Treatment Outcomes in Chronic Hepatitis B Patients on Sequential Therapy with Tenofovir Alafenamide

Mindie H. Nguyen, MD, MAS, FAASLD

Division of Gastroenterology and Hepatology

Liver Transplant Program

Stanford University Medical Center

Palo Alto, CA 94304

mindiehn@stanford.edu

650-736-1731 (O)

[redacted] (M)

Protocol Version 15, March 06, 2019

Table of contents:

1. General Information

Protocol title: Treatment Outcomes in Chronic Hepatitis B Patients on Sequential Therapy with Tenofovir Alafenamide (TAF)

Stanford eProtocol #: 45054 IND: IND Exempt (see attachment for documentation)

Version date: March 06, 2019

Principal investigator, sponsor, and monitor, medical expert (responsible for all trial-site related medical decisions), contact information:

Name: Mindie H. Nguyen, MD, MAS, FAASLD

Title: Professor of Medicine
Division of Gastroenterology and Hepatology
Liver Transplant Program

Address: Stanford University Medical Center
750 Welch Road, #210
Palo Alto, CA 94304

Email: mindiehn@stanford.edu

Phone: 650-736-1731 (o)
650-721-8710(f)
[redacted] (m)

*Coordinating center for overall project: contract, study oversight, data management and analysis:
Stanford University Medical Center, Palo Alto, CA
Lead PI: Mindie H. Nguyen, MD, MAS, FAASLD

*Clinical centers and site PIs:

1. USA: Stanford University Medical Center, Palo Alto, CA
   PI: Mindie H. Nguyen, MD, MAS
2. USA: San Jose Gastroenterology, San Jose, CA
   PI: Huy Trinh, MD

3. USA: Digestive Health Associates of Texas, Plano, TX
   PI: Son Do, MD
4. Japan: Kyushu University Graduate School of Medical Sciences, Fukuoka
   PI: Eiichi Ogawa, MD, PhD
5. Japan: Nagoya City University Graduate School of Medical Sciences, Nagoya
   PI: Yasuhito Tanaka, MD, PhD
6. Japan: Ogaki Municipal Hospital, Ogaki
   PI: Hidenori Toyoda, MD, PhD
7. Japan: Osaka City University Graduate School of Medicine, Osaka
   PI: Masaru Enomoto, MD, PhD
8. Japan: Saga University Hospital, Saga
   PI: Yuichiro Eguchi, MD, PhD
9. Japan: Yamagata University Faculty of Medicine, Yamagata
   PI: Yoshiyuki Ueno, MD, PhD
10. South Korea: Nowon Eulji Medical Center, Eulji University College of Medicine, Seoul
    PI: Hyo Young Lee, MD, M.M.Sc
11. South Korea: Hanyang University Hospital and Liver Research Group, Seoul
    PI: Dae Won Jun, MD, PhD
12. South Korea: Sanggye Paik Hospital, Inje University College of Medicine, Seoul
    PI: Eileen L. Yoon, MD, PhD
13. Taiwan: E-Da Hospital, Kaohsiung
    PI: Cheng-Hao Tseng, MD, PhD
14. Taiwan: Kaohsiung Medical University Hospital, Kaohsiung
    PI: Ming-Lung Yu, MD, PhD

2. Background Information

Investigational product: Tenofovir alafenamide (TAF) is a nucleotide reverse transcriptase inhibitor and a prodrug of tenofovir with higher intracellular active drug concentration allowing for dosing of only 25 mg once daily.

Scientific Rationale: Chronic hepatitis B (CHB) affects ~250 million people worldwide. While mostly endemic to Asia and Sub-Saharan Africa, CHB is also prevalent in the United States among many immigrant groups, with an estimated 0.8 to 1.4 million persons affected in 2006 according to the National Health and Nutrition Examination Survey, although this number is likely an underestimation due to underrepresentation of immigrant populations. Currently, there are several FDA-approved oral anti-HBV agents such as entecavir and tenofovir disoproxil fumarate that are first-line agents recommended by most guidelines. Entecavir 0.5-1.0 mg once daily is suboptimal for patients with known or at risk for

lamivudine resistance due to risk of cross resistance between the two medications. Tenofovir 300 mg once daily has potential, albeit low, risks for renal toxicity and bone loss. Older medications such as lamivudine or adefovir carry high risk of viral resistance and/or higher risk of renal toxicity (adefovir). Tenofovir alafenamide (TAF) is a new formulation of tenofovir with higher intracellular active drug concentration allowing for dosing of only 25 mg once daily and thus can potentially lower the already low risk of renal toxicity and bone loss with tenofovir disoproxil fumarate (TDF).

Summary of known and potential risks and benefits:

Risks: This is a multicenter prospective interventional study of CHB patients who were recommended to switch from any existing antiviral therapy to TAF for any reasons by their treating physicians and as such there is minimal risk involved to the participants. There is a potential risk of breach of confidentiality of medical information or laboratory results that can cause psychological, social, or possibly economic harm to study participants. These risks are extremely unlikely to occur and procedures are in place to minimize these risks. Only de-identified data will be transmitted to the data coordinating center and only aggregate de-identified data will be presented at conferences or in other peer-reviewed publications. The study will be conducted under local IRB oversight at each of the study centers and at the data coordinating center at Stanford University Medical Center.

TAF has been approved for patients with CHB by the U.S. Food and Drug Administration (FDA), Japan's Ministry of Health Labour and Welfare, Taiwan's Food and Drug Administration, and the Ministry of Food and Drug Safety in Korea for the treatment of CHB and subjects who will be given TAF were chosen to do so by their physician and will be followed by their physician as part of their clinical care outside of the study. The following adverse events were identified based on week 48 analysis from 2 ongoing studies in which participants with CHB received TAF:

Common (≥ 5% and < 10%):

- Headache
- Nausea (general feeling of being sick in the stomach)
- Abdominal Pain
- Cough
- Fatigue
- Back pain

There may be unforeseeable risks to the embryo or fetus, for both male and female subjects in this study. Subsequently, extreme care must be taken to avoid pregnancy in female subjects during this study for up to 30 days following completion of study treatment as well as in female partners of male subjects during this study for up to 90 days following completion of study treatment.

In addition to the risks listed above, there are risks that are not known or do not happen often when subjects take TAF, including severe or life-threatening allergic reactions, or interactions with another medication. Subjects will be informed in a timely manner, both verbally and in writing of any new information or changes to the way the research will be done that might influence their willingness to continue to take part in this study.

For more details on adverse reactions please see the Vemlidy® package insert for more information.

Benefits: The medical knowledge gained may be able to guide future research, clinical trial planning, and guideline recommendation for this patient population.

3. Study Overview

Dosage regimen: Patients on any antiviral treatment for chronic HBV who plan to be switched by their physician to be treated with TAF 25 mg for 24 months will be enrolled. Any treatment after will be up to the physician's discretion. The drug will be administered orally, per manufacturers' instructions, and can be taken with food.

Compliance: Patients will be enrolled and monitored according to the protocol, GCP, and clinical practice guidelines.

Study population: Approximately 251 adult patients currently on antiviral therapy and are planned to be switched to TAF by their physicians will receive TAF 25 mg. Enrollment goal will be approximately 185 for prior entecavir patients, 33 for prior tenofovir (TDF) patients and 33 for prior combination therapy patients (any oral nucleos(t)ide combination). Enrollment goal for entecavir is based on relative lack of data for sequential entecavir to TAF therapy. Enrollment goal for TDF is used to avoid bias and as a comparison. Enrollment goal for combination therapy is based on estimates of the small patient population with CHB maintained on long term combination therapy.

Inclusion criteria:

1. Male or female, age ≥18 years
2. CHB diagnosis confirmed by positive HBsAg or HBV DNA or HBeAg or documented history of CHB in physician note
3. Currently maintained on antiviral therapy for at least 48 weeks with any HBV DNA value at Screening/Baseline and planned to be switched to TAF by their physician

4. Routinely monitored for serum HBV DNA PCR, liver chemistry, renal chemistry including by their physicians every 3-6 months and a bone density scan at least every 2 years as per routine clinical care (one at baseline and one 2 years after switch).
5. Estimated creatinine clearance > 15 ml/min for men or >12.75 ml/min for women (using the Cockcroft-Gault method) at Screening/Baseline Visit
6. Willing and able to provide informed consent
7. Able to comply with dosing instructions for study drug administration and able to complete the study schedule of assessments

Exclusion criteria:

1. Pregnant women, women who are breastfeeding or who believe they may wish to become pregnant during the course of the study
2. Previous recipient of a liver transplant
3. Co-infection with human immunodeficiency virus (HIV) or hepatitis C (HCV) or hepatitis D (HDV)
4. Severe or uncontrolled comorbidities
5. Current or known hepatic decompensation (≤2 years) (e.g ascites, encephalopathy, or variceal hemorrhage) with a Child-Pugh score of B or C
6. Malignancy including liver cancer within 5 years except cancers easily curable by surgical resection (e.g. basal cell skin cancer and squamous cell cancer)
7. Currently receiving any immunosuppressive therapy
8. On any of the disallowed concomitant medications listed in the prior and concomitant medications list (pg. 13). Subjects on prohibited medications who are otherwise eligible will need a wash out period of at least 30 days prior to the Screening/Baseline visit.
9. Males and females of reproductive potential who are unwilling to use "effective" protocol-specified method(s) of contraception during the study.
10. Current substance or alcohol abuse judged by the investigator to potentially interfere with subject compliance.
11. Any other clinical conditions that, in the opinion of the Investigator, would make the subject unsuitable or unable to comply with any of the study procedures

4. Study Objectives

Primary objective:

- To describe rate of persistence and/or improvement of viral suppression with TAF as with previous anti-HBV treatment

Secondary objective:

- To describe persistence of ALT normalization and/or improvement of ALT levels with TAF as with previous anti-HBV treatment

- To describe trends in serum creatinine and calculated creatinine clearance as available by local labs.
- To describe trends in bone mass from baseline to 24 months after switch.

5. Study Design

Study design: Open label prospective interventional cohort study.
Study Timelines:

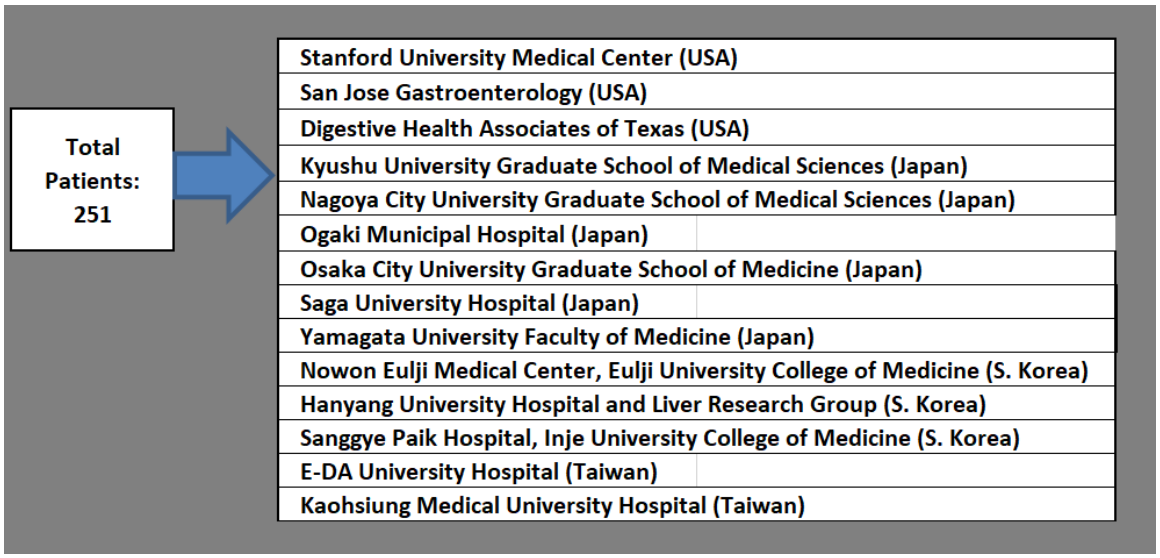
- Total study duration: 36 months
- Study Start-Up: 3 months
- Patient enrollment: 6 months
- Patient follow-up: 24 months
- Final analysis & Manuscript Preparation: 3 months
- Publication plan: Interim analysis 2018 – 2019, Final analysis 2020

Primary endpoint: Rate of viral suppression at 6, 12, 18, 24 months after switch, as available.

Secondary endpoints(s):

- ALT levels at 6, 12, 18, 24 months after switch
- Serum creatinine, calculated creatinine clearance (Cockcroft-Gault) at 6, 12, 18, 24 months after switch
- % change in bone mineral density from baseline to 24 months after switch

Study schematic:



The following table below describes all study procedures:

Study Procedures	Screening/Baseline	Treatment Months*							
		3*	6	9*	12	15*	18	21*	24/ED
Informed Consent	x								
Inclusion/ Exclusion Criteria	x								
Medical History[1]	x								
Vital Signs	x		x		x		x		x
Physical Examination	x		x		x		x		x
Adverse Events			x		x		x		x
Concomitant Medications	x		x		x		x		x
Bone Density Scan (DEXA)[4,5]	x								x
HBeAg[2]	x		x		x		x		x
HBV DNA PCR	x	x	x	x	x	x	x	x	x
α-fetoprotein (AFP)	x		x		x		x		x
Ultrasound (to rule out HCC)	x		x		x		x		x
International Normalized Ratio (INR)[3]	x				x				x
CBC Panel with WBC, Hb, Platelet, HCT	x		x		x		x		x
Complete Metabolic Panel with Na, K, Cr, Tb, CO2/HCO3, BUN, GLU, AST, ALT, ALK, ALBU	x	x	x	x	x	x	x	x	x
Serum Phosphorus	x	x	x	x	x	x	x	x	x
Fasting Cholesterol Panel with Total Cholesterol, HDL, direct LDL, TG	x		x		x		x		x
Vitamin D Assessment	x								
Fibrotest, Fibrosure, Fibrospect, FIB-4 or Elastography	x								
HCV, HDV, HIV Testing[6]	x								
Urinalysis	x	x	x	x	x	x	x	x	x

Data capture/case report forms	x		x		x		x		x
Study Drug Dispensing	x		x		x		x		

*Every visit can be 3-6 months as per routine clinical care. Clinical visit for Month 3 is optional but Month 3 lab is required for all sites. Month 9, 15, and 21 labs are optional.
1. For women of childbearing potential, last menstrual period must be documented
2. HBeAg serology to be done only in patients with positive HBeAg at Screening
3. INR testing to be done only in cirrhotic patients
4. Bone density scan will be charged and billed to the study as applicable.
5. Additional scan at 12 months is optional per investigator.
6. HCV RNA or antibody testing can be used to rule out co-infection. HDV and HIV antibody test are optional if test is not available to order at site or is not routinely performed.

Study Procedures:

Pre-Screening: Patients who are planned to be switched from their current antiviral therapy to TAF will be identified by their primary physician and approached to enroll in this prospective interventional cohort study. If a patient is deemed eligible to participate, the site will evaluate the potential patient using the inclusion/exclusion criteria and fill out the CRF for the screening visit. The local coordinator will transmit the pre-screening data to the central coordinator prior to the actual screening/baseline visit. If the patient is deemed eligible by the sponsor, the patient will be given a study ID and allowed to enter the study.

Screening/Baseline: Written and informed consent will be obtained prior to any study protocol related procedures or data abstraction. If patient has been pre-screened approved and all lab data are available they will begin treatment with TAF on the screening/baseline visit. The screening/baseline visit consists of obtaining written and informed consent, reviewing the inclusion/exclusion criteria, confirming medical history, completing a physical examination with vital signs and body weight, reviewing any concomitant medications and study drug dispensing. HBV DNA can be done within 3 months prior to study enrollment and Vitamin D assessment can be done within 12 prior to study enrollment. Serum AFP and liver ultrasound can be done within 6 months prior to enrollment. DEXA scan can also be done within 6 months prior to enrollment.

Procedures: In general, labs should include CBC (complete blood count, e.g. WBC, PLT, Hb, HCT), CMP (complete metabolic panel, e.g. CO_2 or HCO_3^-, Na^+, K^+, Creatinine, Albumin, ALT, AST, ALK, Glucose, Total Bilirubin, BUN, Serum Phosphorous), INR (international normalized ratio), AFP (alpha-fetoprotein), fasting cholesterol panel, (e.g. Total cholesterol, HDL, direct LDL, Triglycerides (TG), Urinalysis, HBV DNA quantification and HBeAg status. Screening will also include HCV, HIV and HDV testing, if not previously done. All laboratory tests including the DEXA scan for all sites except South Korea will be ordered and billed as per routine care. For South Korea, all laboratory and DEXA scans will be ordered and billed to the study per standard of procedures in South Korea for all studies that provide medication. For Taiwan and the US, all DEXA scans will be ordered and billed to the study. Blood will be drawn at the site at which the patient was recruited, and processed by a lab technician in the clinical laboratory at that respective site. Standard of care for HCC surveillance should include radiology and AFP every 6 months per AASLD and APASL guidelines. All scans should be billed to patient's insurance or patient. At site PI's discretion, higher level imaging or frequency can be done.

Treatment Visits: Treatment will consist of taking TAF 25 mg daily with food for 24 months. Treatment visits will occur at approximately every 3-6 months as per routine clinical care, except for those listed in section 13. Clinical visit for Month 3 is optional but Month 3 lab is required for all sites. Month 9, 15, and 21 labs are optional. Each visit will consist of reviewing adverse

events and concomitant medications, completing a physical examination with vital signs and body weight, completing all necessary routine labs including DEXA scan and study drug dispensing. At every visit the patient must bring all study drugs (including empty bottles) so that the study staff can count compliance using the number of remaining pills.

This schedule of clinic visits and laboratory tests are routine and standard practice for investigators in their treatment of similar patients with CHB. Patients will be encouraged to adhere to these recommendations. Results of these laboratory tests and clinical evaluations will be recorded as well as any additional evaluations that are done as part of the patient's clinical care that are pertinent to the objective of the study.

Prior and Concomitant Medications

Medications not permitted before and during the study treatment phase will be up to the discretion of the treating physician. Disallowed concomitant medications include:

- Drugs that reduce renal function or compete for active tubular secretion may increase concentrations of tenofovir and the risk of adverse reactions (e.g., cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir)
- Nephrotoxic agents (e.g., aminoglycosides, amphoterecin B, vancomycin, cidofovir, foscarnet, cisplatin, pentamidine, cyclosporine, tacrolimus)
- Other products containing TAF
- Oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, or St. John's wort. Such co-administration is expected to decrease the concentration of TAF, reducing the therapeutic effect of TAF.
- Drugs that strongly affect P-gp and BCRP activity may lead to changes in TAF absorption.

Monitoring subject compliance: Patients will be encouraged by their physician to adhere to clinical and lab visitation recommendations per routine clinical care.

Measures to minimize/avoid bias: Not applicable. This study does not include randomization of subjects or blinding.

Description of study treatment: See Dosage regimen in Section 3 (Study Overview).

Duration of subject participation: Patient participation is expected to take approximately 2.5 years. Study treatment period, continuation and choice of therapeutic agents are at the discretion of the local primary investigator and treating physician and patient.

Discontinuation criteria: The study can be terminated at any time for any reasons with written notice by Dr. Mindie Nguyen (Study Sponsor). For discontinuation criteria for individual subjects, see Withdrawal criteria in section 6 (Selection and withdrawal of subjects). Though there are no formal treatment stopping rules in this study, patients will be asked to stop early if there are any adverse events that the investigator feels make it the patient's best interest to stop treatment.

Accountability procedures for TAF:

U.S.A, S. Korea and Taiwan Sites

TAF used for US sites will be shipped to the Stanford Hepatology Office where the study coordinator confirms that all bottles are present and undamaged. At Stanford, the medication is logged into a Pharmacy Binder and stored in a temperature-controlled room and a locked cabinet to which only Dr. Mindie Nguyen and the designated research staff have access. When the medication is to be dispensed at Stanford, the study coordinator transports the study drugs to the Stanford Hepatology Clinic in a protective container. Dr. Nguyen reviews and confirms the study drugs before they are dispensed to study participants. The Pharmacy Binder is updated when the study drugs are dispensed and returned.

Drug dispensing at U.S.A. sites outside of Stanford University: After enrollment of each patient, study drugs will be shipped from Stanford University to US site(s).

TAF for non-US sites will be shipped directly by Gilead to a third party in S. Korea and Taiwan, where Stanford will contract directly with this third party payer to further distribute the study medications to each participating site within that country. Trained staff at each site will dispense study drugs to subjects accordingly. Storage and dispensing of study drugs will be per local pharmacy and/or site PI and will be required to follow this procedure: the medication is logged into a Pharmacy Binder and stored in a locked cabinet in a temperature-controlled room and a to which only the designated pharmacist and/or PI and/or the designated research staff have access. When the medication is to be dispensed at the study site, the study coordinator transports the study drugs to the clinic in a protective container. The PI reviews and confirms the study drugs before they are dispensed to study participants. The Pharmacy Binder is updated when the study drugs are dispensed and returned.

Japan Sites

No medications will be provided for Japan sites. Per local investigators' preference by local practice, medications will be prescribed by physicians and covered by patients' insurance as per standard clinical care.

6. Selection and Withdrawal of Subjects

Selection of Subjects: Patients planning to be switched to TAF will be identified/referred by their physician. Written informed consent will be obtained prior to study initiation in all patients. See Study population in Section 3 (Trial overview for study inclusion and exclusion criteria).

Withdrawal Criteria:

- Failure to follow study instructions or protocol violation (subject to investigator)
- Adverse events (subject to investigator)
- Any medical, psychosocial or administrative or other reasons that would, in judgment of the investigator, be detrimental to the patient's well-being.
- Death
- Withdrawal of informed consent – They may be considered withdrawn if they state an intention to withdraw or fail to return for study visits, or become lost to follow-up for any other reasons.

Procedures for Subject Withdrawal:

When and how to withdraw subjects from trial: Subjects will be withdrawn during the study at any time if they meet any of the withdrawal criteria above. If premature withdrawal occurs for any reason a report will be generated by investigator describing reasons and nature of the withdrawal and will include documentation of last patient encounter and laboratory testing prior to or at time of withdrawal. If patient stops the study treatment early, documentation outlining the reasoning will be drawn.

Data to be collected for withdrawn subjects: For patients not lost to follow-up, viral suppression and pertinent clinical and laboratory data to be collected will be those which are done as part of standard clinical care including bone and renal function tests.

Follow-up for subjects withdrawn from investigational product: If patients are withdrawn from the study early, they will complete an Early Discontinuation (ED) Visit, during which they will have a physical exam, review their concomitant medication and any adverse events, review their drug accountability, and complete any routine laboratory, bone density or imaging tests. All patients that have withdrawn from the study early will also complete a follow-up visit 3 to 6 months after their ED visit.

7. Adverse Events and Toxicity Management

Assessment of safety: Safety assessments will include monitoring of laboratory results, vital signs, treatment emergent adverse events, serious adverse events, etc. Safety assessments will be performed at every clinic visit as part of clinical care and during follow-up visits.

Adverse events definitions:

Adverse Event (AE): Any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and an unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Serious Adverse Event (SAE): An adverse event or suspected adverse reaction is considered ‘‘serious’’ if, in the view of Dr. Mindie Nguyen, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event, an adverse event or suspected adverse reaction is considered ‘‘life-threatening’’ if, in the view of Dr. Mindie Nguyen, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions such as a congenital anomaly/birth defect.
- Is a suspected transmission of infectious agents by a medicinal product

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Management of Adverse Events, Serious Adverse Events: In general, Dr. Nguyen (the sponsor) must immediately report to Gilead Sciences and IRB, any serious adverse event whether or not considered drug related. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol regardless if there is evidence suggesting a causal relationship between the drug and the event (e.g., death as a result of anaphylactic reaction or fatal hepatic necrosis). In any case, the investigator must immediately report the event to the sponsor and their IRB.
For each subject, AEs and SAEs should be recorded after informed consent is obtained until the subject has completed participation in the study as follows:

- A serious adverse event must be reported if it occurs during a subject's participation in the study and within **30 days** of receiving the last dose of study drug.
- Any serious adverse event that is ongoing when a subject completes his/her participation in the study must be followed until any of the following occurs:
    - The event resolves or stabilizes;
    - The event returns to baseline condition or value (if a baseline value is available);
    - The event can be attributed to agents(s) other than the study drug, or to factors unrelated to study conduct.

Recording of Adverse Events, Serious Adverse Events: Recording should be done in a concise manner using standard, acceptable medical terms. The adverse event recorded should not be a procedure or a clinical measurement (i.e. a laboratory value or vital sign) but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement. Preexisting conditions that worsen in severity or frequency during the study should also be recorded (a preexisting condition that does not worsen is not an adverse event).

Furthermore, a procedure or surgery is not an adverse event; rather, the event leading to the procedure or surgery is considered an adverse event. Any event requiring in-patient hospitalization that occurs during the course of a subject's participation in a trial must be reported as an SAE. Hospitalizations that do not meet the criteria for SAE reporting are:

- Reasons described in the Protocol, e.g. drug administration, Protocol-required testing
- Surgery or procedure planned prior to entry into the study.

If, in Dr. Mindie Nguyen's judgment, a clinical significant worsening from baseline is observed in any laboratory or other test parameter, physical exam finding, or vital sign, a corresponding clinical adverse event should be recorded.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the adverse event, whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, "hepatitis" and not "elevated liver function tests" should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an adverse event, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema).

Maintenance of Safety Information: Safety information will be maintained in a clinical database/repository in a retrievable format. At a minimum, at the end of the treatment phase (="last patient off treatment") as well as the end of the follow-up phase (="last patient out") of

the study, Dr. Mindie Nguyen shall provide all adverse events, both serious and non-serious, in report format.

Reporting Timelines: All safety information covered in SAEs should be reported within **24 hours** of becoming aware of the event(s) to the sponsor. All non-serious AEs should be recorded in a CRF and reported to the site's IRB as per their guidelines for prompt reporting.

Pregnancy Precaution and Contraceptive Requirements: Because the full effects of TAF on an unborn baby or a nursing infant are not known, any female who is pregnant or breast feeding an infant will not be enrolled in this study. Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 30 days after the end of relevant systemic exposure.

If a subject becomes pregnant or suspects that they have become pregnant while in the study or within 30 days after the last dose of study drug, they must stop taking all the study drugs and notify their study doctor immediately. They will be discontinued from the study. If their partner becomes pregnant while they are in the study, the subject must notify the study doctor immediately. The study doctor will request to track the pregnancy and will report the pregnancy to the Study Sponsor.

If a subject is a sexually active female, it is required that they use an effective method of birth control from the Screening/Baseline visit as well as during the study and for at least 30 days after stopping the last dose of study drug. Effective protocol specified methods of birth control in this study are as follows:

Complete abstinence from intercourse of reproductive potential or consistent and correct use of 1 of the following methods of birth control listed below:

- Intrauterine device (IUD) with a failure rate of < 1% per year
- Intrauterine hormone-releasing system (IUS) with a failure rate of < 1% per year
- Tubal sterilization
- Essure micro-insert system (provided confirmation of success 3 months after procedure)
- Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)
- Barrier methods (one female barrier and one male barrier must be used in combination)
    - -Female barriers: Diaphragm with spermicide or Cervical cap with spermicide
    - -Male barriers: Male condom (with or without spermicide)
- Hormonal methods
    - -Oral contraceptives (either combined or progesterone only)
    - -Injectable progesterone
    - -Implants of levonorgestrel
    - -Transdermal contraceptive patch

-Contraceptive vaginal ring

During the study, male subjects with female partners of childbearing potential should use condoms when engaging in intercourse of reproductive potential.

Birth control methods that are unacceptable include periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). Female condom and male condom should not be used together.

8. Statistics

Data management and analysis will be performed at Stanford.

Sample size to be used in the analysis: Sample size will be estimated by enrollment feasibility at all study sites.

Statistical methods to be employed: Descriptive and comparative statistics will be performed for all demographic and clinical variables that are outcome endpoints for this pilot study.

Level of significance: A 95% confidence interval will be used.

Termination of trial: Termination of the trial will be upon completion of follow-up of all 251 subjects enrolled and/or up to the discretion of the sponsor, Dr. Mindie Nguyen.

Procedure for missing, unused, spurious data: Data that is missing, unused or spurious data will all be treated as missing data. This data will be marked as an empty field.

Deviation from original statistical plan: Any deviation from the original statistical plan will be up to the discretion of the study sponsor.

Selection of subjects to be included in analyses: All eligible subjects that have not been withdrawn from the study will be included in analyses.

9. Direct Access to Source Data/Documents

PIs at local centers will have access to their corresponding source documents. Dr. Mindie Nguyen and central coordinators will have access to de-identified source documents from all clinical sites and will conduct study related monitoring and audits as necessary. All participating centers will allow for IRB review and regulatory inspections of documentation by providing

access to the source data/documents. All participating centers will also transmit de-identified source documents to central coordinators for review.

10. Quality Control and Quality Assurance

Dr. Mindie Nguyen will ensure quality control and quality assurance by:

a. Periodic coordinator conference calls and investigator conference calls as needed.
b. In-person investigator meetings 1-2 times a year: APASL (Feb) or EASL (April), and AASLD (October).

One of Dr. Mindie Nguyen's staff will conduct monitoring visits at each non-Stanford location after enrollment of each site's first patient and before closure of the study to resolve all queries. Additional monitor visits may be carried out during the duration of the study, based on Dr. Mindie Nguyen's discretion. Within reasonable notice, site PI and research staff will agree to provide desk space for central coordinator site visits and will cooperate in providing needed source documents for the purpose of data monitoring.

11. Ethics

The study will be approved by each site's institutional review board (IRB) to comply with ethical conduct guidelines and has been registered on *http://www.ClinicalTrials.gov,* as required by U.S. Law.

12. Data Handling and Recordkeeping

Each patient is uniquely identified in the study by a combination of the center ID and patient number. The center ID is assigned by the sponsor, Dr. Mindie Nguyen. The patient number is generated after record is deemed eligible and all data in the CRF is submitted to the central coordinator. This identification code will be used for the duration of the study. Information linking this identification code to the patient will be kept on a password protected file stored securely at each local site.

Data will be transferred through email, fax, and courier. Patient identifying information (except for study ID) will be removed before transmittal. Data will be shared through a password protected, secure online database provided by the sponsor. All electronic data transfers of study information will be done only with approved encryption methods in place.

All sites will be instructed to keep study participants' source documents in locked cabinet files. Each CRF with PHI will be kept in individual subject binders and will be taken out of cabinet files only when necessary. Research staff will be instructed to not discuss participant/study information to persons outside of the research team and outside of the work area. All research staff have received proper HIPAA training.

As required, patient information may be provided to the Food and Drug Administration and other federal and regulatory agencies.

13. Financing and Insurance

Gilead Sciences will provide financial support for the study in the form of a research grant to Stanford University, which will provide funds to all participating centers via subcontract between Stanford University and participating institutions. For all sites except Japan, Gilead Sciences will also supply TAF 25 mg for all study participants. Reimbursement for bone density tests will be provided to patients in US and Taiwan sites as these may not be part of routine care for all participants there. Reimbursement for bone density tests, routine clinical visits with blood tests to be captured for study analysis will be provided for participants in Korea as per local standard. No other patient stipends will be provided. Other than drug provision and clinical care reimbursement as mentioned in this paragraph, all other clinical care including but not limited to visits, radiologic, laboratory tests done as per routine clinical care will be the responsibility of each study participant and/or his/her insurance.

14. Publication Policy

Findings from the interim analysis will be submitted for 1 to 2 abstracts at the following conferences: APASL, EASL/DDW and/or AASLD 2019. Findings from the final analysis of this study will be submitted for 1 to 2 abstracts at following conferences: APASL. EASL, DDW, and/or AASLD 2020 and 1 manuscript to be submitted to the following journals: Hepatology, Clinical Gastroenterology & Hepatology, Alimentary Pharmacology & Therapeutics, or Journal of Viral Hepatitis in 2020-2021. All sites agree to not publish data from their centers independently.

15. References

1. Martin P, Lau D T-Y, Nguyen MH, Janssen HLA, Dieterich DT, Peters MG, Jacobson IM. A Treatment Algorithm for the Management of Chronic Hepatitis B Virus Infection in the United States: 2015 Update. Clin Gastroentrol Hepatol 2015;13(12):2071-2087. 26188135.
2. Terrault N et al. AASLD HBV Clinical Practice Guideline. Hepatology 2015 Epub ahead of print.
3. Anna S.F. Lok, Brian J. McMahon, et al. Antiviral Therapy for Chronic Hepatitis B Viral Infection in Adults: A Systematic Review and Meta-Analysis. Hepatology 2015. Epub ahead of print.
4. Schweitzer A, Horn J, Mikolajczyk RT, et al. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet 2015;386:1546-55.
5. CDC. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. MMWR 2008;57:1-20.

6. Ward JW, Byrd KK. Hepatitis B in the United States: A major health disparity affecting many foreign-born populations. Hepatology 2012;56:419-421
7. Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int*. 2016; 10:1-98.
8. VEMLIDY (tenofovir alafenamide) [package insert]. Foster City, CA: Gilead Sciences Inc; 20015.