endoscopic evaluation

Definite diagnosis: Presence of esophageal/gastric varices or portal hypertensive gastropathy,[5,6] coupled with morphologic evidence of cirrhosis, based on liver biopsy and/or imaging study, as outlined earlier, supporting the conclusion that endoscopy findings are the result of cirrhosis rather than other processes proximal to the liver (eg, portal vein thrombosis). Findings are new, as compared with prior studies performed 12 or fewer months before study randomization.

Probable diagnosis: Presence of esophageal/gastric varices or portal hypertensive gastropathy.[5–8] Morphologic evidence of cirrhosis is lacking.

• Fibroscan (Ecosens, Paris, France) evaluation

Taking into consideration the best data on the sensitivity and specificity of transient elastography findings for a diagnosis of cirrhosis in the setting of CHB,[9] optimal cut-off values to provide a diagnosis of probable or definite cirrhosis can be defined and are outlined as follows:

Definite diagnosis: transient elastography liver stiffness measurement greater than 15 kPa;

Probable diagnosis: transient elastography liver stiffness measurement greater than 9.5 kPa.

Development of decompensated cirrhosis. Patients enrolled in this study will be followed up for the development of decompensated cirrhosis at the discretion of the treating physician/investigator. However, investigators will be provided with guidance on monitoring for HBV disease progression and the development of decompensated cirrhosis and will be asked to provide certain supporting documents for the specific event reported.

Development of decompensated cirrhosis is defined as any of the following clinical events:

• New-onset ascites

Definite diagnosis: Presence of at least moderate ascites by imaging study (ultrasound, computed tomography scan, magnetic resonance imaging),[7,8,10,11] or the presence of moderate to marked ascites on physical examination. Supporting evidence that ascites is the result of cirrhosis, based on the presence of cirrhosis (ie, liver nodularity by ultrasound or other imaging study) or portal hypertension (eg, esophageal/gastric varices by upper endoscopy). No other cause of ascites considered likely in the opinion of the investigator (and evaluating physician, when evaluating physician is other than the investigator).

• Spontaneous bacterial peritonitis

Definite diagnosis: Ascitic fluid culture positive for bacteria or fungi and/or that has a polymorphonuclear leukocyte count of 250 cells/μL or greater.[7,8,12,13]

Monomicrobial non-neutrocytic bacterascites (ie, positive ascitic fluid culture but ascitic fluid polymorphonuclear count is <250 cells/μL).[7,8,12,13]

• Hepatic encephalopathy

Definite diagnosis: Any alteration in mental status, occurring in the setting of cirrhosis (the latter based on liver biopsy or imaging study criteria) and in the

absence of another identifiable cause for the change in neurologic status, in the opinion of the investigator (and evaluating physician, when the evaluating physician is other than the investigator).[7,14] An identifiable precipitant for hepatic encephalopathy (eg, temporally associated upper gastrointestinal bleed, event of spontaneous bacterial peritonitis) provides further supporting evidence for the diagnosis.

- Portal hypertensive-related bleeding

Definite diagnosis:

A. Active variceal bleeding (esophageal or gastric) visualized on upper endoscopy

B. Endoscopic stigmata of recent variceal bleed[15–17]

   i. Presence of esophageal/gastric varices with the presence of adherent clot and/or white nipple on at least 1 varix; or

   ii. Esophageal/gastric varices without any of the aforementioned findings in (i), but with the presence of blood in the esophagus or stomach and no other cause for upper gastrointestinal bleeding identified on upper endoscopy.

C. Endoscopic or angiographic demonstration of active gastrointestinal bleeding or stigmata of recent gastrointestinal bleeding through ectopic, stomal, anastomotic varices, or portal hypertensive gastropathy

D. An episode of gastrointestinal bleed for which upper endoscopy was either not performed or upper endoscopy failed to confirm the bleeding source still can be considered indicative of a portal hypertension–related-bleed if the patient underwent emergent surgery or an interventional procedure aimed at controlling the bleed (ie, surgical devascularization, sugiura-like procedure (esophageal or upper stomach blood vessel surgery), portacaval surgical shunt, transjugular intrahepatic portosystemic shunt, or angiographic obliteration technique.[1] These procedures have in common that they provide evidence (direct or radiologic) of portal hypertension as well as extensive portal-systemic collateralization.

Probable diagnosis: Any given episode of gastrointestinal bleeding in which the presence of esophageal/gastric varices or other potential source (ie, stomal, anastomotic, or ectopic varices, portal hypertensive gastropathy, gastric antral vascular ectasia) is documented in the absence of blood or other stigmata in patients with cirrhosis, and there is no evidence of an alternative source of upper or lower gastrointestinal bleeding.

- Hepatorenal syndrome

Definite diagnosis: Azotemia, defined as serum creatinine concentration greater than 1.5 mg/dL and/or 24-hour creatinine clearance less than 40 mL/min, coupled with urine proteinuria less than 500 mg/d; no improvement in renal function after diuretic withdrawal and plasma volume expansion with 1.5 L or more of normal saline; absence of alternate prerenal (hypovolemia), intrarenal (eg, acute tubular necrosis, allergic interstitial nephritis) or postrenal explanation for the acute renal failure, in the opinion of the investigator (and evaluating physician, when the evaluating physician is other than the investigator).[18,19]

- Pulmonary complications

  - Hepatopulmonary syndrome

Definite diagnosis: An association of chronic liver disease with arterial hypoxemia (Pao_2 <70 mm Hg), an O_2 alveoarterial gradient greater than 20 mm Hg, and pulmonary vasodilation. Diagnosis based on vasodilation and shunts by 2 noninvasive tests: contrast echocardiography, perfusion pulmonary scintigraphy, or other diagnostic study.[8]

  - Portopulmonary hypertension

Definite diagnosis: The finding, in the presence of chronic liver disease, of a mean pulmonary arterial pressure greater than 25 mm Hg, a pulmonary capillary pressure less than 15 mm Hg, and a pulmonary vascular resistance greater than 120 dynes S/cm.[5] Diagnosis based on cardiac echocardiography or right heart catheterization. Other causes of pulmonary hypertension ruled out by clinical evaluation.[8]

  - Hepatic hydrothorax

Definite diagnosis: Pleural effusion(s) associated with the presence of cirrhosis, later as documented by liver imaging (ie, liver nodularity) or as supported by findings on other studies (ie, esophageal/gastric varices by upper endoscopy), and concurrent or recent presence of ascites. No other identifiable cause for the pleural effusion(s) (eg, empyema, tuberculous infection, malignancy, hemothorax, and so forth) in the opinion of the investigator (and treating physician, when the treating physician is other than the investigator).[8]

Progression of decompensated cirrhosis. Development of a new, recurrent, or progressive liver-related manifestation of decompensated cirrhosis, based on manifestations of decompensated cirrhosis that the patient manifested at study entry (ie, as documented on baseline case report form for medical history and hepatitis disease history). Definitions for liver-related manifestations of decompensated cirrhosis as outlined earlier the section, "Development of decompensated cirrhosis."

Hepatocellular carcinoma. Patients enrolled in this study will be monitored for the development of HCC at the discretion of the treating physician and/or

investigator (when the investigator is the treating physician). However, investigators will be provided with a copy of the available guidelines on the surveillance and management of HCC (ie, American Association for the Study of Liver Diseases Practice Guidelines for HCC).[20]

Definite diagnosis:

- HCC based on cytohistologic criteria
  - Tissue biopsy recommended for hepatic lesions 1 cm or greater in size that fail to include findings considered typical for HCC on dynamic imaging.
- HCC based on either of the following noninvasive criteria
  - Single radiologic criteria: the finding on a single imaging study (ie, triphasic abdominal computed tomography scan, gadolinium-enhanced magnetic resonance imaging) of a focal hepatic lesion, greater than 1 cm in size, which either shows changes considered typical for HCC (ie, arterial vascularization in addition to washout in the early or delayed venous phase of the study), and/or is coupled with a serum α-fetoprotein level greater than 200 ng/mL, and/or vascular invasion. These criteria are not restricted to patients with cirrhosis, but also may apply to patients who have not yet developed cirrhosis or who could have regressed from their cirrhosis.

Probable diagnosis:

- HCC based on either of the following noninvasive criteria
  - Finding of a serum α-fetoprotein level greater than 400 ng/mL in the absence of an identifiable liver lesion. No alternate explanation for the serum α-fetoprotein level (eg, no evidence for other tumor that can cause an increase in serum α-fetoprotein level).
  - Presence of a liver lesion that is increasing in size over time, as evidenced by serial liver imaging, but that does not meet other imaging criteria for HCC, as outlined earlier.

Dysplastic liver nodules. Patients enrolled in this study will be monitored for the development of a dysplastic liver nodule(s). A dysplastic nodule generally is defined as a nodular region of hepatocytes at least 1 mm in diameter with dysplasia but without definite histologic criteria for malignancy. These nodules usually, but not always, are found within cirrhotic liver. Dysplastic nodules typically are subclassified as low grade or high grade based on the presence of mild or moderate atypia, respectively.[21]

Definite diagnosis:

- Based on histopathology findings meeting accepted criteria for a dysplastic nodule, in the opinion of the viewing pathologist.
- Based on the requirement for histologic confirmation of diagnosis (ie, there are currently no probable criteria for diagnosis, based on liver imaging, tumor markers, and so forth), events of liver dysplasia that are reported to the sponsor or designee will be submitted to the EAC for review only when histologic confirmation of diagnosis is available. Otherwise, data for submitted events will be stored electronically, and the event will be submitted for EAC review when histologic data eventually become available and/or the patient develops HCC, for which a history of liver dysplasia is a risk factor. In the latter instance, the data for the dysplastic liver nodule will be merged with the reported HCC event, and submitted as one package to the EAC for review/adjudication of the HCC event.

Death. The Hepatology EAC Subcommittee will be expected to adjudicate the primary cause of death for all liver-related deaths as follows:

- Liver-related;
- Non–liver-related;
- Unable to distinguish.

For deaths reported as liver-related, in many, but not all, cases, the investigator may report the specific liver-related event leading to death (eg, death owing to variceal bleed and hepatic coma, death owing to ascites, spontaneous bacterial peritonitis, and secondary septic shock). In such cases, the adjudicator will need to affirm or refute the specific causes outlined by the investigator as leading to the liver-related death. Similarly, this may be the case for death owing to nonliver, nonmalignancy causes (eg, cardiovascular death owing to myocardial infarction and pulmonary edema; or cerebrovascular death owing to aspiration and aspiration pneumonia).

In all cases, the adjudicator will need to have documentation verifying that the subject has died. Such documentation may include a death certificate, medical discharge summary, or physician note verifying that the patient has died and detailing the events leading up to death and failed resuscitation efforts. When such documentation is not available, the reviewing EAC member(s) may conclude that they are unable to adjudicate the event of death (with cause) because of insufficient data.

Definitions of Events of Non–Hepatocellular Carcinoma Malignant Neoplasms

COEs requiring adjudication by the Oncology EAC Subcommittee (and EAC Full Committee, when necessary) are broadly defined as follows:

- Non-HCC malignant neoplasm (including carcinoma in situ but excluding nonmelanoma skin cancer).

Patients will be monitored for occurrence of a non-HCC malignant neoplasm (including carcinoma in situ but excluding nonmelanoma skin cancer). Events of

recurrent malignant neoplasm or second malignant neoplasm also will require adjudication. Patients additionally will be monitored for occurrence of HCC and dysplastic liver nodules, for a non-HCC event of HBV disease progression (refer to section Diagnostic criteria for liver-related events of hepatitis B virus disease progression) and for death (liver-related, malignancy-related, or the result of another cause).

Non–hepatocellular carcinoma malignant neoplasm, including carcinoma in situ but excluding nonmelanoma skin cancer.

- Tissue biopsy

Definite diagnosis: Pathology report from tissue obtained antemortem (ie, via tissue biopsy or tissue/organ resection) or post mortem notes the presence of malignant neoplasm. Diagnosis based on gross and microscopic pathology. Depending on the particular tumor, results of immunohistochemistry, other special stains, and/or tumor marker studies may help make the diagnosis.

- Imaging studies

Probable diagnosis: Pathology results are not available because tissue biopsy/resection either was not performed or could not be performed safely, owing to location of tumor, host factors, or other reason. Hence, tumor diagnosis must rely on other information, such as results of imaging studies and/or serum tumor markers, coupled with medical history, physical examination, and routine laboratory studies (for clinical presentation) and medical plus family history (for malignancy risk factors).

Death. The Oncology EAC Subcommittee will be expected to adjudicate the primary cause of death for all malignancy-related deaths as follows:

- Malignancy-related
- Non–malignancy-related
- Unable to distinguish.

For deaths reported as malignancy-related, in many, but not all, cases, the investigator may report the specific malignancy-related event leading to death (eg, death resulting from superior vena cava syndrome and pulmonary embolism; death caused by catheter-related infection and septic shock). In such cases, the adjudicator will need to affirm or refute the specific causes outlined by the investigator as leading to the malignancy-related death. Similarly, this may be the case for death owing to nonliver, nonmalignancy causes (eg, cardiovascular death, owing to myocardial infarction and pulmonary edema; or cerebrovascular death owing to aspiration and aspiration pneumonia).

In all cases, the adjudicator will need to have documentation verifying that the subject has died. Such documentation may include a death certificate, medical discharge summary or physician note, verifying that the patient has died and detailing the events leading up to death and failed resuscitation efforts. When such documentation is not available, the reviewing EAC member(s) may conclude that they are unable to adjudicate the event of death (with cause) because of insufficient data.

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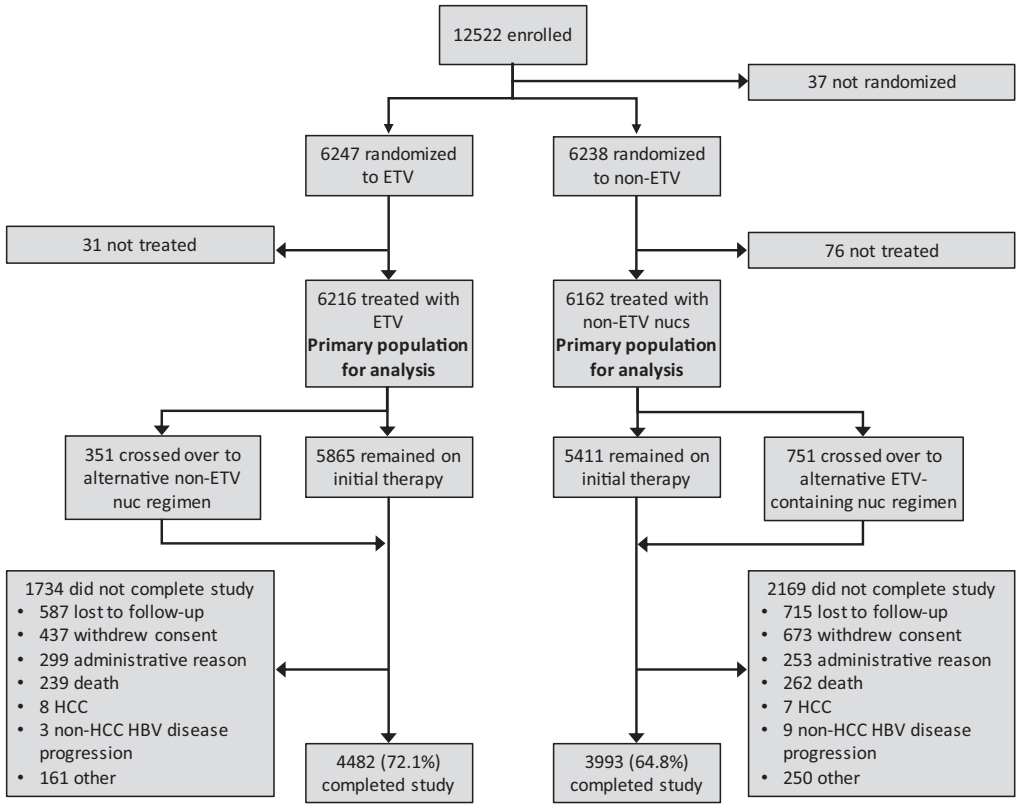
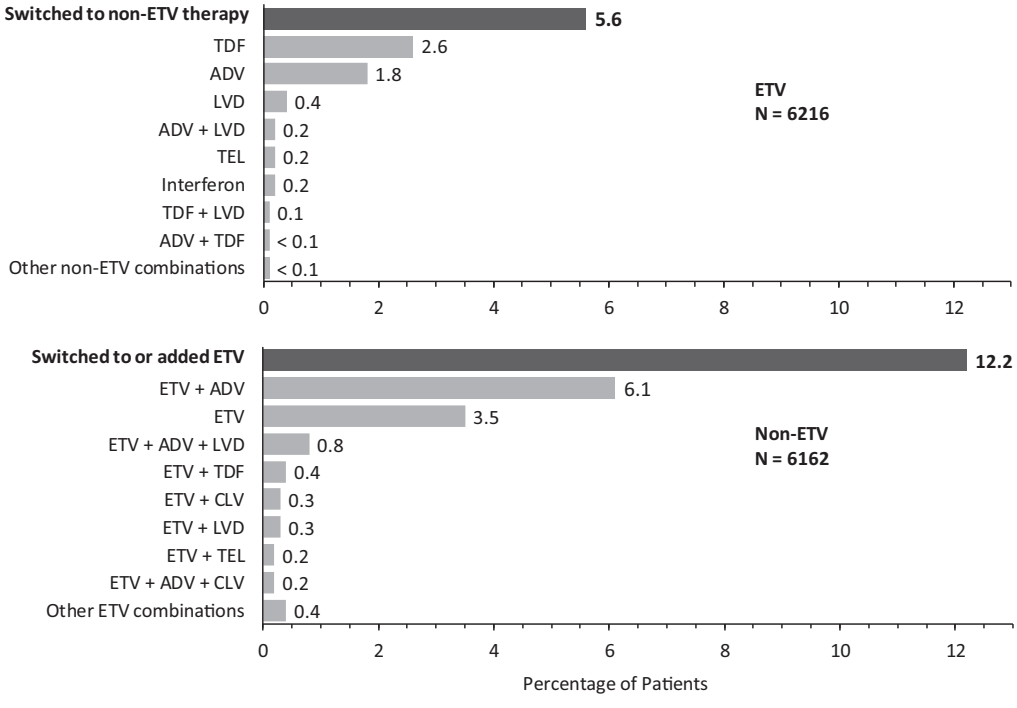
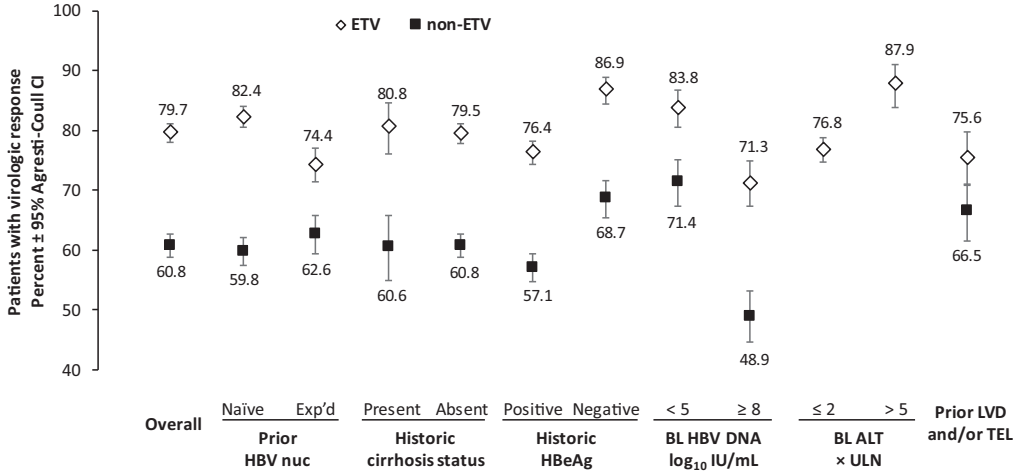


Supplementary Figure 1. Patient disposition. The flow of patients through the study is shown. Outcome analyses were based on all patients who were randomized and treated. Reasons for not completing the study are shown for each treatment group; discontinuations for administrative reasons were primarily the result of early site closures associated with site conduct issues, dissolution of site ethics committees, or related issues. ETV, entecavir; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.



Supplementary Figure 2. HBV therapy cross-over. The proportion of patients in each treatment group who switched to an alternative therapy are shown in bold, with the specific regimens to which patients switched shown below. ADV, adefovir; CLV, clevudine; ETV, entecavir; LVD, lamivudine; TEL, telbivudine; TDF, tenofovir.



Supplementary Figure 3. China cohort: virologic response rate by subgroup. The proportion of patients who achieved virologic response (HBV DNA level $<$50 IU/mL at $\geq$2 consecutive follow-up visits, maintained during the study without subsequent virologic rebound) are shown by treatment arm in the overall study population and in different baseline subgroups. ALT, alanine aminotransferase; BL, baseline; ETV, entecavir; Exp'd, experienced; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; LVD, lamivudine; non-ETV, standard of care hepatitis B virus nucleos(t)ide analogue; TEL, telbivudine; ULN, upper limit of normal.

Supplementary Table 1. Contributing Sites and Lead Investigators

	Principal investigator	Institution
China		
1	Yan-Yan Ji, MD	Jing-An District Center Hospital, Shanghai
2	Mo-Bin Wan, MD	Changhai Hospital of Shanghai, Shanghai
3	Shun-Cai Zhang, MD	Zhongshan Hospital, affiliated with Fudan University, Shanghai
4	Cheng-Wei Chen, PhD	The 85th Hospital of People Liberation Army, Shanghai
5	Ai Min Sun, MD	Henan Academy of Medical and Pharmaceutical Science, Zhengzhou
6	Jin Lin Hou, MD	Guangzhou Nanfang Hospital, Guangzhou
7	Jifang Sheng, MD Ya-Gang Chen, MD (previous)	First Affiliated Hospital of College of Medicine, Zhejiang University, Hangzhou
8	DeMing Tan, MD	Xiangya Hospital of Central South University, Changsha
9	Qing Xie, DR	Shanghai Ruijin Hospital, Jiaotong University of Medical Science, Shanghai
10	De Ying Tian, MD	Tongji Hospital of Tongji Medical College of Huazhong University, Wuhan
11	Hong Ren, MD	No. 2 Hospital, Chongqing Medical University, Chongqing
12	Yu Ming Wang, MD	Southwest Hospital, Chongqing
13	Dao-Zhen Xu, MD	Beijing Ditan Hospital, Beijing
14	Ling-Xia Zhang, MD	320 Military Hospital of China, Beijing
15	Lai Wei, MD	Peking University People's Hospital, Beijing
16	Qin-Huan Wang, MD	Peking University First Hospital, Beijing
17	Wukui Cao, MD	Tianjin Second People's Hospital, Tianjin
18	Min De Zeng, MD	Shanghai Renji Hospital, Jiaotong University of Medical Science, Shanghai
19	Jiefei Wang, MD Liang Chen, MD (previous) Yin Jiang, MD (previous)	Shanghai Public Health Clinical Center, Shanghai
20	Zhi-Liang Gao, PhD	Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou
21	Guangfeng Shi, MD	Huashan Hospital, Fudan University, Shanghai
22	Ji-Dong Jia, MD	Beijing Friendship Hospital, Beijing
23	Guozhong Gong, MD	Second Xiangya Hospital of Central South University, Changsha
24	Hong Tang, MD	West China Hospital, Sichuan University, Chengdu
25	Weibo Yang, MD Jia Wei, MD (previous)	First Affiliated Hospital of Kunming Medical College, Kunming
26	Xiaoguang Dou, MD	Shengjing Hospital of China Medical University, Shenyang
27	Gang Liu, MD	Fifth People's Hospital of Shanghai, Fudan University, Shanghai
28	Xiaoping Tang, MD	Guangzhou No. 8 People's Hospital, Guangzhou
29	Boping Zhou, MD	Shenzhen Third People's Hospital (Donghu Hospital), Shenzhen
30	Huazhong Chen, MD	Taizhou Hospital of Zhejiang Province, Linhai
31	Shijun Chen, MD	Jinan Infectious Disease Hospital, Jinan
32	Jianhe Gan, MD	First Affiliated Hospital of Soochow University, Suzhou
33	Maorong Wang, MD	No. 81 Hospital of the People's Liberation Army, Nanjing
34	Wei Zhao, MD	Second Hospital of Nanjing, Nanjing
35	Xuefan Bai, MD	Second Affiliated Hospital of the Fourth Military Medical University of the People's Liberation Army, Xi'an
36	Zhongping Duan, MD	Beijing Youan Hospital, Capital Medical University, Beijing
37	Tao Han, MD	Tianjing Third Central Hospital, Tianjin
38	Shumei Lin, MD	First Affiliated Hospital of the Medical Center of Xian Jiaotong University, Xi'an
39	Jia Shang, MD	Henan Provincial People's Hospital, Zhengzhou
40	Zujiang Yu, MD	First Affiliated Hospital of Zhengzhou University, Zhengzhou
41	Longfeng Zhao, MD	First Affiliated Hospital of Shanxi Medical University, Taiyuan
42	Huimin Liu, MD	Sixth People's Hospital of Hangzhou, Hangzhou
43	Mingliang Cheng, MD	Affiliated Hospital of Guiyang Medical College, Guiyang
44	Junqi Niu, MD	First Hospital of Jilin University, Changchun
45	Hao Ying, MD	Ningbo No. 2 Hospital, Ningbo
46	Donghui Zhou, MD	First Affiliated Hospital with Nanjing Medical University, Nanjing
47	Shaofeng Wei, MD	First Affiliated Hospital of Anhui Medical University, Hefei
48	Jie Jia, MD	Hainan Provincial People's Hospital, Haikou
49	Yingchun Yan, MD	Shenyang No. 6 People's Hospital, Shenyang
50	Wei Liu, MD	The Sixth People's Hospital, Dalian
Taiwan		
51	Hsing-Tao Kuo, MD	Chi Mei Medical Center, Young Kang City
52	Cheng-Yuan Peng, MD, PhD	China Medical University Hospital, Taichung
53	Sheng-Shun Yang, MD, PhD	Taichung Veterans General Hospital, Taichung
54	Wan-Long Chuang, MD, PhD	Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsiung
55	Sien-Sing Yang, MD	Cathay General Hospital, Taipei
56	Chuan-Mo Lee	Chang Gung Memorial Hospital, Kaohsiung

Supplementary Table 1. Continued

Principal investigator	Institution
57 Chi-Jen Chu, MD	Taipei Veterans General Hospital, Taipei
58 Ting-Tsung Chang, MD	National Cheng Kung University Hospital, Tainan
59 Chun-Jen Liu, MD, PhD Ming-Yang Lai, MD, PhD (previous)	National Taiwan University Hospital, Taipei
60 Chun-Che Lin, MD	Chung-Shan Medical University Hospital, Taichung
Korea	
61 Myeong Jun Song, MD Sang-Bum Kang, PhD (previous) Soon Woo Nam, PhD (previous)	Daejeon St. Mary's Hospital, Daejeon
62 Kwan Sik Lee, MD, PhD	Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul
63 Soon Koo Baik, MD, PhD	Wonju Christian Hospital, Wonju
64 Kwan-Soo Byun, MD, PhD	Korea University Guro Hospital, Seoul
65 Gab-Jin Cheon, MD, PhD	Gangneung Asan Hospital, Gangneung
66 Sang-Young Han, MD, PhD	Dong-A University Medical Center, Busan
67 Jeong Heo, MD, PhD	Pusan National University Hospital, Busan
68 Jae Young Jang, MD, PhD Soung Won Jeong, MD (previous)	Soon Chun Hyang University Seoul Hospital, Seoul
69 Dong Joon Kim, MD, PhD	Chuncheon Sacred Heart Hospital, Chuncheon
70 Hyun Ju Min, MD Tae-Hyo Kim, PhD	Gyeong-Sang National University Hospital, Jinju
71 Byung-Ho Kim, PhD	Kyung Hee University Medical Center, Seoul
72 Sang Gyune Kim, PhD Yun-Nah Lee, MD (previous)	Soonchunhyang University Hospital, Bucheon
73 Yung-Sang Lee, MD	Asan Medical Center, Seoul
74 Heon-Young Lee, MD, PhD	Chungnam National University Hospital, Daejeon City
75 Chang-Hyeong Lee, PhD	Dnegu Catholic University Hospital, Daegu
76 June Sung Lee, MD, PhD	Inje University Ilsan Paik Hospital, Koyang City
77 Jae-Dong Lee, MD	Konkuk University Chungju Hospital, Chungju
78 Youn-Jae Lee, MD, PhD	Inje University College of Medicine, Busan Paik Hospital, Busan
79 Chun-Kyon Lee, PhD	National Health Insurance Corporation Ilsan Hospital, Goyang
80 Myung-Sek Lee, MD, PhD	Hallym University College of Medicine, Kangnam Sacred Heart Hospital, Seoul
81 Se-Hyun Cho, MD, PhD	St. Mary's Hospital, Seoul
82 Si-Hyun Bae, MD, PhD	St. Mary's Hospital, Seoul
83 Neung Hwa Park, MD, PhD	Ulsan University Hospital, Ulsan
84 Gun-Young Hong, PhD Sang-Wook Park, PhD (previous)	Kwangju Christian Hospital, Gwangju
85 Jeong Ill Suh, PhD	Dongguk University Hospital, Gyeongju
86 Sung-Won Cho	Ajou University Hospital, Suwon
87 Kwang-Hyub Han, MD, PhD	Severance Hospital, Yonsei University College of Medicine, Seoul
88 Chang-Wook Kim, MD, PhD Chang-Don Lee, MD, PhD (previous)	Uijeongbu St Mary's Hospital, Uijeongbu
89 Bung-Hoon Han, PhD	Kosin University Gospel Hospital, Busan
90 Ju Hyun Kim, PhD	Gachon University Gil Medical Center, Incheon
91 Jin Mo Yang, PhD	St. Vincent's Hospital, Suwon
92 Seong-Gyu Hwang, MD, PhD	Bundang Cha Hospital, Sungnam
93 Jin-Woo Lee, MD	Inha University Hospital, Incheon
94 Jae-Seok Hwang, PhD Woo Jin Chung, MD, PhD (previous)	Keimyung University Dongsan Hospital, Daegu
95 Young-Kul Jung, MD Hyung Joon Yim, MD, PhD (previous)	Korea University Ansan Hospital, Ansan
96 Seung Woon Paik, MD, PhD	Samsung Medical Center, Seoul
97 Young-Min Park, PhD	Bundang Jesaeng General Hospital, Sungnam
98 Joung-Il Lee, PhD	Kyunghee East-West Neo Medical Center, Seoul
99 Joong-Won Park, MD	National Cancer Center, Gyeonggi
Thailand	
100 Wattana Sukeepaisarnjaroen, MD	Srinagarind Hospital, Khon Kaen
101 Tawesak Tanwandee, MD	Siriraj Hospital, Mahidol University, Bangkok
102 Anuchit Chutaputti, MD	Phramongkutklao Hospital, Bangkok
103 Teerha Piratvisuth, MD	NKC Institute of Gastroenterology and Hepatology, Hat Yai
104 Ratha-Korn Vilaichone, MD, PhD	Thammasat University Hospital, Pathumthani
105 Piyawat Komolmit, MD	Chulalongkorn University Hospital, Bangkok
Singapore	
106 Seng Gee Lim, MBBS	National University Hospital, Singapore

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Principal investigator	Institution
Philippines	
107 Jane Ricaforte Campos, MD	Medical Center Manila, Manila
108 Higinio Mappala, MD	Jose R. Reyes Memorial Medical Center, Manila
109 Felix Domingo, MD	East Avenue Medical Center, Quezon City
110 Lamberto H. Garcia Sr, MD	Cebu Doctors Hospital, Cebu City
111 Eulenia Rasco-Nolasco, MD	Philippine General Hospital, Manila
112 Diana Alcantara-Payawal, MD	Cardinal Santos Medical Center, Manila
113 Marilyn Arguillas, MD	Davao Doctors Hospital, Davao City
114 Jose D. Sollano Jr, MD	Cardinal Santos Medical Center, Manila
India	
115 Sandeep Lakhtakia, MD	Asian Institute of Gastroenterology, Hyderabad
116 Ajay Kumar Jain, MD	Choithram Hospital and Research Centre, Indore
117 Ajit Sood, MD	Dayanand Medical College and Hospital, Ludhiana
118 Palakurthy Murali Krishna, MBBS Eadara Peda Veerraju, MBBS (previous)	King George Hospital, Visakhapatnam
119 Mahesh Kumar Goenka, MD	Apollo Gleneagles Hospital, Kolkata
120 Roy J. Mukkada, MD Abraham Koshy, MD	Lakeshore Hospital and Research Centre, Kochi
121 Mohan Prasad, MD	Gem Hospital, Coimbatore
122 Samir Mohindara, DM, MD Gourdas Choudhuri, MD (previous)	Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow
123 Randhir Sud, MD	Medanta–The Medicity, Gurgaon
124 Aejaz Habeeb, MD CM Habibullah, MD (previous)	Deccan College of Medical Sciences and Allied Hospital, Hyderabad
125 Premashis Kar, MD	Maulana Azad Medical College and Associated Lok Nayak Hospital, New Delhi
126 Gitanjali Pawar, MD Sanjay Gupta, MD (previous)	Christian Medical College and Hospital, Ludhiana
127 Bonthala Subbaraj Satyaprakash, MD	M.S. Ramaiah Memorial Hospital, Bangalore
128 Pravin Rathi, MD	B.Y.L Nair Charitable Hospital and TN Medical College, Mumbai
129 Panduranga Rao Kondadasula, MD Umadevi Malladi, MD (previous)	Osmania General Hospital, Hyderabad
130 Janavikulam Sankaran Rajkumar, MD	Lifeline Multispeciality Hospital, Chennai
131 Nitin Chintaman Borse, MD, MBBS	Nasik Digestive Disease and Endoscopy Centre, Nasik
132 Prashant Vasant Bhandarkar, MD	Gastroenterology and Endoscopy Centre, Dhantoli
133 Kaushal Y. Vyas, DM, MD	V.S. General Hospital, Ahmedabad
134 Ramanjeneyulu Erukulla, MD	Kamineni Hospitals, Hyderabad
135 Rajendra Kumar Jain, MD	Dr. Jain's Clinic, Arera Colony, Bhopal
136 Ramesh Ardhanari, MS	Meenakshi Mission Hospital, Madurai
137 Rupesh Mehta, MS	Mehta Hospital, Ahmedabad
138 Thayumanavan L. Bharathi, MD	Vadamalayan Hospitals, Madurai
139 Nagarjuna Kumar Yarlagadda, MD	Krishna Institute of Medical Sciences, Secunderabad
140 Sunil Gupta, MD	Apex Hospital, Jaipur
141 Yarlagadda Krishna Mohan, MD	Leads Medical Center, Hyderabad
142 Lalit Dongre, MD	Suretech Hospital and Research Centre, Nagpur
143 Harshad Devarbhavi, MD	St. John's Medical College Hospital, Bangalore
144 K Sundara Bhat, MD	Father Muller Medical College Hospital, Mangalore
Germany	
145 Thomas Berg, MD	Universitaetsklinikum Leipzig, Leipzig
146 Hartwig Klinker, MD	Klinikum Julius-Maximilians-Uni Würzburg, Würzburg
147 Ulrike Heinzel-Pleines, MD	Universitätsklinikum Düsseldorf, Düsseldorf
148 Christoph Berg, MD Stephan Kaiser, MD (previous)	Universitätsklinikum Tübingen, Tübingen
149 Marie-Luise Schneider Lorenz, MD Jurgen Bauditz, MD (previous) Johann Ockenga, MD (previous)	Campus Charite Mitte, Berlin
150 Joerg Petersen, MD, PhD	IFI Institute at Asklepios Klinik St Georg, University of Hamburg, Hamburg
151 Ulrich Spengler, MD	Universitätsklinikum Bonn, Bonn
Spain	
152 Manuel Garcia Bengoechea, MD	Hospital Donostia, San Sebastian Guipuzcoa
153 Javier Salmeron Escobar, MD	Hospital Universitario San Cecilio, Granada
154 Moises Diago, MD	Clinica Quiron, Valencia
155 Manuel Romero-Gomez, MD	Hospital Universitario de Valme, Sevilla
156 Luisa Gonzalez-Dieguez, MD	Hospital Universitario Central de Asturias, Oviedo
157 Ricardo Moreno Otero, MD, PhD	Hospital de la Princesa, Madrid
158 Jose Luis Calleja, MD, PhD	Hospital Universitario Puerta De Hierro Majadahonda, Majadahonda

Supplementary Table 1. Continued

Principal investigator	Institution
Italy	
159 Nicola Caporaso, MD	Universita di Napoli Federico II, Napoli
160 Pietro Andreone, MD	Azienda Ospedaliero-Universitaria di Bologna Policlinico S. Orsola Malpighi, Bologna
161 Gianpiero D'Offizi, MD Giorgio Antonucci, MD (previous) Pasquale Narciso, MD (previous)	Istituto Nazionale per le Malattie Infettive, Roma
Portugal	
162 Carla Rolanda, MD R Goncalves, MD (previous) G Macedo, MD, PhD (previous)	Hospital de Braga, Braga
163 Antonio Filipe Calinas, MD	Hospital de Santo Antonio Dos Capuchos, Lisbon
164 Armando Carvalho, MD, PhD	Hospitais da Universidade de Coimbra, Coimbra
165 Ana Horta e Vale, MD, PhD	Hospital São Joao, Porto
France	
166 Jean-Pierre Bronowicki, MD	Hôpitaux de Brabois-CHU de Nancy, Vandoeuvre
167 Stanislas Pol, MD	Hôpital Cochin, Paris
168 Jean-Pierre Zarski, MD	Hôpital Albert Michallon-CHU De Grenoble, Grenoble
169 Thierry Poynard, MD	Centre Hospitalier de la Pitié-Salpêtrière, Paris
170 Christian Trepo, MD, PhD	Hôpital de la Croix-Rousse
171 Jean-Didier Grange, MD	Hôpital Tenon, Paris
172 Philippe Mathurin, MD, PhD	CHRU Lille, Hôpital Claude Huriez, Lille
173 Veronique Loustaud-Ratti, MD	CHU Dupuytren, Limoges
174 Christophe Hezode, MD	CHU Henri Mondor, Creteil
Czech Republic	
175 Pavel Chalupa, MD	Fakultni Nemocnice Na Bulovce, Prague
176 Petr Husa, MD	Klinika Infekcnich Chorob, Brno
177 Luděk Rožnovský, MD	University Hospital Ostrava, Ostrava
178 Pavel Dlouhy, MD	Sdružení Lékařů Pro Infekční A Interní Nemoci, Ústí nad Labem
178 Stanislav Plíšek, MD, PhD	Klinika Infekčních Nemocí, Hradec Králové
Poland	
180 Iwona Mozer-Lisewska, MD, PhD Jacek Juszczyk, MD, PhD (previous)	Wielospecjalistyczny Szpital Miejski im. Józefa Strusia, Poznan
181 Anna Piekarska, MD, PhD Jan Kuydowicz, MD (previous)	Wojewodzki Specjalistyczny Szpital im. Dr. Władysław Bieganskiego, Lodz
182 Włodzimierz Mazur, MD, PhD	Specjalistyczna Praktyka Lekarska Wytwórnia Aparatury Medycznej Włodzimierz Mazur, Zawiercie
183 Tomasz Mach, MD	Szpital Uniwersytecki W. Krakowie, Krakow
184 Marta Wawrzynowicz-Syczewska, MD, PhD Anna Boroń -Kaczmarska, MD, PhD (previous)	Samodzielny Publiczny Wojewódzki Szpital Zespolony, Szczecin
185 Barbara Baka-Cwierz, MD	Wojewodzkie Centrum Diagn I Terapii Wzw I Hepatologii, Krakow
186 Iwona Olszok, MD	Szpital Rejonowy Im. Dr. Józefa Rostka W. Raciborzu, Raciborz
Turkey	
187 Ulus Akarca, MD	Ege University Medical Faculty, Izmir
188 Mehmet Yucesoy, MD	Erciyes University Medical Faculty, Kayseri
189 Sukran Kose, MD	Tepecik Research and Training Hospital, Izmir
190 Halis Simsek, MD	Hacettepe University Faculty of Medicine, Ankara
191 Iftihar Koksal, MD	Karadeniz Technical University, Trabzon
192 Hasan S. Z. Aksu, MD	Cukurova University Medical School, Balcali
193 Gaye Usluer, MD	Eskisehir Osmangazi University Medical Faculty, Meselik
Romania	
194 Irinel Raluca Parepa, MD, PhD	Constanta Emergency County Clinical Hospital, Constanta
195 Adrian Streinu Cercel, MD	Matei Bals Infectious Disease, Bucharest
196 Mihai Voiculescu, MD	Fundeni Clinical Institute of Uronephrology and Renal Transplant, Bucharest
197 Florin Alexandru Caruntu, MD, PhD	Matei Bals Infectious Disease, Bucharest
198 Dan Olteanu, MD	Bucharest Emergency University Hospital, Bucharest
199 Emanoil Ceausu, MD, PhD	Dr. Victor Babes Infectious and Tropical Diseases Hospital, Bucharest
200 Mihail-Radu Voiosu, MD	Colentina Clinical Hospital, Bucharest
201 Mihai Mircea Diculescu, MD	Fundeni Clinical Institute of Digestive Diseases and Hepatic Transplant, Bucharest
202 Carol Stanciu, MD	Gastroenterology and Hepatology Institute, Iasi
203 Ioan Sporea, MD, PhD	County Emergency Hospital, Timisoara

Supplementary Table 1. Continued

Principal investigator	Institution
Greece	
204 Dimitrios Dimitroulopoulos, MD Emmanuel Paraskevas, MD (previous)	Agios Savas Anti-Cancer Oncology Hospital of Athens, Athens
205 Konstantinos Mimidis, MD	University General Hospital, Alexandroupolis
206 Dimitrios Karamanolis, MD	General Hospital of Athens "Evangelismos," Athens
207 Irene Vafiadis-Zouboulis, PhD	Laiko General Hospital of Athens, Athens
Russia	
208 Sergey Martyushov, MD	Regional Clinical Hospital, Arkhangelsk
209 Nina Shironina, MD, PhD	Regional AIDS and Infectious Diseases Center, Kirov
210 Viacheslav Morozov, MD	Medical Company, Hepatolog, Samara
211 Olga Korochkina, MD, PhD	Hospital of Infectious Diseases, Nizhniy Novgorod
212 Vladimir N. Abrosimov, MD, PhD	Regional Clinical Hospital N.A. Semashko, Ryazan
213 Snezhana Sleptosova, MD Marfa Alexeeva, MD, PhD (previous)	Municipal Institution Yakutsk Municipal Clinical Hospital, Yakutsk
214 Ludmila Kirillova, MD	Lipetsk Region Center Prophylaxis and Treatment AIDS and Infectious Diseases, Lipetsk
215 Firaya Nagimova, MD, PhD Margarita Makarova, MD, PhD (previous)	Tatarstan Republic's Center for AIDS and Infectious Disease, Kazan
216 Vladimir Ivashkin, MD, PhD	I.M. Sechenov Moscow Medical Academy, Moscow
217 Nonna Nikolaeva, MD, PhD	Municipal Institution of Health Care, Krasnoyarsk
218 Igor Malov, MD	Irkutsk Regional Clinical Diagnostic Center, Irkutsk
219 Tatiana Lopatkina, PhD	M. Sechenov Moscow Medical Academy, Moscow
220 Natalia Blokhina, MD, PhD	Moscow Clinical Infectious Diseases Hospital #1 Hepatocenter, Moscow
United States	
221 Paul Kwo, MD Hong Shen, MD (previous)	Indiana University, Indianapolis, IN
222 Edwin Dejesus, MD	Orlando Immunology Center, Orlando, FL
223 Eugene Schiff, MD	University of Miami Center for Liver Diseases, Miami, FL
224 Edmund J. Bini, MD	Veterans Affairs New York Harbor Healthcare System, New York, NY
225 Nikunj Shah, MD Stanley B. Cohen, MD (previous)	Rush University Medical Center, Chicago, IL
226 Hie-Won L. Hann, MD	Thomas Jefferson Medical College, Philadelphia, PA
227 Tarek I. Hassanein, MD	SCTI Research Foundation, Coronado, CA
228 Fredric Regenstein, MD Luis Balart, MD (previous) Shobha Joshi, MD (previous)	Tulane University Health Sciences Center, New Orleans, LA
229 William M. Lee, MD	University of Texas Southwestern Medical Center, Dallas, TX
230 Enrique Jesus Martinez, MD	Atlanta Gastroenterology Associates, Atlanta, GA
231 Albert Min, MD	Beth Israel Medical Center, New York, NY
232 Frederick Nunes, MD	Pennsylvania Hospital, Philadelphia, PA
233 Tram Tran, MD	Cedars Sinai Medical Center, Los Angeles, CA
234 Mordechai Rabinovitz, MD	University of Pittsburgh Medical Center, Center For Liver Diseases, Pittsburgh, PA
235 Joykumar Girishbhai Patel, MD Hany Elbeshbeshy, MD (previous) Harlan Wright, MD (previous)	Integris Baptist Medical Center, Oklahoma City, OK
236 Walford Jeffrey Fessel, MD	Kaiser Permanente Medical Center, San Francisco, CA
237 Sing Chan, MD	Office of Sing Chan, MD, Flushing, NY
238 Mark Russo, MD	Carolinas Medical Center, Charlotte, NC
239 Calvin Q. Pan, MD	Medical Procare, Flushing, NY
240 George Y. Wu, MD, PhD	University of Connecticut Health Center, Farmington, CT
Canada	
241 Edward Tam, MD Frank H. Anderson, MD (previous)	Liver and Intestinal Research Centre, Vancouver, British Columbia
242 Carla S. Coffin, MD	Heritage Medical Research Clinic, Calgary, Alberta
243 Morris Sherman, MD	Toronto Hospital, Toronto, Ontario
244 David Lorne J. Tyrrell, MD	University of Alberta, Edmonton, Alberta
245 Jean-Pierre Villeneuve, MD	Hospital Saint-Luc Du Chum, Montreal, Quebec
Argentina	
246 Adrian Carlos Gadano, MD	Society Italiana de Beneficiencia en Buenos Aires-Hospital Italiano, Buenos Aires
247 Bernardo Frider, MD	Hospital General De Agudos Cosme Argerich, Buenos Aires
248 Carlos Eduardo Remondegui, MD	Hospital San Roque, San Salvador De Jujuy
249 Roberto Perez Alvarez, MD	Hospital Italiano De Mendoza, Guaymallén
250 Liliana Maria Calanni, MD	Cein Unidad Infectologica De Prevencion, Neuquén
251 Eduardo L. Fassio, MD	Hospital Nacional Profesor Alejandro Posadas, Buenos Aires

Supplementary Table 1. Continued

Principal investigator	Institution
252 Beatriz Margarita Ameigeiras, MD	Hospital General De Agudos J.M. Ramos Mejia, Buenos Aires
253 Tomas Exequiel Smith Casabella, MD Gustavo J. Guaymas, MD (previous)	Prevencion Cardiovascular Salta, Salta
Colombia	
254 Antonio Carlos Jaramillo, MD	Fundacion Salud Bosque Comite De Infecciones, Bogota
255 Antonio Carlos Jaramillo, MD	Medicos Asociados Nueva Clinica San Sebastian, Bogota
256 Henry Mendoza Ramirez, MD	Riesgo de Fractura, Bogota
Brazil	
257 Carlos E. Brandao Mello, MD, PhD	Hospital Universitário Gaffrée e Guinle, Rio de Janeiro
258 Fernando Lopes Goncales Jr, MD	Hospital das Clinicas da Universidade Estadual de Campinas, Campinas
259 Francisco Souto, MD, PhD	Hospital Universitário Júlio Muller da Fundação Universidade Federal de Mato Grosso, Cuiabá
260 Hugo Cheinquer, MD	Hospital de Clinicas de Porto Alegre, Porto Alegre
261 Jose Luiz de Andrade Neto, MD	Instituto A-Z de Pesquisa e Ensino, Curitiba
262 Raymundo Parana Ferreira Filho, MD	Universidade Federal da Bahia, Salvador
263 Rosangela Teixeira, MD	Hospital da Clínicas da Universidade Federal de Minas Gerais, Belo Horizonte
264 Antonio T. de Faria Freire, MD	Santa Casa de Misericordia de Belo Horizonte, Belo Horizonte
265 Ana de Lourdes Candolo Martinelli, MD	Hospital das Clinicas De Ribeirao Preto, Ribeirão Preto
266 Antonio Barone, MD	Instituto de Medicina Tropical, São Paulo
267 Carlos Francisconi, MD	Hospital São Lucas–Pontificia Universidade Católica do Rio Grande do Sul, Porto Alegre
268 Claudio Figueiredo-Mendes, MD	Hospital Geral da Santa Casa da Misericordia, Rio de Janeiro
269 Delzi Vinha Nunes de Gongora, MD	Hospital de Base, São Jose do Rio Preto
270 Paulo Abrao Ferreira, MD Esper Georges Kallas, MD (previous)	Escola Paulista de Medicina Universidade Federal São Paulo, São Paulo
271 Fernando Jose Goes Ruiz, MD	Nici Infectologia, Sorocaba
272 Andre Castro Lyra, MD	Hospital Universitário Profesor Edgard Santos, Salvador
273 Marcio Rodrigues de Castro, MD	Clinica São Vicente, Ipatinga
274 Maria Patelli Juliani Souza Lima, MD	Hospital e Maternidade Celso Pierro da Pontificia Universidade Católica-Campinas, Campinas
275 Olavo Henrique Munhoz Leite, MD Maria C. J. Mendes Correa, MD (previous)	Unidade de Referência para Doenças Infecciosas Preveníveis–Faculdade de Medicina do ABC, Santo Andre
276 Maria Eugenia Valias Didier, MD	Hospital Felicio Rocho, Atraves da Fundacao Felice Rosso, Belo Horizonte
277 Paulo Renato Petersen Behar, MD	Hospital Santa Clara, Santa Casa de Porto Alegre, Rio Grande do Sul
278 Pedro Duarte Gaburri, MD	Santa Casa de Misericórdia de Juiz de Fora, Juiz de Fora
279 Ana Ruth Silva de Araujo, MD	Fundação de Medicina Tropical, Manaus
280 Lúcio Filgueiras Pacheco Moreira, MD	Hospital Geral de Bonsucesso, Rio de Janeiro
281 Luiz Gustavo Escada Ferreira, MD	Hospital Regional Homero de Miranda Gomes, São Jose
282 Leila Maria Beltrão Pereira, MD, PhD	Instituto do Fígado de Pernambuco, Recife
283 Diana Brasil Pedral Sampaio, MD	Universidade Federal da Bahia, Hospital Professor Edgard Santos, Salvador
284 Heitor Rosa, MD	Hospital das Clinicas da Universidade Federal de Goiás, Goiania
285 Luciana Pedral Sampaio Sgarbi, MD	Faculdade De Medicina De Marilia-Famema, Marilia
286 Deborah Crespo, MD	Nucleo de Estudos e Pesquisas em Hepatologia da Amazonia, Belem
287 Cirley Maria de Oliveira Lobato, MD	Fundação Hospital Estadual do Acre (Hospital das Clinicas), Rio Branco
Mexico	
288 Guillermo Cabrera Alvarez, MD	Clinica De Higado and Gastroenterologia Integral, Cuernavaca
289 Francisco J. Bosques Padilla, MD	Hospital Universitario Dr. Jose Eleuterio Gonzalez, Monterrey
290 Adrian Flores Gaxiola, MD	Issste-Hospital Regional Manuel Cardenas De La Vega, Culiacan
291 Juan Francisco Sanchez Avila, MD	Instituto Nacional De Ciencias Medicas y Nutricion S.Z., Distrito Federal
292 Hector Raul Perez Gomez, MD	Antiguo Hospital Civil De Guadalajara Fray Antonio Alcalde, Guadalajara
293 Jose Maria Remes Troche, MD	Centro De Diagnostico Integral, Boca del Rio
294 Francisco Israel Guerrero Díaz, MD	Hospital Universitario de Saltillo, Saltillo
295 Laura E. Cisneros Garza, MD	Practica Privada de la Dra Laura Esthela Cisneros Garza, Morones
296 Gerardo Amaya, MD	Hospital de Especialidades del Centro Medico Puerta de Hierro, Zapopan
297 Alma Minerva Pérez Rios, MD	Centro de Investigación Farmacéutica Especializada, Guadalajara
298 Isidro German Zavala Trujillo, MD	Hospital Dr. Angel Leano, Zapopan
299 José Carlos Tecalero Hernández, PhD	Centro Ambulatorio de Prevención y Atención de Sida e Infecciones de Transmisión Sexual, Durango

Supplementary Table 2. Initial Anti-HBV Treatment

Treatment, n (%)	ETV N = 6216	Non-ETV N = 6162
Monotherapy	6111 (98.3)	6018 (97.7)
ETV monotherapy	6108 (98.3)	6 (<0.1)
Non-ETV monotherapy	3 (<0.1)	6012 (97.6)
ADV	2 (<0.1)	4419 (71.7)
CLE	0	337 (5.5)
LVD	0	446 (7.2)
TDF	0	151 (2.5)
TEL	0	659 (10.7)
Unknown	1 (<0.1)	0
Combination therapy	105 (1.7)	144 (2.3)
ETV combination therapy	105 (1.7)	9 (0.1)
ETV + ADV	33 (0.5)	4 (<0.1)
ETV + ADV + LVD	0	1 (<0.1)
ETV + CLE	1 (<0.1)	1 (<0.1)
ETV + IFN	15 (0.2)	0
ETV + LVD	51 (0.8)	1 (<0.1)
ETV + TDF	2 (<0.1)	0
ETV + TEL	2 (<0.1)	2 (<0.1)
ETV + THY	1 (<0.1)	0
Non-ETV combination therapy	0	135 (2.2)
ADV + CLE	0	3 (<0.1)
ADV + IFN	0	9 (0.1)
ADV + IFN + LVD	0	1 (<0.1)
ADV + LVD	0	91 (1.5)
ADV + LVD + TEL	0	1 (<0.1)
ADV + TDF	0	2 (<0.1)
ADV + TEL	0	11 (0.2)
CLE + LVD	0	3 (<0.1)
IFN + LVD	0	3 (<0.1)
IFN + TDF	0	2 (<0.1)
IFN + TEL	0	2 (<0.1)
LVD + TEL	0	5 (<0.1)
LVD + THY	0	1 (<0.1)
TDF + TEL	0	1 (<0.1)

ADV, adefovir; CLE, clevudine; ETV, entecavir; HBV, hepatitis B virus; IFN, interferon; LVD, lamivudine; TEL, telbivudine; TDF, tenofovir; THY, thymosin.

Supplementary Table 3. Time to Overall Adjudicated Malignant Neoplasm

	ETV N = 6216				Non-ETV N = 6162			
Interval, *mo*[a]	N at risk[b]	N events[c]	N censored[c]	KM proportion[d]	N at risk[b]	N events[c]	N censored[c]	KM proportion[d]
0–12	6216	45	162	0.0073	6162	47	194	0.0078
12–24	6009	96	295	0.0159	5921	103	376	0.0173
24–36	5825	137	416	0.0229	5683	157	575	0.0268
36–48	5663	187	549	0.0316	5430	202	767	0.0350
48–60	5480	229	696	0.0391	5193	246	984	0.0433
60–72	5291	268	891	0.0463	4932	287	1250	0.0515
72–84	5057	306	1226	0.0537	4625	317	1646	0.0579
84–96	4684	320	2348	0.0568	4199	330	2654	0.0612
96–108	3548	331	5088	0.0611	3178	337	5088	0.0639
108–120	797	331	5885	0.0611	737	337	5825	0.0639

ETV, entecavir; KM, Kaplan-Meier.
[a]Intervals include right end point.
[b]At risk entering interval.
[c]Cumulative.
[d]Kaplan–Meier cumulative proportion with events at end of interval.

Supplementary Table 4. Time to Adjudicated All-Cause Death

	ETV N = 6216				Non-ETV N = 6162			
Interval, *mo*[a]	N at risk[b]	N events[c]	N censored[c]	KM proportion[d]	N at risk[b]	N events[c]	N censored[c]	KM proportion[d]
0–12	6216	40	131	0.0065	6162	40	166	0.0066
12–24	6045	72	244	0.0118	5956	72	331	0.0120
24–36	5900	101	349	0.0167	5759	115	513	0.0195
36–48	5766	128	476	0.0213	5534	163	692	0.0281
48–60	5612	164	614	0.0277	5307	193	898	0.0337
60–72	5438	196	796	0.0335	5071	218	1166	0.0386
72–84	5224	211	1138	0.0363	4778	246	1570	0.0444
84–96	4867	230	2300	0.0405	4346	259	2617	0.0477
96–108	3686	238	5147	0.0441	3286	264	5147	0.0496
108–120	831	238	5978	0.0441	751	264	5898	0.0496

ETV, entecavir; KM, Kaplan-Meier.
[a]Intervals include right end point.
[b]At risk entering interval.
[c]Cumulative.
[d]Kaplan–Meier cumulative proportion with events at end of interval.

Supplementary Table 5. Time to Adjudicated Liver-Related HBV Disease Progression

	ETV N = 6216				Non-ETV N = 6162			
Interval, *mo*[a]	N at risk[b]	N events[c]	N censored[c]	KM proportion[d]	N at risk[b]	N events[c]	N censored[c]	KM proportion[d]
0–12	6216	98	146	0.0160	6162	82	181	0.0135
12–24	5972	147	270	0.0241	5899	154	359	0.0257
24–36	5799	188	384	0.0311	5649	211	550	0.0357
36–48	5644	238	514	0.0397	5401	260	739	0.0446
48–60	5464	269	658	0.0452	5163	295	954	0.0512
60–72	5289	306	852	0.0520	4913	329	1218	0.0580
72–84	5058	339	1186	0.0584	4615	357	1612	0.0639
84–96	4691	345	2312	0.0597	4193	368	2631	0.0667
96–108	3559	350	5065	0.0616	3163	375	5056	0.0696
108–120	801	350	5866	0.0616	731	375	5787	0.0696

ETV, entecavir; HBV, hepatitis B virus; KM, Kaplan-Meier.
[a]Intervals include right end point.
[b]At risk entering interval.
[c]Cumulative.
[d]Kaplan–Meier cumulative proportion with events at end of interval.

Supplementary Table 6. Time to Adjudicated HCC

	ETV N = 6216				Non-ETV N = 6162			
Interval, *mo*[a]	N at risk[b]	N events[c]	N censored[c]	KM proportion[d]	N at risk[b]	N events[c]	N censored[c]	KM proportion[d]
0–12	6216	34	163	0.0055	6162	36	196	0.0059
12–24	6019	73	298	0.0121	5930	81	381	0.0136
24–36	5845	103	420	0.0172	5700	124	584	0.0211
36–48	5693	143	556	0.0242	5454	162	780	0.0281
48–60	5517	166	706	0.0283	5220	195	1000	0.0344
60–72	5344	200	907	0.0346	4967	227	1270	0.0408
72–84	5109	228	1248	0.0400	4665	248	1671	0.0452
84–96	4740	236	2389	0.0418	4243	258	2703	0.0478
96–108	3591	240	5169	0.0435	3201	263	5157	0.0495
108–120	807	240	5976	0.0435	742	263	5899	0.0495

ETV, entecavir; HCC, hepatocellular carcinoma; KM, Kaplan-Meier.
[a]Intervals include right end point.
[b]At risk entering interval.
[c]Cumulative.
[d]Kaplan–Meier cumulative proportion with events at end of interval.

Supplementary Table 7. As-Treated Covariate-Adjusted Sensitivity Analysis of Time-to-Adjudicated COEs

Patients with events, n	ETV N = 6221	Non-ETV N = 6159	ETV exposure coefficient estimate (95% CI)
Primary end points			
Overall malignant neoplasm	332	336	-0.014 (-0.0157 to -0.0117)
Death	352	373	-0.017 (-0.0193 to -0.0150)
Liver-related HBV disease progression	240	262	-0.014 (-0.0168 to -0.0121)
Secondary end points			
Non-HCC malignant neoplasm	95	81	-0.011 (-0.0150 to -0.0077)
HCC[a]	241	262	-0.015 (-0.0170 to -0.0123)
Liver-related death	47	47	-0.019 (-0.0258 to -0.0126)
Post hoc exploratory end point			
Non-HCC HBV disease progression	138	145	-0.021 (-0.0254 to -0.0175)

NOTE. Analyses are stratified by geographic region and prior HBV nuc experience. Nine patients who received different initial treatment from randomized treatment were grouped according to the initial treatment received, and 2 treated patients who were not randomized were included. Covariates are cumulative ETV exposure up to event time and baseline age, sex, race, historic cirrhosis status, cigarette smoking ever, alcohol drinking ever, and body mass index.
COE, clinical outcome events; ETV, entecavir; HBV, hepatitis B virus.
[a]One patient had pretreatment HCC and therefore was excluded.

Supplementary Table 8. EAC Reviewed and Adjudicated Non-HCC Malignant Neoplasms

Patients with events, n (%)	ETV N = 6216	Non-ETV N = 6162
Total adjudicated as non-HCC malignant neoplasm	95 (1.5)	81 (1.3)
Gastrointestinal malignancies	30 (0.5)	27 (0.4)
Reproductive system and breast malignancies	13 (0.2)	13 (0.2)
Renal and urinary malignancies	9 (0.1)	7 (0.1)
Respiratory, thoracic, and mediastinal malignancies	10 (0.2)	6 (<0.1)
Blood and lymphatic system malignancies	7 (0.1)	8 (0.1)
Endocrine malignancies	7 (0.1)	5 (<0.1)
Hepatobiliary malignancies	4 (<0.1)	10 (0.2)
Head and neck malignancies	2 (<0.1)	4 (<0.1)
Skin and subcutaneous tissue malignancies	4 (<0.1)	0
Nervous system malignancies	1 (<0.1)	0
Unspecified organ system malignancies	8 (0.1)	1 (<0.1)

EAC, event adjudication committee; ETV, entecavir; HCC, hepatocellular carcinoma.

Supplementary Table 9. EAC-Reviewed and Adjudicated COEs by Historic Cirrhosis Status

	Cirrhosis		No cirrhosis	
Patients with events, n (%)	ETV N = 1260	Non-ETV N = 1261	ETV N = 4956	Non-ETV N = 4901
Death	163 (12.9)	184 (14.6)	75 (1.5)	80 (1.6)
HCC	172 (13.7)	195 (15.5)	69 (1.4)	68 (1.4)
Non-HCC malignant neoplasm	29 (2.3)	29 (2.3)	66 (1.3)	52 (1.1)
Non-HCC HBV disease progression	83 (6.6)	84 (6.7)	54 (1.1)	62 (1.3)

COE, clinical outcome event; EAC, event adjudication committee; ETV, entecavir; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

Supplementary Table 10. Treatment-Related Serious Adverse Events

Patients with events, n (%)	ETV N = 6216	Non-ETV N = 6162
Total patients with an event	12 (0.2)	50 (0.8)
Investigations	3 (<0.1)	5 (<0.1)
Alanine aminotransferase level increased	2 (<0.1)	0
Blood bilirubin level increased	1 (<0.1)	0
Blood creatine phosphokinase level increased	0	3 (<0.1)
Blood creatine level increased	0	1 (<0.1)
Weight decreased	0	1 (<0.1)
Gastrointestinal disorders	2 (<0.1)	0
Pancreatitis	1 (<0.1)	0
Acute pancreatitis	1 (<0.1)	0
Blood and lymphatic system disorders	1 (<0.1)	0
Thrombocytopenia	1 (<0.1)	0
Hepatobiliary disorders	1 (<0.1)	1 (<0.1)
Chronic hepatitis	1 (<0.1)	0
Hepatitis	0	1 (<0.1)
Infections and infestations	1 (<0.1)	1 (<0.1)
Chronic hepatitis B	1 (<0.1)	0
Hepatitis B virus	0	1 (<0.1)
Injury, poisoning, and procedural complications	1 (<0.1)	2 (<0.1)
Overdose	1 (<0.1)	0
Atypical femur fracture	0	1 (<0.1)
Toxicity to various agents	0	1 (<0.1)
Musculoskeletal and connective tissue disorders	1 (<0.1)	24 (0.4)
Myalgia	1 (<0.1)	1 (<0.1)
Muscular weakness	0	5 (<0.1)
Myopathy	0	15 (0.2)
Myositis	0	1 (<0.1)
Polymyositis	0	2 (<0.1)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	1 (<0.1)	0
Hepatocellular carcinoma	1 (<0.1)	0
Renal and urinary disorders	1 (<0.1)	7 (0.1)
Renal impairment	1 (<0.1)	1 (<0.1)
Acute kidney injury	0	1 (<0.1)
Nephropathy	0	3 (<0.1)
Nephropathy toxic	0	2 (<0.1)
General disorders and administration site conditions	0	2 (<0.1)
Edema peripheral	0	1 (<0.1)
Pelvic mass	0	1 (<0.1)
Metabolism and nutrition disorders	0	5 (<0.1)
Hypophosphatemia	0	4 (<0.1)
Lactic acidosis	0	1 (<0.1)
Nervous system disorders	0	5 (<0.1)
Hypoesthesia	0	1 (<0.1)
Mononeuropathy	0	1 (<0.1)
Mononeuropathy multiplex	0	1 (<0.1)
Neuropathy peripheral	0	2 (<0.2)

ETV, entecavir.

Supplementary Table 11. China Cohort: COEs by Baseline Subgroup

Parameter, n/N (%)	Overall malignant neoplasms		HCC		Liver-related HBV disease progression		Deaths	
	ETV N = 2659	Non-ETV N = 2646	ETV N = 2659	Non-ETV N = 2646	ETV N = 2659	Non-ETV N = 2646	ETV N = 2659	Non-ETV N = 2646
All	90/2659 (3.4)	104/2646 (3.9)	69/2659 (2.6)	87/2646 (3.3)	95/2659 (3.6)	114/2646 (4.3)	62/2659 (2.3)	74/2646 (2.8)
Age, *y*								
<30	0/734	2/778 (0.3)	0/734	2/778 (0.3)	2/734 (0.3)	4/778 (0.5)	2/734 (0.3)	2/778 (0.3)
30–49	51/1580 (3.2)	52/1534 (3.4)	38/1580 (2.4)	42/1534 (2.7)	56/1580 (3.5)	55/1534 (3.6)	35/1580 (2.2)	39/1534 (2.5)
50–54	13/207 (6.3)	18/191 (9.4)	11/207 (5.3)	16/191 (8.4)	14/207 (6.8)	22/191 (11.5)	5/207 (2.4)	13/191 (6.8)
≥55	26/138 (18.8)	32/143 (22.4)	20/138 (14.5)	27/143 (18.9)	23/138 (16.7)	33/143 (23.1)	20/138 (14.5)	20/143 (14.0)
BMI, kg/m^2								
<25	59/1954 (3.0)	73/1956 (3.7)	45/1954 (2.3)	64/1956 (3.3)	65/1954 (3.3)	85/1956 (4.3)	42/1954 (2.1)	50/1956 (2.6)
25–30	26/598 (4.3)	25/597 (4.2)	20/598 (3.3)	18/597 (3.0)	25/598 (4.2)	24/597 (4.0)	15/598 (2.5)	19/597 (3.2)
>30	5/106 (4.7)	6/85 (7.1)	4/106 (3.8)	5/85 (5.9)	5/106 (4.7)	5/85 (5.9)	5/106 (4.7)	5/85 (5.9)
Sex								
Men	71/2148 (3.3)	92/2128 (4.3)	56/2148 (2.6)	79/2128 (3.7)	76/2148 (3.5)	100/2128 (4.7)	53/2148 (2.5)	67/2128 (3.1)
Women	19/511 (3.7)	12/518 (2.3)	13/511 (2.5)	8/518 (1.5)	19/511 (3.7)	14/518 (2.7)	9/511 (1.8)	7/518 (1.4)
Historic cirrhosis								
Present	42/317 (13.2)	52/307 (16.9)	40/317 (12.6)	49/307 (16.0)	56/317 (17.7)	59/307 (19.2)	39/317 (12.3)	37/307 (12.1)
Absent	48/2342 (2.0)	52/2339 (2.2)	29/2342 (1.2)	38/2339 (1.6)	39/2342 (1.7)	55/2339 (2.4)	23/2342 (1.0)	37/2339 (1.6)
Historic HBeAg								
Positive	38/1752 (2.2)	54/1733 (3.1)	31/1752 (1.8)	45/1733 (2.6)	45/1752 (2.6)	60/1733 (3.5)	31/1752 (1.8)	45/1733 (2.6)
Negative	49/862 (5.7)	48/846 (5.7)	36/862 (4.2)	40/846 (4.7)	47/862 (5.5)	50/846 (5.9)	30/862 (3.5)	28/846 (3.3)
HBV DNA, log_{10} *IU/mL*								
<5	31/544 (5.7)	30/525 (5.7)	25/544 (4.6)	26/525 (5.0)	32/544 (5.9)	34/525 (6.5)	21/544 (3.9)	24/525 (4.6)
5 to <6	15/365 (4.1)	20/389 (5.1)	13/365 (3.6)	17/389 (4.4)	18/365 (4.9)	19/389 (4.9)	12/365 (3.3)	15/389 (3.9)
6 to <7	22/422 (5.2)	26/395 (6.6)	16/422 (3.8)	24/395 (6.1)	24/422 (5.7)	32/395 (8.1)	12/422 (2.8)	18/395 (4.6)
7 to <8	14/744 (1.9)	21/761 (2.8)	11/744 (1.5)	15/761 (2.0)	15/744 (2.0)	23/761 (3.0)	13/744 (1.7)	14/761 (1.8)
≥8	7/537 (1.3)	4/515 (0.8)	3/537 (0.6)	2/515 (0.4)	5/537 (0.9)	2/515 (0.4)	4/537 (0.7)	2/515 (0.4)
HBV nuc experience								
Naive	57/1766 (3.2)	69/1760 (3.9)	44/1766 (2.5)	58/1760 (3.3)	60/1766 (3.4)	77/1760 (4.4)	43/1766 (2.4)	56/1760 (3.2)
Experienced	33/893 (3.7)	35/886 (4.0)	25/893 (2.8)	29/886 (3.3)	35/893 (3.9)	37/886 (4.2)	19/893 (2.1)	18/886 (2.0)
Cigarette smoking ever								
Yes	34/716 (4.7)	40/711 (5.6)	27/716 (3.8)	34/711 (4.8)	36/716 (5.0)	41/711 (5.8)	29/716 (4.1)	34/711 (4.8)
No	56/1933 (2.9)	64/1935 (3.3)	42/1933 (2.2)	53/1935 (2.7)	59/1933 (3.1)	73/1935 (3.8)	32/1933 (1.7)	40/1935 (2.1)
Alcohol drinking ever								
Yes	25/574 (4.4)	32/578 (5.5)	20/574 (3.5)	28/578 (4.8)	26/574 (4.5)	34/578 (5.9)	14/574 (2.4)	22/578 (3.8)
No	65/2075 (3.1)	72/2068 (3.5)	49/2075 (2.4)	59/2068 (2.9)	69/2075 (3.3)	80/2068 (3.9)	47/2075 (2.3)	52/2068 (2.5)

BMI, body mass index; COE, clinical outcome event; ETV, entecavir; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; nuc, nucleos(t)ide.

Supplementary Table 12. China Cohort: Rates of Incomplete Viral Suppression by Year

Group, n/N (%)	Year 1	Year 3	Year 5	Year 7	Year 10
ETV	893/2497 (36)	485/2385 (20)	411/2288 (18)	196/1495 (13)	85/683 (12)
Experienced	378/832 (45)	215/789 (27)	186/778 (24)	96/505 (19)	45/269 (17)
Naive	515/1665 (31)	270/1596 (17)	225/1510 (15)	100/990 (10)	40/414 (10)
Non-ETV	1526/2375 (64)	1011/2242 (45)	702/2098 (33)	357/1353 (26)	130/603 (22)
Experienced	524/795 (66)	358/751 (48)	249/712 (35)	119/459 (26)	43/247 (17)
Naive	1002/1580 (63)	653/1491 (44)	453/1386 (33)	238/894 (27)	87/356 (24)
Total	2419/4872 (50)	1496/4627 (32)	1113/4386 (25)	553/2848 (19)	215/1286 (17)
P value, ETV vs non-ETV	<.001	<.001	<.001	<.001	<.001

NOTE. Rates of incomplete viral suppression (HBV DNA level >50 IU/mL) are shown at each time point according to treatment group and prior treatment status. Differences between treatment groups were tested using chi-square analysis; all statistical tests were 2-sided and conducted using SPSS version 23.0 (IBM, Armonk, NY).
ETV, entecavir.

Supplementary Table 13. China Cohort: Virologic Response and Covariate-Adjusted Time-to-EAC–Adjudicated HBV-Related COEs

Patients with events, n	Responder N = 2119	Nonresponder N = 540	Responder:nonresponder hazard ratio (95% CI)
ETV			
Liver-related HBV disease progression	70	25	0.09 (0.038–0.221)
Non-HCC liver-related HBV disease progression	30	6	0.18 (0.053–0.647)
HCC	48	21	0.03 (0.009–0.113)
Liver-related death	1	2	Not applicable[a]
	Responder N = 1608	Nonresponder N = 1038	
Non-ETV			
Liver-related HBV disease progression	59	55	0.11 (0.056–0.201)
Non-HCC liver-related HBV disease progression	21	23	0.10 (0.041–0.250)
HCC	41	46	0.05 (0.022–0.105)
Liver-related death	0	6	Not applicable[a]

COE, clinical outcome event; EAC, event adjudication committee; ETV, entecavir; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; non-ETV, standard-of-care hepatitis B virus nucleos(t)ide analogue.
[a]Iteration limit was reached without convergence.