TITLE PAGE

Protocol Title: A multi-centre, one-arm prospective study to evaluate efficacy and safety of switching from Entecavir (ETV) to Tenofovir Disoproxil Fumarate (TDF) in Japanese chronic hepatitis B HBeAg-positive and HBV-DNA undetectable subjects

Protocol Number: 205883
Short Title: A study of switching from Entecavir to Tenofovir in subjects with chronic hepatitis B

Compound Number: GSK548470

Sponsor
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Approval Date: [5-Jul-2018]

SPONSOR SIGNATORY:

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[VP & Head, Development & Medical Affairs Division]

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1. SYNOPSIS

Protocol Title: A multi-centre, one-arm prospective study to evaluate efficacy and safety of switching from Entecavir (ETV) to Tenofovir Disoproxil Fumarate (TDF) in Japanese chronic hepatitis B HBeAg-positive and HBV-DNA undetectable subjects

Short Title: A study of switching from Entecavir to Tenofovir in subjects with chronic hepatitis B

Study Rationale:
This study has been planned to evaluate the virological effects and safety of switching at Day 1 from entecavir hydrate (ETV) to tenofovir disoproxil fumarate (TDF) in chronic hepatitis B HBeAg-positive and HBV-DNA undetectable subjects [< 1.3 log IU/mL (< 20 IU/mL) or < 2.1 Log_{10} copies/mL].

Objectives and Endpoints:

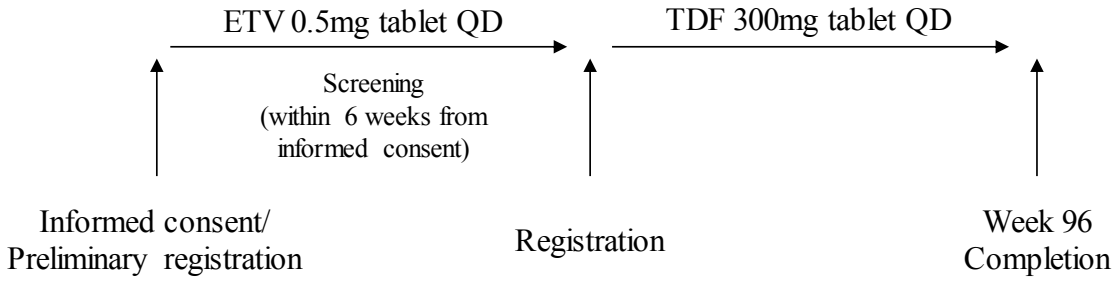
Objectives	Endpoints
Primary	
• To evaluate the HBsAg reduction potential at Week 48	• Proportion of subjects achieving 0.25 Log_{10} HBsAg reduction from the baseline at Week 48
Secondary	
• To evaluate the virological effects	• Proportion of subjects achieving 0.25 Log_{10} HBsAg reduction from the baseline at Week 24 and 96 • Proportion of subjects achieving HBsAg loss and HBsAg/Ab seroconversion at Week 24, 48 and 96 • Proportion of subjects achieving HBeAg loss and HBeAg/Ab seroconversion at Week 24, 48 and 96 • Reduction of HBsAg titer from the baseline at Week 24, 48 and 96 • Reduction of HB core-related antigen (HBcrAg) titer from the baseline at Week 24, 48 and 96
• To evaluate the safety	• Adverse events (AEs) • Clinical Laboratory values (hematology, clinical chemistry, urinalysis) • Vital signs (blood pressure, pulse rate, temperature) • 12-lead ECG

	• Bone density

Study Design:
This is a multi-center, one-arm, open-label study. The study will evaluate the efficacy and safety of TDF by switching at Day 1 from ETV to TDF in chronic hepatitis B HBeAg-positive and HBV-DNA undetectable subjects [< 1.3 log IU/mL (< 20 IU/mL) or < 2.1 Log_{10} copies/mL].

Number of Subjects:
Screening, 80 subjects; Subjects eligible for evaluation, 65 subjects

Treatment Groups and Duration:



2. SCHEDULE OF ACTIVITIES (SOA)

Procedure	**Screening (up to 42 days before Day 1)[1]**	**Treatment period**					**Discontinuation/Completion (Week 96) (±14)[2]**
		Day 1	**Week 4 (±14)**	**Week 12, 24, 36 (±14)**	**Week 48 (±14)**	**Week 60, 72, 84 (±14)**	
Informed Consent	X[1]						
Demography	X						
Abdominal imaging test[3]	X	(X)	(X)	(X)	(X)	(X)	X
Inclusion/Exclusion Criteria[4]	X						
Pregnancy Test (females of childbearing potential only)[5]	X	X	X	X	X	X	X
[HIV and HCV screening]	X						
12-lead ECG	X				X		X
Bone densinometry	X[6]		(X)[7,8]	(X) [7,8]	(X) [7,8]	(X) [7,8]	X[8]
Vital Signs[9]	X	X	X	X	X	X	X
Study treatment dispensation		X		X	X	X	
Confirmation of investigational product compliance			X	X	X	X	X
AE Assessment		X	←	—	—	→	X
SAE Assessment		X	←	—	—	→	X
Concomitant Treatment Review	X	X	←	—	—	→	X
Hematology [10]	X	X	X	X	X	X	X
Clinical Chemistry [11]	X	X	X	X	X	X	X
Urinalysis [12]	X	X	X	X	X	X	X
HBV-DNA	X	X	X	X	X	X	X
HBeAg/Anti-HBe	X	X	X	X	X	X	X

Procedure	Screening (up to 42 days before Day 1)[1]	Treatment period					Discontinuation/Completion (Week 96) (±14)[2]
		Day 1	Week 4 (±14)	Week 12, 24, 36 (±14)	Week 48 (±14)	Week 60, 72, 84 (±14)	
HBsAg/Anti-HBs	X	X	X	X	X	X	X
HBcrAg		X	X	X	X	X	X
Resistant Assay [13]			(X)	(X)	(X)	(X)	(X)
HBV Genotype	X						

1. Perform the screening examinations surely within 42 days before starting the study treatment.
2. On completing or discontinuing the study, perform these items within 72 hours after the last dose of the study treatment.
3. For diagnosis of cirrhosis, see Appendix 7.
4. For subject in whom HBsAg value range is confirmed before screening, enter values at 2 time points (with an interval of at least 3 months, and at least one point within 1 year from screening) into electronic Case Report Form (eCRF).
5. Perform the pregnancy test (urine test) for only women of childbearing potential or women with less than two years after the last menstruation. On the day of starting the study treatment, perform the pregnancy test before the first dose of the study treatment.
6. If the assessment was performed within 1 year prior to screening, it can be substituted as a score at screening.
7. Perform the assessment when the investigator considered necessary from laboratory results.
8. Perform bone densimetry with an interval of at least 4 months. If the assessment was performed within 3 months prior to each visit, do not duplicate the procedure.
9. Assess height, weight, blood pressure, pulse rate and temperature. Height is collected at screening only.
10. Red blood cell count, hemoglobin, hematocrit, white blood cell count (including differential count), platelet count, prothrombin time
11. AST, ALT, γ-GTP, ALP, LDH, total bilirubin, direct bilirubin, total protein, serum albumin, serum creatinine, creatinine kinase, amylase, lipase, AFP, antinuclear antibody titer, electrolyte (Na, K, Cl, Ca, P), blood glucose, uric acid, BUN, hyaluronate, lactic acid (however, assess antinuclear antibody titer at screening only, hyaluronate must be assessed at screening but for the visits afterwards assess when necessary), CLcr (calculate from serum creatinine based on Cockcroft-Gault formula described in section 6.1) and eGFR.
12. Urinary sediment, β2-microglobulin, urine creatinine, urine glucose, urine protein, electrolyte (P)

13. Perform resistance analysis on lamivudine (LAM), adefovir (ADV), ETV and TDF. In a case where a virological breakthrough has been observed (a case where the serum HBV-DNA level has increased from the nadir by at least 1 log IU/mL or an increase of at least 2 log IU/mL (100 IU/mL) if the nadir is under 10 IU/mL), perform the resistance analysis. The blood specimen for the resistance analysis must be taken at every visit (excluding the starting date of the study treatment).

3. INTRODUCTION

Tenofovir Disoproxil Fumarate (TDF) is a nucleos(t)ide analogue that inhibits HBV growth, and is marketed in Japan with an indication for inhibition of HBV growth in patients with chronic hepatitis B associated with HBV growth and abnormal liver function.

3.1. Study Rationale

This study has been planned to evaluate the virological effects and safety of switching at Day 1 from ETV to TDF in chronic hepatitis B HBeAg-positive and HBV-DNA undetectable subjects.

3.2. Background

Chronic hepatitis B (CHB) generally shows exacerbation over a long term by repeating liver inflammation persistently or intermittently. It is known that when chronic hepatitis B is left untreated, liver fibrosis proceeds toward the risk for onset of liver failure or liver cancer [Mizokami, 2010].

There are two options in CHB treatment. One is interferon preparation used by injection and the other is nucleos(t)ide analogue used by oral administration. The interferon therapy does not show a high response rate, since the therapeutic effect is markedly different depending on the initial HBV-DNA level, ALT level and HBV genotype. On the other hand, nucleic acid analogues show a very potent effect to suppress HBV growth, but appearance of HBV strains resistant to each nucleos(t)ide analogue is problematic. Furthermore, the long-term goal of treatment, the loss of HBsAg, is rarely achievable.

It has been reported that TDF demonstrated a superior HBsAg reduction compared to ETV in the Japanese phase 3 study [Koike,2018]. Recently, a topic on the effect of TDF on HBsAg reduction is often seen at conferences in Japan and HBsAg reduction by nucleos(t)ide analogue is drawing attention from the hepatologists. Loss of HBsAg is one of the goals in the 10-year strategy for hepatitis research by the Ministry of Health, Labour and Welfare, and HBsAg is considered an important surrogate marker in CHB treatment.

Based on the above, evaluation of HBsAg reduction in this study is considered medically and clinically significant.

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of TDF may be found in the Package Insert.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Investigational Product[GSK548470]	
Renal toxicity	In nonclinical studies, high levels of serum creatinine and chloride, urinary glucose or urinary protein, and increase in urine volume, karyomegaly, denaturation or reproduction, and necrosis of tubular epithelium, interstitial nephritis, etc. were observed in rats, dogs, and monkeys. The kidney is considered as the target organ of TDF. Although not reported in Japanese clinical studies conducted in subjects infected with HBV, serious renal dysfunction such as renal failure, Fanconi syndrome and other proximal renal tubular disorders have been reported in overseas clinical studies. Serious renal dysfunction such as acute renal failure and renal tubular necrosis has been spontaneously reported overseas during the post-marketing use of TDF including preparations with the same ingredients indicated for HIV-1 infection.	Set the inclusion criteria for subjects with creatinine clearance ≥70 mL/min. Set the exclusion criteria for subjects with proximal renal tubular disorders. Set the dose adjustment when creatinine clearance reaches 50 mL/min. Included prohibited concomitant drugs that affects the kidney. Monitor renal function by assessing serum creatinine, etc. during this study period and set the discontinuation criteria based on the renal function values. Collect detailed information on the incidence, seriousness, and outcome of renal toxicity during this study period.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Bone events (fracture, osteomalacia, etc.)	Effect on serum and urinary phosphorus, range in bone metabolism markers, decrease in bone mineral density or bone density, etc. were observed in rats and monkeys in non-clinical studies. The bone is considered the target organ of TDF. Tubular epithelium disorder caused by TDF is considered to lead to a loss of phosphonate into the urine. Accelerated bone resorption associated with decreased intestinal absorption of phosphonate is also considered responsible for bone metabolism disorders leading to bone fractures. Although not reported in Japanese clinical studies, skeletal events such as osteopenia and osteoporosis have been reported in overseas clinical studies. Fractures and osteomalacia, etc. have been spontaneously reported during overseas post-marketing use of TDF including preparations with the same ingredients indicated for HIV-1 infection.	Exclude subjects with proximal renal tubular disorders through exclusion criteria. Monitor serum phosphorus, urinary phosphorus, and β2-microglobulin levels, etc. and perform bone densinometry as necessary, during this study period. Collect detailed information on the incidence, seriousness, and outcome of bone events such as fracture and osteomalacia during this study period.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Hepatic dysfunction (exacerbation of hepatitis after discontinuation of administration etc)	Hepatitis may occur by regrowth of virus after discontinuation of TDF administration. In the overseas clinical study conducted in subjects infected with HBV, exacerbation of hepatitis at 2-3 month post treatment discontinuation was observed in 8.75% (7/80 subjects) of the subjects who discontinued TDF during the treatment period of up to 240 weeks. Hepatitis flare may occur during oral antiviral therapy in relation to a rapid decrease of virus, characterized by abnormal changes in laboratory results such as a rapid elevation of ALT and other hepatic function.	Monitor hepatic function by measuring ALT, etc. during this study period and set the liver chemistry stopping criteria. Allow the subjects who meet the stopping criteria and who have been withdrawn from TDF treatment can start alternative treatment. Collect detailed information on the incidence, seriousness, and outcome of hepatic dysfunction during this study period.
Pancreatitis	Increased lipase levels were observed in the Japanese clinical study in subjects infected with HBV (2.10%, 3/143 subjects). Also, pancreatitis and acute pancreatitis were observed in overseas clinical studies. Although the incidence is lower than in subjects infected with HIV, pancreatitis has been spontaneously reported in subjects infected with HBV in overseas post-marketing studies.	Collect detailed information on the incidence, seriousness, and outcome of pancreatitis during this study period.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Lactic acidosis and severe hepatomegaly associated with fatty degeneration	Lactic acidosis may occur due to the DNA polymerase inhibiting function of TDF. Occurrence of lactic acidosis has been observed in overseas clinical studies of TDF. Although the incidence is lower than in subjects infected with HIV, lactic acidosis has been spontaneously reported in subjects infected with HBV in overseas post-marketing studies.	Collect detailed information on the incidence, seriousness, and outcome of lactic acidosis and severe hepatomegaly associated with fatty degeneration during this study period.
Lipodystrophy	Although not reported in the Japanese or overseas clinical studies in subjects infected with HBV, lipodystrophy has been reported in overseas clinical studies in subjects infected with HIV-1. Although the incidence is lower than in subjects infected with HIV-1, lipodystrophy has been spontaneously reported in subjects infected with HBV in overseas post-marketing studies.	Collect detailed information on the incidence, seriousness, and outcome of lipodystrophy during this study period.
Drug resistance and cross resistance	Although clinical resistance to TDF has not been confirmed, appearance of TDF-resistant viruses may exacerbate CHB by causing virologic breakthrough (rebound of viral load). Although cross-resistance with other drugs has not been observed in overseas long-term clinical studies of up to 240 weeks, partial cross-resistance among HBV reverse transcriptase inhibitors has been observed in vitro.	Monitor HBV DNA levels during this study period and perform resistance analysis if virologic breakthrough (increase in serum HBV DNA by ≥1 log IU/mL from the nadir or an increase of at least 2 log IU/mL (100 IU/mL) if the nadir is under 10 IU/mL) is observed.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study procedures		
Change in safety data such as on renal impairment and change in efficacy data such as on antiviral effect by switching from ETV to TDF	Although clinical studies conducted overseas showed no difference in the change in eGFR levels, proportion of subjects with a 20% decrease in eGFR was reported to be higher in the TDF group than in the ETV group at Week 96 [Sriprayoon 2017]. Although clinical resistance to TDF has not been confirmed, appearance of TDF-resistant viruses may exacerbate CHB by causing virologic breakthrough (rebound of viral load).	In addition to the mitigation strategy for each of the above items, set up a visit at Week 4 to obtain/confirm safety and efficacy data at an early stage after switching to study treatment.

3.3.2. Benefit Assessment

In the JSH Guidelines for the Management of Hepatitis B Virus Infection [Drafting Committee for Hepatitis Management Guidelines, the Japan Society of Hepatology 2017], short-term goals of antiretroviral therapy include continuous normalization of ALT level and negative conversion of HBeAg, and short-term goal for subjects on sequential treatment with nucleos(t)ide analogues is negative conversion of HBV DNA. Among these, loss of HBeAg has not been achieved in subjects in this study. As a preliminary step to achieve the long-term goal, HBsAg loss, the decrease in HBsAg level must be observed. However, subjects in this study show high HBsAg levels or no tendency of decrease (fluctuation range of $\geq$ -0.1 Log_{10} IU/mL/year). Since HBsAg reduction was significantly higher in the TDF group compared to the ETV group in the Japanese Phase 3 study [Koike, 2018], switching from ETV to TDF to achieve toward the long-term goal, HBsAg loss, is considered beneficial.

3.3.3. Overall Benefit: Risk Conclusion

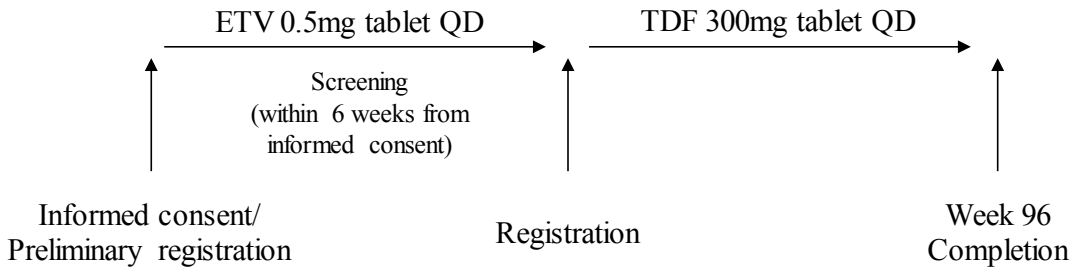
Considering the endpoints to minimize risks to the subjects enrolled in the study, the known potential risks of TDF are justified by the potential benefits to CHB subjects.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the HBsAg reduction potential at Week 48	• Proportion of subjects achieving 0.25 Log_{10} HBsAg reduction from the baseline at Week 48
Secondary	
• To evaluate the virological effects	• Proportion of subjects achieving 0.25 Log_{10} HBsAg reduction from the baseline at Week 24 and 96 • Proportion of subjects achieving HBsAg loss and HBsAg/Ab seroconversion at Week 24, 48 and 96 • Proportion of subjects achieving HBeAg loss and HBeAg/Ab seroconversion at Week 24, 48 and 96 • Reduction of HBsAg titer from the baseline at Week 24, 48 and 96 • Reduction of HB core-related antigen (HBcrAg) titerfrom the baseline at Week 24, 48 and 96
• To evaluate the safety	• Adverse events (AEs) • Clinical laboratory results (hematology, clinical chemistry and urinalysis) • Vital signs (blood pressure, pulse rate, temperature) • 12-lead ECG • Bone density

5. STUDY DESIGN

5.1. Overall Design



This study is designed as a multi-center, one-arm, post-marketing clinical study.
The study will be conducted in CHB HBeAg-positive and HBV-DNA undetectable [< 1.3 log IU/mL (< 20 IU/mL) or < 2.1 Log_{10} copies/mL] treated with ETV.
After switching ETV to TDF at Day 1, TDF will be administered for 96 weeks.

5.2. Number of Subjects

Approximately 80 subjects will be screened to achieve 65 evaluable subjects.

5.3. Participant and Study Completion

A subject is considered to have completed the study if he/she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SOA).

The end of the study is defined as the date of the last scheduled procedure shown in the SOA for the last subject in the trial.

5.4. Scientific Rationale for Study Design

In this study, on-going ETV treatment is switched to TDF treatment at Day 1 in CHB HBV-DNA undetectable subjects [< 1.3 log IU/mL (< 20 IU/mL) or < 2.1 Log_{10} copies/mL]. With regards to the negative conversion of HBV-DNA which is listed as a short-term goal of antiretroviral therapy in the JSH Guidelines for the Management of Hepatitis B Virus Infection, the target subjects are those who are well controlled by ETV treatment. However, as for the negative conversion of HBeAg which is also listed as a short-term goal, the target subjects are those who have not achieved this goal. In addition, this study is designed to investigate the HBsAg reduction in subjects who have not achieved the long-term goal, the loss of HBsAg. The Japanese phase 3 study demonstrated superior HBsAg reduction in TDF treated group compared to the ETV treated group.
The switching of treatment in this study is performed by starting TDF on the day ETV is discontinued, without having overlapping treatment periods. Since both ETV and TDF are once-daily drugs and the blood concentration of TDF reaches its peak at 1.2 ± 0.5 hr, the method of switching treatment is considered appropriate.

5.5. Dose Justification

As this is a post-marketing clinical study, the dosage and administration of TDF will be 300 mg once daily in accordance with the product package insert.

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

Inclusion Criteria	**Screening**	**Day** 1
1. Subjects must be 20 to 69 years of age inclusive, at the time of signing the informed consent	X	
2. Male and female A female subject is eligible to participate if she is not pregnant and not breastfeeding (see Appendix 4), and at least one of the following conditions applies: i) Not a woman of childbearing potential (WOCBP) as defined in Appendix 4 OR ii) A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 during the treatment period and for at least 4 days after the last dose of study treatment	X	(X: For females, confirmation of pregnancy test only)
3. Capable of giving signed informed consent form (ICF) as described in Appendix 2, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.	X	
4. Subjects with CHB (excluding hospitalized patients)	X	
5. Subjects treated with ETV for at least 2 years prior to initiation of study treatment.		X
6. The serum HBV-DNA level at screening is below the limit of quantitation [< 1.3 log IU/mL (< 20 IU/mL) or < 2.1 Log_{10} copies/mL].		X
7. Subjects with serum HBeAg positive at screening		X
8. Meet either of the following serum HBsAg levels at screening. • Serum HBsAg ≥ 800 IU/ml • Serum HBsAg 80 < to < 800 IU/ml and fluctuation decrease is within -0.1 Log_{10} IU/ml per year (Confirming the fluctuation range before screening must be determined using the value which has already been measured. Using preserved serum specimen for retest is prohibited.)		X
9. Meet all of the following criteria at screening • Creatinine clearance (CLcr) ≥ 70 mL/min CLcr is calculated using the following Cockcroft-Gault formula. Male: CLcr = (body weight [kg] × [140-age in years]) / (72 × serum creatinine [mg/dL]) Female: CLcr = CLcr (male) × 0.85 • Hemoglobin ≥ 8 g/dL		X

• WBC ≥ 1,000 /mm^3		

6.2. Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

Exclusion Criteria	**Screening**	**Day** 1
1. QTc > 450 msec or > 480 msec for subjects with bundle branch block Note: • QT interval (QTcB) corrected by the Bazett formula, QT interval (QTcF) corrected by the Fridericia formula and/or QT intervals corrected by other formulae. Interpreted by computer or re-interpreted manually. • The QT Interval correction formula used for inclusion/exclusion criteria and discontinuation criteria for each subject should be determined prior to study initiation. Multiple correction formulae cannot be used for QTc calculation for each subject and the lowest QTc value cannot be used for enrolment or discontinuation of subjects.	X	
2. Received any interferon or HB vaccine therapy within 24 weeks prior to initiation of the study treatment.		X
3. Received overdose of nonsteroidal anti-inflammatory drugs (NSAIDs) (excluding temporary or topical use) within 7 days prior to initiation of the study treatment.		X
4. Received any of the following drugs within 8 weeks prior to initiation of the study treatment (excluding topical products such as ointment and/or cream etc). • Drugs causing renal impairment (e.g., aminoglycosides, amphotericin B, vancomycin, foscarnet, cisplatin, pentamidine, tacrolimus, cyclosporine, some contrast mediums [ionic high-osmolar contrast media, ionic low-osmolar contrast media] • Competitors of renal excretion (except temporary use, e.g., probenecid) • Immunosuppressants (e.g., azathioprine, cycolphosphamide) or chemotherapeutics (e.g., etoposide) • Glucocorticoid preparation		X
5. Received TDF, ADV or TAF within 2 years prior to initiation of the study treatment		X
6. Participation in another clinical study within 6 months prior to screening, or planned participation in another clinical study simultaneously with this study.	X	
7. Co-infection with HIV or HCV		X
8. Subjects with serious complication other than compensated CHB (cancer, significant renal, cardiovascular, pulmonary, or neurological disease, uncontrollable diabetes, etc.)	X	

9. Received or have a plan for solid organ or bone marrow transplantation	X	
10. Has proximal tubulopathy.	X	
11. Subjects with decompensated CHB who meet the following. • Direct bilirubin > 1.5 × ULN, PT < 60%, platelets < 75,000/mm^3 and serum albumin < 3.0 g/dL		X
12. Diagnosed as an autoimmune hepatitis, excluding CHB		X
13. Subjects with or suspected of having hepatocellular carcinoma (HCC) (including both primary and metastatic) from diagnostic imaging at screening, or with serum α-fetoprotein (AFP) > 50 ng/mL at screening		X
14. History of HCC (except subjects who underwent resection or received curative treatment by radiofrequency, and with AFP ≤ 10 ng/mL at screening)		X
15. Woman who is pregnant, possibly pregnant, lactating or planning a pregnancy during the study period.	X	(X: confirmation of pregnancy test only)
16. Psychiatry disorder or cognitive disorder that may affect the subject's ability to give informed consent or to follow specified study procedures.	X	
17. Subjects with a history of alcohol or drug abuse	X	
18. Subjects whom the investigator (or sub-investigator) considers ineligible for the study.	X	
19. Subjects with hypersensitivity to study treatments or their components, nucleoside and/or nucleotide analogues. Subjects with drug allergy that, in the investigator's (sub-investigator's) [or medical monitor's] opinion, labelled contraindication for participation in the study, or other allergy.	X	

6.3. Lifestyle Restrictions

There are no specific lifestyle restrictions in this study.

6.4. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Information on screen failures as to which participation criteria was not met should be entered into electronic Case Report Form (eCRF) dividing into categories, "failures at screening" and "failures prior to study treatment." For participation criteria to be confirmed at screening and Day 1, refer to Inclusion Criteria and Exclusion Criteria sections.

Individuals who do not meet the criteria for participation in this study (screen failure), regarding to inclusion criteria 4 to 9 or exclusion criteria 2 to 6, may be rescreened for one time only if it is

confirmed that all inclusion criteria are met and exclusion criteria are not met except exclusion criterion 3 after the next visit. There should be an interval of 12 weeks before rescreening. Rescreened subjects should be assigned to the new subject number as from the initial screening.

7. TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol. The study treatment in this study indicates Tenozet tablet 300 mg as described in Section 7.1.

7.1. Treatments Administered

Study Treatment Name:	Tenofovir Disoproxil Fumarate (Tenozet Tablet 300 mg)
Dosage formulation:	Film-coated tablets
Unit dose strength(s)/Dosage level(s):	300 mg/dose, once daily
Route of Administration	Oral
Dosing instructions:	1 tablet per dose
Packaging and Labeling	A commercially available product, Tenozet Tablets 300 mg, will be used for study treatment.
Manufacturer:	GlaxoSmithKline K.K.

7.2. Dose Modification

In case of CLcr < 50 mL/min, study treatment dose intervals are adjusted in accordance with Table 1:

Table 1 Guidelines for administration corresponding to decreased renal function

CLcr (mL/min)	Administration method
30 - 49 mL/min	300 mg once every 2 days
10 - 29 mL/min	300 mg once every 3-4 days
Hemodialysis subjects	300 mg following dialysis every 7 days[note)] or 300 mg after a total of approximately12 hours of dialysis

Note) After hemodialysis. Pharmacokinetics in subjects with CLcr <10 mL/minute without hemodialysis has not been evaluated.

7.3. Method of Treatment Assignment

There is no randomization in this study.

7.4. Blinding

This is an open-label study.

7.5. Preparation/Handling/Storage/Accountability

1. The study treatment, Tenozet Tablets, will be used from existing stock of the medical institution or dispensed by the medical institution. The sponsor will not provide study treatments.
2. Storage and management of study treatment should follow the package insert and procedures of each medical institution.
3. Prescription and medication instruction to subjects should follow the procedures of each medical institution.
4. The investigator (sub-investigator)/designated staff of the medical institution should document the amount of study treatment dispensed to and the amount taken by subject in the chart (source document).

- Under normal conditions of handling and administration, study treatment is not expected to pose a significant safety risks to the site staff.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from the medical institution.

7.6. Treatment Compliance

- When subjects self-administer study treatment(s) at home, compliance with Tenozet Tablets 300 mg will be assessed through querying the subject during the site visits and documented in the source documents and eCRF. A record of the number of Tenozet Tablets 300 mg dispensed to and taken by each subject must be maintained. Treatment start and stop dates, including those for dose reductions will also be recorded in the eCRF.

7.7. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrolment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Permitted Concomitant Drugs

Appendix 6: Drug not specified in “Prohibited Drugs” may be used concomitantly. However, on using the following drugs concomitantly, the instructions shown below should be taken into consideration. It is permitted to use a contrast medium considered less influential on the kidney, only in a case where an imaging test by CT or MRI needing a contrast medium is clinically necessary in order not to miss the onset of liver cancer.

- Non- ionic low osmolar contrast media, contrast media for MRI

Note: Each contrast medium should be administered carefully paying attention to the renal functions by, e.g., securing the urine amount with transfusion of physiological saline before and

after using the contrast medium as the measures to prevent renal impairment of the contrast medium. Furthermore, more careful administration is necessary in case of using the contrast medium in subjects with decreased renal function.

Prohibited Concomitant Drugs
During the period from the start to completion of study treatment, concomitant use of the drugs listed in "Appendix 6: Prohibited drugs" will be prohibited due to the possibility of having the impact on efficacy and safety evaluation.
However, the following drug, which is listed in "Appendix 6: Prohibited drugs," may be used for the purpose of liver supporting therapy.

1. Ursodeoxycholic acid preparations

When the ALT or AST level exceeds 10 times the ULN, rescue medication may be used after consultation with the medical monitor of the sponsor. Rescue medication name, date administered, and administration method must be documented.

7.8. Treatment after the End of the Study

After the completion of study treatment and subject's last visit, the investigator (sub-investigator) will perform the treatment considered most appropriate for each subject. The investigator (sub-investigator) is responsible for considering the subject's medical care whether or not the sponsor provides specific treatment after study completion.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

8.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology.
If a subject corresponds to any of the following conditions, discontinuation of study treatment due to abnormal liver function test result is required.

- When a subject corresponds to any of the following conditions
  - Bilirubin ≥ 2 times ULN and direct bilirubin > 35%
  - International Normalized Ratio (INR) > 1.5 without the administration of warfarin
  - Evidence of clinical liver decompensation (development of encephalopathy, ascites, hypoalbuminemia [albumin ≤ 3 g/dL]) or variceal bleeding
  - ALT ≥ 20 times ULN in the absence of increased bilirubin or evidence of clinical decompensation, if persisting ≥ 2 weeks or accompanied by worsening hepatitis symptoms.

OR

The investigator (sub-investigator) considered it to be in the best interest of the subject to discontinue study treatment, although the abnormal liver function test values of the subject do not meet the criteria for discontinuation specified in the protocol.

Required actions after liver event and the follow-up assessment section are shown in Appendix 5.

8.1.2. QTc Stopping Criteria

- The same QT correction formula must be used for each individual subject to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the subject has been enrolled.
    - For example, if a subject is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual subject as well.
    - Once the QT correction formula has been chosen for a subject's eligibility, the same formula must continue to be used for that subject for all QTc data being collected for data analysis. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTc should be based on single ECG.

If ECG results show the following, the subject should be withdrawn from the study.

- QTc > 500 msec or uncorrected QT > 600 msec

For subjects with bundle branch block, the following stopping criteria should be followed.

Baseline value in subjects with bundle branch block	Stopping criteria in subjects with bundle branch block
< 450 msec	> 500 msec
450 - 480 msec	≥530 msec

See the SOA for data to be collected at the time of treatment discontinuation of study and follow-up and for any further evaluations that need to be completed.

8.1.3. Discontinuation Criteria Related to Renal Function Test Values

The **discontinuation criteria and follow-up observation criteria related to renal function test values** will be specified in order to secure the safety of the subjects.

Serum creatinine values ≥ 0.5 mg/dL above baseline should be confirmed by repeat testing within 3 calendar days of receipt of results before the study treatment is discontinued. (However, if such a delay of study treatment discontinuation concerns the safety of subject, study treatment should be discontinued immediately.) For serum creatinine elevation ≥ 0.5 mg/dL above baseline, subjects may continue all study medication, but it is recommended that subjects should be monitored weekly until the serum creatinine returned to the original baseline value or ≤ 0.3 mg/dL from baseline.

All study treatments should be permanently discontinued in the event that repeated testing of serum creatinine confirms > 2 mg/dL. The subject should be followed weekly until the serum creatinine reaches within 0.3 mg/dL elevation of the baseline value.

8.1.4. Temporary Discontinuation

Subjects who stopped study treatment will be withdrawn from this study.

8.1.5. Rechallenge

8.1.5.1. Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge is not allowed if study subject meets any of the stopping criteria specified in each section under 8.1.

8.1.6. Treatment after Discontinuation of Study Treatment

Subjects who meet stopping criteria and who have been withdrawn from study treatment can start alternative treatment.

8.2. Withdrawal from the Study

If one of the following events 1) to 6) occurs in a subject, the investigator (or sub-investigator) should withdraw that subject from the study:

1） When the subject is lost to follow-up.
2） When the subject or subject's legally acceptable representative wishes to withdraw from the study.
3） When it is confirmed that the subject is pregnant.
4） When the subject meets QTc stopping criteria (refer to 8.1.2. QTc stopping criteria).
5） When the subject stopping criteria related to hepatic or renal function test values (refer to 8.1.1. Liver Chemistry Stopping Criteria or 8.1.3. Discontinuation Criteria Related to Renal Function Test Values).
6） When the study is prematurely terminated for other reasons not directly related to the study

If one of the following events 7) to 11) occurs in asubject, the investigator (or sub-investigator) may, at their discretion, withdraw that subject from the study:

7） When it is difficult to continue the study due to an adverse event (s) (Refer to the package insert of Tenozet Tablets 300 mg).
8） When a protocol deviation is found
9） When it is difficult to continue the study due to exacerbation of the primary disease or a complication
10） When the disease being studied resolved
11） When the investigator (or sub-investigator) considers necessary to withdraw the subject from the study for other reasons.

If one of the following events 1) to 11) occurs, reason for withdrawal and date of withdrawal should be entered into eCRF while taking necessary measures. If the consent is withdrawed, the reason must be entered into eCRF.

- A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons.
- If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to the SOA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.3. Lost to Follow Up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SOA.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SOA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SOA.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1. Efficacy Assessments

9.1.1. Virus test

According to theSOA, the following virus tests will be performed on the specified days. These tests will be performed centrally at SRL Inc. in principle. The test results will be reported to each study site and the sponsor.

- HIV, HCV (only at the time of screening)
- HBV Genotype (only at the time of screening)
- HBV-DNA levels (at screening, Day 1 of administration, Week 4, every 12 weeks)
- HBe Ag/Ab, HBs Ag/Ab (quantitation) (at the time of screening, Day 1 of administration, Week 4, every 12 weeks)
- HB cr Ag (Day 1 of administration, Week 4, every 12 weeks)
- LAM resistance analysis, ADV resistance analysis, ETV resistance analysis, TDF resistance analysis (a case where the serum HBV-DNA level has increased from the nadir by at least 1 log IU/mL or an increase of at least 2 log IU/mL (100 IU/mL) if the nadir is under 10 IU/mL)

The blood sample for the resistance analysis should surely be taken at each visit and the resistance analysis will be performed in the above cases. Blood samples taken for resistance analysis will be stored at SRL Inc. until completion of study.

9.1.2. Endpoints

Primary Endpoint

1. Proportion of subjects achieving 0.25 Log_{10} HBsAg reduction from the baseline at Week 48

Secondary Endpoints

1. Proportion of subjects achieving 0.25 Log_{10} HBsAg reduction from the baseline at Week 24 and 96
2. Proportion of subjects achieving HBsAg loss and HBsAg/Ab seroconversion at Week 24, 48 and 96
3. Proportion of subjects achieving HBeAg loss and HBeAg/Ab seroconversion at Week 24, 48 and 96
4. Reduction of HBsAg titer from the baseline at Week 24, 48 and 96
5. Reduction of HBcrAg titer from the baseline at Week 24, 48 and 96

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.
The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the subjectto discontinue the study treatment (see Section 8).

9.2.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the start of study treatment until completion/discontinuation of study at the time points specified in the SOA (Section 2). However, study participation (e.g., study treatment, procedures specified in the protocol, invasive testing, or change from the current therapy) or all SAEs considered associated with GSK products will be recorded from the time the subjectgave consent to participation in the study.
- All AEs will be collected from the start of treatment until completion/discontinuation of the study at the time points specified in the SOA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported immediately, but no longer than 24 hours in any circumstances, to the sponsor or designee as indicated in Appendix 3. The investigator (sub-investigator) will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators (sub-investigators) are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subjecthas been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.
- All non-serious AEs considered associated with the study treatment in the post-marketing clinical study will be recorded and reported to the sponsor or designee within 24 hours of it being available as indicated in Appendix 3.

9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the subjectis the preferred method to inquire about AE occurrence.

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subjectat subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the subjectis lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 3.

Non-serious AEs considered associated with the study treatment in the post-marketing clinical study will also be followed.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.
- Prompt notification to the sponsor of non-serious AEs considered associated with the study treatment in post-marketing clinical study is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

9.2.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.
The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

9.2.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

Not applicable

9.2.7. Pregnancy

- Details of all pregnancies in female subjects will be collected after the start of study treatment until 4 days after the last dose.
- If a pregnancy is reported, the investigator (sub-investigator) should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

9.2.8. Medical Device Incidents (Including Malfunctions)

Not applicable

9.3. Treatment of Overdose

For this study, any dose of TDF greater than 300 mg within a 1-day period will be considered an overdose.
The package insert of TDF (Tenozet Tablets 300 mg) describes overdose as follows.

No case of overdose of TDF has been reported and specific signs and symptoms at the time of overdose are unknown. Closely monitor the subjectfor adverse reactions to TDF at the time of overdose and perform symptomatic therapy as needed. TDF can partially be removed by hemodialysis. Tenofovir removal by peritoneal dialysis has not been examined.

In the event of an overdose, the investigator (sub-investigator) should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the subject for AE/SAE and laboratory abnormalities until Tenofovir can no longer be detected (at least 4 days).
3. Obtain a plasma sample for PK analysis within 24 hours from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator (sub-investigator) in consultation with the sponsor's Medical Monitor based on the clinical evaluation of the subject.

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the SOA.

9.4.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigator (sub-investigator) should pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Vital Signs

- Temperature (axillary), pulse rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subjectin a quiet setting without distractions (e.g., television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the CRF.

9.4.3. Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SOA (Section 2) at screening, Week 48, at discontinuation or completion of study, and that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 8.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- The measured ECG Waveforms will be retained at each medical institution in paper or electronic form.

9.4.4. Clinical Safety Laboratory Assessments

- Refer to Table 2 for the list of clinical laboratory tests to be performed and to the SOA for the timing and frequency.
- The investigator (sub-investigator) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator (sub-investigator) to be more severe than expected for the subject's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 4 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Table 2, must be conducted in accordance with the laboratory manual and the SOA.
- The laboratory tests detailed in Table 2 will be performed by the central laboratory.

- Protocol-specific inclusion/exclusion criteria for subjects are included in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator (sub-investigator) or required by local regulations.

Table 2 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count	Hemoglobin	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	RBC Count	Hematocrit	Prothrombin time	
Clinical Chemistry[1]	Blood urea nitrogen (BUN)	LDH	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	CLcr	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose [fasting not required]	eGFR	Alkaline phosphatase (ALP)	γ-GTP
	Albumin	Creatine kinase	Amylase	Lipase
	AFP	Antinuclear antibody titer [only at the time of screening]	Electrolyte (Na, K, Cl, Ca, P)	Uric acid
	Hyaluronic acid [Required at screening and as needed thereafter.]	Lactic Acid		
Urinalysis	Glucose, protein, creatinine, electrolyte (P), urinary sediment, β2-microglobulin			
Other screening tests	Human chorionic gonadotrophic hormone (hCG) pregnancy test (for women of childbearing potential and if required)[2]			

Notes:

1. Details of liver chemistry stopping criteria, required actions after liver events and follow-up assessments are provided in Section 8.1 and Appendix 5.

2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

9.4.5. Abdominal Imaging Test

Abdominal imaging test will be performed to diagnose HCC and hepatic cirrhosis in accordance with the SOA (Section 2).

9.4.6. Bone Densitometry

Bone densitometry will be performed using DEXA, SEXA, or ultrasound in accordance with the SOA (Section 2). Refer to Appendix 7.

9.5. Pharmacokinetics

PK parameters are not evaluated in this study.

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7. Genetics

Genetics are not evaluated in this study.

9.8. Biomarkers

Biomarkers are not evaluated in this study.

9.9. Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

This is an open-label uncontrolled study to evaluate the virological effects and safety of switching at Day 1 from ETV to TDF 300 mg once daily in Japanese CHB HBeAg-positive and HBV-DNA undetectable subjects [< 1.3 log IU/mL (< 20 IU/mL) or < 2.1 Log_{10} copies/mL].
Exploratory investigation will therefore be performed and no confirmatory hypotheses will be tested. Descriptive summary will be used to assess the efficacy and safety objectives.

10.1. Sample Size Determination

10.1.1. Sample Size Assumptions

Although no confirmatory hypotheses will be tested in this study, the sample size has been examined using the expected responder rate and threshold rate. Assuming the proportion of subjects achieving 0.25 Log_{10} HBsAg reduction from the baseline (proportion of HBsAg responder) at Week 48 to be 20%, the proportion of HBsAg responder in subjects not switched to TDF-based regimens on the basis of results of ETV treatment to be 6% (threshold rate), and significance level (two tailed) to be 5%, the sample size with at least 90% power is calculated to be 57. Allowing for a dropout rate of 10%, the sample size is calculated to be 64 and thus the target sample size was set at approximately 65.

10.1.2. Sample Size Sensitivity

Table 3 shows the sample sizes needed to have an at least 80% or 90% power, assuming a 15% to 25% expected proportion of subjects achieving 0.25 Log_{10} HBsAg reduction from the baseline and a 6% to 10% threshold proportion of subjects.

Table 3 Sample size calculation

Threshold (%)	The proportion of HbsAg responder at Week 48 (%)	≥ 80% power (N)	≥ 90% power (N)
6	15	82	116
	20	55	57
	25	55	55
8	15	156	215
	20	61	86
	25	40	45
10	15	341	455
	20	94	132
	25	49	64

10.1.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation will be performed.

10.2. Populations for Analyses

For analysis purposes, the following populations are defined:

Population	Description
Enrolled	Subjects who provided consent
Screen failures	Subjects who provided consent but were not subsequently administered
Safety Population: SP	Subjects who have received at least 1 dose of study treatment after enrolment.
Full Analysis Set: FAS	A population of all subjects enrolled in the study, excluding those who meet either of the following criteria. • Have not received any dose of study treatment. • Have no efficacy data after the start of study treatment.
Efficacy Evaluable Set: EES	A subset of subjects in the FAS defined above and evaluable for efficacy. Refer to Report and analysis plan (RAP) for more details.

10.3. Statistical Analyses

The data in this study will be presented in the form of tables and/or graphs and descriptively summarized in accordance with the Integrated Data Standards Library (IDSL) of the sponsor (GSK).

Detailed analyses will be described in the Report and analysis plan (RAP).

10.3.1. Efficacy Analyses

Efficacy analyses will be performed on the FAS. Primary endpoint analyses will be performed also on EES.

Statistical methods
The primary endpoint is the proportion of subjects achieving 0.25 Log_{10} HBsAg reduction from the baseline at Week 48, and the responder rate and its two-sided 95% confidence interval will be calculated. As the secondary analysis, the responder rate (%) at Week 24 and Week 96 and its two-sided 95% confidence interval will also be calculated. Analyses similar to the primary analysis will also be performed in subgroups (disease, genotype, etc.). These subgroup analyses are intended to assess the robustness of results. Subgroup: • Disease (CHB, liver cirrhosis) • Genotype (A, B, C, D) Centrally measured virus testing results will be used for both the primary endpoint and efficacy endpoints

10.3.2. Safety Analyses

Safety analyses will be performed on the SP.

Statistical methods
Adverse events All adverse events occurred during the study period will be coded with the latest version of Medical Dictionary for Regulatory Activities (MedDRA) and classified by System Organ Class (SOC) and Preferred Term (PT). The adverse events, the adverse events causally related with the investigational product, the adverse events resulting in discontinuation of the study, the severe adverse events and the serious adverse events will be summarized, and all the adverse events will be listed. The frequency and incidence of AE of interest (renal adverse events, hepatic adverse events, and skeletal adverse events) will also be summarized. **Clinical Laboratory Tests** As for the clinical laboratory values (hematology, clinical chemistry, urinalysis), the summary statistics (number of subjects, mean, median, SD, minimum, maximum) of observed values at each evaluation time point and variation from baseline will be calculated. Shift table from baseline to each evaluation time point will be generated. The measured value for each parameter will be included in the data listings. In addition, subjects found to have test values out of the reference range will be listed. **Vital Signs** For changes in vital signs (blood pressure, pulse rate, temperature) from baseline to each assessment point, the summary statistics (number of subjects, mean, median, SD, minimum, maximum) will be calculated. The measured value for each parameter will be included in the data listings.

10.3.3. Interim Analyses

No interim analysis to make statistical investigations will be performed in this study. However, the CRF data by Week 48 will be locked when all subjects (excluding withdrawn subjects) complete Week 48 to collect safety and efficacy data.

10.3.4. Handling of Withdrawed Subjects

In analyzing the primary endpoint, unless otherwise stated, withdrawed subjects reported during the study period will be treated as non-responders. Other imputation methods will be examined.

11. REFERENCES

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ADV	Adefovir pivoxil
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Asparate Aminotransferase
CLcr	Creatinine Clearance
eCRF	Electronic Case Report Form
ETV	Entecavir hydrate
eGFR	Estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
γ-GTP	γ-glutamyltranspeptidase
HCC	Hepatocellular carcinoma
IEC	Independent Ethics Committee

INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-To-Treat
LAM	Lamivudine
MedDRA	Medical Dictionary for Regulatory Activities
PCD	Primary completion date
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PP	Per Protocol
PT	Preferred Term
RAP	Reporting and Analysis Plan
SAE	Serious Adverse Event
SD	Standard Deviation
SOA	Schedule of Activities
SOC	System Organ Class
SRM	Study Reference Manual
TAF	Tenofovir Alafenamide Fumarate
TDF	Tenofovir Disoproxil Fumarate
ULN	Upper Limit of Normal

Trademark

Trademarks of the GlaxoSmithKline group of companies

Trademarks not owned by the GlaxoSmithKline group of companies
Tenozet

12.2. Appendix 2: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - The Ordinance on Standards for Conduct of Clinical Trials (MHW Ordinance No. 28 dated March 27, 1997) and applicable laws and regulations regarding quality of medicinal products and medical devices, efficacy and safety assurance, etc.
  - The Ordinance on Good Post-Marketing Study (MHLW Ordinance No.171 dated December 20, 2004)
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site, ICH guidelines, the IRB/IEC, and all other applicable regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

Prior to subjects' participation in the study, the investigator (sub-investigator) will fully explain the study using patient information to the subject considered as appropriate or/and to his/her legally authorized representative. During this period, provide the subjects opportunities to ask questions and sufficient time and obtain the consent form signed or signed/sealed dated with the date of consent by the subject and/or his/her legally authorized representative. Subjects may take home the Patient Information/Consent Form to consider about the participation at home. The person who provides explanation and the study collaborator who provides supplemental explanation will sign or sign/seal with the date signed. If a witness is required, the witness should also sign or sign/seal with the date witnessed. The investigator (sub-investigator) will attach the original of the above signed or signed/sealed, and dated Consent Form (and the Patient Information) to the original medical records such as medical chart, retain (follow the storage

regulations of the medical institution, if any), and hand the copy to the subject or his/her legally authorized representative.

- The investigator (sub-investigator) or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.
- Subjects who are rescreened are required to sign a new ICF.

The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research in accordance with SOP-GSKF-410. The investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate will not provide this separate signature.

Data Protection

- Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

Prior to enrolment of subjects, the study information derived from this protocol will be made publicly available on the Clinical Trial Registry System including the website (www.ClinTrials.gov) of the National Institutes of Health (NIH). 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 provide the investigator with the full summary of the study results. The investigator will share the summary results with the study subjects, as appropriate.
The results summary will be posted to the GSK Clinical Study Register within 12 months of the PCD or LSLV, whichever is earlier, or any decision to terminate the study. In addition, a manuscript will be submitted to a peer-reviewed journal for publication within 18 months of the LSLV or any decision to terminate the study. When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

Data Quality Assurance

- All subject data relating to the study will be recorded on electronic CRF (eCRF) unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the latest approved protocol and any other study agreements, ICH, GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. In addition, current medical records must be available.
- Definition of what constitutes source data can be found in the source document correspondence list.

Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.
The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of marketing of the investigational product

Study Period
August 2017 to December 2019

Implementation system
Attachment 1 provides the sponsor information. Attachment 2 provides a list of medical institutions and investigators.

12.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • 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 study treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • 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 before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug 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 it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses 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. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or changes in other safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • 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. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which 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.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening 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 inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization 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 outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term 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 with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include 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 hospitalization, or development of drug dependency or drug abuse.
g. Events meeting liver chemistry stopping criteria • Bilirubin ≥ 2 times ULN and >35% direct bilirubin • International Normalized Ratio (INR) > 1.5 in absence of warfarin • Evidence of clinical decompensation (development of encephalopathy, ascites, hypoalbuminea [albumin ≤ 3g/dL]), or variceal bleeding • ALT ≥ 20 times ULN in the absence of increased bilirubin or evidence of clinical decompensation, if persisting ≥ 2 weeks or accompanied by worsening hepatitis symptoms

Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF 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 • Revascularization

Recording AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF. • It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories: • Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
• The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator (sub-investigator) will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.
- Any updated data on non-SAEs considered associated with the use of study treatment in the post-marketing study will be submitted by the investigator to GSK within 24 hours of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via eCRF

- The primary mechanism for reporting SAE to GSK will be the eCRF .
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.

- After the study is completed at a given site, the eCRF will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the eCRF has been taken off-line, then the site can report this new or updated information on a paper SAE form (see next section) or to the sponsor's medical monitor/study contact by telephone.
- Contacts for SAE reporting can be found in Attachment 1.
- The non-SAEs considered associated with the use of study treatment in the post-marketing clinical study should be reported in the same manner.

SAE Reporting to GSK via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the sponsor's **medical monitor or the SAE coordinator**.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE pages of the CRF sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in Attachment 1.
- The non-SAEs considered associated with the use of study treatment in the post-marketing clinical study should be reported in the same manner.

12.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of subject's medical records, medical examination, or medical history interview.

3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

Contraception Guidance

Female subjects

Female subjects of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 4.

Table 4 Highly effective contraception methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • Oral
Highly Effective Methods That Are User Independent
• Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS)
Vasectomized partner
(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)

Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects in clinical studies.

b. Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the treatment period and for at least 4 days after the last dose of study treatment.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test.
- Additional pregnancy testing is not required during the treatment and after the last dose of study treatment and as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Pregnancy testing will be performed using the test kit approved by the sponsor and in accordance with instructions provided in its package insert.

Collection of Pregnancy Information

Female Subjects who become pregnant

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on subject and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 3. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating

- Will be withdrawn from the study

12.5. Appendix 5: Liver Safety: Required Actions and Follow-up Assessment and Study Treatment Rechallenge Guidelines

Liver chemistry stopping and follow-up assessment criteria in phase III-IV studies will be specified in order to secure the safety of the subjects and evaluate the etiology of liver events.

Liver chemistry stopping criteria and required follow-up assessment in phase III-IV studies

<table>
<tr><th colspan="2">Liver chemistry stopping criteria</th></tr>
<tr><td>Bilirubin[1]</td><td>Bilirubin ≥ 2 times ULN and >35% direct bilirubin</td></tr>
<tr><td>INR[1]</td><td>INR > 1.5 in absence of warfarin</td></tr>
<tr><td rowspan="2">Symptoms</td><td>Evidence of clinical decompensation (development of encephalopathy, ascites, hypoalbuminea [albumin ≤ 3g/dL]), or variceal bleeding</td></tr>
<tr><td>ALT ≥ 20 times ULN in the absence of increased bilirubin or evidence of clinical decompensation, if persisting ≥ 2 weeks or accompanied by worsening hepatitis symptoms</td></tr>
<tr><th colspan="2">Required actions and liver event endpoints</th></tr>
<tr><th>Actions to be taken</th><th>Liver event endpoints</th></tr>
<tr><td>• Discontinue study treatment immediately
• Report the information to the sponsor within 24 hours.
• If the event meets SAE criteria as well, enter necessary information in the “Liver Event” and “SAE” sections of the CRF.[1]
• Investigate the liver event endpoints (refer to the right column for endpoints).
• Subjects will be followed up until the liver function test value becomes normal, stabilizes or returns to the baseline level (refer to the “Follow-up assessment” below).
• The study treatment must not be re-initiated/re-administered to subjects.

Follow-up assessment:
<u>Bilirubin or INR Criteria:</u>
• The liver function tests (ALT, AST, ALP, bilirubin) should be performed again within 24 hours and liver event endpoints will be examined (refer to the right column for endpoints).
• Follow-up will be performed twice a week until the liver function test value becomes normal, stabilizes or returns to the baseline level.</td><td>• Serum testing[2] related to virus hepatitis
• Measure the INR and monitor each liver function test value until decreasing trend is observed in transaminase levels.
• Only the subjects who were complicated with CHB at the time of enrolment (confirmed by positive hepatitis B surface antigen (HBsAg)): HBV-DNA quantitative analysis
• Obtain blood sample for PK analysis within 24 hours after the last dose.[3]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH)
• Fractionate bilirubin, if total bilirubin ≥ 2 x ULN
• Obtain blood count including WBC differential to assess eosinophilia
• Record the occurrence and worsening of clinical symptoms[4] of hepatic impairment or hypersensitivity on the AE CRF.
• Record use of concomitant medications including acetaminophen, herbal remedies, and other over the counter medications on the concomitant medications CRF.
• Record alcohol intake on the liver event CRF.</td></tr>
</table>

• Complete the liver imaging and/or liver biopsy CRFs if these tests are performed. **<u>Other criteria:</u>** • Subjects with ALT ≥ 20 times ULN who otherwise do not meet other stopping criteria outlined above can continue study medication, but should be monitored weekly. • If, after 2 weeks of monitoring, ALT < 20 times ULN, subjects should be monitored twice monthly until the liver function test value becomes normal, stabilizes or returns to the baseline level. However, if during the monitoring period, subjects meet the liver chemistry threshold stopping criteria or are unable to return for weekly follow-up, investigational product must be stopped and follow-up will be performed until the liver function test value becomes normal, stabilizes or returns to the baseline level.	• HBV-DNA level resistance analysis (only in the subject who has shown virological breakthrough) • HBeAg/Ab • Prothrombin time **<u>Bilirubin or INR criteria:</u>** • Quantitative determinations of antinuclear antibody, antismooth muscle antibody, anti-liver/kidney microsome antibody type I and immunoglobulin G (IgG) or gamma-globulin • Perform liver imaging (ultrasound, magnetic resource, or computerized tomography) and/or liver biopsy to evaluate liver disease and record on the liver event CRF.

1. Events indicating severe liver injury (possible Hy's Law) (bilirubin ≥ 2 times ULN **and** >35% direct bilirubin, or INR > 1.5 in the absence of warfarin) **must be reported as an SAE**.
2. Hepatitis A IgM antibody, hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (IgM), hepatitis C RNA, cytomegalovirus IgM antibody, Epstein-Barr virus capsid antigen IgM antibody (if not feasible, perform the heterophile agglutination test), hepatitis E IgM antibody or hepatitis E RNA
3. Record the date/time of the PK blood sample draw and the date/time of the last dose of investigational product prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Refer to the Study Reference Manual (SRM) for procedures for handling and transferring samples.
4. Symptoms considered to be related to liver impairment (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, etc.), or symptoms considered to be related to hypersensitivity (fever, rash, eosinophilia, etc.).

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of

Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369.

12.6. Appendix 6: Prohibited Drugs

Prohibit the use of the below drugs from the initiation of the study treatment:

- Interleukin-2 preparations
- Ursodeoxycholic acid preparations
- Herbal medicine with positive effects on hepatic dysfunction
- Antiviral drugs with an inhibitory effect on HBV growth (excluding ADV and TAF, which should be prohibited from the day of the informed consent)

TDF is prohibited from the day of the consent until the day before the initiation of the study treatment (TDF will be administered as an investigational product from Day 1)

Prohibit the use of the below drugs from the day of the informed consent:

- Other investigational products
- Interferon preparations
- HB vaccine therapy
- Glucocorticoid preparations (excluding topical preparations such as ointment and cream)
- Immunosuppressants (e.g., azathioprine and cyclophosphamide) or chemotherapeutic agents (e.g., etoposide) (excluding topical preparations such as ointment and cream)
- Drugs influential on the renal functions shown below (excluding topical preparations such as ointment and cream)
    - Nephrotoxic drugs (e.g., aminoglycoside-class antibiotics, amphotericin B, vancomycin, foscarnet, cisplatin, pentamidine, tacrolimus, cyclosporine, some contrast media [ionic high osmolar contrast medium, ionic low osmolar contrast media])
    - Drugs competing in renal excretion (excluding temporary use, e.g., probenecid)

Prohibit the use of the below drugs influential on the renal functions within 7 days prior to initiation of the study treatment:

- Overdose NSAIDs (excluding temporary or topical use)

12.7. Appendix 7: Evaluation of Baseline Values

12.7.1. Participant Backgrounds

At the time of screening, the following items will be examined and recorded in the eCRF.

- Birth year, gender, race
- Time of diagnosis of CHB/cirrhosis B
- Cardiovascular history/risk factors
- History related to liver disease
- Complications
- Name of the drug for the treatment of CHB and treatment period within 2 years
- History of alcohol consumption and smoking
- Family history of cardiovascular risk factors
- Measured values at 2 time points (with an interval of at least 3 months, and at least one point within 1 year from screening) for subjects in whom changes in HBsAg before screening can be confirmed.

12.7.2. Diagnosis of Cirrhosis B

Cirrhosis will be diagnosed when applicable to either of the following.

- A case where definite diagnosis of cirrhosis has been made by liver biopsy or abdominoscopy performed within one year before obtaining consent
- A case where cirrhosis can be diagnosed in clinical overall diagnosis including abdominal imaging tests (ultrasonography, CT, MRI, etc.) (see Table 5)

Table 5 Cirrhosis diagnosis criteria[1]

	Test item	Criterion
Hematology	Platelet count	≤ 120,000 /μL
Clinical Chemistry	Hyaluronate level	≥ 100 ng/mL
Abdominal imaging test[2]	Ultrasonography, CT, MRI, etc.	1. Concavity and convexity on the liver surface 2. Echo pattern changes in the hepatic parenchyma 3. Findings of portal hypertension

1. Cirrhosis is diagnosed when all the criteria are met. Use the results of hematology, clinical chemistry and abdominal imaging test obtained at the time of screening.
2. One of the criteria 1 to 3 must be met for abdominal imaging tests.

12.7.3. Bone densitometry

Perform densitometry on either lumbar spine or femur, using DEXA (refer to Table 6). If there is a difficulty to perform with DEXA or on either lumbar spine or femur, other region (radius or calcaneus) or other method (SEXA or ultrasound) may be selected.

Table 6 Region to perform bone densitometry

	Preferred	Substitute	
Method	DEXA	SEXA	Ultrasound

Region	lumbar spine femur radius[1] calcaneus[1]	radius calcaneus	calcaneus

1. Measure this region if the lumbar spine or femur is not available

If densitometry is required during the study or at study completion/discontinuation, use the same method and region performed at baseline.