TITLE PAGE

Protocol Title: Effectiveness and Safety of Tenofovir Disoproxil Fumarate in Chronic Hepatitis B Patients: A 3-Year, Prospective, Real-World Study in China

Protocol Number: 207667

Short Title: Three-Year Effectiveness and Safety of TDF in Chinese CHB Patients in Real World

Compound Number: GSK548470

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Regulatory Agency Identifying Number(s): Not Applicable

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1. SYNOPSIS

Protocol Title: Effectiveness and Safety of Tenofovir Disoproxil Fumarate (TDF) in Chronic Hepatitis B Patients: A 3-Year, Prospective, Real-World Study in China

Short Title: Three-Year Effectiveness and Safety of TDF in Chinese CHB patients in real world

Rationale: Chronic infection with hepatitis B virus (HBV) represents a major global public health problem. It is estimated by WHO that around 257 million people are living with HBV infection. Chronic HBV infection leads to an increased risk of cirrhosis, hepatic decompensation, hepatocellular carcinoma (HCC), and liver-related premature mortality. HBV infection is particularly important in the Asian-Pacific region and China. Tenofovir disoproxil fumarate (TDF) was approved for the treatment of Chronic Hepatitis B (CHB) in the U.S. in 2008 and in China in 2013 based on Phase III clinical trials results. Since launching in China in 2014, the treatment experience of TDF is limited due to poor access. One important reason was the lack of real world evidence on long-term effectiveness and safety of TDF among Chinese CHB patients to guide clinical practice. The generation of real-world evidence from this study will provide clinical guidance to Chinese healthcare care professional (HCPs), address their concerns, and aid public health decision making on resource allocation.

Objectives and Research Questions:

Objectives	Research Questions
Primary Objective To assess the effectiveness among overall and sub-group Chinese CHB patients who receive TDF treatment in real-world	Among the overall analysis population and relevant sub-group* populations: • Proportion of patients who achieve complete virologic response (CVR) at weeks of 48, 96, and 144. • Proportion of patients who achieve HBeAg loss and/or HBeAg. seroconversion in HBeAg positive patients at weeks of 48, 96 and 144. • Proportion of patients who achieve HBsAg loss and/or HBsAg seroconversion at weeks of 48, 96 and 144. • Proportion of patients who achieve transaminase normalization at weeks of 48, 96 and 144. • Time to CVR, defined as time from baseline to the first occurrence of CVR (if

Objectives	Research Questions
	applicable)
Secondary Objective To assess the renal function change among overall and sub-group CHB patients during TDF treatment	Among the overall analysis population and relevant sub-group* populations: • Proportion of patients whose eGFR decline >20% from baseline at weeks of 48, 96, and 144. • Percentage of change from baseline in eGFR at weeks of 48, 96, and 144 • Change from baseline in eGFR values at weeks of 48, 98 and 144 • Proportion of patients with confirmed serum phosphate Grade 3 or 4 abnormality (<2.0 mg/dL) at weeks of 48, 98 and 144. • The percentage of change from baseline in serum phosphate at weeks of 48, 98 and 144. • Change from baseline in phosphorus values at weeks of 48, 98 and 144

Overall Design: This is a China-based multi-centre, prospective, longitudinal, non-interventional study conducted in a real-world setting. This study will take a naturalistic approach, capturing real world medical practice and patient outcomes. Patients with diagnosed CHB will be recruited from general and specialized hospitals, where patients will receive medical care according to their physicians' standard practice without interventions and procedures. Patients will only be approached for participation after their treatment decision is made naturally at hospital visit. As per CHB treatment guideline, patients on anti-viral treatment will need to be monitored at least every 6 months in terms of therapy response, drug-related side effect and disease progression. The minimal essential lab test in line with routine clinical practice requested by CHB management guideline will be performed in central lab. Patient data will be collected using an innovative electronic approach (i.e. Smartphone APP) from routine lab tests, medical records, and investigators' evaluation at the entry of this study and at 6-month intervals thereafter for 3 years.

Number of Participants: Approximately 2000 CHB patients who newly initiate TDF and who already started TDF prior to entry of study will be recruited from general and specialized hospitals across China.

Treatment Groups and Duration: The recruited 2000 TDF-treated CHB patients will be followed up to 3 years as treatment group to evaluate the effectiveness of safety of TDF in real-world setting in China.

2. SCHEDULE OF ACTIVITIES (SOA)

The exact timing of each assessment is listed in the Schedule of Activities Table 1

Table 1 Schedule of Activities

Procedure	Baseline data collection[5]			Follow-up data collection period (3 years)[6]					
	Patients who have started TDF prior to entry of study		Patients who newly initiate TDF						
	Initiation of TDF treatment	Entry of study	Entry of study	6 months	12 months	18 months	24 months	30 months	36 months
Informed consent		X	X						
Inclusion and exclusion criteria		X	X						
Baseline assessments[1]									
Sociodemographic		X	X						
Health behaviour		X	X						
Physical examination		X	X						
Medical history	X	X	X						
Regular assessments[2,3]									
HBV serology	X	X	X	X	X	X	X	X	X
HBV DNA *	X	X	X	X	X	X	X	X	X
ALT and/or AST	X	X	X	X	X	X	X	X	X
Serum creatinine and eGFR [MDRD equation] *	X	X	X	X	X	X	X	X	X
Serum phosphate*	X	X	X	X	X	X	X	X	X
TDF treatment status or update	X	X	X	X	X	X	X	X	X
Comorbidity and concomitant medication review	X	X	X	X	X	X	X	X	X

Procedure	Baseline data collection[5]			Follow-up data collection period (3 years)[6]					
	Patients who have started TDF prior to entry of study		Patients who newly initiate TDF						
	Initiation of TDF treatment	Entry of study	Entry of study	6 months	12 months	18 months	24 months	30 months	36 months
Patients adherence to TDF treatment		X		X	X	X	X	X	X
Other assessments[2,3]									
AFP		X	X	X	X	X	X	X	X
Hepatic ultrasound		X	X	X	X	X	X	X	X
Genotype		X	X	X	X	X	X	X	X
Bone mineral density (BMD)		X	X	X	X	X	X	X	X
Liver biopsy		X	X	X	X	X	X	X	X
Transient elastography		X	X	X	X	X	X	X	X
computed tomography (CT) /magnetic resonance imaging (MRI)		X	X	X	X	X	X	X	X
Spontaneous AE/SAEs and pregnancy exposure data collection[4]									
Spontaneous AE/SAEs reporting		X	X	X	X	X	X	X	X
Pregnancy exposure reporting		X	X	X	X	X	X	X	X

Abbreviations and notes:
AEs = Adverse events; CT= computed tomography; DNA = Deoxyribonucleic acid; eGFR = estimated Glomerular filtration rate; HBV = Hepatitis B virus; HBeAg = Hepatitis B envelope antigen; HCC = Hepatocellular carcinoma; MDRD = Modification of Diet in Renal Disease; MRI = Magnetic resonance imaging; SAEs = Serious adverse events AFP = Alpha feto protein * the essential lab test performed in central lab at or after entry of study

1. Sociodemographic: a brief baseline survey will be administered to collect a minimal amount of information. Additional study relevant information (only for enrolled patients) will be collected to enable study analyses.
2. Laboratory assessments and other clinical assessments: patients will only be monitored according to their physicians' standard practice without additional study-specified interventions and evaluations. Only available assessments will be collected from routine testing/evaluations using electronic approaches.

3. Assessments may not be conducted at the exact scheduled time intervals as there will be no intervention for patients' clinical care. Only available assessments will be collected from routine testing/evaluations. The schedule is to remind physicians to collect data regularly.

4. Adverse event and pregnancy exposure reporting: only spontaneous AEs/SAEs and pregnancy exposure related to any GSK products will be reported and summarized.

5. The baseline assessment filling with grey colure is mandatory and requested for baseline data collection.

6. Follow-up data collection period (e.g. months 6, 12, 18, 24, 30, 36) for patients who have started TDF before the entry of study will be anchored to their actual TDF initiation dates.

3. INTRODUCTION

3.1. Background

Chronic infection with hepatitis B virus (HBV) represents a major global public health problem. It is estimated by WHO that around 257 million people are living with HBV infection (defined as hepatitis B surface antigen positive) [WHO HBV Face Sheet]. Chronic HBV infection leads to an increased risk of cirrhosis, hepatic decompensation, hepatocellular carcinoma (HCC), and liver-related premature mortality. In 2015, HBV infection accounted for 887 000 deaths, mostly from complications (including cirrhosis and hepatocellular carcinoma) [WHO HBV Face Sheet]. HBV infection is particularly important in the Asian-Pacific region and China. More than one-third of the world's chronic HBV carriers live in China. It is estimated that over half a million of Chinese people die annually from end-stage liver diseases. HBV infection and progression to end-stage disease is also associated with significant economic burden to the healthcare system and the society. Successful prevention of HBV infection and disease progression will considerably reduce humanistic sufferings and socioeconomic burden [Sun, 2010].

Over the past decades, five oral nucleoside/nucleotide analogues (NUCs) have been approved for antiviral treatment of chronic hepatitis B (CHB) including Tenofovir Disoproxil Fumarate (TDF), Entecavir (ETV), Telbivudine (LdT), Adefovir (ADV) and Lamivudine (LAM). It has been established that the risk of disease progression is decreased through the sustained reduction in HBV deoxyribonucleic acid (DNA) to undetectable levels. NUCs have been shown to effectively reduce serum HBV DNA and alanine aminotransferase (ALT) levels and therefore improve patients' hepatic reserve and liver histology. For NUCs, lifetime treatment is suggested for Chronic Hepatitis B (CHB) patients with advanced liver disease or in some instances with chronic Immunosuppressive therapy. The generally favourable side-effect profiles of the five NUCs demonstrated in registration trials coupled with the low rates of antiviral drug resistance with the newer agents make them attractive for use beyond 1 year.

However, infrequent but serious adverse events such as myopathy, neuropathy, and pancreatitis as well as renal impairment and reduced Bone Mineral Density (BMD) have been reported [Terrault, 2016]. NUCs-dependent nephrotoxicity was first observed in human immunodeficiency virus (HIV)-infected patients treated with adefovir (ADV) and primarily results in proximal tubular toxicity rather than glomerular toxicity, which was susceptible to the effects of mitochondrial toxicity [Fisher, 2001, Lampertico, 2016]. It was reported that proportion of patients with GFR-shifting from ≥90 to 60 – 89 mL/min/1.73 m2 from baseline was 15%, 17.8% and 14.5% among LAM, ETV and TDF-treated non-cirrhotic compensated CHB patients respectively [Koklu, 2015]. However, HBV-infection, aging, comorbidity, e.g. hypertension, diabetes mellitus, is also linked to occurrence of chronic kidney disease in CHB patients besides NUC usage [Levey, 2012]. Hence, regular monitoring of renal function (including serum phosphate) as well as viral response is required in the management of CHB patients [Chinese Medical Association, 2015, Terrault, 2016, EASL, 2017]. Reduced BMD is another possible manifestation of renal toxicity due to renal proximal tubule damage leading to serum phosphate reduction and inadequate bone mineralisation [Kumar, 2012]. The

reported adverse effects of TDF on bone mineral density (BMD) are well known from its use in HIV treatment [Woodward, 2009].

3.2. Rationale

TDF was approved for the treatment of CHB in the U.S. in 2008 and in China in 2013. TDF is recommended as the first line anti-viral therapy either for naïve patients or as a rescue regimen by CHB clinical practice guidelines based on its high potency in supressing HBV DNA, good tolerance profile and low incidence of drug resistance [Chinese Medical Association, 2015, Sarin, 2016, Terrault, 2016, EASL, 2017]. Two global registered multicentred, randomized, controlled Phase III studies, GS-US-174-0102 (NCT00117676; Study 102) and GS-US-174-0103 (NCT00116805; Study 103), have shown that, during 48 weeks of TDF treatment period, 76.0% hepatitis B envelope antigen (HBeAg) positive and 93% HBeAg negative CHB patients achieved complete viral suppression (defined as HBV-DNA<69IU/ml, 400copies/ml) [Marcellin, 2008]; 98.0% and 99.6% achieved complete viral suppression among HBeAg positive and HBeAg negative respectively during 8 years of treatment [Marcellin, 2014]. No cases of TDF drug resistance were observed through the 8 years of treatment [Corsa, 2015]. The 48-week Chinese multicentred, randomized, controlled Phase III trials showed similar reports and the following open-label study up to 192 weeks reported similar results [Hou, 2015, Hou, 2016].

Besides the high potency of TDF in viral suppression, TDF was well-tolerated in the 8-years follow-up studies 102 & 103 [GS-US-174-0102 and GS-US-174-0103) and 192-week follow-up Phase III study from China [Hou, 2016]. For Studies 102 & 103, no renal toxic effects were observed during the 48 weeks of TDF treatment among patients with CHB who had preserved renal function at baseline; and the incidence of all individual renal adverse events in the 8-year follow up period was reported ≤2.2% (either ≥ 0.5 mg/dL increase in serum creatinine, or serum phosphate <2 mg/dL, or creatinine clearance <50 mL/min). Nearly 1% of renal adverse events was observed in the long-term follow up period in the Chinese Phase III study [Hou, 2016]. In TDF global registry study, BMD was also monitored, it was observed that T scores of hip and spine were stable between years 4-8.

Since launch, accumulating data from observational or real-world studies have added to our understanding of the efficacy and safety of TDF: the VIREAL study conducted in France, the GEMINIS in Germany, and a Taiwanese study [Marcellin, 2016, Petersen, 2015, Wang, 2016]. In these studies, treatment-naïve and experienced patients from diverse practice settings who were newly initiated on TDF therapy, were included. Hypertension, diabetes, renal disease, cardiovascular diseases, and other comorbidities were present in approximately 40% of patients, with up to 28% having estimated glomerular filtration rate (eGFR) <90 ml/min. The primary measurement of treatment effectiveness was HBV DNA suppression. HBV DNA suppression was achieved by >89% of those completing 3 years of treatment with no incidences of drug resistance. However, there have been inconsistent conclusions associated with the safety. In GEMINIS cohorts, the mean eGFR decreased by -3.50 mL/min over 3 years of TDF treatment. Similar findings were reported in the Taiwanese study where the greatest decrease in eGFR occurring in the first year (from 96.0±32.4 to 88.3±21.1). While the

VIREAL study showed that median eGFR was not remarkably affected during the 3-years of treatment even in patients aged ≥65 years old or patients having baseline creatinine clearance of <90ml/min. In the 3-year retrospective analyses done by Wang et al [Wang, 2016]. Mean eGRF reduced in the first year of TDF treatment. However, it did not decrease significantly during 2-3 years of treatment; but BMD did not change significantly during the treatment.

The effectiveness and renal safety results of TDF varies between registered clinical trials [complete virological response (CVR) over 95%] and real-world research (CVR approximately 71 to 92%) [Pol, 2012, Idilman, 2015, Kim, 2015], partly due to the difference between clinical trial patient population and real world study population. Phase III clinical trials are conducted under well-controlled conditions among pre-selected patients with strict in/exclusion criteria, generally eliminating older patients and those with co-infections or comorbidities (such as cirrhosis). Compared with most patients seen in real world practice, those participating in clinical trials are typically younger and healthier with less comorbidity and better treatment adherence. Understanding how antivirals perform in real world general patient population is more important to guide routine clinical practice. The results from high-quality real-world cohorts will continue to provide clinical guidance for physicians by providing safety and effectiveness evidence across diverse treatment settings and in a broader array of patients and enable more patients to benefit from the available treatment options.

Lampertico et al. [Lampertico, 2016] reviewed recent real-world evidence on the safety of TDF treatment among HBV-monoinfected patients. Overall, TDF can lead to minor reduction in eGFR and BMD, which was mainly observed during early stage of treatment and remained stable in long-term follow up in most patients. Although TDF was well tolerated with no clinically significant renal toxicity, evidence from cohort studies seems to be conflicting. Reductions in GFR/Creatinine among HBV patients treated with TDF were reported, the clinical significance of these changes needs more discussion and the degree of association between TDF and changes in renal function indicators varies across studies. The inconsistency might result from small sample size, different baseline population with different renal function, varying measures of renal function. Few studies observed BMD during TDF treatment among CHB patients. Gill et al. carried out a single-centre cohort study in the UK, specifically to assess the impact of TDF on BMD in 170 HBV-monoinfected patients. There was no difference in T-score between treatment groups for lumbar or femoral neck measures, but TDF was associated with a lower hip T-score compared with no TDF (P = 0.02) [Gill, 2015].

Since launching in China since 2014, the treatment experience of TDF is limited due to its late entry, high price, and lack of real world evidence on long-term effectiveness and safety of TDF among Chinese CHB patients to guide clinical practice. Safety outcomes among CHB patients in existing real-world studies were inconsistent due to limited sample size, different patient's socio-demographic and clinical characteristics, and varying clinical criteria for renal function assessment. In addition, there is a general concern on renal safety of TDF among Chinese HCPs because of the NUC-associated renal toxicity observed in HIV-infected patients, although it was assumed to be mostly related to either co-medication or co-morbidities associated with HIV.

Therefore, the primary purpose of the current real-world study is to evaluate the long-term effectiveness of TDF in the treatment of Chinese CHB patients. A secondary purpose is to explore TDF safety among Chinese CHB patients to address HCPs' concerns. The real-world data collected from this study will provide clinical guidance to Chinese HCPs, and aid public health decision making on resource allocation.

3.3. Benefit/Risk Assessment

Not applicable for this non-interventional real-world study.

4. OBJECTIVES AND RESEARCH QUESTIONS

Study objectives and research questions are listed in the Table 2.

Table 2 Objectives and Research Questions

Objectives	Research Questions
Primary Objective To assess the effectiveness among overall and sub-group Chinese CHB patients who receive TDF treatment in real-world	Among the overall analysis population and relevant sub-group* populations: • Proportion of patients who achieve complete virologic response (CVR) at weeks of 48, 96, and 144. • Proportion of patients who achieve HBeAg loss and/or HBeAg. seroconversion in HBeAg positive patients at weeks of 48, 96 and 144. • Proportion of patients who achieve HBsAg loss and/or HBsAg seroconversion at weeks of 48, 96 and 144. • Proportion of patients who achieve transaminase normalization at weeks of 48, 96 and 144. • Time to CVR, defined as time from baseline to the first occurrence of CVR (if applicable)
Secondary Objective To assess the renal function change among overall and sub-group CHB patients during TDF treatment	Among the overall analysis population and relevant sub-group* populations: • Proportion of patients whose eGFR decline >20% from baseline at weeks of 48, 96,

Objectives	Research Questions
	and 144. • Percentage of change from baseline in eGFR at weeks of 48, 96, and 144 • Change from baseline in eGFR values at weeks of 48, 98 and 144 • Proportion of patients with confirmed serum phosphate Grade 3 or 4 abnormality (<2.0 mg/dL) at weeks of 48, 98 and 144. • The percentage of change from baseline in serum phosphate at weeks of 48, 98 and 144. • Change from baseline in phosphorus values at weeks of 48, 98 and 144
Exploratory Objectives To explore the Bone Mineral Density (BMD) change among overall and sub-group CHB patients during TDF treatment	Percentage of BMD change from baseline at weeks of 48, 96, and 144
To investigate predictors of effectiveness among CHB patients who receive long-term TDF treatment	Baseline or on-treatment predictors (e.g. baseline characteristics, etc). • Treatment effectiveness, including CVR, HBeAg loss and/or HBeAg, transaminage normalization
To explore risk factors of safety among CHB patients who receive long-term TDF treatment	Baseline or on-treatment risk factors (e.g. baseline characteristics, co-morbidities, and concomitant treatment etc). • Renal impairment, including eGFR decline and serum phosphate • Bone impairment, including BMD decline
To investigate patient adherence to therapy	Duration of TDF therapy during the study period

Objectives	Research Questions
	• Summary of reasons of treatment discontinuation
To summarize the spontaneous AEs/SAEs and pregnancy exposures occurred during the study period (with special interest in AEs/SAEs due to TDF)	Summary of the occurrence of spontaneous AEs/ SAEs and pregnancy cases by GSK products and categorization. Incidence of decompensated cirrhosis/liver disease and related complications, at weeks of 48, 98 and 144

Abbreviations:
AEs = Adverse events; CHB = Chronic hepatitis B; CVR = Complete virological response; DNA = Deoxyribonucleic acid; eGFR = estimated Glomerular filtration rate; HBV = Hepatitis B virus; HBeAg = Hepatitis B envelope antigen; HCC = Hepatocellular carcinoma; MDRD = Modification of Diet in Renal Disease; SAEs = Serious adverse events
* Sub-group of interest may include important baseline socio-demographic, health behaviour, and clinical characteristics.

According the relevance and importance to the clinical practice and patient outcomes, sub-groups are defined by patients sociodemographic, health behaviour and clinical characteristics and on treatment factors, including age, gender, baseline HBV DNA level, HBeAg status, baseline alanine aminotransferase level in relation to the upper limit of the normal range, receipt or no-receipt of previous treatment with other NUCs, previous history of drug resistance, comorbidities (e.g. chronic kidney disease , hypertension, diabetes), baseline renal function, patient treatment adherence, etc.

5. STUDY DESIGN

5.1. Overall Design

This is a China-based multi-center, prospective, longitudinal, real-world study, taking a naturalistic approach, capturing real-world medical practice and patient outcomes using a non-interventional design. Patients with diagnosed CHB who newly initiate and continue TDF monotherapy or combination therapy will be consecutively recruited from general and specialized hospitals across China. Site/hospital selection will consider geographic and hospital type/tier representativeness, investigators' research interest, as well as feasibility such as electronic data collection approaches. For non-enrolled subjects, reasons of exclusion will be collected.

During the study, patients will seek and receive medical care as they do in regular clinical practice setting without investigational product tested. Specifically, patients' diagnosis, treatment, and monitoring will be left to their physicians' routine practice without study-

dictated visits and procedures. Minimal patient evaluations will be done by physicians, e.g. baseline patient demographics and clinical characteristics and patients' treatment adherence. Minimal lab tests in line with routine clinical practice (HBV DNA, serum creatinine, and serum phosphate) will be conducted in a central lab on the basis of the judgement of treating physicians and willingness of patients.

Other patient data will be collected using electronic approaches, mainly from lab test reports or medical records at the entry of this study and thereafter at 6-month intervals for 3 years. As this is a real-world study without mandatory scheduled visits, patients may not seek medical care and conduct assessments (e.g. lab tests) exactly at 6-month intervals. The 6-month interval is set to remind investigators to collect data regularly.

5.2. Number of Participants

Approximately 2000 eligible CHB patients will be recruited from general and specialized hospitals across China.

5.3. Participant and Study Completion

The recruited 2000 TDF-treated CHB patients will be followed up to 3 years as treatment group to evaluate the effectiveness of safety of TDF in real-world setting in China without study-specified intervention and procedure. All the recruited patients will seek and receive medical care as they do in regular clinical practice setting during the study follow-up and after the study completion with no study medicine provided.

5.4. Scientific Rationale for Study Design

Although evidence on TDF efficacy and safety has been accumulated in traditional clinical trials, there is a lack of real-world evidence on its effectiveness and safety, especially among Chinese CHB patients. CHB patients are a heterogeneous population, with a wide range of age, morbidities and comorbidities, such as renal impairment. However, many of these patients are usually excluded from traditional clinical trials. The importance of real-world evidence is increasingly acknowledged because real-world studies provide valuable information about the use of treatments in daily clinical practice, as they include patient populations usually under-represented in clinical trials and capture real-world practice and patient outcomes.

To explore the effectiveness and safety of TDF, this study will take a naturalistic approach using a non-interventional and prospective design, reflecting the real-world patient population and disease management. Evidence from this real-world study will be of great relevance and value to inform physicians, patients and payers to better understand the benefits and risks of TDF, guide physicians' practice on managing CHB patients, aid payers in decision-making on resource allocation, and ultimately provide more benefits to Chinese CHB patients.

5.5. Dose Justification

Not applicable for this study in which no study intervention will be administered.

6. STUDY POPULATION

TDF-naïve patients with confirmed diagnosis of CHB who newly initiate (Viread) monotherapy or combination therapy for the treatment of CHB will be invited to participate in this study. Those who have already started TDF treatment and meet all the inclusion and exclusion criteria will be also considered eligible. To minimize selection bias, investigators are encouraged to follow their routine clinical practice and consecutively recruit all eligible patients at their practice. More importantly, patients will only be approached for participation after his/her treatment choice has been naturally made between him/her and the physician/investigator (e.g. whether to get treatment or what anti-viral treatment). Willing participants (or their legal guardian) will be asked to voluntarily provide the informed consent to allow their past, current and follow-up medical information to be collected within the study period. For non-enrolled subjects, the reasons for exclusion will be collected whenever possible.

Hospitals and investigators will be selected mainly based on the representativeness of hospital tier, geographic, the research interest of a specific physician to this study, and the potential CHB patient flow. To better understand the real-world practice in Chinese hospitals, we performed a feasibility assessment among infectious disease physicians in 17 hospitals across the country, including 8 Tier 3 Grade A general hospitals, 6 Tier 3 Grade A infectious disease specialized hospitals, and 3 Tier 2 Grade A general hospitals. 11 out of 17 physicians showed interest in this study and the evidence on TDF's effectiveness and safety in real world setting. The majority of interviewed physicians stated that over 50 CHB patients could be recruited in their practice within 3 months.

6.1. Inclusion Criteria

Participants will be eligible to be included in this study only if all of the following criteria apply:

1. Male or female participants aged 12 years and above, at the time of signing the informed consent.
2. Participants who are diagnosed with CHB and meet the criterion of antiviral treatment for HBV infection judged by certified physicians.
3. Participants who newly initiate TDF ((only including brand TDF, Viread, and generic TDF, Beixin and Naxinde, which passed China generic quality consistency evaluation by Apr. 1 2018) monotherapy or combination therapy for the treatment of CHB by the judge of investigators at the study entry.
4. Participants who have already started TDF at the entry of study and will continue to be treated TDF (including brand TDF, Viread, and generic TDF, Beixin and Naxinde, which passed China generic quality consistency evaluation by Apr. 01 2018) with essential medical information record and lab test reports available at the initiation of TDF treatment and follow-up visit.

   Essential medical information record and lab test reports:

   - *At the initiation of TDF treatment:*

i. TDF treatment detail: TDF dose, brand name, start date;

ii. Lab test (within +/-4 weeks of TDF treatment initiation): HBV DNA quantification (using high sensitive real-time PCR assays for HBV DNA quantification with lower limit of detection of 20IU/ml), ALT and/or AST, Serum creatinine and Serum phosphate, HBsAg/Anti-HBs and HBeAg/Anti-HBe

iii. Medical information: CHB diagnosis and treatment history, co-morbidity, concomitant treatment

- *The following visits under TDF treatment prior to entry of the study (At least once following visit record if TDF treatment >6 months):*

i. Lab test: HBV DNA quantification (using high sensitive real-time PCR assays for HBV DNA quantification with lower limit of detection of 20IU/ml), Serum creatinine and Serum phosphate

ii. Medical information: co-morbidity, concomitant treatment, TDF treatment information

The proportion of patients who have already started TDF at the study entry will be monitored closely during study recruitment and will be kept less than 10% of the total study population.

5. Participants who are able to perform normal activities and seek regular medical care, e.g., willing to regularly perform lab test to monitor the treatment response.
6. Participants or their legal guardians who are capable of providing signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

6.2. Exclusion Criteria

Participants will be excluded from the study if any of the following criteria apply:

1. Participants who have HIV/HCV co-infection.
2. Participants who initiate or continue antiviral treatment of generic TDF which did not pass China generic quality consistency evaluation by Apr. 01, 2018
3. Participants who initiate antiviral treatment of unauthorized TDF in China.
4. Participants with a prior history of receiving any TDF monotherapy or combination therapy without essential lab test report (e.g. HBV DNA level, eGFR, serum phosphate) and medical records available at the initiation of TDF treatment and thereafter follow-up.
5. Participants who participate in any concurrent clinical trials or within 3 months prior to the entry into this study.
6. Participants who are NOT able to upload their information electronically using the study-designed smartphone APP.
7. Inability to comply with study requirements as determined by the study Investigator.

6.3. Lifestyle Restriction

Not applicable for this study in which no study-specified intervention will be administered.

6.4. Screen Failure

When screening, relevant information will be collected as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for study exclusion.

7. STUDY ASSESSMENTS AND PROCEDURES

Given the naturalistic nature of the study design, all participated patients will be diagnosed, treated, and monitored as in real clinical practice according to their physicians' judgement without additional interventions and procedures. Protocol-specified information relevant to CHB diagnosis and treatment will be collected from assessments generated from routine clinical care, including lab tests and medical records, complemented with investigators' evaluation at the entry of this study and thereafter at 6-month intervals for up to 3 years until the end of the study or until participant withdraws from this study. It is expected that diagnosis and treatment practice will vary across study hospitals and physicians.

Data will be collected using an innovative electronic approach, i.e. Smartphone App, with the intention to reduce the data collection burden on patients, investigators, and sites and also improve data collection efficiency and quality. The use of Smartphone App enables patients and investigators to upload lab tests and medical records and complete brief online evaluations (e.g. whether the patient remains on TDF? Any changes on TDF treatment?) via their smartphones.

There are no mandatory visits during the study period, however, according to the CHB clinical practice and CHB management guideline, CHB patients on anti-viral treatment should be monitored for at least every 6 months, e.g. HBV DNA, liver and renal function. Data collected and their timing are summarized in the SoA (See Section 2). The 6-month data collection interval is set to remind investigators to collect patient's data regularly. A minimal necessary medical evaluation in line with routine clinical practice following the guideline recommendation is required for all eligible patients at the entry of study for basic medical assessment on the basis of the judgement of treating physicians and willingness of patients. Other lab tests and procedures in the SoA will be judged by the treating physician and carried out by patients. Only available and identifiable assessments will be collected.

All the lab test and procedures in the SoA will be performed based on the judgement of investigators/treating physicians and patients' willingness as in real-world practice. To achieve consistent evaluation of the effectiveness and safety of TDF treatment, the minimal essential lab test requested by CHB management guideline, including HBV DNA, eGFR and serum phosphate, will be performed in central lab during patients'

routine clinical visits. Other lab tests and procedures will be performed in local hospitals where patients seek care. Results will be collected by the innovative electronic approach.

Supplementary central lab operation information would be provided in the accompanying study procedure manual (SPM). The SPM will provide the site personnel with administrative and detailed information on how to minimize the impact of the introduction of central lab to routine practice.

7.1. Baseline Evaluation

Necessary and mandatory baseline evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria (refer to Section 6). The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for study exclusion, as applicable. Information collected as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening purposes provided the information met the protocol-specified criteria and was collected within the time frame defined in the SoA (Table 1).

The investigator will maintain a log to confirm eligibility or record reasons for study exclusion.

7.2. Baseline Data Collection

Baseline information collected (assessment values and date of assessment) includes:

- Socio-demographic information, e.g. age, sex, economic status, medical insurance coverage
- Health behaviour information, e.g. smoking status, alcohol consumption, health care seeking behaviour
- Physical examinations, e.g. weight, height
- Medical information, e.g. medical history, anti-Hep B diagnosis and treatment history, NUC drug resistance history, co-morbidity, concomitant treatment, decompensated cirrhosis/liver disease and related complications
- TDF treatment details，e.g. TDF dose, brand name, start date
- Initial tests when initiating TDF therapy, including
    - HBV serology
    - HBV DNA
    - Serum creatinine and eGFR [MDRD equation]
    - Serum phosphate
    - Alanine transaminase (ALT) and aspartate transaminase (AST)
- Other tests and procedures collected if available
    - AFP

- Hepatic ultrasound
- Genotype
- Bone mineral density
- Liver biopsy
- Transient elastography (fibrotouch or fibroscan)
- Hepatic ultrasound/ computed tomography (CT) /magnetic resonance imaging (MRI)

- Spontaneous AEs if available

To evaluate renal function, the estimated glomerular filtration rate (eGFR) will be calculated using the modification of Diet in Renal Disease (MDRD) equation:

Where the unit of creatinine is ml/min/1.73m^2. Baseline data will be collected using a specifically designed survey. For patients who initiate TDF treatment at the entry of the study, baseline information can be completed from investigator interviewing the patient.

For patients who have already been on TDF treatment at the study entry, their previous data related to initiation of TDF treatment and follow-up will be collected from (electronic) medical records as needed if available.

Three essential lab tests, HBV DNA, serum creatinine, and serum phosphate, will be performed in a central lab. Patients' other data will be collected using electronic approaches, mainly from lab test reports or medical records at baseline and follow-ups.

7.3. Follow Up Data Collection

Study participants will be followed up for 3 years or until they withdraw from the study. Follow-up information will be collected at 6-month intervals:

- Regular tests
  - HBV serology
  - HBV DNA
  - Serum creatinine and eGFR [MDRD equation]
  - Serum phosphate
  - Alanine transaminase (ALT) and aspartate transaminase (AST)
- Other tests and procedures
  - AFP
  - Hepatic ultrasound
  - Genotype
  - Bone mineral density

  - Liver biopsy
  - Transient elastography (fibrotouch or fibroscan)
  - Hepatic ultrasound /computed tomography (CT) /magnetic resonance imaging (MRI)
- Updated CHB treatment details, e.g. any change to regimen or dosage and reason for change
- Comorbidity and concomitant medication review
- Spontaneous AEs if available
- For treatment adherence, it will be evaluated by the treating physician according to the patients' care seeking care, e.g. whether take the medication as prescribed, have you ever discontinued your medications and for how long?
- For participants who discontinue TDF prematurely, duration of treatment and reasons for TDF discontinuation will be recorded, e.g. SAEs, non-SAEs, and insufficient effectiveness.

7.4. Adverse Events and Pregnancy Events Data Collection

As this study takes a naturalistic design and minimizes the level of interventions, only spontaneous AEs will be collected, i.e. all serious and non-serious adverse events (AEs) and pregnancy exposures related to any GSK product (e.g., Viread) will be collected and reported as described in the study-specific pharmacovigilance plan (sPVP). Our special interest is the renal and bone toxicity related to TDF. In routine clinical practice, collecting and reporting spontaneous AEs including pregnancy exposure is the obligation of physicians. Such events will be evaluated and reported by investigators completing the Spontaneous AE Reporting Form for HCPs, Pregnancy Initial Notification Form for HCPs and Pregnancy Outcome Form for HCPs. The study SAP will oversee the spontaneous AE reports to be forwarded by CRO to local safety team who will report to GSK central safety department.

See study Pharmacovigilance Plan (sPVP) for details. sPVP will include the following elements to ensure a comprehensive approach to safety event collection and reporting:

- Supplier pharmacovigilance training
- Investigator and site staff pharmacovigilance training
- Safety-specific roles
- AEs / SAEs and pregnancy exposures collection and reporting processes
- AEs / SAEs and pregnancy exposures collection forms
- Frequency of data review
- Reporting process and timelines

- Interim reports
- Study-specific PVP monitoring process
- Provision of final study report

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Not applicable. No investigational treatment will be tested.

8.2. Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

In this real-world study, participants will be considered withdrawal from the study if any of the following events occurs within the 3-year study period:

Discontinuation of TDF (Viread, Beixin or Naxinde) for at least 28 days

Participation in clinical trials for any new drugs not limited to CHB-related ones during the 3-year study period

Study closed/terminated

Withdrew consent

The overall duration of TDF treatment and the reason for discontinuation of TDF treatment will be collected and the patient's adherence will be evaluated by the investigator a designed questionnaire.

8.3. Loss to Follow Up

There will be no protocol-dictated interventions to improve patient compliance besides what physicians do in practice. This study will use an innovative electronic data capture approach (e.g. Smartphone APP), which is expected to minimize the data collection burden and reduce patients' loss to follow up.

9. STATISTICAL CONSIDERATIONS

9.1. Sample Size Determination

9.1.1. Hypotheses

No formal hypotheses will be tested, as this will be a descriptive study. The objective of this study is to observe the effectiveness and safety among Chinese CHB patients who receive long-term TDF treatment in real-world setting.

9.1.2. Sample Size Assumptions

Sample sizes are estimated based on feasibility and precision level achieved as no formal hypothesis will be tested in this study.

The primary objective of this study is to assess the effectiveness of TDF, with one important indicator being the proportion of subjects who achieve the CVR (i.e. HBV-DNA undetectable) at weeks of 48, 96, and 144. To be able to assess the CVR achievement at week 144, a sample size of 2,000 patients will provide a precision of no more than 2.2%, assuming the percentage of patients achieving CVR is 80% and the rate of loss-to-follow-up and discontinuation is 35%. The precision is calculated by the following: precision = $Z_{(1\alpha/2)}$*SQRT(p*(1-p)/N), where Z is the critical value of normal distribution corresponding to the probability of 1-α/2 (corresponding to (1- α)*100% confidence interval), and p is the percentage of patients achieving CVR. It is half of the width of 95% confidence interval for the point estimate, which means that the lower and upper bounds of the 95% confidence interval for the patient proportion of interest will be within 2.2% of the point estimate (point estimate +/- 2.2%). In addition, there will be approximately a 73% probability of identifying a least one AE with a true AE rate of 0.1%.

For an exploratory purpose, more calculations about the precisions of evaluating the CVR achievement percentage are also provided for difference sub-populations, such as HBeAg positive or Cirrhosis. Assuming HBeAg positive (Cirrhosis) is made of 54.5% (20%) of HBV patients, the percentage of patients achieving CVR is 80% and 3 -year drop-out rate is 35%, a sample size of N=2000 will have 1090 (400) patients in the interested group and about 708 (260) completers and a precision of no more than 0.029 (0.049) [You, 2016].

9.1.3. Sample Size Sensitivity

Different sample sizes and corresponding precisions are provided in the Table 3 below. It assumes the percentage of patients achieving CVR is 80%, and the drop-out rate is 35%.

Table 3 Different Sample Sizes and Corresponding Precisions

Total Sample Size (N)	Completers after 35% drop out	Precision (Half width of 95% confidence interval)
3000	1950	0.018
2500	1625	0.019
2000	1300	0.022
1500	975	0.025
1000	650	0.031
750	488	0.036
500	325	0.043

9.2. Populations for Analyses

The main population for analyses will consist of all consented participants who have the requested baseline data and at least one post-baseline assessment data.

9.3. Statistical Analyses

A detailed Reporting and Analysis Plan (RAP) outlining details of data analyses will be created and described below. Besides the 144-week analysis, key analyses may be conducted annually with the 48-week and 96-week cut-off data to look at short-term patient outcomes. No adjustment for multiplicity will be made for these analyses.

Continuous variables will be summarized for overall population and various subgroups using mean (standard deviation) and/or median (range), while categorical variables will be summarized in tables of frequencies and percentages. Comparative analyses will be performed across sub-groups using Student's t test or analyses of variance for quantitative variables, and Pearson's Chi-square test (Fisher exact test might be used when necessary) for qualitative variables. Nonparametric tests will be used when necessary.

In primary and secondary analyses, as this is a real-world study without mandatory scheduled visits, the assessments (e.g. lab test) may not be conducted exactly at 6-month intervals, but to keep the robustness of the estimation for effectiveness and renal function change, a time window that ±28 days for week 48, 96 and 144 will be applied in each cut-off analyses. As the supportive analyses, the analyses with time windows that ± 3 months will be conducted. More details will be included in Reporting and Analyses Plan (RAP).

9.3.1. Baseline Description

Among eligible patients approached by investigators or site staff, the proportion who agreed to participate this study will be estimated. The basic socio-demographic and health status information will be summarized and compared between those who were enrolled and those who refused to participate to examine the potential difference between the two groups of CHB patients., a brief screening survey will be administered to all eligible patients (including non-enrolled patients) to collect a minimal amount of socio-demographic and health information. This is to enable the evaluation of possible patient selection bias and potential confounding factors in study analysis. All individual identifiers will be removed for non-enrolled patients., a brief screening survey will be administered to all eligible patients (including non-enrolled patients) to collect a minimal amount of socio-demographic and health information..

For the analysis population, baseline patients' characteristics (e.g. socio-demographic, clinical, and genotype) will be summarized using descriptive statistics for the overall population and by subgroups (e.g. gender, age group, clinical characteristics).

9.3.2. Primary Analyses

In order to evaluate the effectiveness of TDF for the treatment of CHB patients, the following estimates will be summarized for the overall analysis population and sub-populations (e.g. gender, age group, clinical characteristics).

- The proportion of patients who achieve CVR at week of 144
- The proportion of patients who achieve CVR at weeks of 48 and 96
- The proportion of patients who achieve HBeAg loss and/or HBeAg seroconversion in HBeAg positive patients at weeks of 48, 96, and 144
- The proportion of patients who achieve HBsAg loss and/or HBsAg seroconversion at weeks of 48, 96, and 144
- The proportion of patients who achieve transaminase normalization at weeks of 48, 96, and 144

Sub-groups are defined according to patients sociodemographic, lifestyle and clinical characteristics and on treatment factors, including age, gender, baseline HBV DNA level, HBeAg status, baseline alanine aminotransferase level in relation to the upper limit of the normal range, receipt or no-receipt of previous treatment with other NUCs, previous history of drug resistance, baseline genotype, comorbidities (cirrhosis, hypertension, diabetes, renal disease), patient treatment adherence.

A time window that ±28 days for week 48, 96 and 144 will be applied in each cut-off analyses. As the supportive analyses, the analyses with time windows that ± 3 months will be conducted.

9.3.3. Secondary Analyses

Patients' renal functional change during TDF treatment period will be explored.

- The proportion of patients whose eGFR (MDRD equation) decline >20% from baseline at weeks of 48, 96 and up to week 144 will be summarized for the overall study analysis population and sub-group populations.
- Mean and 95% confidence intervals for the change from baseline in eGFR values will be calculated for the overall analysis population, as well as for the sub-populations of interests. A mixed effect model will be fitted to explore the impacts on the mean change from baseline in eGFR of fixed effects of age, gender, treatment-naïve or experienced, ADV or non-ADV, type of baseline co-morbidities (Cirrhosis, Hypertension, diabetes mellitus (DM), non-overlapping), baseline eGFR values, baseline HBV-DNA counts, baseline HBeAg status, and other factors as appropriate, and random effects of subject ID.
- The percentage of change from baseline in eGFR will be estimated for the overall analysis population and by sub-populations at weeks 48, 96, and 144. Figures of mean eGFR values overall and the sub-populations of interests will be generated.
- The proportion of patients with confirmed a serum phosphate Grade 3 or 4 abnormality (<2.0 mg/dL) at weeks of 48, 98 and 144 will be summarized for the overall study analysis population and sub-group populations.
- The percentage of change from baseline in serum phosphate will be estimated for the overall analysis population and by sub-populations at weeks 48, 96, and 144. Figures of mean serum phosphate values overall and the sub-populations of interests will be generated.
- Mean and 95% confidence intervals for the change from baseline in serum phosphate values will be calculated for the overall analysis population, as well as for the sub-populations of interests. A mixed effect model will be fitted to explore the impacts on the mean change from baseline in serum phosphate of fixed effects of age, gender, treatment-naïve or experienced, ADV or non-ADV, type of baseline co-morbidities (Cirrhosis, Hypertension, DM, non-overlapping), baseline eGFR values, baseline HBV-DNA counts, baseline HBeAg status, baseline phosphorus and other factors as appropriate, and random effects of subject ID.

9.3.4. Exploratory Analyses

9.3.4.1. Bone safety

Patients' BMD change from baseline during TDF treatment period will be explored.

- Percentage of BMD change at weeks of 48, 96, and 144 will be summarized using appropriate descriptive statistics for the overall analysis population and by subgroup populations.

9.3.4.2. Risk factors/Predictors of TDF effectiveness

To explore risk factors or predictors (e.g. baseline characteristics, co-morbidities, and concomitant treatment etc.) for effectiveness:

- Treatment effectiveness, including CVR, HBeAg loss and/or HBeAg. Seroconversion, transaminase normalization

Fisher exact test will be performed for the comparisons of the above treatment effectiveness endpoints in sub-groups of interest.

If data permits, generalized linear mixed model will be used to analyze CVR, HBeAg loss and/or HBeAg Seroconversion, transaminase normalization. More details will be included in RAP.

Time to CVR will be analysed by Kaplan-Meier curve, log-rank test will be performed separately for risk factors or predictors of interest, and multivariate analysis by Cox regression model will be conducted if data is applicable.

9.3.4.3. Patient Treatment Adherence

The duration of patients on TDF treatment and the primary reason of discontinuation will be summarized using descriptive statistics as appropriate. The difference between CHB patients who continued TDF and those who discontinued will be explored in terms of socio-demographic and clinical characteristics (e.g. baseline HBV DNA level, HBeAg status, baseline alanine aminotransferase level, receipt or no-receipt of previous treatment with other NUCs, previous history of drug resistance, treatment-naïve or experienced, ADV or non-ADV, type of baseline co-morbidities).

9.3.4.4. Spontaneous Adverse Events and Pregnancy Events

- Spontaneous AEs/SAEs will be summarized using descriptive statistics.

  Adverse events will be assigned preferred terms and categorized into body systems according to the medical dictionary for regulatory activities (MedDRA) classification of the World Health Organisation terminology.

  The proportion of subjects who experienced AEs will be calculated by dividing the number of subjects who experienced the AE during the treatment period by the number of subjects evaluable for safety analysis. Adverse events will be summarised by treatment group, and by body system and event within each body system. The following summaries of AEs will be provided:

  All AEs.

  All treatment related AEs.

  All SAEs.

  All treatment related SAEs.

  All AEs leading to permanent discontinuation of study drug.

  All AEs leading to permanent discontinuation from the study.

- Pregnancy events will be summarized using descriptive statistics. In addition, change from baseline of serum phosphate, serum creatinine, and creatinine clearance will also be summarized to evaluate the drug safety.
- The incidence of decompensated cirrhosis/liver disease and related complications, such as HCC, will be calculated for weeks of 48, 98 and 144, for the overall analysis population, and for certain sub-populations of interests, such as elderly and baseline Cirrhosis patients

9.3.5. Other Analyses

Missing data is inevitable in this real-world study and can have an impact upon the interpretation of the data. In general, values for missing data will not be imputed unless otherwise specified. As this study takes a naturalistic approach, there will be no protocol-dictated interventions or approaches to improve patient compliance besides what physicians do in practice. The study will use innovative electronic data capture approaches to increase the efficiency of data collection and reduce the effort on patients, physicians and sites, hopefully to reduce the chance of missing data.

The duration of patients on TDF, the reason for discontinuation if possible, and patients' adherence will be evaluated and recorded. Missing data issue will be explored in data analyses. For example, the reason and occurrence time of missing data will be summarized. It might be informative to know more the missing data and improve the adherence of treatment in the future.

When applicable, additional analyses may be conducted on primary, secondary, and exploratory objectives and research questions and will be described in RAP.

10. STUDY GOVERNANCE CONSIDERATIONS

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors （or delegators） will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.

GSK （or delegators）will monitor the study to ensure that the:

Data are authentic, accurate, and complete.

Safety and rights of subjects are being protected.

Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

Data will be collected using an innovative electronic approach, i.e. Smartphone APP, with the intention to reduce the data collection burden on patients, investigators, and sites and also improve data collection efficiency and quality in this study. All the data uploaded must be managed and retained in order to comply with all applicable law/regulatory requirements and GSK standard operating procedures.

11. INFORMED CONSENT PROCESS

Electronic informed consent form would be provided via the innovative digital approach in this study. Written informed consent must be obtained from each subject prior to participation in the study.

12. STUDY LIMITATIONS

This is a China-based multi-centre, prospective, longitudinal, non-interventional study conducted in a real-world setting in order to investigate long-term effectiveness and safety of TDF among Chinese CHB patients to guide clinical practice. The absence of comparison group is one of the major limitations to this study, which can be mitigated by a historical comparison leveraging previous trial data from literature or in-house alternatively. The mixing of the new initiator and on-treatment patients is another limitation, which may complicate the analysis due to varied treatment duration and inconsistent baseline information. Potential solutions include setting restriction on the inclusion criteria to the patients who have already started TDF prior to the entry of study in line with those of new initiators.

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14. APPENDICES

Appendix 1: Abbreviations and Trademarks

Abbreviations

AE	Adverse event
ADV	Adefovir
ALT	Alanine aminotransferase
AFP	Alpha feto protein
BMD	Bone mineral density
CV	Cardiovascular
CHB	Chronic hepatitis B
CVR	Complete virological response
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
ETV	Entecavir
eGFR	Estimated glomerular filtration rate
HBeAg	Hepatitis B envelope antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCP	Healthcare care professional
HIV	Human immunodeficiency virus
ICF	Informed consent form
IU/mL	International unit per millilitre
LAM	Lamivudine
LdT	Telbivudine
mL	Milliliter
mL/min/m^2	Milliliter per minute per meter square
MedDRA	Medical dictionary for regulatory activities
MDRD	Modification of diet in renal disease
NUC	Nucleos(t)ide analogues
PI	Principal investigator
RAP	Reporting and analysis plan
SAE	Serious adverse event
SD	Standard deviation
SOA	Schedule of activity
sPVP	study pharmacovigilance plan
TE	Transient elastography
TDF	Tenofovir disoproxil fumarate
%	Percentage

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