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**Study ID: 201213**

**Official Title of Study:** A prospective, multi-center, cohort study to evaluate the efficacy and safety of Tenofovir Disoproxil Fumarate (TDF) therapy in Chinese chronic hepatitis B (CHB) subjects with advanced fibrosis & compensated cirrhosis

**Version Date:** 27-Mar-2016
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| **Title:** | A prospective, multi-center, cohort study to evaluate the efficacy and safety of Tenofovir Disoproxil Fumarate (TDF) therapy in Chinese chronic hepatitis B (CHB) subjects with advanced fibrosis & compensated cirrhosis |

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**Author(s):** PPD

**SPONSOR SIGNATORY:**

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**Regulatory Agency Identifying Number(s):** NA

# INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: _____

| | |
|---|---|
| Investigator Signature | Date |

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| ADV | Adefovir dippivoxil |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| ANA | Anti-nuclear antibody |
| AST | Aspartate aminotransferase |
| BP | Blood pressure |
| CFDA | China Food and Drug Administration |
| CHB | Chronic hepatitis B |
| CRF | Case report form(s) |
| DAPD | (2*R*,4*R*)-4-(2,6-Diaminopurin-9-yl)-1,3-dioxolan-2-yl]methanol |
| DNA | Deoxyribonucleic acid |
| EC | Ethics committee |
| ETV | Entecavir |
| FTC | Emtricitabine |
| GCP | Good Clinical Practice (Guidelines) |
| GFR | glomerular filtration rate |
| HAV | Hepatitis A virus |
| HBeAg | Hepatitis B e antigen |
| HBsAg | Hepatitis B s antigen |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| HCC | Hepatocellular carcinoma |
| HDV | Hepatitis delta virus |
| HIV | Human immunodeficiency virus |
| IB | Investigator brochure |
| IFN | Interferon |
| INR | International normalised ratio |
| IP | Investigational product |
| IUD | Inter uterine device |
| IUS | Inter uterine system |
| L-FMAU | 1-(2-fluoro-5-methyl-beta, L-arabinofuranosyl) uracil |
| LAM | Lamivudine |
| LdT | Telbivudine |
| LFT | Liver function test |
| LLD | Lower limit of detection |
| LSLV | Last subject last visit |
| LSM | Liver stiffness measure |
| mITT | Modified Intent-to-treat (population) |
| MedDRA | Medical dictionary for regulatory activities |
| NA | Nucleos(t)ide analogues |
| PP | Per protocol population |
| PT | Prothrombin time |
| PTA | Prothrombin time activity |
| QD | *quaque die* (Once daily) |
| RAP | Reporting and analysis plan |
| SA | Safety analysis population |

| | |
|---|---|
| SAE | Serious adverse event |
| SOP | Standard operating procedure |
| SPM | Study procedures manual |
| TDF | Tenofovir disoproxil fumarate |
| TE | Transient elastography |
| ULN | Upper limit of the normal range |

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# PROTOCOL SUMMARY

## Rationale

Chronic hepatitis B infection affects over 240 million people worldwide, of whom about 93 million live in China. Chronic hepatitis B infection is known as the most frequently identified cause of liver disease that predisposes patients to the development of hepatocellular carcinoma (HCC). It is now clear that active HBV replication is the key driver of liver injury and disease progression.

Over the past decades, four oral nucleos(t)ide analogues (NA) have been approved for antiviral treatment of CHB in China. They have been shown to be effective in decreasing serum HBV DNA and alanine aminotransferase (ALT) levels, improving hepatic reserve and liver histology. Seven years of tenofovir DF (TDF) therapy in treatment naïve patients results in sustained viral suppression with no development of resistance and was associated with either the halting or regression of fibrosis in 96%, and reversal of cirrhosis in 74% of previously cirrhotic patients(Marcellin et al., 2013).

Only a few long-term studies of patients with advanced liver diseases undergoing antiviral treatment are available, mostly using LAM. However, LAM is associated with a high rate of resistance, which may cause disease progression and reduce benefit of antiviral therapy. Newer NAs with low resistance rates, such as entecavir (ETV) and TDF, show good efficacy in suppressing HBV DNA, but the long-term effects on the prevention of decompensation and HCC are not well characterised.

This prospective multi-center cohort study is designed (1) to investigate the long-term effect of TDF on prevention of HCC and disease progression in Chinese CHB subjects with compensated cirrhosis; (2) to evaluate the efficacy and safety of long-term TDF in Chinese CHB subjects with compensated cirrhosis; (3) to explore baseline and on-treatment risk factors associated with disease progression and development of HCC in Chinese CHB subjects with compensated cirrhosis

## Objective(s)

## Primary Objective

- To evaluate the incidence of hepatocellular carcinoma (HCC) during 240-weeks of TDF 300mg QD treatment in Chinese CHB subjects with advanced fibrosis and compensated cirrhosis.
- To evaluate the rate of disease progression during 240-weeks of TDF 300mg QD treatment in Chinese CHB subjects with advanced fibrosis and compensated cirrhosis.

## Secondary Objective

- To evaluate the efficacy and safety of 240 weeks of TDF 300mg QD treatment in Chinese CHB subjects with advanced fibrosis and compensated cirrhosis

## Study Design

This is a prospective, multi-centre, open-label, cohort study to investigate efficacy and safety of TDF treatment in Chinese chronic hepatitis B (CHB subjects with advanced fibrosis and compensated cirrhosis. The study will enrol 186 subjects.

Screen phase (≤4 weeks): Subjects considered eligible to enroll into the study will be assessed at a screening visit as described in Table 1 to decide if they meet the study criteria (see section 4.2 and 4.3). Between Screen visit and baseline visit, subjects will not receive investigational product.

Treatment phase (0 Day ~Week 240): 186 subjects will be administered TDF 300 mg QD and undergo regular safety and efficacy assessments every 12 weeks for a total of up to 240 weeks(see Table 1). Subjects will be questioned about adverse events, concurrent medications, and study drug accountability; blood will be taken for hematology and biochemistry profiles; serum samples well be tested for HBV markers, and the prothrombin time will be measured. Serum samples will be collected at Week 12, 24, 36,48, 60, 72, 84, and 96 and every 24 weeks thereafter and analyzed for HBV DNA levels at a central laboratory. Abdominal ultrasound and serum alpha-fetoprotein test will be performed every 12 weeks for HCC surveillance. If abdominal ultrasound reports a liver mass or nodule, CT of MRI will be performed. At baseline and W216, a subset of 100 subjects will undergo liver biopsy to evaluate liver histological changes pre- and post- TDF treatment. All subjects will be followed up to Week 240.

Rescue treatment could be optionally initiated, at the discretion of the investigator if

- subjects have confirmed virological breakthrough as defined as a $\geq 1$ $\log_{10}$ IU/mL increase in HBV DNA from nadir determined by two sequential HBV DNA measurements at least 1 month apart, OR
- subjects have HBV DNA ⩾200IU/ml at week 48 and afterwards have ≤ one log decrease in HBV DNA at two consecutive tests, confirmed by a third visit at least one month apart.

Confirmation of HBV DNA test will require an additional visit to collect serum sample. To receive rescue treatment subjects must have investigational product (IP) compliance > 80% in the last regular visits period (usually 12 weeks). Add-on combination with a second nucleoside agent (LAM, ETV or telbivudine (LdT)) is acceptable rescue treatment in this study, to be decided by the investigator. Before rescue treatment, serum sample should be collected for resistance testing.

Subjects who reach primary endpoint (i.e. develop liver complications or HCC) may withdraw from study. Investigator and subjects can decide whether to continue study drug. Subjects who continue to take study drug will be followed as per the original schedule until Week 240. During the follow-up period, AEs, concomitant medication, vital signs, hepatitis B virus DNA, haematology, chemistry and prothrombin will be evaluated. Serum/plasma storage also will be conducted.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not affect subject safety.

## Study Endpoints/Assessments

## Primary Endpoint

- Incidence of hepatocellular carcinoma at Week 240.
- Incidence of disease progression at Week 240, defined as the first occurrence of any one of the following criteria:
  - An increase in Childs-Pugh score (as defined in Appendix 1) of 2 or more points from baseline. an increase in Childs-Pugh score of 2 or more points, solely based on laboratory parameters (i.e. bilirubin, prothrombin time and/or albumin), confirmed between two consecutive visits at least one month apart;
  - spontaneous bacterial peritonitis (with proven sepsis);
  - renal insufficiency defined as a decrease in creatinine clearance rate to ⩽50 mL/minute confirmed on two occasions at least one week apart (calculated from serum creatinine concentration, see section 11.2 Appendix 2);
  - bleeding gastric/oesophageal varices;
  - hepatocellular carcinoma;
  - liver-related death

## Secondary Endpoints

- Incidence of HCC at Week 48, Week 96 Week 144, and Week 192
- Cumulative incidence of HCC at Week 48, Week 96, Week 144, Week 192 and Week 240
- Cumulative incidence of disease progression at Week 48, Week 96, Week 144 and Week 192, and Week 240
- The mean changes of liver stiffness measurement (LSM) at Week 48, Week 96, Week 144, Week 192 and Week 240
- Proportion of subjects with serum HBV DNA <20 IU/mL (Roche COBAS Taqman HBV Test) at Week 48, Week 96, Week 144, Week 192 and Week 240.
- The mean $\log_{10}$ reduction in serum HBV DNA at Week 48, Week 96, Week 144, Week 192 and Week 240 compared with baseline.
- The proportion of subjects with ALT normalization at Week 48, Week 96, Week 144, Week 192 and Week 240 in subjects who have abnormal ALT at baseline.

- For HBeAg positive subjects: the proportion of subjects achieving HBeAg loss, HBeAg seroconversion or HBsAg loss and HBsAg seroconversion at Week 24, Week 48, Week 96, Week 144, Week 192 and Week 240.
- For HBeAg negative subjects: the proportion of subjects achieving HBsAg loss and HBsAg seroconversion at Week 48, Week 96, Week 144, Week 192 and Week 240.
- Incidence of virological breakthrough as defined by $\geq 1$ $\log_{10}$ increase in HBV DNA from nadir (as determined by two sequential HBV DNA measurements at least 1 month apart, or the last on-treatment measurement) up to Week 48, Week 96, Week 144, Week 192 and Week 240
- The proportion of subjects with histological improvement (a reduction of two or more points in the Knodell necroinflammatory score with no increase in fibrosis) at Week 216 in the subset of subjects with paired baseline and W216 liver biopsies.
- The proportion of subjects with cirrhosis reversal (a reduction of one or more points in the Ishak score and no evidence of cirrhosis) at Week 216 in the subset of subjects with paired baseline and W216 liver biopsies and with a baseline Ishak score higher than or equal to five.
- Subject safety as determined by adverse events and laboratory assessments.

## Other Endpoints

- Incidence of TDF resistance substitutions (if identified) at Week 48, Week 96, Week 144, Week 192 and Week 240.
- Baseline or on-treatment risk factors for HCC/disease progression (e.g. gender, age, HBV DNA, genotype, HBeAg sero-status, ALT, treatment response etc)

# 1. INTRODUCTION

## 1.1. Background

Chronic hepatitis B infection affects over 240 million people worldwide, of whom about 93 million live in China(Chinese Society of Hepatology & Chinese Society of Infectious Diseases, 2011). And It has been reported that 15–20% of CHB patients progress to cirrhosis within 5 years. Over 70% of Chinese patients with cirrhosis are HBsAg positive(Zhang, Zhang, Elizabeth, & Liu, 2012). CHB infection is also known as the most frequently identified cause of liver disease that predisposes patients to the development of hepatocellular carcinoma (HCC), accounting for approximately 70%-80% of cases(Lai & Yuen, 2013). HCC is the second most common type of malignancy in China, developing at an annual incidence of 3–6 % in patients with cirrhosis and far less frequently in non-cirrhotic patients(Nguyen, Law, & Dore, 2009)' (Chen, Chu, Yeh, & Liaw, 2007). It is now clear that active HBV replication is the key driver of liver injury and disease progression.

Over the past decades, four oral nucleos(t)ide analogues (NA) have been approved for antiviral treatment of CHB in China(Chinese Society of Hepatology & Chinese Society of Infectious Diseases, 2011). They have been shown to be effective in decreasing serum HBV DNA and alanine aminotransferase (ALT) levels, improving hepatic reserve and liver histology. The goal of antiviral therapy in cirrhotic patients is to prevent hepatic decompensation, reduce or prevent progression and/or HCC, and prolong survival(Chinese Society of Hepatology & Chinese Society of Infectious Diseases, 2011)'(Liaw et al., 2012).

Only a few long-term studies of patients with advanced liver diseases undergoing antiviral treatment are available. A randomized placebo-controlled study in 651 patients showed that LAM therapy for a median of 32.4 months could reduce the incidence of HCC (hazard ratio 0.49, P = 0.047) and the incidence of liver complications (hazard ratio 0.45, P=0.02) in patients with advanced fibrosis or compensated cirrhosis (Liaw et al., 2004). A large Korean cohort of lamivudine-treated patients was compared with historical controls and reported that long-term viral suppression reduced the rate of HCC compared with those with viral breakthrough or untreated controls in patients with cirrhosis at baseline (Eun, Lee, Kim, & Lee, 2010). However, LAM is associated with a high rate of resistance, especially with long-term therapy. Clinical studies have shown that the greatest benefit in preventing disease progression was observed in patients without drug resistance, and the benefit decreased after emergence of drug resistance (Liaw et al., 2004)'(Di Marco et al., 2004). Newer NAs with low resistance rates, such as entecavir (ETV), show good efficacy in suppressing HBV DNA, but the long-term effects of ETV treatment are not well characterised. In one report the 5-year cumulative incidence of HCC in a retrospective-prospective cohort undergoing ETV treatment were 2.1% and 12.9% in the non-cirrhosis and cirrhosis subgroups, respectively (Wong et al., 2013). Hosaka et al reported that long-term ETV treatment may reduce the incidence of HCC (versus historical control, hazard ratio: 0.37, P = 0.030) (Hosaka et al., 2013). However, Papatheodoridis et al reported that risk of HCC continued to increase in their large mutlicenter study of predominantly Caucasian patients treated with ETV or TDF (Papatheodoridis, Dalekos, & Yurday-, 2013).

Until now, liver biopsy (LB) remains the gold standard for assessing the degree of liver fibrosis. But recently many non-invasive methodologies have been developed. Among them, transient elastography (FibroScan, Echosens, France) has been widely accepted for the measure of liver stiffness and helping to stage liver fibrosis. Some researchers have proposed diagnostic algorithms that use dual TE cut-offs, for positive and negative prediction of significant fibrosis. And based on their results, China's Review Panel for Liver Stiffness Measurement offered recommendations for the clinical application of transient elastography in liver fibrosis assessment(Review Panel for Liver Stiffness Measurement, 2013).

## 1.2. Rationale

Two Phase III studies (GS-US-174-0103, GS-US-174-0102) have shown that seven years of tenofovir disoproxil fumarate (TDF) therapy in treatment naïve patients results in sustained viral suppression with no development of resistance and was associated with either the halting or regression of fibrosis in 96%, and reversal of cirrhosis in 74% of previously cirrhotic patients (Marcellin et al., 2008) ,(Marcellin et al., 2013), (Kitrinos et al., 2013). However, the long-term effect of TDF on the prevention of decompensation and HCC has not been well established.

Additionally, the characteristics of Chinese CHB population differ from those enrolled in studies referred to above in which the majority of cirrhotic subjects were NAs treatment naïve and genotype A/D, while in China the majority of cirrhotic patients are NAs treatment experienced and genotype B/C (Liaw et al., 2012). Due to these differences the efficacy and safety of TDF on CHB patients with compensated cirrhosis in China may differ from those seen in the cirrhosis subgroup analysis above.

Despite the success of nucleot(s)ide (NA) treatment of CHB infection, antiviral treatment has failed to reduce the risk of subsequent HCC. Established risk factors for the development of HCC in untreated chronic HBV patients include subject age, male gender, presence of cirrhosis, hepatitis B e antigen (HBeAg) positive serostatus, and high levels of serum HBV-DNA. Thus it is important to identify those at higher risk of HCC even with potent NAs treatment.

This prospective multi-center cohort study is designed (1) to investigate the long-term effect of TDF on prevention of HCC and disease progression in Chinese CHB subjects with compensated cirrhosis; (2) to evaluate the efficacy and safety of long-term TDF in Chinese CHB subjects with compensated cirrhosis; (3) to explore baseline and on-treatment risk factors associated with disease progression and development of HCC in Chinese CHB subjects with compensated cirrhosis

## 1.3. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with Tenofovir can be found in the Investigator's Brochure and China-specific prescribing information for TDF in CHB. The following section outlines the risk assessment and mitigation strategy for this protocol:

### 1.3.1. Risk Assessment

| Potential Risk of Clinical Significance | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Investigational Product (IP)** | | |
| Renal toxicity | Tenofovir is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of VIREAD. | • Exclusion of CHB patients with creatinine clearance <70 mL/min<br>• Monitor renal function every 12 weeks<br>• Dosing interval adjustment of VIREAD is recommended in all patients with creatinine clearance below 50 mL/min.<br>• Stopping criteria based on renal function with serum creatinine confirms >2.5 mg/dL have been clearly defined.(see section 6.3.2) |
| Bone events | Decreases in Bone mineral density (BMD) has been reported in adults and pediatric patients. The effects of VIREAD-associated changes in BMD and biochemical markers on long-termbone health and future fracture risk are unknown. | • Monitoring the serum calcium and phosphate every 12 weeks<br>• In every regular visits, the information of bone related symptoms will be collected.<br>• Assessment of BMD and related treatment should be considered by the investigator's judgement. |
| Lactic acidosis/severe hepatomegaly with steatosis and lipodystrophy | Lactic acidosis/ severe hepatomegaly with steatosis, including fatal cases, havebeen reported with the use of nucleoside analogs, including VIREAD, in combination with other antiretrovirals. | • Guidelines for management of lactic acidosis are outlined in Appendix 4. |
| Drug-Drug Interaction Potential | Since tenofovir is primarily eliminated by the kidneys, coadministration of VIREAD with drugs that reduce renal function or compete for active tubular secretion may increase | • Estimated creatinine clearance will be assessed in all patients every 12 weeks during treatment with TDF<br>• TDF should be avoided |

| | | |
|---|---|---|
| | serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir,aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs | with concurrent or recent use of a nephrotoxic agent according to the protocol(See section5.6.2) |
| Post-treatment hepatic flares | Discontinuation of anti-HBV therapy, including VIREAD, may be associated with severe acute exacerbations of hepatitis and must only take place under careful supervision. | • Patients who withdraw from the investigational product during treatment period will be followed as per the original schedule.<br>• No post-study medication is provided; the investigator is responsible for ensuring that consideration has been given to the post-study care of the patient's medical condition. |

### 1.3.2. Benefit Assessment

The benefits and risks of TDF have now been characterized in a large range of subject populations with HIV-1 and HBV infection enrolled in clinical studies and a large number of patients who have received TDF in clinical practice.

*Chronic Hepatitis B Infection*

The effectiveness of TDF has been characterized in a large range of adult populations, cirrhotic population included, and in pediatric patients ≥ 12 years of age, with HBV infection.

TDF demonstrates potent and selective inhibition of HBV replication in vitro and in vivo.

No mutations associated with TDF resistance have been identified in viremic subjects (HBV DNA > 400 copies/mL) treated with TDF.

TDF has been studied in an extensive clinical development program. The strength of evidence supporting the overall efficacy of TDF is provided by large-scale long term phase III clinical studies, which demonstrate effective reduction of HBV viral load and histologic improvement both in general and cirrhotic population. No significant data weakness or uncertainties remain.

### 1.3.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with TDF are justified by the anticipated benefits that may be afforded to patients with CHB.

# 2. OBJECTIVE(S)

## 2.1. Primary Objective

- To evaluate the incidence of hepatocellular carcinoma (HCC) during 240-weeks of TDF 300mg QD treatment in Chinese CHB subjects with advanced fibrosis and compensated cirrhosis.
- To evaluate the rate of disease progression during 240-week of TDF 300mg QD treatment in Chinese CHB subjects with advanced fibrosis and compensated cirrhosis.

## 2.2. Secondary Objectives

- To evaluate the efficacy and safety of 240 weeks of TDF 300mg QD treatment in Chinese CHB subjects with advanced fibrosis and compensated cirrhosis

# 3. INVESTIGATIONAL PLAN

## 3.1. Study Design

This is a prospective, multi-centre, open-label, cohort study to investigate efficacy and safety of Tenofovir Disoproxil Fumarate (TDF) treatment in Chinese CHB subjects with advanced fibrosis and compensated cirrhosis. The study will enrol 186 subjects with a diagnosis of CHB and advanced fibrosis or compensated cirrhosis.

Screen phase (≤4 weeks): Written informed consent must be obtained from each subject prior to participation in the study. Subjects considered eligible to enroll in the study will be assessed at a screening visit as described in Table 1 to decide if they meet the study criteria (see that in 4.2 and 4.3). Between Screen visit and baseline visit, subjects will not receive investigational product.

Treatment phase: 186 subjects will be administered TDF 300 mg QD and undergo regular safety and efficacy assessments every 12 weeks for a total of up to 240 weeks (see Table 1). Subjects will be questioned about adverse events, concurrent medications, and study drug accountability; blood will be taken for hematology and biochemistry profiles; serum samples well be tested for HBV markers, and the prothrombin time will be measured. Serum samples will be collected at Week 12, 24,36, 48, 60, 72, 84, and 96 and every 24 weeks thereafter and analyzed for HBV DNA levels at a central laboratory. Abdominal ultrasound, the prothrombin time and serum alpha-fetoprotein test will be performed every visits. If abdominal ultrasound reports a liver mass or nodule, CT or MRI will be performed. At baseline and W216, 100 of subjects will take liver biopsy to

evaluate liver histological changes pre and post TDF treatment. All subjects will be followed through to Week 240.

Rescue treatment could be optionally initiated in subjects with unsatisfied response to TDF, at the discretion of the investigator if

- subjects have confirmed virological breakthrough as defined by ≥ one log increase in HBV DNA from nadir determined by two sequential HBV DNA measurements at least 1 month apart, or
- subjects have HBV DNA ⩾200IU/ml at week 48 and afterwards have ≤ one log decrease in HBV DNA at two consecutive visits, confirmed by a third visit at least one month apart.

Confirmation of HBV DNA test will require an additional visit to collect serum sample. To receive rescue treatment subjects must have investigational product (IP) compliance > 80% in the last regular visits period (usually 12 weeks). Add-on combination with a nucleoside agent (LAM, ETV or LdT) is acceptable rescue treatment in this study, as to investigator's decision. Before rescue treatment, serum sample should be collected for resistance testing.

Subjects who reach primary endpoint (i.e. develop liver complications or HCC) may withdraw from study. Investigator and subjects can decide whether to continue study drug. Subjects who continue to take study drug will be followed as per the original schedule until Week 240. During the follow-up period, AEs, concomitant medication, vital signs, hepatitis B virus DNA, haematology, chemistry and prothrombin will be evaluated. Serum/plasma storage also will be conducted.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not affect subject safety.

## 3.2. Discussion of Design

This study is designed to evaluate the cumulative incidence of newly diagnosed HCC in patients with advanced fibrosis and compensated cirrhosis during 240 weeks of TDF treatment. It will also provide long-term efficacy and safety data (up to 240 weeks) of TDF 300 mg QD.

It is accepted that long-term antiviral therapy benefits cirrhotic patients as will be investigated in this study with TDF. As HCC develops at an annual incidence of approximately 3–6 % in patients with cirrhosis it will take some time to observe an effect of TDF on prevention of HCC, and on histological improvement.

CHB patients with advanced fibrosis and cirrhosis have severe liver disease and reducing viral replication and acheiving HBV DNA undetectability is particularly important in this group. In this study subjects with poor response or virological breakthrough after Week 48 (See Section3.1) may receive rescue treatment, with add-on treatment of additional NAs. Before rescue treatment, serum sample should be collected for resistance testing.

# 4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

## 4.1. Number of Subjects

186 Chinese CHB subjects with advanced fibrosis & compensated cirrhosis will be administered to TDF 300 mg QD.

| | |
|---|---|
| Screened | 260 |
| Enrolled | 186 |
| Completed/evaluable | 158 |

## 4.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB/IB supplement(s) and product label.

Deviations from inclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects eligible for enrolment in the study must meet all of the following criteria:

1. Age 18-60 years(inclusive);
2. Presence of HBsAg in serum at screening and for at least 6 months before screening assessment;
3. Serum HBV DNA≥ 2000 IU/mL if HBeAg positive at screening (with or without ALT elevation); or serum HBV DNA≥ 200IU/mL if HBeAg negative at screening (with or without ALT elevation);
4. Pathologically or clinically diagnosed as advanced fibrosis or compensated cirrhosis defined as one of following(a or b) :
    a. Liver biopsy showing advanced fibrosis or cirrhosis (Ishak score ≥4 or Fibrosis stage≥S3 by Scheuer Score, or within the previous 6 months before baseline and provided that no treatment likely to improve liver histology has been taken since). The slides must be available for review by an independent histopathologist.
    b. Clinical diagnosis: liver stiffness measure (LSM) >12.4 kpa (ALT> ULN) or LSM>9.0 kpa (ALT≤ULN), (See section 6.2.7) plus one of the following:
        i. Endoscopy-proven gastroesophageal or gastric varices, non-cirrhotic portal hypertension excluded;
        ii. Abdominal ultrasound or CT found changes indicating cirrhosis, irregular liver surface or nodularity, with/without splenomegaly(depth of spleen>4.0cm or spleen length>13cm);
        iii. Blood platelets <100 $x10^9$/L (and other causes of thrombocytopenia excluded);

5. Ability to give written informed consent;
6. A female is eligible to enter and participate in this study if she is of:
    a. non-childbearing potential (i.e., physiologically incapable of becoming pregnant, including any female who is post-menopausal), or
    b. Child-bearing potential, has a negative urine pregnancy test at screening, and agrees to one of the following methods for avoidance of pregnancy during the period of the study and until 30 days after last dose of study medication:
        i. Oral contraceptive, either combined or progestogen alone.
        ii. Injectable progestogen.
        iii. Implants of levonorgestrel.
        iv. Oestrogenic vaginal ring.
        v. Percutaneous contraceptive patches.
        vi. Intrauterine device (IUD) or intrauterine system (IUS) showing that the expected failure rate is less than 1% per year as stated in the IUD or IUS product label.
        vii. Has a male partner who is sterilised.
        viii. Double barrier method: condom and an occlusive cap (diaphragm orcervical/vault caps) with a vaginal spermicidal agent (foam/gel/film /cream/suppository).
7. Agreement not to participate in any other investigational trials or to undertake other HBV systemic antiviral or IFN regimens during participation in this study.

## 4.3. Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Hepatocellular carcinoma as evidenced by one of the following:
    - Suspicious foci on ultrasound or radiological examination.
    - Normal ultrasound serum alpha-fetoprotein >50 ng/mL at screening.
2. Serum ALT >10 times ULN at screening or history of acute exacerbation leading to transient decompensation;
3. Documented co-infection with hepatitis A (HAV), hepatitis C (HCV), hepatitis delta virus (HDV), hepatitis E virus (HEV) or HIV. For HCV co-infection, subjects who are anti-HCV positive and in whom HCV RNA is undetectable are considered to be not eligible for enrolment.
4. Evidence of active liver disease due to autoimmune hepatitis (antinuclear antibody (ANA) titre >1:160)
5. Decompensated liver disease as indicated by any of the following:
    a. serum bilirubin >1.5 xULN
    b. prothrombin time activity <60% or INR>1.5
    c. serum albumin <32 g/L
    d. history of previous clinical hepatic decompensation (e.g.,

ascites, variceal bleeding, or encephalopathy);

6. Planned for liver transplantation or previous liver transplantation;
7. Creatinine clearance less than 70 mL/min;
8. Haemoglobin <10 g/dL, white blood cell (WBC) count <1.5 x $10^9$/L, platelets ≤50 x $10^9$/L;
9. Any serious or active medical or psychiatric illnesses other than hepatitis B which, in the opinion of the Investigator, would interfere with subject treatment, assessment or compliance with the protocol. This would include any uncontrolled clinically significant renal, cardiac, pulmonary, vascular, neurogenic, digestive, metabolic (diabetes, thyroid disorders, adrenal disease), immunodeficiency disorders, pathological fractures or cancer;
10. Active alcohol or drug abuse or history of alcohol or drug abuse considered by the Investigator to be sufficient to hinder compliance with treatment, participation in the study or interpretation of results;
11. A female who is breastfeeding or plan to breastfeed;
12. Use of immunosuppressive therapy, immunomodulatory therapy (including IFN or thymosin α,), systemic cytotoxic agents, chronic antiviral agents including Chinese herbal medicines known to have activity against HBV (e.g., LAM, adefovir, ETV LdT or hepatitis B immunoglobulin (HBIg)) within the previous 6 months prior to screening into this study;
13. Have ever received TDF or any medicinal products containing the above mentioned antiviral agents or any investigative anti-HBV treatments (e.g., emtricitabine (FTC), (2*R*,4*R*)-4-(2,6-Diaminopurin-9-yl)-1,3-dioxolan-2-yl]methanol (DAPD) and 1-(2-fluoro-5-methyl-beta, Larabinofuranosyl) uracil (L-FMAU));
14. History of hypersensitivity to nucleoside and/or nucleotide analogues and/or any component of study medication;
15. Therapy with nephrotoxic drugs (e.g., aminoglycosides, amphotercin B, vancomycin, cidofovir, foscarnet, cis-platinum, pentamidine etc.) or competitors of renal excretion (e.g., probenecid) within 2 months prior to study screening or the expectation that subject will receive any of these during the course of the study;
16. Inability to comply with study requirements as determined by the study Investigator.

## 4.4. Withdrawal Criteria

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and re-schedule the missed visit as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study based on previous non-compliance. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls and if necessary a certified letter to the subject's last known mailing address) so that they can appropriately be withdrawn from the study. These contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, then and only

then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up". For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF.

Subjects who temporarily interrupted treatment for <28 consecutive days were allowed to continue in the study. Subjects with treatment interruptions of ≥ 28 consecutive days were required to withdraw from the study.

A subject may voluntarily discontinue participation in this study at any time. The investigator also have the right to withdraw patients from treatment or the study in the event of intercurrent illness, adverse events, protocol violations, administrative reasons or other reasons at any time. Any female subject who becomes pregnant while participating should withdraw from the study. The reason for withdrawal from the study must be recorded in the case report form (CRF).

Subjects will also be withdrawn from the study if they reached primary end-point. These subjects will be eligible for study drugs and originally scheduled follow-up.

Subjects who have received at least one dose of study drug and permanently discontinued the study drug should be followed up by the investigator as described in Table 1.

### 4.5. Screening/Run-in Failures

If a blood sample has been collected and it is determined that the subject does not meet the inclusion and exclusion criteria for participation in the study, then the investigator must withdraw those subjects and complete the appropriate documentation to request sample destruction within the timeframe specified by GSK.

## 5. STUDY TREATMENTS

### 5.1. Investigational Product and Other Study Treatment

Tenofovir disoproxil fumarate (9-[(R)-2-[[bis[[(isopropoxy-carbonyl) oxy] methoxy] phosphinyl] methoxy] propyl] adenine fumarate (1:1)); GS4331-05) is an oral pro-drug (bisPOC-PMPA) of tenofovir (PMPA), an acyclic nucleoside phosphonate (nucleotide) analogue of adenosine 5'-monophosphate. Tenofovir disoproxil fumarate has demonstrated antiviral activity against HBV and HIV and is indicated for use in combination with other antiretroviral agents in the treatment of HIV infection.

Tenofovir disoproxil fumarate tablets are white, almond-shaped, film-coated tablets containing 300 mg of TDF, debossed with "GSK" and "300" on one side of the tablet. Each tablet contains the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, pregelatinised starch, croscarmellose sodium, and magnesium stearate. The tablets are film coated with Opadry II White 32K18425.

Study drugs (TDF) are packaged in white, high-density polyethylene bottles with a white child resistant cap. There are 30 tablets per bottle. Each bottle also contains silica gel canister(s) to protect the product from humidity and fibre packing to protect the product during handling and shipping.

For subjects who experienced virological breakthrough or partial virological response will add another drug without cross resistant to Tenofovir including LAM (Heptodin, GlaxoSmithKline, 100mg QD), ETV (Baraclude, Bristol-Myers Squibb, 0.5mg QD) and LdT(Sebivo,Novartis,600mg QD).Investigator will make the decision for the drug selection.

### 5.1.1. Handling and Storage of Investigational Product

No preparation of investigational product is required at site.

The contents of the label will be in accordance with all applicable regulatory requirements.

Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

Investigational product must be stored in a secure area under the appropriate physical conditions for the product at lower than 25° C. Access to and administration of the investigational product will be limited to the investigator and authorised site staff. Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

### 5.1.2. Dosage and Administration

Subjects will be assigned to receive open-label TDF 300 mg treatments for 240 weeks in the study. Subjects will be instructed to take one pill once daily. Investigational product absorption is not affected by food intake so the tablets do not have to be taken with a meal.

Subjects who receive add-on rescue treatment may take LAM 100 mg, ETV 0.5 mg or LdT 600 mg per day upon investigator’s decision in addition to TDF tablet.

Subjects will be dispensed study drug at all visits except for the Week 240 or early study drug discontinuation visit. Subjects will be instructed to return unused study medication in the original container at each post-baseline study visit. The Investigator will be responsible for maintaining accurate records for all study drug and study drug bottles dispensed and returned. The inventory must be available for inspection by the study monitor. Study medication supplies, including partially used or empty bottles, must be accounted for and the dispensing logs must be verified by the study monitor prior to destruction or return.

If subjects develop renal insufficiency (defined by serum creatinine clearance) during study treatment, the following dose reduction criteria should be used when subjects have a serum creatinine clearance of <50 mL/minute:

| Calculated Creatinine Clearance (mL/minute)[a] | | | Requiring Haemodialysis |
|---|---|---|---|
| ≥ 50 | 30–49 | 10–29 | |
| Tenofovir disoproxil fumarate 300 mg every 24 h | Tenofovir disoproxil fumarate 300 mg every 48 h | Tenofovir disoproxil fumarate 300 mg every 72 h | Tenofovir disoproxil fumarate 300 mg every 7 days or after a total of approximately 12 h of dialysis[b] |
| Lamivudine 100 mg every 24 h | Lamivudine is prohibited in such patients. | | |
| Entecavir 0.5 mg every 24 h | Entecavir 0.5 mg every 48 h | Entecavir 0.5 mg every 72 h | Entecavir 0.5 mg every 5-7 days post-haemodialysis[c] |
| Telbivudine 600mg every 24 h | Telbivudine 600mg every 48 h | Telbivudine 600mg every 72 h | Telbivudine 600mg every 96 h or after dialysis[c] |

a. Calculated using ideal (lean) body weight.
b. Generally once weekly assuming three haemodialysis sessions a week of approximately 4 h duration. Medication should be administered following completion of dialysis.
c. Medication should be administered following completion of dialysis.

## 5.2. Treatment Assignment

This is an open label, single arm study.

## 5.3. Blinding

N/A

## 5.4. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study.

## 5.5. Treatment Compliance

The importance of compliance with the treatment regimen will be emphasised at each visit.

The subject must be reminded to return all unused medication (including empty containers). The Investigator or designated study site personnel should count the number of tablets returned by the subject to establish the number of tablets used, and compare this to the number of tablets expected to be used for the period. A record of this reconciliation must be maintained using the accountability forms provided, and any issues of non-compliance discussed with the subject.

## 5.6. Concomitant Medications and Non-Drug Therapies

### 5.6.1. Permitted Medications and Non-Drug Therapies

All concomitant medication and the reason(s) for their use must be entered into the CRF. Effort should be made to give only medications which are clearly indicated for a specific medical reason.

### 5.6.2. Prohibited Medications and Non-Drug Therapies

No other investigational drugs, immunosuppressive therapy, immunomodulatory therapy (including IFN or thymosin α), systemic cytotoxic agents, chronic antiviral agents(e.g., LAM, adefovir, ETV, LdT, other medicinal products containing tenofovir, ganciclovir, famciclovir, FTC, DAPD, LFMAU, HBIg), agents containing glycyrrhizic acid(e.g., compound glycyrrhizin, compound ammonium glycyrhetate, diammonium glycyrrihizinate), agents containing bicyclol or bifendate will be permitted, unless defined in protocol .

TDF should be avoided with concurrent or recent use of a nephrotoxic agent including but are not limited to cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir, aminoglycosides (e.g., gentamicin), high-dose or multiple NSAIDs,,and herbal medications (e.g., tripterygium wilfordii,  leonuri and plant medicine containing aristolochic acid).

Traditional Chinese medicines and other herbal medicines intended to improve/protect liver function are prohibited during the study and must be discontinued at the time of screening. Such medicines include, but are not restricted to, oxymatrine and agents containing schisandra. Medicines intended to improve liver fibrosis are prohibited during the study and must be discontinued at the time of screening. Such medicines include, but are not restricted to,Fuzheng Huayu Capsule.

In the events mentioned in Section 6.3.1, medicines intended to improve/protect liver function will be allowed based on the Investigator’s judgement after consulting with the GlaxoSmithKline medical monitor. All concomitant medication and reasons for their use

must be entered into the CRF. However, agents containing bicyclol, bifendate or schisandra will not be permitted in any situation.

## 5.7. Treatment after the End of the Study

No post-study medication is provided as part of this protocol.

Discontinuation of anti-HBV therapy, including VIREAD, may be associated with severe acute exacerbations of hepatitis and must only take place under careful supervision.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the patient's medical condition whether or not GSK is providing specific post study treatment. TDF study medication is commercially available in China.

## 5.8. Treatment of Study Treatment Overdose

If a subject in the study takes an overdose, whether intentional or otherwise, the subject will be referred to a hospital at the Investigator's discretion. Management of such a subject should be symptomatic and supportive. In these circumstances it is the responsibility of the Investigator to obtain as much clinical data as possible, including blood samples for TDF or LAM/LdT/ETV assay, and to communicate this to GlaxoSmithKline. An SAE form must be completed if the overdose is associated with any signs or symptoms. For the purposes of this study, an overdose will be defined as any dose administration exceeded the recommended dose of TDF 300 mg, LAM 100mg, LdT 600mg or ETV 0.5mg per day.

# 6. STUDY ASSESSMENTS AND PROCEDURES

## Table 1 Time and Events Table

| **Procedures** | **Screening[1] ( ≤ 4 weeks prior to dosing) Visit 1** | **Baseline (Day 0) Visit 2** | **First Year (Week)[2] Visit 3~6** | | | | **Second year (Week)[2] Visit 7~10** | | | | **third Year to Fourth year (Week)[2] Visit 11~18** | | | | **Last Year (Week) [2] Visit 19-22** | | | | **Withdraw[3] (Week off treatment)** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 12 ±6 d | 24 ±6 d | 36 ±6 d | 48 ± 6 d | 60 ±6 d | 72 ±6 d | 84 ±6 d | 96 ±6 d | 108 ±6d<br>156 ±6d | 120 ±6d<br>168 ±6d | 132 ±6d<br>180 ±6d | 144 ±6d<br>192 ±6d | 204 ±6d | 216 ±6d | 228 ±6d | 240 ±6d | 12 |
| Written informed consent | √ | | | | | | | | | | | | | | | | | | |
| Subject demography[14] | √ | | | | | | | | | | | | | | | | | | |
| Medical history | √[4] | √[5] | | | | | | | | | | | | | | | | | |
| Inclusion/exclusion criteria | √ | | | | | | | | | | | | | | | | | | |
| Concomitant medication[6] | | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Physical examination[7] | √ | √ | √ | √ | | √ | | √ | | √ | | √ | | √ | | √ | | √ | √ |
| Vital signs[8] | √ | √ | √ | √ | | √ | | √ | | √ | | √ | | √ | | √ | | √ | √ |
| Adverse events | | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Serious adverse events | | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| **Laboratory assessments** | | | | | | | | | | | | | | | | | | | |
| Haematology | √ | √ | | √ | | √ | | √ | | √ | | √ | | √ | | √ | | √ | √ |
| Chemistry(Liver & Renal function, electrolyte(phosphate and calcium inclusive)) | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Pregnancy test[9] | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| HAV/HCV/HDVHEV/HIV / ANA | √ | | | | | | | | | | | | | | | | | | |
| B-ultrasound[15] | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Fibroscan | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | | √ | | √ | | √ | | √ | |
| AFP | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Urinalysis[16] | √ | √ | | √ | | √ | | √ | | √ | | √ | | √ | | √ | | √ | √ |
| Prothrombin time and INR | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| HBV DNA[10, 13] | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | | √ | | √ | | √ | | √ | √ |
| HBeAg/Anti-HBe | √ | √ | | √ | | √ | | √ | | √ | | √ | | √ | | √ | | √ | √ |
| HBsAg/Anti-HBs | √ | √ | | √ | | √ | | √ | | √ | | √ | | √ | | √ | | √ | √ |
| Genotyping[13,18] | | √ | | | | | | | | | | | | | | | | | |
| Genotypic analysis[13,17] | | | | | | | √ | √ | √ | √ | | √ | | √ | | √ | | √ | √ |
| **Investigational product** | | | | | | | | | | | | | | | | | | | |
| Study drug dispensed and reconciliation of drug dupply[11] | | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | |
| **Liver biopsy[12]** | √ | | | | | | | | | | | | | | | √ | | | |
| **Serum and plasma storage** | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |

1 All results to be obtained before baseline visit.

2 No more than 6 days before or 6 days after the date scheduled based on the time from baseline visit not from the previous visit.

3 In the event of early study drug discontinuation, the evaluation should be performed in 12 weeks after discontinuation of study treatment.

4 Medical history will include any acute and chronic medical conditions including prior surgery, information related to hepatitis B history, any current and prior HBV medications, and previous HBV-related procedures.

5 Update any new medical conditions and/or concomitant medications that have occurred since study screening.

6 Concomitant medications including traditional Chinese medicines and/or herbal remedies.

7 At screening, a complete physical examination will be performed. For all following indicated visits, a brief physical examination will be performed.

8 Including blood pressure, pulse, respiratory rate and temperature.

9 Urine pregnancy test will be performed at screening, baseline and every 3 months after dosing.

10 HBV DNA will be tested using Roche COBAS Taqman HBV test(LLD 20 IU/mL).

11 Each study visit: All study medication to be collected and reconciled.

12 Liver biopsy will be done in 100 subjects in sites at baseline and week 216. Liver biopsy can be done at screening (Visit 1) or at baseline (Visit 2), at the discretion of investigator. Liver biopsy slides within 6 months prior to baseline can be accepted as baseline evaluation.

13 Tests will be performed at central lab

14 Demographic data includes birth date, gender and race

15 B ultrasound examination include liver, pancreas, spleen, gall bladder and kidney

16 Urinalysis: urine glucose, ketones, specific gravity, blood, pH and protein

17 Serum will be colleted as scheduled for potential resistance surveillance. Genotypic analysis will be performed under the condition defined in protocol (see section 6.2.8)

18 Genotyping will be performed at central lab at screen

## 6.1. Critical Baseline Assessments

Prior to dispensing study medication on Day 1, the procedures listed in Table 1 must be performed and documented in the CRF.

The first dose of study medication will be administered at this visit, after all the study procedures have been completed. Subjects can be discharged immediately after dosing.

## 6.2. Efficacy

Samples for efficacy analysis will be collected at times outlined in Table 1. Collection and processing procedures for each type of sample will be detailed in the SPM.

### 6.2.1. Serum/Plasma Storage

Serum and plasma will be stored at the central laboratory and frozen at or below -20°C to allow possible evaluation of changes in laboratory markers of HBV infection (including resistance testing) observed during the course of the study.

### 6.2.2. Primary Endpoint

To determine the incidence of newly diagnosed HCC (from week 24 to week 240), the subject must meet one of the following criteria:

- A histological diagnosis of HCC (i.e. by biopsy or at post-mortem)
- In patients with nodules >2 cm, identification of typical HCC characteristics (hypervascular in the arterial phase with washout in the portal venous or delayed phases) by 4-phase multidetector CT scan or dynamic contrast-enhanced MRI
- In patients with nodules > 1 cm, , identification of typical HCC characteristics by both techniques (4-phase multidetector CT and dynamic contrast-enhanced MRI )

### 6.2.3. Clinical Endpoint

The cumulative incidence of disease progression during the study timepoints will be defined as the first occurrence of any one of the following criteria:

- an increase in Childs-Pugh score (as defined in section 11.1 Appendix 1) of 2 or more points from baseline.
- An increase in Childs-Pugh score of 2 or more points, solely based on laboratory parameters (i.e. bilirubin, prothrombin time and/or albumin), confirmed at two consecutive visits at least one month apart;
- spontaneous bacterial peritonitis (with proven sepsis);

- renal insufficiency defined as a decrease in creatinine clearance to ⩽50 mL/minute confirmed on two occasions at least one week apart (calculated from serum creatinine concentration);
- bleeding gastric/oesophageal varices;
- hepatocellular carcinoma;
- liver-related death

### 6.2.4. Virological Endpoint

To evaluate the proportion of subjects with HBV DNA< 20 IU/mL and viral load change over time, HBV DNA level will be quantified using the Roche COBAS Taqman HBV test(LLD 20IU/mL) at times outlined in Table 1.

### 6.2.5. Biochemical Endpoint

To evaluate the biochemical response, ALT will be measured at times outlined in Table 1.

### 6.2.6. Serological Endpoint

To evaluate the serological response, HBeAg/anti-HBe and HBsAg/anti-HBs will be measured at times outlined in Table 1.

### 6.2.7. Liver fibrosis endpoint

Liver fibrosis will be assessed using non-invasive FibroScan in all study subjects, and by formal liver biopsy in a subset of study subjects.

To assess liver fibrosis changes non-invasively a liver stiffness measure (LSM) will be obtained for all patients by transient elastography using FibroScan (EchoSens) at times outlined in Table 1.

. The LSM result will be expressed as a median value of the total measurements in kiloPascal (kPa). Only subject examinations with at least 10 validated measurements, a success rate of at least 60%, and an interquartile range (IQR) of all validated measurements of less than 30% will be considered a reliable LSM measure. Mean changes of LSM at Week 48, Week 96, Week 144, Week 192 and Week 240 will be reported.

To evaluate the proportion of subjects who experience an improvement in histology at Week 216 a subset of study subjects (approximately 100 subjects) will undergo liver biopsies at times outlined in Table 1.

A single central pathologist will evaluate all baseline and final biopsy slides in a pairedfashion and blinded to timing of biopsy. The baseline and end of treatment biopsies will be read at the same time. (See Appendix 3)

### 6.2.8. Resistance Surveillance

To evaluate the resistance (if identified) rate, genotypic analysis of the HBV polymerase gene will be performed on storage serum at times outlined in Table 1 using a central laboratory in the following situations:

- Subjects with HBV DNA ≥20 IU/mL at their last visit. (i.e. week 240 or last visit before withdrawl)
- Subjects with virological breakthrough, defined as HBV DNA level increase ≥1 $\log_{10}$ IU/mL above the treatment nadir (confirmed on two consecutive visits at least 1 month apart).
- Subjects have HBV DNA ⩾200IU/ml at week 48 and afterwards have ≤ one log decrease in HBV DNA at two consecutive visits, confirmed by a third visit at least one month apart.

## 6.3. Safety

### 6.3.1. On-Treatment ALT Flare, ALT Elevation With or Without Hepatic Dysfunction, and Post-Treatment Exacerbation of Hepatitis Management

DEFINITIONS

| | | |
|---|---|---|
| ALT FLARE | ALT Both >2x baseline value and >10x ULN | See Section 6.3.1.1 |
| ALT ELEVATION With HEPATIC DYSFUNCTION | ALT Both >2x nadir value and >5xULN with evidence of worsened hepatic function (e.g. Direct Bilirubin >1.5mg/dL INR ≥1.7, or abnormal serum albumin ≤2.7) | See Section 6.3.1.1 |
| ALT ELEVATION ALONE | ALT Both >2x nadir value and >5x ULN | See Section 6.3.1.2 |

#### 6.3.1.1. Management of ALT Flare or ALT Elevation With Hepatic Dysfunction in Subjects Receiving Study Medication

If laboratory results indicate **ALT Flare** or **ALT Elevation With Hepatic Dysfunction** the following is recommended:

Schedule the subject to return to the clinic as soon as possible (ideally within 3 days after initial laboratory results were drawn). During the visit, a clinical assessment of the subject will be performed. The assessment should include a physical examination and evaluation of the subject's mental status.

Check the following laboratory parameters: serum ALT and AST, alkaline phosphatase, total and direct bilirubin, INR, and serum albumin.

If the **ALT Flare** or **ALT Elevation With Hepatic Dysfunction** is confirmed, request the clinical laboratory to conduct reflex testing for plasma HBV DNA, serology for HBV (HBsAg, HBeAg, HBeAb, and HBsAb), HDV, HAV IgM, HCV, and HEV

Based on the results of the confirmatory tests, the following treatment modifications are recommended:

**Evidence of worsening HBV infection:**

- If Plasma HBV DNA is increasing (≥1 log increase), the investigator should discuss initiation of additional therapy with the medical monitor.

**In the absence of evidence of worsening HBV infection:**

- If ALT levels are elevated (+/- direct bilirubin/INR/albumin) as above, the subject may remain on study medication and should be monitored with ALT and AST, alkaline phosphatase, total and direct bilirubin, INR, and serum albumin at least weekly until laboratory abnormalities return to baseline level.

- During monitoring, if the ALT values (+/- direct bilirubin/INR/albumin) are worsening or remain persistently abnormal or elevated after 4weeks, the Investigator should discuss with the Medical Monitor regarding the monitoring schedule and whether the study drug should be discontinued.

For subjects with bridging fibrosis or cirrhosis, study drug discontinuation with treatment-free follow-up is to be avoided due to the potential risk of exacerbation of hepatitis in the setting of low hepatic reserve which could lead to decompensation. Subjects with bridging fibrosis or cirrhosis should be placed on commercially available HBV therapy following study drug discontinuation.

Subjects should be followed until laboratory parameters return to baseline up to a maximum of 6 months after the initial occurrence of the event.

#### 6.3.1.2. Increased monitoring for On-Treatment ALT Elevation Alone

- In patients with confirmed **ALT Elevation Alone** (**both** >2x nadir **and** also >5xULN) but have not reached **ALT Flare** (**Both** ALT >2x baseline value **and** >10x ULN) and do not have evidence of worsened hepatic function (e.g. Direct Bilirubin >1.5mg/dL INR ≥1.7, or abnormal serum albumin <=2.7) the subject may remain on study medication and should be monitored weekly until ALT levels return to baseline level. During monitoring, if after 4 weeks the ALT values remain stable but persistently abnormal, the Investigator should discuss with the Medical Monitor regarding the monitoring schedule.

If patients worsen to reach ALT Flare definition or ALT Elevation with hepatic dysfunction,manage as above in Section 6.3.1.1.

Subjects should be followed until laboratory parameters return to baseline up to a maximum of 6 months after the initial occurrence of the event.

#### 6.3.1.3. Management of Exacerbation of Hepatitis in Subjects who have Discontinued Study Medication

If laboratory results indicate **ALT Flare** or **ALT Elevation With Hepatic Dysfunction** and the subject is on no post-study therapy for HBV, the following is recommended:

- Schedule the subject to return to the clinic as soon as possible (ideally no later than 3 days after the initial laboratory values were drawn). During the visit, perform a clinical assessment of the subject.

- Check the following laboratory parameters: serum ALT and AST, alkaline phosphatase, total and direct bilirubin, INR, and albumin.

- If the **ALT Flare** or **ALT Elevation With Hepatic Dysfunction** is confirmed, request the clinical laboratory to conduct reflex testing for plasma HBV DNA, serology for HBV (HBsAg, HBeAg, HBeAb, and HBsAb), HDV, HAV IgM and HCV. If Plasma HBV DNA is increasing (≥1 log increase), the investigator should consider immediate initiation of approved therapy.

- Subjects should be followed until laboratory parameters return to baseline up to a maximum of 6 months after the initial occurrence of the event.

Please refer to Appendix 4: Lactic Acidosis Guidelines for the recommend method for managing lactic acidosis.

### 6.3.2. Serum Creatinine Elevation

Serum creatinine values ≥ 0.5 mg/dL above baseline should be confirmed by repeat testing within 3 calendar days of receipt of results.

For serum creatinine elevations ≥ 0.5 mg/dL above baseline, subjects may continue all study medication, but it is recommended that subjects be monitored weekly until the serum creatinine returns to the original baseline value or ≤ 0.3 mg/dL from baseline.

All study drugs should be permanently discontinued in the event that repeat testing of serum creatinine confirms >2.5 mg/dL. The subject should be followed weekly until the serum creatinine reaches within 0.3 mg/dL of the baseline value.

### 6.3.3. Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

#### 6.3.3.1. Definition of an AE

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Any noxious or unintended response to a medicinal product related to any dose should be considered an adverse drug reaction (ADR).

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE) unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.

“Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject’s condition

#### 6.3.3.2. Definition of an SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

   NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalisation or prolongation of existing hospitalisation

   NOTE: In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

   Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

g. All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN and INR>1.5, if INR measured) termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants).

   NOTE: bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating

direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥ 2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

#### 6.3.3.3. Sentinel Events

A Sentinel Event is a GSK-defined SAE that is not necessarily drug-related but has been associated historically with adverse reactions for other drugs and is therefore worthy of heightened pharmacovigilance. Medical monitor review of all SAEs for possible Sentinel Events is mandated at GSK. The GSK medical monitor may request additional clinical information on an urgent basis if a possible Sentinel Event is identified on SAE review. The current GSK-defined Sentinel Events are listed below:

- Acquired Long QT Syndrome
- Agranulocytosis/Severe Neutropenia
- Anaphylaxis & Anaphylactoid Reactions
- Hepatotoxicity
- Acute Renal Failure
- Seizure
- Stevens Johnson syndrome/Toxic epidermal necrosis

### 6.3.4. Cardiovascular Events

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularisation

### 6.3.5. Death Events

In addition, all deaths will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding cardiovascular (including sudden cardiac death) and noncardiovascular death.

This information should be recorded in the specific death eCRF within one week of when the death is first reported.

### 6.3.6. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator are to be recorded as AEs or SAEs. However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.

### 6.3.7. Pregnancy

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to GSK.

In addition, the investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to GSK as described above.

### 6.3.8. Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the start of study treatment and until the follow up contact.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed **as related** to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to and including any follow up contact. All SAEs will be reported to GSK within 24 hours, as indicated in Section 6.3.9.

### 6.3.9. Method of Detecting AEs and SAEs

Care must be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

"How are you feeling?" or for paediatric studies, "How does your child seem to feel?"

"Have you had any (other) medical problems since your last visit/contact?" or for paediatric studies, "Has your child had any (other) medical problems or seem to act differently in any way since his/her last visit/contact?"

"Have you taken any new medicines, other than those provided in this study, since your last visit/contact?" or for paediatric studies, "Has your child needed to take any medicines, other than those provided in this study, since his/her last visit/contact?"

### 6.3.10. Prompt Reporting of Serious Adverse Events and Other Events to GSK

SAEs, pregnancies, medical device incidents, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to GSK as described in the following table once the investigator determines that the event meets the protocol definition for that event.

| | Initial Reports | | Follow-up Information on a Previous Report | |
|---|---|---|---|---|
| **Type of Event** | **Time Frame** | **Documents** | **Time Frame** | **Documents** |
| All SAEs | 24 hours | "SAE" data collection tool | 24 hours | Updated "SAE" data collection tool |
| Pregnancy | 2 weeks | "Pregnancy Notification Form" | 2 weeks | "Pregnancy Follow-up Form" |
| ADR(Adverse Drug Reaction) | 5 days | ADR form | 5 days | ADR form |

The method of recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in the SPM. Procedures for post-study AEs/SAEs are provided in the SPM.

Procedures for documenting, transmitting and follow-up of medical device incidents along with the regulatory reporting requirements for medical devices are provided in the SPM.

#### 6.3.10.1. Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Prompt notification of SAEs and non-serious AEs related to study treatment, by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

### 6.3.11. Other Safety Outcome

Protocol required laboratory assessments, as defined in Table 1, must be performed by the central laboratory, [Peking University Hepatology Institute]. Laboratory assessments must be conducted in accordance with the Central Laboratory Manual and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by [Peking University Hepatology Institute]. Reference ranges for all safety parameters will be provided to the site by [Peking University Hepatology Institute].

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in patient management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the subject's CRF. Refer to the SPM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

## 6.4. Viral Genotyping and Phenotyping

HBV genotyping will be performed in central lab at screening.

# 7. DATA MANAGEMENT

For this study (1-eDM) subject data will be entered into GSK defined electronic case report forms (eCRFs), transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications

terms will be coded using MedDRA and an internal validated medication dictionary, GSKDrug. In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

# 8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

## 8.1. Hypotheses

No hypotheses applicated.

## 8.2. Study Design Considerations

### 8.2.1. Sample Size Assumptions

Sample sizes are chosen based on feasibility and precision because no hypothesis is tested in this study.

The primary endpoint is the cumulative incidence of newly diagnosed as HCC in treatment group from Week 24 to Week 240.

To decide the number of subjects for analysis, some precision calculations have been performed. In the retrospective analysis of GS-US-174-0102 and GS-US-174-0103 trials, HCC incidence over 7 years was approximately 4.5% among patients (23% of whom were Asian, 25 of whom were genotype B or C) with cirrhosis at baseline. Accordingly, we hypothesize that the accumulative incidence of HCC at 240 weeks will be 5% in Chinese compensated cirrhotic patients treated with TDF. A sample size of 158 patients will allow us to estimate the confidence interval of the incidence with a margin of error at 3.4%( 0.016-0.084) Assuming a 15% drop out rate, 186 patients are to be recruited.

- Sample size formula: $\mathrm{N} = \mathrm{p}(1-p)\left(\frac{z_c}{e}\right)^2$

The main analyses will be performed on mdodified intent-to-treat (mITT) basis, including all patients who are assigned to treatment and received study medication. All endpoint analyses will use a last observation carried forward (LOCF) approach; that is, the last available visit is used as the end point. Changes from baseline to endpoint (LOCF) will be analyzed by Wilcoxon signed-rank test.

### 8.2.2. Sample Size Sensitivity

The sample size estimates are dependent upon the assumed incidence. If the actual treatment difference is around 5%, then the current planned sample size will provide adequate power. If the actual treatment difference is smaller than 5%, the actual power could be much lower.

**Table 2 Sample Size Sensitivity Table**

| P | 1-p | Width (half CI) | N |
|---|---|---|---|
| 5% | 0.95 | 0.04 | 115 |

| | | | |
|---|---|---|---|
| **5%** | **0.95** | **0.034** | **158** |
| 5% | 0.95 | 0.033 | 168 |
| 5% | 0.95 | 0.032 | 179 |
| 5% | 0.95 | 0.03 | 203 |
| 5% | 0.95 | 0.02 | 457 |

### 8.2.3. Sample Size Re-estimation

No sample size re-estimation is planned.

## 8.3. Data Analysis Considerations

### 8.3.1. Analysis Populations

Three populations will be used in the analysis:

- Mdodified Intent to Treat (mITT) Population

The mITT population is defined as all randomised subjects who receive at least one dose of study medication.

- Per Protocol (PP) population

The PP population will consist of subjects in the mITT population with the exception of major protocol violators. Details on the definitions of major protocol violators will be included in the reporting and analysis plan (RAP).

- Safety Analysis (SA) population

The SA population is defined as all subjects who receive at least one dose of study medication and have at least one post baseline safety assessment.

All efficacy endpoints will be analysed using the mITT and PP population according to the treatment groups to which they were randomised. As this is a superiority study, the mITT population is the most conservative approach to statistical analysis; hence, the mITT population is of primary interest.

All safety endpoints will be analysed using the SA population according to the actual treatment they received.

### 8.3.2. Analysis Data Sets

For information on the analysis data sets please refer to the RAP.

### 8.3.3. Treatment Comparisons

#### 8.3.3.1. Primary Comparisons of Interest

This is a single-arm cohort study to observe HCC incidence in patients with HBV related advanced fibrosis and cirrhosis under TDF treatment. No comparisons are planned.

#### 8.3.3.2. Other Comparisons of Interest

No comparisons are planned.

### 8.3.4. Interim Analysis

No interim analysis is planned for this study.

### 8.3.5. Key Elements of Analysis Plan

Missing data can have an impact upon the interpretation of the trial data. In general, values for missing data will not be imputed.

For the primary analysis of HCC incidence at Week 240, data from non-completers will use the last available visit as the end point.

All serum HBV DNA results below the lower limit of detection will be analysed as being the value of the lower limit of detection.

#### 8.3.5.1. Efficacy Analyses

In this study, data will be summarised as mean, medium, standard deviation, maximum, and minimum for continuous variables, and in tables of frequencies and percentages for categorical variables.

The primary outcomes of this study were the 5-year cumulative incidence rates of HCC, calculated by the Kaplan–Meier method.

Univariate and multivariable analysis by Cox proportional hazards regression model was performed to identify factors associated with HCC. Variables may include serum albumin, total bilirubin, and ALT levels, HBeAg status, serum HBV DNA titter and response to treatment, etc. Effect sizes are expressed as hazard ratios (HRs) and 95% confidence intervals (CIs).

The detail of primary, secondary and other efficacy endpoint analysis will be included in the RAP.

#### 8.3.5.2. Safety Analyses

Clinical safety observations will include: extent of exposure information, AEs, deaths, laboratory abnormalities and withdrawals from study. The safety data will be tabulated and, where appropriate, a Fisher's exact test comparing treatment groups will be run.

Extent of exposure to study drug data will be generated from the study drug administration page of CRF. Exposure data will be summarised by treatment group.

Adverse events will be assigned preferred terms and categorized into body systems according to the 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.

All AEs that caused a change in dose or temporary interruption of study drug.

#### 8.3.5.3. Viral Genotyping/Phenotyping Analyses

Viral genotyping of HBV will be performed and recorded at screening. Proportion of subjects infected with HBV genotype B/C will be analysed.

# 9. STUDY CONDUCT CONSIDERATIONS

## 9.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

## 9.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.

Subject informed consent.

Investigator reporting requirements.

GSK will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each subject prior to participation in the study.

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments, unless otherwise indicated. Where permitted by regulatory authorities, approval of the optional assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the optional assessments is being deferred and the study, except for the optional assessments, can be initiated. When the optional assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, the optional assessments will not be conducted.

## 9.3. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors 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. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK 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.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

## 9.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

## 9.5. Study and Site Closure

Upon completion or termination of the study, the GSK monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, GCP, and GSK Standard Operating Procedures.

GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe non-compliance. If GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, GSK will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

## 9.6. Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

## 9.7. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the

opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK will provide the investigator with the randomisation codes for their site only after completion of the full statistical analysis.

The results summary will be posted to the Clinical Study Register no later than eight months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal for publication no later than 18 months after the last subject's last visit (LSLV). When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

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# 11. APPENDICES

## 11.1. Appendix 1: CHILDS-PUGH SCORE*

| Component | Score Given |
|---|---|
| | CCI |

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

**Childs-Pugh Classification**

Childs-Pugh Class CCI = score CCI
Childs-Pugh Class CCI = score CCI
Childs-Pugh Class CCI = score CCI

* Reference: Haozhu Chen, Guowei Lin. Practice of internal medicine. Edition 13. Beijing: People's Medical Publishing House, 2009:2082

## 11.2. Appendix 2: Estimated creatinine clearance rate (CLcr) Formula and Estimated Glomerular Filtration Rate (GFR) Equation

**CLcr using Cockcroft-Gault (CG) formula：**

CLcr=[(140-Age)×Ideal Body Weight(kg)]/[72×Scr(mg/dL)]

Scr=Serum Creatinine in mg/dL； for female Multiplied by the coefficient of 0.85

Note: If actual body weight (ABW) is lower than ideal weight body (IBW), ABW should be used. Calculation Formula for IBW:

（Male）IBW=50kg+2.3kg×[Height(Inch)-60]

（Female）IBW=45.5kg+2.3kg×[Height(Inch)-60]

1Inch=2.54cm

**GFR Equation:**

Glomerular filtration rate is estimated by Chronic kidney disease (CKD)-Epidemiology Collaboration (EPI) equation:

GFR(mL/min per 1.73 $m^2$) = 141 × min(Scr/κ, 1)$^{\alpha}$ × max(Scr/κ, 1)$^{-1.209}$ × $0.993^{Age}$ [ × 1.018 if female] [ × 1.159 if black],

where Scr is serum creatinine (mg/dl), κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min is the minimum of Scr/κ or 1, and max is the maximum of Scr/κ or 1

## 11.3. Appendix 3: Histological Score

Modified Knodell scoring system

| Category | Score |
|---|---|
| CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded. | |

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## 11.4. Appendix 4: Lactic Acidosis Guidelines

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with other antiretrovirals. Most of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors; however, cases have also been reported in subjects with no known risk factors.

Guidelines for management of symptomatic hyperlactatemia and asymptomatic hyperlactatemia are outlined in Section A and B below and are derived from the AACTG Lactic Acidosis Guidelines. Section C outlines venous lactate collection techniques.

### Section A. Symptomatic Hyperlactatemia

Symptomatic hyperlactatemia is defined as a clinical suspicion of hyperlactatemia characterised by new, otherwise unexplained and persistent (≥ 2 weeks) occurrence of one or more of the following symptoms:

- Nausea and vomiting.
- Abdominal pain or gastric discomfort.
- Abdominal distention.
- Increased LFTs.
- Unexplained fatigue.
- Dyspnoea.

AND

Venous lactate level >2 x ULN confirmed by repeat venous lactate analysis within 1 week and, if persistently elevated, arterial lactate with blood gas analysis.

If the repeat venous lactate is elevated confirmation with an arterial lactate specimen and arterial blood gas (pH, $PO_2$, $PCO_2$, bicarbonate, oxygen saturation) should be performed within 48 h. If the arterial specimen contains lactate at a level >2 x ULN, the subject should be discontinued from the study and alternative therapy started. Subjects should be monitored weekly until signs and symptoms resolve. Hyperlactatemia should be followed until levels return to <2 x ULN.

An elevated anion gap in a subject with metabolic acidosis suggests the diagnosis of lactic acidosis. It can be suspected when the sum of anions minus the sum of cations $[(Na^+ + K^+) – (Cl^- + HCO_3)]$ exceeds 18 mEq/L (18 mmol/L) in the absence of other causes of increased anion gap such as renal failure, salicylate ingestion or other poisoning, or significant ketonemia (e.g., diabetic ketoacidosis, alcohol).

Management of symptomatic subjects with lactate levels of 1–2 x ULN is left to the discretion of the Investigator. As some of the symptoms are sufficiently vague (e.g., fatigue) to be present in everyone, serial repeat testing is encouraged with plans to modify the regimen if the lactate level rises to >2 x ULN as outlined above.

## Section B. Asymptomatic Hyperlactatemia

In asymptomatic subjects, lactic acidosis will be defined as hyperlactatemia >4 x ULN. Any subject with a lactate level >2 x ULN but ≤ 4 x ULN, should be questioned closely for symptoms (described above) and have a repeat venous sample obtained in 1 week, and, if confirmed, subsequently at monthly intervals.

If the subject fulfils the definition for asymptomatic hyperlactatemia, repeat venous lactate should be obtained within a week with confirmation of a more than four-fold venous elevation in lactate by arterial lactate measurement and arterial blood gas (pH, $PO_2$, $PCO_2$, bicarbonate, oxygen saturation) within 48 h. If confirmed, the subject should be discontinued from the study and alternative therapy instituted. Hyperlactatemia should be followed until levels return to <2 x ULN.

## Section C. Specimen Collection

Venous lactate levels are highly dependent on collection techniques. It is therefore recommended that the instructions below be followed closely. High lactate levels should be repeated for verification. If carefully collected, venous lactate level is equivalent to an arterial collection in most clinical situations. If it is not possible to collect the specimen without hand clenching or prolonged tourniquet time, an arterial lactate should be considered, as this will help exclude falsely elevated lactate levels.

Have subject sit, relaxed for 5 minutes prior to venepuncture.

1. Instruct subject not to clench the fist before or during the procedure and to relax the hand as much as possible.
2. If possible, do not use a tourniquet. If a tourniquet is necessary, then apply tourniquet lightly and draw lactate first before the other samples with the tourniquet still in place.
3. Collect the blood in a chilled gray-top (sodium fluoride-potassium oxalate) tube.
4. Place the specimen immediately on ice and send to the laboratory for immediate processing, preferably within 30 minutes of collection.
5. If random lactate is elevated, then repeat as above with the following additional subject instructions: no alcohol within 24 h, no exercise within 8 h, and no food or drink except water within 4 h of the draw.