ClinicalTrials.gov ID (NCT Number): NCT03753074

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Unique Protocol Id: IN-KR-320-5358

Clinical Trial Protocol

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A Multinational, Multicenter, Open-label, Randomized Controlled **T**rial to Investigate the Effectiveness of **TEN**ofovir Alafenamide in Reducing Clinical Events in Chronic Hepatitis B Patients beyond Treatment Indica**TION**s by Current Guidelines **(ATTENTION)**

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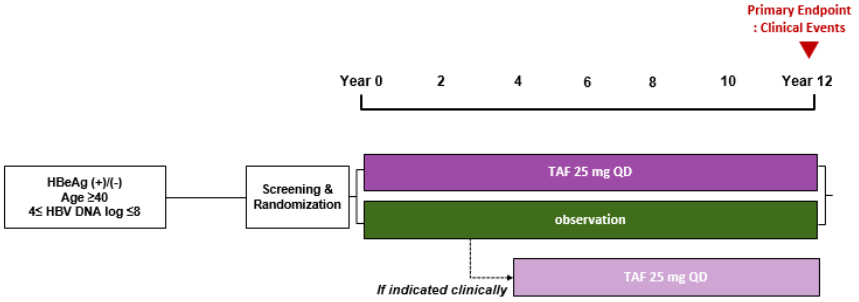
Protocol Version	Master Version Number 5.0 (Ver. Date: 26/SEP/2023) Local Version for Taiwan, Number 5.0(Ver. Date: 26/SEP/2023)
Clinical Study Type	Investigator Initiated Trial
Chief Investigator	Young-Suk Lim Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, South Korea
Clinical Phase	Phase IV

Confidentiality

Synopsis

Protocol Title	A Multinational, Multicenter, Open-label, Randomized Controlled Trial to Investigate the Effectiveness of Tenofovir Alafenamide in Reducing Clinical Events in Chronic Hepatitis B Patients beyond Treatment Indications by Current Guidelines (ATTENTION)
Chief Investigator	Professor Young-Suk Lim, Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine
Investigators	International and Multicenter
Study Sites	10 sites in Korea + 12 sites in Taiwan
Clinical Phase	Phase IV
Study Design	Multinational, Multicenter, Open-label, Randomized Controlled Trial
Number of Subjects to be Enrolled	780 subjects • Treatment Arm: TAF 25 mg QD • Observation Arm: Best Supportive Care
Number of Subjects Planned	780 subjects • Treatment Arm: 390 subjects • Observation Arm: 390 subjects Group-Sequential Two-Sided Log-rank Tests(O'Brien-Fleming) Maximum follow-up = 12 years (1st interim = 4 years, 2nd interim = 8 years, final analysis = 12 years) -Proportional hazards assumption model, assumed survival rates (12 years) = 0.889/0.801 (Treatment Arm/Observation Arm) -Hazard ratio Treatment Arm/Observation Arm) = 0.53 -Required number of events: 115 (assuming hazard ratio of 0.53) -Power: 0.85 -Type I error rate: 0.025
Study Population	Chronic hepatitis B male and female adults, without cirrhosis who are not currently receiving treatment for hepatitis B and are beyond treatment indications by current guidelines
Objectives	To assess the efficacy of Tenofovir Alafenamide (TAF) in reducing liver-related events (hepatocellular carcinoma [HCC], liver-related death, liver transplantation, and decompensated liver disease) in chronic hepatitis B patients beyond treatment indications by current guidelines, compared with best supportive care
Duration of Study Planned	Until December 31, 2031., from the date of IRB approval. • The study's end is defined as the last date of information collection for the primary and secondary outcome variable analyses for the first subject
Investigational Products	Tenofovir Alafenamide 25 mg (Vemlidy®)
Methodology	Approximately 780 subjects meeting eligibility criteria will be enrolled. Subjects will be randomized (1:1) to Treatment Arm or Observation Arm, below: • Treatment Arm (n=390): TAF 25 mg once daily with food • Observation Arm (n=390): Best supportive care Participants will be randomly allocated to each study arm in order to prevent bias and ensure comparability between the Treatment arm and Observation arm. Centralized stratified block randomization will be utilized in which participants will be stratified by HBeAg status (positive or negative) and, in

	each stratum, randomly allocated to either Treatment or Observation arm in 1:1 ratio as HBeAg status is expected to affect the primary outcome based on the clinical evidence stating that HBeAg status may influence the primary outcome. This study will be followed up for 12 years. Observation arm (treatment arm B) will initiate TAF treatment if the participants in the observation arm satisfy the criteria of TAF treatment issued by American Association for the Study of Liver Disease 2018. The criteria of TAF treatment in the observation arm is as follows: ● ALT level ≥70 IU/L (males) or ≥50 IU/L (females) by local laboratory test ● 40≤ALT levels<70 IU/L (males) or 40≤ ALT levels<50 IU/L (females) with evidence of significant fibrosis (F2 ≥7.2 kPa) as measured by either liver biopsy, Fibroscan, or MR elastography performed within 3 months ● If they were clinically judged to have cirrhosis by investigators and confirmed with Fibroscan (≥ 12.0 kPa). * Study Design 
Efficacy Evaluation	**Primary Efficacy Endpoint:** The primary efficacy endpoint of this study is the occurrence of composite events during follow-up observation. including death, liver transplantation, or decompensated liver diseases [Child-Pugh score≥7], complications of portal hypertension [ascites, gastroesophageal varices] or HCC in the full analysis set. **Secondary Efficacy Endpoints:** The secondary endpoints of this study include: ● Cumulative incidence of composite clinical events (Composite endpoint: death, liver transplantation, decompensated cirrhosis [Child-Pugh score≥7], portal hypertension complications [ascites, esophageal varices], HCC) ● Cumulative incidence of HCC ● Cumulative incidence of death ● Cumulative incidence of liver transplantation ● Cumulative incidence of decompensated liver diseases[Child-Pugh score ≥7] ● Cumulative incidence of complications of portal hypertension [ascites, gastroesophageal varices] ● Proportion of subjects who start treatment with TAF in Observation Arm ● Cumulative Proportion with viral response (HBV < 15 IU/mL) ● Cumulative Proportion with normal ALT ● Cumulative Proportion with HBeAg seroclearance (only for subjects

	who are HBeAg-positive at baseline) ● Serial changes of Fibroscan ● Serial changes of APRI index ● Serial changes of FIB-4 index ● Serial changes in the quality of life of the study patients according to treatment, treatment response, treatment duration, outcomes (hepatitis, cirrhosis, HCC) *Subgroup analysis for HBeAg(+) or HBeAg(-) -Cumulative incidence of HCC -Cumulative incidence of mortality -Cumulative incidence of liver transplantation -Cumulative incidence of decompensated liver diseases [Child-Pugh score≥7] -Cumulative incidence of portal hypertension complications [ascites, gastroesophageal varices] -Cumulative Proportion with viral response (HBV < 15 IU/mL) -Cumulative Proportion with normal ALT *Subgroup analysis of subjects according to baseline ALT level (normal ALT and elevated ALT) -Cumulative incidence of HCC -Cumulative incidence of mortality -Cumulative incidence of liver transplantation -Cumulative incidence of decompensated liver diseases [Child-Pugh score≥7] -Cumulative incidence of portal hypertension complications [ascites, gastroesophageal varices] -Cumulative Proportion with viral response (HBV < 15 IU/mL) ● Cumulative and annual rate of patients with clinical events (death, liver transplantation, liver decompensation, portal hypertensive complications, and HCC) after excluding patients who occurs clinical events within 6 months of enrollment ● Cumulative and annual rate of patients with clinical events (death, liver transplantation, liver decompensation, portal hypertensive complications, and HCC) after excluding patients who occurs clinical events within 12 months of enrollment ● Cumulative and annual rate of patients with clinical events (death, liver transplantation, liver decompensation, portal hypertensive complications, and HCC) in patients with normal ALT (<40 U/L) at the time of enrollment, after excluding patients who occurs clinical events within 6 months of enrollment ● Cumulative and annual rate of patients with clinical events (death, liver transplantation, liver decompensation, portal hypertensive complications, and HCC) in patients with normal ALT (<40 U/L) at the time of enrollment, after excluding patients who occurs clinical events within 12 months of enrollment

Eligibility Criteria (Inclusion/Exclusion)	**Inclusion Criteria** 1) Willing and able to provide written informed consent prior to study entry. 2) Age ≥40 years and ≤80 years at the time of screening. 3) Chronic hepatitis B infection defined as HBsAg (+) or HBV DNA (+) for at least 6 months prior to the Screening visit, or the subject is not regarded to have acute hepatitis B according to the clinical assessment of the investigator. 4) Either HBeAg (+) or HBeAg (-) 5) Subject must be documented as non-cirrhotic (Platelet ≥ 100,000/ mm^3) 6) Serum HBV DNA levels ≥1.0 x 10^4 IU/mL and ≤1.0 x 10^8 IU/mL (4.00 $\log_{10}$ IU/mL ≤ Serum HBV DNA levels ≤ 8.00 $\log_{10}$ IU/mL) 7) Serum ALT levels<70 IU/L (males) or <50 IU/L (females) 8) Estimated creatinine clearance ≥ 30 ml/min (CrCl or CKD-EPI) 9) Ability to comply with all study requirements **Exclusion Criteria** 1) Confirmed known co-infection with HCV, HIV, or HDV 2) Current alcohol (60g/day) or substance abuse judged by the investigator that will potentially interfere with subject compliance 3) History or current evidence of clinically hepatic decompensation (e.g., ascites, encephalopathy, variceal hemorrhage) 1 year prior to Screening, or a Child-Pugh grade 7 (with the exception of Gilbert syndrome) at the time of Screening. 4-1) Evidence of liver cirrhosis defined as meeting any of the following criteria: a) Platelet count <100,000/mm^3 b) Clinically significant portal hypertension c) Presence of esophageal or gastric varices by endoscopy in 2 years before the time of screening d) Fibroscan ≥ 12.0 kPa (If the test was done in 3 months before the time of screening.) and confirmed to have liver cirrhosis by an investigator 4-2) 40≤ALT levels<70 IU/L (males) or 40≤ ALT levels<50 IU/L (females) with evidence of significant fibrosis (F2 ≥7.2 kPa) as measured by either liver biopsy, Fibroscan, or MR elastography performed within 3 months 5) Currently on or have received therapy with Interferon or immunosuppressant (including systemic chemotherapy) within 12 months prior to the screening 6) Requirement for chronic use of systemic immunosuppressant including, but not limited to, corticosteroid (prednisone equivalent of >40 mg/day for >2 weeks), azathioprine, or monoclonal antibodies 7) Received solid organ or bone marrow transplant 8) History of severe, life-threatening or other significant sensitivity to any excipients of the study drugs 9) Any other clinical conditions (cardiovascular, respiratory, neurologic, or renal conditions) or prior therapy that, in the opinion of the investigator, would make the subject unsuitable for the study or unable to comply with dosing requirements. 10) Currently on or have received antiviral treatment for ≥ 2 weeks within 6 months prior to the screening 11) History or current evidence of HCC, or high α-fetoprotein (AFP) > 20 ng/mL. (Patients with AFP>20ng/mL can be enrolled, however if imaging investigations, such as dynamic CT or MRI, provide no evidence of HCC within 4 months prior to Screening) 12) Malignancy other than HCC within 5 years prior to the screening, with the exception of specific cancers that are cured by surgical resection (within 2

	years prior to screening with confirmation of no evidence of disease). Subjects under evaluation for possible malignancy are not eligible. 13) Concurrent enrollment in another clinical study for other type of antiviral treatment for CHB or immune modulatory drug within 3 months prior to randomization,, Participation to an observational (non-interventional) clinical studies or interventional studies not using anti-HBV or immune modulatory drugs, or during the follow-up period of an interventional study are not exclusion criteria. 14) Pregnant women, women who are breastfeeding or who believe they may wish to become pregnant during the course of the study
Statistical Analysis	The primary analysis set for efficacy analysis is the full analysis set (FAS), defined as all subjects who were randomized to Treatment Arm or Observation Arm (intention-to-treat analysis). Subjects will be analyzed according to the randomized or enrolled treatment assignment. Demographic and baseline characteristics will be summarized by Treatment Arm and Observation Arm using standard descriptive methods. Continuous endpoints will be summarized using conventional descriptive statistics by the initially assigned group. Categorical endpoints will be summarized by number and percentage of subjects that meet the endpoint by the initially assigned group. Exploratory analyses will be also performed to evaluate the effect of TAF treatment in the rate of HCC development using Cox proportional hazard model by adjusting potential confounders including age, sex, HBeAg positivity, serum HBV DNA level at baseline, ALT level, and platelet counts. Exploratory analyses for secondary endpoints will be performed by on-treatment analysis. $P<0.05$ considers statistically significant. SPSS (SPSS, Chicago, IL, USA) and R program (https://cran.r-project.org/) will be used for statistical analyses. Serial changes in the quality of life (EQ-5D and EQ-VAS) of the study patients according to treatment, treatment response, treatment duration, outcomes (hepatitis, cirrhosis, HCC) will be analyzed by Generalized Estimation Equation (GEE) adjusted by age, gender, and baseline clinical characteristics of the patients. Interim analyses will be conducted at 4 and 8 years after the start of the study, including all randomly assigned patients. If the null hypothesis is not rejected, a final analysis will be performed at the 12-year mark to demonstrate statistical significance.

Signature Page

Protocol Agreement

Clinical Study Title

A Multinational, Multicenter, Open-label, Randomized Controlled Trial to Investigate the Effectiveness of Tenofovir Alafenamide in Reducing Clinical Events in Chronic Hepatitis B Patients beyond Treatment Indications by Current Guidelines (ATTENTION)

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by primary site of this study. I will discuss this material with them to ensure that they are fully informed about the drugs and the study

Investigator

_____	_____	_____
Printed Name	Signature	Date (DD/MM/YYYY)

Table of Contents

1 Study Title and Phase

1.1 Study Title

A Multinational, Multicenter, open-label, Randomized Controlled Trial to Investigate the Effectiveness of Tenofovir Alafenamide in Reducing Clinical Events in Chronic Hepatitis B Patients beyond Treatment Indications by Current Guidelines (ATTENTION)

1.2 Study Phase

Phase IV (Investigator Initiated Trial)

2 Study Sites and Investigators

Korea Sites

Study Sites	Investigators
Asan Medical Center	Young-Suk Lim
Samsung Medical Center	Wonseok Kang
Kyung-Hee University Hospital	Gi-Ae Kim
Chung-Ang University Hospital	Hyung Joon Kim
Seoul National University Hospital	Yun Bin Lee
Ulsan University Hospital	Neung-Hwa Park
Konkuk University Medical Center	So Young Kwon
Kyungpook National University Hospital	Soo Young Park
Korea University Guro Hospital	Ji Hoon Kim
Seoul National University Bundang Hospital	Gwang Hyeon Choi

Taiwan Sites

Study Sites	Investigators
Kaohsiung Medical University Hospital	Ming-Lung Yu
Kaohsiung Chang Gung Memorial Hospital OF THE G.G.M.F	Chien-Hung Chen
E-Da Hospital	Yao-Chun Hsu
Taitung Mackay Memorial Hospital	Ming-Jong Bair
National Cheng Kung University Hospital	Pin-Nan Cheng
Chi Mei Hospital, Liouying	Hung-Da Tung

Chang Gung Memorial Hospital, Chia-Yi	Te-Sheng Chang
Ditmanson Medical Foundation Chia-Yi Christian Hospital	Chi-Yi Chen
St. Martin De Porres Hospital	Ching-Chu Lo
Dalin Tzu Chi General Hospital	Kuo-Chih Tseng
Taichung Veterans General Hospital	Sheng-Shun Yang
China Medical University Hospital	Cheng-Yuan Peng

3 Purpose and Background

3.1 Purpose

To determine whether or not TAF treatment in the patients beyond treatment indications by current guidelines who have high risk of HCC, deaths and events associated with hepatic diseases reduces the incidence of HCC, deaths and events associated with hepatic diseases.

3.2 Background

The goal of treatment for patients with chronic hepatitis B (CHB) is to improve survival by preventing disease progression and HCC.[1,2] Ideally, for hepatitis B therapies to be approved, they should demonstrate efficacy in preventing HCC and liver-related deaths. However, these clinical endpoints evolve over years or decades. Therefore, intermediate surrogate endpoints that are easy to assess, occur frequently, and are considered to correlate with clinical outcomes have been used for the evaluation of treatment efficacy. Those surrogate endpoints include virological, biochemical, and serological biomarkers.[1,2]

The natural course of CHB is typically divided into several phases based on hepatitis B e antigen (HBeAg) status, serum hepatitis B virus (HBV) DNA levels, and alanine aminotransferase (ALT) activity. The first, which is the immune-tolerant (IT) phase, is characterized by high circulating HBV DNA and normal ALT level. Antiviral treatment is generally not recommended for these patients by most practice guidelines because of the notion that the histological activity is dormant and the risk of disease progression is low in the IT phase.[3-5]However, recent studies have claimed that the histological activity and HBV-specific immune response do occur in the IT phase and are comparable with those occurring in the immune active (IA) phase. [6,7] Moreover, a high level of chromosomal HBV DNA integration and clonal hepatocyte expansion was found in patients considered to be in the IT phase, indicating that hepatocarcinogenesis could be under way in these patients.[8] These findings suggest that therapeutic interventions to minimize further damage to the hepatocytes should be

considered for IT-phase patients. However, virtually no clinical evidence exists regarding whether long-term antiviral treatment of IT-phase patients reduces the risk of HCC and mortality. A recently large-scale historical cohort study revealed that untreated IT-phase patients were associated with significantly higher risk of HCC and death/transplantation than the IA-phase patients treated with nucloes(t)ide analogues.[9] Moreover, the risks of HCC and death/transplantation were further increased among patients in the mildly active phase (ALT levels, 1-2 x upper limit of normal).[9] This historical cohort study also found out that older age, male, lower HBV DNA levels (but above 20,000 IU/mL) and low platelet counts were independently associated with a significantly higher risk of clinical events.[9]

Most HBeAg-negative CHB patients remain in an inactive hepatitis phase with low HBV DNA levels (<2000 IU/ mL) and persistently normal ALT. Approximately 10%–20% of patients progress to "HBeAg-negative active hepatitis phase" characterized by high levels of serum HBV DNA (≥2000 IU/mL), elevated ALT levels (≥2 upper limits of normal [ULN]), and continued necroinflammation, and are indicated for antiviral treatment.[10]However, approximately 30%–35% of HBeAg-negative CHB patients are in the "grey zone" having persistently normal or only mildly elevated ALT (<2ULN) despite high HBV DNA levels (≥2000 IU/mL).[8,11]Antiviral treatment for these patients is generally not recommended by most practice guidelines unless the liver biopsy show significant disease activity.InHBeAg-negative CHB patients with persistently normal ALT, high HBV DNA levels were independently associated with histologically significant hepatic inflammation and fibrosis. Furthermore, in a prospective cohort study that mostly included HBeAg-negative CHB patients (REVEAL-HBV cohort), high levels of HBV DNA (>2000 IU/mL) were associated with a high risk of hepatocellular carcinoma (HCC) and disease progression, irrespective of serum ALT levels.[12,13] However, little clinical evidence exists for whether antiviral treatment would reduce the risks of HCC and death/transplantation in the patients with high HBV DNA levels and persistently normal ALT levels or mildly elevated ALT levels.In a recently conducted large observational cohort study of 5,414 HBeAg-negative CHB patients, compared with the treated group, the untreated patients with high HBV DNA levels showed a significantly higher risk of HCC and death/transplantation by propensity score-matched analysis.[14]

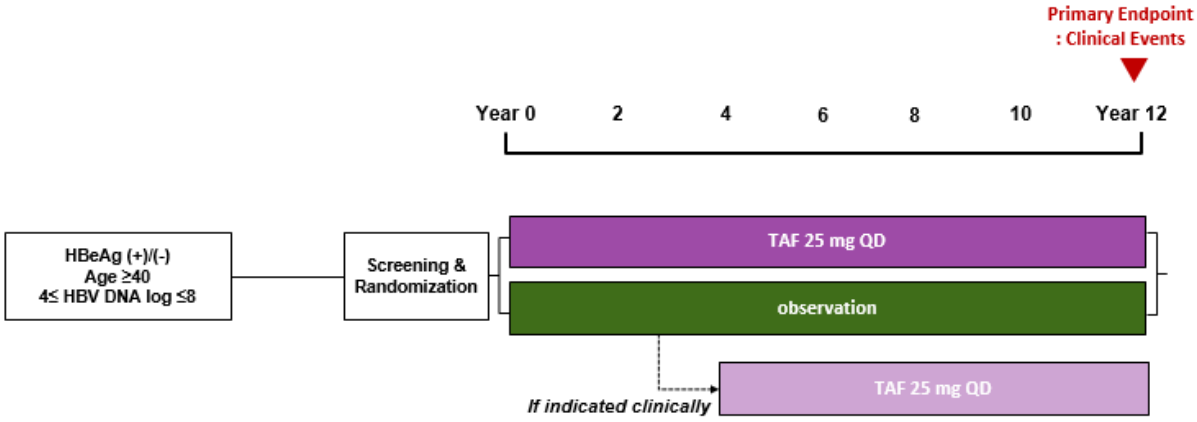
In the aforementioned two large observational studies, older age (≥40 years old) and serum HBV DNA levels between $1.0x10^4$ IU/mL and $1.0x10^8$ IU/mL were predictive factors of

development of HCC and death/transplantation. With these two predictive factors, the cumulative rate of clinical events including HCC or death/transplantation) were 2.77/100 person-years in untreated group, whereas 1.45/100 person-years in antiviral treatment groups. (Hazard ratio = 0.53)

Collectively, patients beyond treatment indication by current practice guidelines of CHB are not thoroughly researched. Few study exists whether long-term antiviral treatment for CHB in patients with above characterization can improve the long-term clinical outcomes. In particular, older age (≥40 years old) with intermediate range of serum HBV DNA (10^4-10^8 IU/mL) should be further evaluated.

4 Study Design

This is a Phase 4, randomized, open-label, international, multicenter study to evaluate the efficacy of Tenofovir Alafenamide in reducing clinical events (HCC, death, liver transplantation or decompensated liver diseases) in CHB patients beyond treatment indication by current practice guidelines for CHB, compared with patients who receive best supportive care.



5 Projected Duration of the Study

Until December 31,, 2031., from the date of IRB approval.

The study's end is defined as the last date of information collection for the primary and secondary outcome variable analyses for the first subject

6 Study Population

The study population consists of chronic hepatitis B male and female adults, without cirrhosis

who are not currently receiving treatment for hepatitis B and are beyond treatment indications by current guidelines

7 Study Subjects Criteria (Inclusion/Exclusion)

7.1 Inclusion Criteria

1) Willing and able to provide written informed consent prior to study entry.

2) Age ≥40 years and ≤80 years at the time of screening.

3) Chronic hepatitis B infection defined as HBsAg (+) or HBV DNA (+) for at least 6 months prior to the Screening visit, or the subject is not regarded to have acute hepatitis B according to the clinical assessment of the investigator.

4) Either HBeAg (+) or HBeAg (-)

5) Subject must be documented as non-cirrhotic (Platelet ≥ 100,000/ mm^3)

6) Serum HBV DNA levels ≥1.0 x 10^4 IU/mL and ≤1.0 x 10^8 IU/mL (4.00 $\log_{10}$ IU/mL ≤ Serum HBV DNA levels ≤ 8.00 $\log_{10}$ IU/mL)

7) Serum ALT levels<70 IU/L (males) or <50 IU/L (females)

8) Estimated creatinine clearance ≥ 30 ml/min (CrCl or CKD-EPI)

9) Ability to comply with all study requirements

7.2 Exclusion Criteria

1) Confirmed known co-infection with HCV, HIV, or HDV

2) Current alcohol (60g/day) or substance abuse judged by the investigator that will potentially interfere with subject compliance

3) History or current evidence of clinically hepatic decompensation (e.g., ascites, encephalopathy, variceal hemorrhage) 1 year prior to Screening, or a Child-Pugh grade 7 (with the exception of Gilbert syndrome) at the time of Screening.

4-1) Evidence of liver cirrhosis defined as meeting any of the following criteria:

a) Platelet count <100,000/mm^3

b) Clinically significant portal hypertension

c) Presence of esophageal or gastric varices by endoscopy in 2 years before the time of screening

d) Fibroscan ≥ 12.0 kPa (If the test was done in 3 months before the time of screening.) and confirmed to have liver cirrhosis by an investigator

4-2) 40≤ALT levels<70 IU/L (males) or 40≤ ALT levels<50 IU/L (females) with evidence of

significant fibrosis(F2; ≥7.2 kPa) as measured by either liver biopsy, Fibroscan or MR Elastography performed within 3 months.

5) Currently on or have received therapy with Interferon or immunosuppressant (including systemic chemotherapy) within 12 months prior to the screening

6) Requirement for chronic use of systemic immunosuppressant including, but not limited to, corticosteroid (prednisone equivalent of >40 mg/day for >2 weeks), azathioprine, or monoclonal antibodies

7) Received solid organ or bone marrow transplant

8) History of severe, life-threatening or other significant sensitivity to any excipients of the study drugs

9) Any other clinical conditions (cardiovascular, respiratory, neurologic, or renal conditions) or prior therapy that, in the opinion of the investigator, would make the subject unsuitable for the study or unable to comply with dosing requirements.

10) Currently on or have received antiviral treatment for ≥ 2 weeks within 6 months prior to the screening

11) History or current evidence of HCC, or high α-fetoprotein (AFP) > 20 ng/mL. (Patients with AFP>20ng/mL can be enrolled, however if imaging investigations, such as dynamic CT or MRI, provide no evidence of HCC within 4 months prior to Screening)

12) Malignancy other than HCC within 5 years prior to the screening, with the exception of specific cancers that are cured by surgical resection (within 2 years prior to screening with confirmation of no evidence of disease). Subjects under evaluation for possible malignancy are not eligible.

13) Concurrent enrollment in another clinical study for other type of antiviral treatment for CHB or immune modulatory drug within 3 months prior to randomization,, Participation to an observational (non-interventional) clinical studies or interventional studies not using anti-HBV or immune modulatory drugs, or during the follow-up period of an interventional study are not exclusion criteria.

14) Pregnant women, women who are breastfeeding or who believe they may wish to become pregnant during the course of the study

8 Study Procedures and Methods

8.1 Treatment Allocation

(1) Treatment Arm (Treatment Arm A): Tenofovir Alafenamide (25mg/day)

(2) Observation Arm (Treatment Arm B): Best supportive care

(3) Allocation Method: An independent statistician will generate the code to randomly allocate participants to either Treatment Arm or Observation Arm in 1:1 ratio by stratified block randomization. Centralized stratified block randomization will be utilized in which participants will be stratified by HBeAg status (positive or negative) and, in each stratum, randomly allocated to either Treatment or Observation arm in 1:1 ratio. The ratio of HBeAg(+) to HBeAg(-) in each arm may be variable. Study sites will then randomly allocate the eligible patients who provide the informed consent to each study arm. Interactive Web Response System (IWRS) will be utilized to randomly allocate the participants to either Treatment Arm or Observation Arm in 1:1 ratio. Both investigators and patients will be aware of the allocation as this study is the open-label trial.

(4) Allocated patients: A total number of patients in the study – 780 (Treatment Arm: 390, Observation Arm: 390)

(5) Treatment Method: Investigational Product, Administration Method and Dosage

Group	Number of subjects	Treatment
Treatment Arm	390	Tenofovir Alafenamide 25 mg oral once daily
Observation Arm	390	Best supportive care

Observation arm (Treatment Arm B) will initiate TAF treatment if the participants in the Observation arm satisfy the criteria of TAF treatment issued by American Association for the Study of Liver Disease 2018. The criteria of TAF treatment in the Observation arm is as follows:

- ALT level ≥70 U/L (males) or ≥50 U/L (females) by local laboratory test
- 40≤ALT levels<70 IU/L (males) or 40≤ ALT levels<50 IU/L (females) with evidence of significant fibrosis(F2; ≥7.2 kPa) as measured either liver biopsy, Fibroscan or MR Elastography performed within 3 months.
- If they were clinically judged to have cirrhosis by investigators and confirmed with Fibroscan (≥ 12.0 kPa).

8.2 Evaluation Assessments

8.2.1 **Timetable of the study**

Assessment / Procedure	**Screening[1]**	**Baseline**	**On-Treatment[2]**					**EOT**
	Baseline ≤ 28days	**M0**	**M6/M18/ M30/M42**	**M12/M 24/M36**	**M48**	**M54/M66/ M78/M90/ M102/M11 4/M126/M1 38**	**M60/M 72/M84 /M96/M 108/M1 20/M13 2**	**M144**
Informed consent	X							
Re-consent for extension					X			
Medical History	X							
Inclusion/Exclusion Criteria	X	X						
Physical Examination[3]	X	X	X	X	X	X	X	X
Randomization		X						
Vital signs[4]	X	X	X	X	X	X	X	X
EQ-5D questionnaire[15]		X		X	X		X	X
Hematology[5]	X	X	X	X	X	X	X	X
Chemistry[6]	X[7]	X[7]	X	X	X	X	X	X
Lipid profile[7]		X	X	X	X	X	X	X
Prothrombin Time	X	X	X	X	X	X	X	X
HBV DNA	X	X	X	X	X	X	X	X
HBsAg[8]	X[10]	X[10]		X	X		X	X
HBsAb	X[11]							
HBeAg/HBeAb	X	X	X	X	X	X	X	X
Alpha-fetoprotein	X	X	X	X	X	X	X	X
US or CT or MRI	X[9]	X	X	X	X	X	X	X
Bone densitometry		X[10]		X[11]	X[11]		X[11]	X[11]
Fibroscan	X[12]			X[11]	X[11]	X[11]	X[11]	X[11]
HbA1C		X[11]		X	X		X	X
Serum for storage[13]		X	X	X	X	X	X	X
Buffy coat		X[14]						
Dispense study drug		X	X	X	X	X	X	
Adverse Events			X	X	X	X	X	X
Compliance check			X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X

1. Screening and baseline evaluation can be done once on the same day. Laboratory tests can be replaced if the tests were done within 2 months prior to the screening.
2. Window period of 2 months from the designated visit date is allowed for each follow-up visit during the study period.
3. A complete physical examination will be taken at screening, and a symptom based physical examination will be performed at each visit
4. Vital Signs: Blood pressure, pulse rate, weight. Height will be measured at the screening visit only. And waist circumference will be measured at Baseline, M12, M24, M36, M48 visit only.
5. Hematology: Hemoglobin, WBC, platelet count, ANC
6. Chemistry: Sodium, potassium, BUN, creatinine, total protein, albumin, AST, ALT, ALP, Total/direct bilirubin, phosphorus, calcium. Just sodium, potassium, BUN, calcium, direct bilirubin, phosphorus could be optional.
7. Lipid profile: Triglyceride, Total Cholesterol, HDL, LDL, it will be done accordance with the decision of the investigator.
8. HBsAg can be measured by either quantitative or qualitative methods at each study site. Study sites can measure HBsAg with stored serum by quantitative methods after the end of this study.

9. Can be replaced if relevant imaging tests (abdominal USG, CT, or MRI) were done within 4 months prior to the screening
10. Can be replaced if the Bone mineral density was done within 12 months prior to the baseline, not mandatory
11. Not mandatory
12. Can be replaced if the Fibroscan was done within 3 months prior to the Screening
13. At every visit serum samples are collected and distributed 0.3-0.5 mL to each cryo tubes (aliquot into at least 4 tubes). These samples will be stored under -70 Celsius degree.
14. If the sample is not collected at screening, it may be collected at any other visit during the study.
15. The questionnaire is optional in Taiwan sites.

8.2.2 **Study Procedures**

1) Screening visit (Baseline ≤28 days)

- Obtain written informed consent
- Basic information and medical history
- Review of inclusion/exclusion criteria
- Complete physical examination and vital signs
  - Physical examination: Lower leg edema, Ascites
  - Vital signs: blood pressure, pulse rate, body weight, height (height can be measured only one time at screening visit)
- Laboratory assessments(Can be replaced if tests were done within 2 months prior to the screening)
  - Blood: Hematology, Chemistry, Prothrombin Time, HBV DNA, HBsAg, HBsAb, HBeAg/HBeAb, AFP
    - HBsAg assessment can be replaced by HBV DNA (+) test results.
    - HBsAb assessment is recommended to be performed at the screening visit, but it can be still completed during baseline or M6.
    - Sodium, potassium, BUN, calcium, direct bilirubin and phosphorus are not mandatory Chemistry assessments.
- Evaluate last clinical imaging (Abdominal US, CT, or MRI, which can be replaced if relevant imaging tests were done within 4 months prior to the screening)
- Fibroscan (Can be replaced if the test was done within 3 months prior to the Screening)
- Review concomitant drugs

2) Baseline (Month 0)

- Review of inclusion/exclusion
- Complete physical examination and vital signs
  - Physical examination: Lower leg edema, Ascites

- Vital signs: blood pressure, pulse rate, body weight, waist circumference

- Randomization
- Dispense study drug for patients assigned to “Treatment Arm”
- EQ-5D questionnaire
- Laboratory assessments (Can be replaced if tests were done within 2 months prior to the baseline)
  - Blood: Hematology, Chemistry, Lipid profile, Prothrombin Time, HBV DNA, HBsAg, HBeAg/HBeAb, AFP, HbA1C, Buffy coat &Serum for storage
    - HBsAg assessment can be replaced by HBV DNA (+) test results.
    - HbA1c measurement is not mandatory.
    - Sodium, potassium, BUN, calcium, direct bilirubin and phosphorus are not mandatory Chemistry assessments.
- Bone mineral density (Can be replaced if the test was done within 12 months prior to the baseline, not mandatory)
- Evaluate last clinical imaging (Abdominal US, CT, or MRI, which can be replaced if relevant imaging tests were done within 4 months prior to the baseline)
- Review concomitant drugs

3) Follow-up visits (Month 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, 102, 108, 120, 126, 132 and 138)

- Physical examination: Lower leg edema, Ascites
- Vital signs: blood pressure, pulse rate, body weight
  (Waist circumference at Baseline, M12, M24, M36 and M48 visit only)
- EQ-5D questionnaire (Month 12, 24, 36, 48, 60, 72, 84, 96, 108, 120 and 132 only)
- Laboratory assessments
  - Blood: Hematology, Chemistry, Lipid profile, Prothrombin Time, HBV DNA, HBeAg/HBeAb,AFP, Serum for storage,
  - Blood: HBsAg and HbA1c (Month 12, 24, 36, 48, 60, 72 and 84 only)
- Image tests (Abdominal US, CT, or MRI)
- Bone mineral density (Month 12, 24, 36, 48, 60, 72 and 84 only / Not mandatory)
- Fibroscan (Month 12, 24, 36, 48, 54, 60, 66, 72, 78, 84, 90, 96, 102, 108, 114, 120, 126,132 and 138 only / Not mandatory)
- Review adverse events

- Dispense study drug for patients assigned to “Treatment Arm”
- Perform study drug compliance
- Review concomitant drugs

4) Month 144

- Physical examination: Lower leg edema, Ascites
- Vital signs: blood pressure, pulse rate, body weight
- EQ-5D questionnaire
- Laboratory assessments
  - Blood: Hematology, Chemistry, Lipid profile, Prothrombin Time, HBV DNA, HBsAg, HBeAg/HBeAb, AFP, Serum for storage, HbA1C
- Image tests (Abdominal US, CT, or MRI)
- Bone mineral density (Not mandatory)
- Fibroscan (Not mandatory)
- Review adverse events
- Return study drug
- Perform study drug compliance
- Review concomitant drugs

8.3 Assessments for Premature Discontinuation from Study

If a subject in the Treatment Arm discontinues study drug, every attempt should be made to keep the subject taking study drug in the study and continue to perform the required study-related follow-up and procedures. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study. However, the information regarding the primary outcomes (e.g. survival, HCC occurrence) can be collected for the primary and secondary analyses, even after the withdrawal of the subject from the study.

In case of diagnosis of HCC during the study period, based on the current practice guidelines, TAF should be continued. The study drug (TAF) would be continuously provided to the subject, as long as the subject is willing to do so.

9 Study Drug

During the study period, principal investigators (PI) and pharmacists of study sites are responsible for storage and handling of the study drug.

9.1 Storage and Handling of the Study Drug

TAF tablets should be stored at controlled room temperature of 25°C. Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

At the beginning of the study, the study monitor will evaluate the study center's study drug disposal procedures and provide appropriate instruction for return or destruction of unused study drug supplies. If the site has an appropriate Standard Operating Procedures (SOP) for drug destruction, the site may destroy used and unused study drug supplies performed in accordance with the site's SOP. If the site does not have acceptable procedures in place for drug destruction, arrangements will be made from the primary site of the present study.

9.2 Assessment of Adverse Effects

The investigator or qualified sub-investigator is responsible for assessing the adverse effects using clinical judgment.

The principal sources of safety for TAF consist of 2 Phase 3 studies in subjects with CHB, Study GS-US-320-0108 and GS-US-320-0110. Subjects included in the Safety Analysis Set received at least 1 dose of study drug.[15,16]

A list of expected adverse events associated with Vemlidy treatment is presented in [Appendix 4].

9.3 Concomitant Drugs

Concomitant medications taken at the time of screening, up to and including the date of the last study visit, need to be recorded in the source documents and eCRFs.

9.4 Drugs Prohibited

The antiviral agents which can affect the CHB treatment such as medications containing

Tenofovir (Atripla, Complera and Truvada), Adefovir (Hepsera) and Entecavir (Baraclude) cannot be taken during the clinical trial.
Precautionary and prohibited medications while treating with Vemlidy is listed in [Appendix 4].

10 Adverse Events

10.1 Definition of Adverse Events

All adverse events will be assessed and recorded on the AE CRF page by the investigator. An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation after randomization and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

10.2 Assessment of AEs

All AEs and SAEs occurring after randomization and until the end of follow-up/final visit should be recorded in the CRF.

10.3 Severe Adverse Events (SAEs)

A serious adverse event is any untoward medical occurrence after randomization:

- Death or life-threatening events
- Hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Development of fetal anomalies
- Cases in which other medically important situations, such as drug dependence or abuse, or blood diseases other than the above cases

* Hospitalizations which were already planned prior to the participation in the clinical trial is not considered a SAE.
* Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered a SAE.

10.4 Reporting Procedures

The principal investigator and sub-investigators have to notify IRB all SAEs during the study regardless of causal relationship. They must fax or e-mail the SAE form to Asan medical center within 48 hours of the investigator's acknowledgement of the event.

All the information about serious adverse events should be reported to the principal investigator and IRB until they are completely resolved.

10.5 Intensity of AE

Grade	Description
Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; no disruption of normal daily activity.
Moderate	Minimal, local or noninvasive intervention indicated; discomfort sufficient to reduce or affect daily activity.
Severe	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; inability to work or perform normal daily activity.
Life-threatening	Represents an immediate threat to life.

10.6 Causal Relationship of AE

The following categories and definitions of causal relationship to the study drug should be used for any AE:

1) Definitely related

- Event or laboratory test abnormality, with plausible temporal relationship to the drug intake
- Cannot be explained by the disease or other drugs
- Response by the withdrawal of the study drug (pharmacologically, pathologically)
- Event definitive pharmacologically or clinically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon)

2) Probably related

- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Unlikely to be attributed by the disease or other drugs
- Response to withdrawal clinically reasonable

3) Possibly related

- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Could also be explained by disease or other drugs
- Response to withdrawal clinically reasonable

4) Probably not related

- Event or laboratory test abnormality, could be explained by the disease or other drugs than the study drug intake
- Response to withdrawal unsatisfactory or vague

5) Definitely not related

- Event or laboratory test abnormality, with a temporal relationship to the drug intake unlikely
- The disease or other drugs provide plausible explanations

6) Unknown

- Cannot be judged because information is insufficient or contradictory
- Data cannot be supplemented or verified

11 Statistical Considerations

11.1 Sample Size Justification

The primary outcome variable is the ratio of hazard rates based on the cumulative incidence of liver-related events, including death, liver transplantation, or decompensated liver diseases [Child-Pugh score≥7], complications of portal hypertension [ascites, gastroesophageal varices] or HCC among randomly assigned and treated patients.

The null hypothesis (H_0) states that 'the hazard rate ratio in the treatment group compared to the control group is equal to 1,' and the alternative hypothesis suggests that 'the hazard rate ratio in the treatment group compared to the control group is not equal to 1.' Sample size was calculated using the O'Brien-Fleming adjusted Group-Sequential Two-Sided Log-rank Test to plan for a maximum of 3 statistical analyses over a period of 12 years.

Assuming a proportional hazards model, the estimated 12-year survival rates for the treatment and observation groups are 0.889 and 0.801, respectively (hazard rate ratio = 0.53). With a power of 85% and a Type I error rate of 2.5%, a minimum of 115 cases of composite events is needed. Assuming initial interim analysis at 4 years, a second analysis at 8 years, and the final

analysis at 12 years, and considering a 4.8% drop-out rate, the required number of participants is 390 in each group, with a total of 780 participants.

11.2 Statistical Analyses

The primary analysis for assessing treatment efficacy and safety will be conducted using the Full Analysis Set, including all randomly assigned patients (Modified Intention-to-Treat analysis). Secondary analyses will involve on-treatment analysis, which includes patients participating in the study at the analysis points. Patients who discontinue the clinical trial during the 12-year study period will be considered as having early termination for all endpoints from the discontinuation point onwards.

The cumulative incidence of primary outcome events in the two groups will be estimated using the Kaplan-Meier method, and comparison will be made using the log-rank test statistics (Z_k), where k represents the analysis time point. The first interim analysis will be conducted at 4-year from the study initiation. If the null hypothesis is not rejected, the second interim analysis will be performed at 8-year from the study initiation. If the null hypothesis is not also rejected in the second interim analysis, the final analysis will be conducted at the end of the study. The stopping boundaries for the log-rank test statistics, determined using the O'Brien-Fleming method, are as follows: if the absolute value of the test statistics is less than 4.17084 (first interim analysis) or 2.8458 (second interim analysis), the trial will be continued. However, if the absolute value of the test statistics exceeds 4.17084 (first interim analysis) or 2.8458 (second interim analysis), the null hypothesis is rejected, and the efficacy of the treatment group is declared, leading to the termination of the study.

Additionally, a Cox proportional hazard model adjusted for baseline variables will be performed. Adjustments will be made for variables such as age, gender, HBeAg positivity, HBV DNA level, ALT level, platelet count, and more. Continuous or categorical variables between the two groups will be compared using appropriate tests such as Student’s t-test, Chi-square test, or Fisher’s exact test. The statistical significance level will be set at 5%.

During the interim analysis, changes in secondary outcome variables such as viral response, changes in liver function, and degree of liver fibrosis will also be observed. These changes will be utilized as data for developing indicators for predicting long-term clinical outcomes.

Details when Spending = O'Brien-Fleming, E = 115, S1 = 0.801, S2 = 0.889

Look	Time	Lower Bndry	Upper Bndry	Nominal Alpha	Inc Alpha	Total Alpha	Inc Power	Total Power
1	4	-4.17084	4.17084	0.00003	0.00003	0.00003	0.01160	0.01160
2	8	-2.84580	2.84580	0.00443	0.00441	0.00444	0.42583	0.43743
3	12	-2.26370	2.26370	0.02359	0.02056	0.02500	0.41284	0.85027

Additionally, for economic evaluations, differences in health-related quality of life utility weights (EQ-5D and EQ-VAS) based on treatment, treatment response, disease status (hepatitis, liver cirrhosis, HCC), and duration of illness will be analyzed using Generalized Estimation Equation (GEE). Adjustments will be made for age, gender, and clinical baseline variables. Before performing the GEE analysis, exploratory analyses will compare trends in utility weight changes for each variable using paired t-tests.

All statistical analyses will be performed using SPSS (SPSS, Chicago, IL, USA) and R (http://cran.r-project.org/).

12 Compliance and modification of the clinical trial protocol

Subjects should bring all the study drug to the study drug compliance at every follow-up visits including premature discontinuation. The site will record the number of tablets returned at these visits and determine compliance to the medication

$$\textbf{Compliance (\%)} = \frac{\text{The amount of drug ingested}}{\text{The amount the subject should have ingested}} \times 100$$

13 Discontinuation and Withdrawal

Subjects may be withdrawn from the study at the investigator's discretion in any of the following instances:

- Development of a toxicity or adverse event which warrants drug discontinuation
- The lack of efficacy of the medication or the exacerbation of signs or symptoms determined by the investigators, which warrant drug discontinuation
- The subjects are revealed to be ineligible to participate in the clinical trial regarding the safety of the participants
- The investigators determine that it is inappropriate to continue the clinical trial
- Unexpected pregnancy during the trial

- The subjects withdraw the consent to participate in the clinical trial

Treatment after discontinuation or withdrawal will be determined by the investigator. In case of discontinuation or withdrawal due to adverse events or safety issue, subjects should be followed until full recovery and the events should be recorded in CRFs.

14 Efficacy Evaluation

14.1 Primary endpoint

The primary efficacy endpoint of this study is the occurrence of composite events during follow-up observation including HCC, death, liver transplantation, or decompensated liver diseases (e.g., development of portal hypertensive complications including ascites, gastroesophageal varices, or Child-Pugh score ≥7), in the full analysis set.

If a primary endpoint (HCC, decompensation, etc.) occurs, the provision of the study drug is stopped with the end of the study. However, the investigator could decide the compassionate use of the study drug (tenofovir alafenamide; TAF) up to 8 years from the date of randomization if it is regarded necessary and safe for the subject, as long as there is a sufficient reserve of the study drugs.

14.2 Secondary endpoint

- Cumulative proportion of subjects with undetectable HBV DNA
- Cumulative proportion of subjects with on-treatment normal ALT
- Cumulative incidence of composite clinical events (Composite endpoint: death, liver transplantation, decompensated cirrhosis [Child-Pugh score≥7], portal hypertension complications [ascites, esophageal varices], HCC)
- Cumulative incidence of HCC
- Cumulative incidence of death or liver transplantation
- Cumulative incidence of decompensated liver diseases (e.g., development of portal hypertensive complications including ascites, gastroesophageal varices, or Child-Pugh score ≥7)
- Cumulative proportion of subjects with HBeAg seroclearance (only for subjects who are HBeAg-positive at baseline)

- Proportion of subjects who start treatment with TAF in Observation Arm
- Cumulative ALT flare >5 x UNL by AASLD criteria
- Fibroscan ≥ 12.0 kPa (Optional)
- Serial changes of liver stiffness measured by Fibroscan
- Serial changes of APRI index[17]
- Serial changes of FIB-4 index[18]

$$\text{APRI} = \frac{\frac{AST\ (\frac{IU}{L})}{AST\ (upper\ limit\ of\ normal, \frac{IU}{L})}}{Platelet\ Count\ (\frac{10^9}{L})}\ x\ 100$$

$$\text{FIB} - 4 = \frac{Age\ (years) x\ AST\ (IU/L)}{Platelet\ Count\ \left(\frac{10^9}{L}\right) x \sqrt{ALT\ (\frac{IU}{L})}}$$

- Serial changes in the quality of life of the study patients according to treatment, treatment response, treatment duration, outcomes (hepatitis, cirrhosis, HCC)
- Subgroup analysis for HBeAg(+) or HBeAg(-)
  -Cumulative incidence of HCC
  -Cumulative incidence of mortality
  -Cumulative incidence of liver transplantation
  -Cumulative incidence of decompensated liver diseases [Child-Pugh score≥7]
  -Cumulative incidence of portal hypertension complications [ascites, gastroesophageal varices]
  -Cumulative proportion of subjects with undetectable HBV DNA
  -Cumulative proportion of subjects with on-treatment normal ALT

- Subgroup analysis of subjects according to baseline ALT level (normal ALT and elevated ALT)
  -Cumulative incidence of HCC
  -Cumulative incidence of mortality
  -Cumulative incidence of liver transplantation
  -Cumulative incidence of decompensated liver diseases [Child-Pugh score≥7]
  -Cumulative incidence of portal hypertension complications [ascites, gastroesophageal varices]
  -Cumulative proportion of subjects with undetectable HBV DNA

- Cumulative and annual rate of patients with clinical events (death, liver transplantation, liver decompensation, portal hypertensive complications, and HCC) after excluding patients who occurs clinical events within 6 months of enrollment

- Cumulative and annual rate of patients with clinical events (death, liver transplantation, liver decompensation, portal hypertensive complications, and HCC) after excluding patients who occurs clinical events within 12 months of enrollment

- Cumulative and annual rate of patients with clinical events (death, liver transplantation, liver decompensation, portal hypertensive complications, and HCC) in patients with normal ALT (<40 U/L) at the time of enrollment, after excluding patients who occurs clinical events within 6 months of enrollment

- Cumulative and annual rate of patients with clinical events (death, liver transplantation, liver decompensation, portal hypertensive complications, and HCC) in patients with normal ALT (<40 U/L) at the time of enrollment, after excluding patients who occurs clinical events within 12 months of enrollment

15 Safety Protection for the subjects

As described in this protocol, the clinical trial institution shall have the facilities and professional manpower necessary for the clinical trial so that the clinical trial can proceed appropriately in accordance with the relevant regulations, and do everything possible to protect the safety of the subjects. The person in charge of the clinical trial should fully understand the adverse reactions and precautions specified in this protocol before starting the clinical trial, and if a serious adverse drug reaction occurs during the clinical trial, immediately stop the clinical trial of the subject and take appropriate measures (e.g., additional concomitant treatment with other antiviral drugs). After that, it should be notified to the IRB.

After stopping the clinical trial and taking appropriate measures (e.g. additional concomitant treatment with other antiviral drugs), the Clinical Trial Review Committee should be notified.

16 Informed Consent, Agreement of Compensation, Post-Study Treatment

16.1 Patient Information and Informed Consent

The investigator is responsible for obtaining written informed consent from each participants after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the IRB-approved consent form for the written informed consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally authorized

representative and the person obtaining the consent.
A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative. If the subject or representative cannot read, an impartial witness is needed.

16.2 Compensation Available to the Patients in the Event of Trial Related Injury

In the event of health injury associated with this trial, the sponsor is responsible for compensation based on the contract.

16.3 Treatment of the Subjects after the End of the Clinical Trial

The subjects who have fulfilled the study would follow the standard treatment of CHB by current practice guidelines. The subjects who are terminated in the middle of the study should receive routine care corresponding patients with CHB.

17 Expected study results and development direction

By deriving therapeutic efficacy and safety from tenofovir alafenamide treatment in patients who do not belong to the treatment criteria in the current chronic hepatitis B treatment guidelines through the clinical trial results, it is expected to bring a better prognosis for chronic hepatitis B patients.

18 Additional Ethical Considerations for the Study

18.1 Compliance and Modification of the Clinical Trial Protocol

This study must be conducted according to the clinical trial protocol, including written informed consent approved by the IRB. All protocol modifications should be upfront discussed between the investigators. All protocol modifications, except those intended to reduce immediate risk to subjects, should be submitted to and approved by the IRB. Approvals must be obtained before changes can be implemented. In the event that modification applied to prevent immediate damage to the subjects before the IRB approval, they should be reported to the IRB as soon as possible.

18.2 Monitoring

Assigning the Clinical Research Associate (CRA) in charge of this trial, the CRA will regularly visit and monitor the study sites before starting the study and during the whole

study period. The monitor is responsible for routine review of the CRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the CRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

18.3 Storage of the Documents and Data

The investigator must maintain all the documents and records of this study to be adequate and accurate and should subsequently verify them. The investigator is responsible for maintaining and providing of the essential documents. The essential documents mean ones that allow evaluating conduct of the clinical trial. The clinical trial essential document will contain the protocol/amendments, CRF and query forms, IRB approval with correspondence, informed consent, and monitoring records and other appropriate documents and correspondence.
Subject clinical source documents contain all the observed date, the records of clinical trial activities and all the reports and records for assessment and reconstruction of the clinical trial. Therefore, subject clinical source documents should include the records of all the procedures conducted by the clinical trial protocol.
All clinical study documents must be retained by the investigator in accordance with local rule after the end of the study.

18.4 Confidentiality of the Data and Records of the Subjects

The investigator must assure that subjects' anonymity will be strictly maintained. The subjects should be accessed by only subject initials or an identification code. Their identities have to be protected from unauthorized parties. Only the investigators, study coordinators, those who conduct inspections, IRB, the director of KFDA can review the data of the subjects to verify the reliability and the study process within the range prescribed by the relevant provisions and without violating the confidentiality of research subjects.

18.5 Provision of Personal Information to Third Parties and Secondary Use

After the primary research is done, the follow-up secondary research is set to begin. For the secondary research, no new data needs to be collected. Therefore, the personal information

given by the research subject can be used for statistical analysis in the secondary research for purposes other than those that were originally planned in the primary research.

1) Subjects to whom personal information is provided: A data management institution designated by the Minister of Health and Welfare of Korea

2) Data recipients' intended use: Public purpose for public health promotion

3) Provided information: Personally identifiable information, personal information (medical records, etc.)

4) Period of storage and use of personal information: 5 years after the end of the primary research

Research subjects have the right to refuse consent to the provision of personal information to a third party, and there is no disadvantage in refusing. To keep research information safe, it will be kept in a locked place (data room, etc.) under the supervision of the data management manager. Only authorized administrators will be able to access it.

In the case of obtaining written consent for the provision of personal information from the research subject, the personal information may be provided to a third party in a pseudonymized state for research purposes after deliberation by the institutional review committee. It will be provided and utilized only for research that is judged to be of public interest through deliberation by the institutional review committee, and where the expected outcome is considered to be a contribution to the promotion of public health.

19 Methods for Human Derived Material storage and disposal

Human materials will be transferred and stored to the storage facility of the institution or Asan Medical Center (South Korea). In case of disposal by the institution, it is discarded after obtaining written approval from Asan Medical Center. The identification information of the subjects is anonymized throughout the entire process.

Human materials will be managed under the supervision of Principal Investigator, and each human material management number will be managed separately from personally identifiable information. The personal identification code sheet should be recorded and managed only by the researcher in charge (or the researcher entrusted with it).

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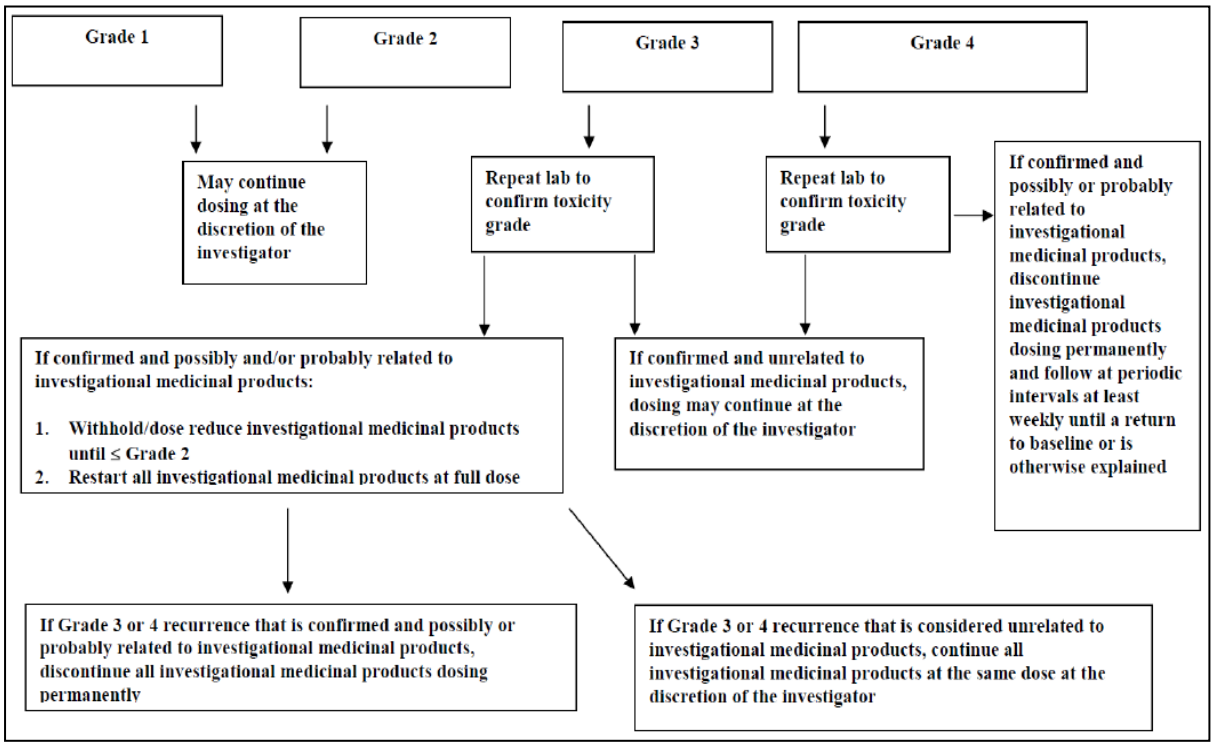
Appendix1. Management of Clinical and Laboratory Adverse Events



Appendix2. GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin	10.0 to 10.9 g/dL 100 to 109 g/L OR Any decrease 2.5 to < 3.5 g/dL 25 to < 35 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L OR Any decrease 3.5 to < 4.5 g/dL 35 to < 45 g/L	7.0 to < 9.0 g/dL 70 to < 90 g/L OR Any decrease ≥ 4.5 g/dL ≥ 45 g/L	< 7.0 g/dL < 70 g/L
Absolute Lymphocyte Count	600 to 650/mm^3 0.60 to 0.65 GI/L	500 to <600/mm^3 0.50 to < 0.60 GI/L	350 to < 500/mm^3 0.35 to < 0.50 GI/L	< 350/mm^3 < 0.35 GI/L
Platelets WBCs	100,000 to < 125,000/mm^3 100.0 to < 125.0 GI/L 2000/mm^3 to 2500/mm^3 2.0 GI/L to 2.5 GI/L	50,000 to < 100,000/mm^3 50.0 to < 100.0 GI/L 1,500 to < 2,000/mm^3 1.5 to < 2.0 GI/L	25,000 to < 50,000/mm^3 25.0 to < 50.0 GI/L 1000 to < 1,500/mm^3 1.0 to < 1.5 GI/L	< 25,000/mm^3 < 25.0 GI/L < 1000/mm^3 < 1.0 GI/L
Prothrombin Time (PT)	> 1.00 to 1.25 × ULN	> 1.25 to 1.50 × ULN	> 1.50 to 3.00 × ULN	> 3.00 × ULN
Activated Partial Thromboplastin (APPT)	> 1.00 to 1.66 × ULN	> 1.66 to 2.33 × ULN	> 2.33 to 3.00 × ULN	> 3.00 × ULN

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 mEq/L to < LLN 130 mmol/L to < LLN	125 to < 130 mEq/L 125 to < 130 mmol/L	121 to < 125 mEq/L 121 to < 125 mmol/L	< 121 mEq/L < 121 mmol/L
Hypernatremia	> ULN to 150 mEq/L > ULN to 150 mmol/L	> 150 to 154 mEq/L > 150 to 154 mmol/L	> 154 to 159 mEq/L > 154 to 159 mmol/L	> 159 mEq/L > 159 mmol/L
Hypokalemia	3.0 mEq/L to < LLN 3.0 mmol/L to < LLN	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L	< 2.0 mEq/ < 2.0 mmol/L
Hyperkalemia	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Hypoglycemia	55 to 64 mg/dL 3.1 to 3.5 mmol/L	40 to < 55 mg/dL 2.2 to < 3.1 mmol/L	30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	< 30 mg/dL < 1.7 mmol/L
Hyperglycemia, Nonfasting and No Prior Diabetes	> ULN to 160 mg/dL > ULN to 8.9 mmol/L	> 160 to 250 mg/dL > 8.9 to 13.9 mmol/L	> 250 to 500 mg/dL > 13.9 to 27.7 mmol/L	> 500 mg/dL > 27.7 mmol/L
Hypocalcemia (corrected for albumin)	7.8 mg/dL to < LLN 1.94 mmol/L to < LLN	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L	< 6.1 mg/dL < 1.51 mmol/L
Hypercalcemia (corrected for albumin)	> ULN to 11.5 mg/dL > ULN to 2.88 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypocalcemia (ionized)	3.0 mg/dL to < LLN 0.74 mmol/L to < LLN	2.5 to < 3.0 mg/dL 0.62 to < 0.74 mmol/L	2.0 to < 2.5 mg/dL 0.49 to < 0.62 mmol/L	< 2.0 mg/dL < 0.49 mmol/L
Hypercalcemia (ionized)	> ULN to 6.0 mg/dL > ULN to 1.50 mmol/L	> 6.0 to 6.5 mg/dL > 1.50 to 1.63 mmol/L	> 6.5 to 7.0 mg/dL > 1.63 to 1.75 mmol/L	> 7.0 mg/dL > 1.75 mmol/L
Hypomagnesemia	1.45 mg/dL to < LLN 0.60 mmol/L to < LLN	1.09 to < 1.45 mg/dL 0.45 to < 0.60 mmol/L	0.72 to < 1.09 mg/dL 0.30 to < 0.45 mmol/L	< 0.72 mg/dL < 0.30 mmol/L
Hypophosphatemia	2.0 mg/dL to < LLN 0.63 mmol/L to < LLN	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L	< 1.0 mg/dL < 0.31 mmol/L
Hyperbilirubinemia	> 1.0 to 1.5 × ULN	> 1.5 to 2.5 × ULN	> 2.5 to 5.0 × ULN	> 5.0 × ULN
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Hyperuricemia	> ULN to 10.0 mg/dL > ULN to 597 micromol/L	> 10.0 to 12.0 mg/dL > 597 to 716 micromol/L	> 12.0 to 15.0 mg/dL > 716 to 895 micromol/L	> 15.0 mg/dL > 895 micromol/L
Hypouricemia	1.5 mg/dL to < LLN 90 micromol/L to < LLN	1.0 to < 1.5 mg/dL 60 to < 90 micromol/L	0.5 to < 1.0 mg/dL 30 to < 60 micromol/L	< 0.5 mg/dL < 30 micromol/L
Creatinine	> 1.5 to 2.0 mg/dL > 137 to 181 micromol/L	> 2.0 to 3.0 mg/dL > 181 to 269 micromol/L	> 3.0 to 6.0 mg/dL > 269 to 535 micromol/L	> 6.0 mg/dL > 535 micromol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bicarbonate	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Triglycerides (Fasting)	— 	500 to 750 mg/dL 5.64–8.47 mmol/L	> 750 to 1200 mg/dL > 8.47–13.55 mmol/L	> 1200 mg/dL > 13.55 mmol/L
Hypercholesterolemia (Fasting)	200 to 239 mg/dL 5.16 to 6.19 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	—
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

Appendix 3. Internal Monitoring Committee (IMC) and Scientific Oversight Committee (SOC)

The IMC will perform periodic safety data review to ensure that continuation of the study does not pose a health hazard to participants.

IMC meetings will be scheduled following each of the planned interim analyses.
Additional review meetings may be scheduled as determined by the IMC. Membership of the IMC will include representatives from Clinical Science (Translational Medicine), Clinical Safety, Biostatistics. If required, additional functional representatives may attend an IMC meeting.

A SOC will act as a consultative body to the Sponsor, providing external expert opinions on the safety data collected during the study. This committee will consist of an external group of at least two CHB therapeutic area experts who will advise the Sponsor on the interpretation of study data.

Data being evaluated by the SOC will include demographic, adverse event, serious adverse event, and relevant laboratory data. SOC may review efficacy data if safety concerns necessitate benefit-risk assessments. The Sponsor will retain all decision making authority for this study.