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INVESTIGATOR PROTOCOL AGREEMENT PAGE

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

Investigator Name: _____

Investigator Signature	Date

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LIST OF ABBREVIATIONS

ADV	Adefovir
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BP	Blood pressure
CHB	Chronic hepatitis B
CRF	Case report form(s)
CFDA	China Food and Drug Administration
DAPD	(2R,4R)-4-(2,6-Diaminopurin-9-yl)-1,3-dioxolan-2-yl]methanol
DNA	Deoxyribonucleic acid
EC	Ethics committee
ETV	Entecavir
GCP	Good Clinical Practice (Guidelines)
HAV	Hepatitis A virus
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B s antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDV	Hepatitis delta virus
HIV	Human immunodeficiency virus
IB	Investigator brochure
IFN	Interferon
INR	International Normalized Ratio
IP	Investigational product
mITT	Modified Intent-to-treat (population)
IUD	Inter uterine device
IUS	Inter uterine system
LAM	Lamivudine
LdT	Telbivudine
L-FMAU	1-(2-fluoro-5-methyl-beta, L-arabinofuranosyl) uracil
LFT	Liver function test
LSLV	Last subject last visit
MedDRA	Medical dictionary for regulatory activities
NAs	Nucleos(t)ide analogues
PP	Per protocol population
PT	Prothrombin time
QD	quaque die (Once daily)
RAP	Reporting and analysis plan
SA	Safety analysis population
SAE	Serious adverse event
SOP	Standard operating procedure
SPM	Study procedures manual
TDF	Tenofovir disoproxil fumarate
TFV	Tenofovir
ULN	Upper limit of the normal range

GSK GlaxoSmithKline

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PROTOCOL SUMMARY

Rationale

Due to the widely use of the low genetic barrier drugs as LAM(lamivudine), ADV(adefovir), and LdT(telbivudine), the number of patients who experienced treatment failure to different NA-treatment regimens has rapidly increased and poses a growing problem in daily clinical practice in China.

Tenofovir disoproxil fumarate (TDF), the oral pro-drug of tenofovir (TFV), is a potent treatment for treatment-naïve and LAM-resistant CHB patients.

Until recently, data on the efficacy of TDF treatment following failure of multiple NA regimens were limited. Patterson [Patterson, 2011]and Van Bommel [van Bommel, 2010] have both examined the impact of prior LAM and ADV sequential therapy on response to TDF. Although LAM resistance did not influence the efficacy of TDF, the effect of pre-existing ADV resistance was more variable. In the Patterson study, the presence of detectable ADV resistance mutations at baseline did not affect the rate of HBV DNA decline during TDF therapy which was not the case in the study by van Bommel.The apparent discrepancy between these may be the difference in baseline HBV DNA titre. The mean baseline HBV DNA viral load in van Bommel's study was much higher compared to the baseline HBV DNA in the Patterson study (>8.0 $\log_{10}$ copies/mL and 6.0 $\log_{10}$ copies/ml, respectively).Due to the fact that both studies had relatively small numbers of patients, it is still yet to be determined how ADV-R impacts response rates to TDF.
Our study is a phase IV study and will evaluate the efficacy and safety of TDF treatment in Chinese CHB patients following failure of multiple NAs. In addition, the efficacy in patients harboring multi-drug resistance mutations prior to initiating TDF will be also evaluated. The result ofthis study will help Chinese physicians better manage the CHB patients following failure of multiple NAs.

Objective(s)

Primary Objective

- To assess the proportion of multiple NA treatment failure chronic hepatitis B patients that achieve HBV DNA<20 IU/mL at week 144 of TDF treatment.

Secondary Objective

- To assess the efficacy of TDF following failure of multiple NAs by evaluating serum HBV DNA, ALT and serological responses at week 48, 96 and 144.
- To assess the efficacy of TDF in patients harboring multi-drug resistance mutations prior to initiating TDF.
- To evaluate the safety of TDF following failure of multiple NAs.
- Evaluate the impact of the baseline characteristics (viral titer, mutation patterns, etc.) and early HBV DNA suppression on response to TDF.

Study Design

This is a single-arm, open-label, multi-centre study to assess the efficacy of TDF in CHB patients following failure of multiple NAs.

The study will enrol 200 CHB patients following failure of multiple NAs. All the eligible study subjects will undergo safety and efficacy assessments every 12 weeks for a total of 14 visits.

Screen phase (Visit 1): About 230 subjects will be assessed for eligibility at a screening visit, with eligible patients returning for a baseline assessment after approximately 4 weeks. Multiple NAs treatment failure is defined as HBV DNA higher than 200 IU/ml after two or more different NA(s) treatments (i.e. initiate with mono-therapy, followed by add-on/switch rescue therapy; at least 6 months continuous treatment for each regimen, total duration to be no less than 12 months). At Visit 1 all the testing will be performed locally except for the HBV DNA quantification which will be measured by a central lab. The subjects will maintain their pre-existing treatment from screening visit to baseline visit. All subjects will provide written informed consent before screening.

Treatment phase (Visits 2 to 14): In the 144 weeks open label period, all enrolled subjects will receive open label TDF at a dose of 300mg orally once daily. At each visit, subjects will be questioned about adverse events, concurrent medications, and study drug accountability; take chemistry (liver function, blood glucose, creatine phosphokinase) test; take electrolytes (sodium, potassium, chloridum, phosphorus and calcium) test; take pregnancy test; take urinalysis test; take renal function (blood creatinine clearance, blood urea nitrogen and blood uric acid) test. Blood routine and International Normalized Ratio(INR) and HBV markers will be measured every 24 weeks. Abdominal ultrasound and serum alpha-fetoprotein test will be tested every 24 weeks. Serum samples will be collected and analyzed for HBV DNA levels in a central lab from visit 2 to 14.At visit 2, resistance surveillance of the HBV polymerase gene will be performed for all subjects at baseline by direct sequencing.

During the treatment phase, rescue therapy will be initiated in those study subjects that do not achieve satisfied response to TDF, defined as

- Experiencing virological breakthrough (defined as HBV DNA level increase $\geqslant$1 $\log_{10}$ IU/ml above the treatment nadir, confirmed on an additional visit),OR
- Subjects have HBV DNA $\geqslant$200IU/ml at week 48 and afterwards have $\leq$ 1 $\log_{10}$ IU/ml decrease in HBV DNA at two consecutive tests, confirmed by a third visit (additional visit) at least one month apart.

Meanwhile, subjects to be received rescue therapy must have investigational product (IP) compliance > 80% in the last regular visits period (usually 12 weeks).

Another NA(s) without cross-resistance (eg. LAM, LdT, or ETV) will be added, the choice to be decided by the investigator.

Additional Visit: During the treatment phase, subjects who do not achieve satisfied response to TDF(eg.experience virological breakthrough or HBV DNA level does not continue to decline,) need to perform another HBV DNA test at an additional visit at least one month apart. Before rescue treatment initiation, serum sample should be collected for resistance testing.

During the treatment phase, patients that have evidence of HBsAg loss or seroconversion and HBeAg loss/seroconversion (for baseline HBeAg positive subjects) and HBV DNA < 20 IU/ml at any two consecutive visits at least 3 months apart will enter a non-treatment observational arm of the study, and will be followed up until the end of the study according to protocol-defined assessments and procedures. Study treatment should be stopped within 15 days of the result confirming that the subject meets the criteria.

If a patient in the non-treatment observational arm subsequently develops HBV DNA ≥20 IU/ml, HBsAg re-emerges, and ALT > 1.5 ULN, they will be eligible to be re-treated with TDF up to week 144 of the study. Once the treatment is restarted, the patients should be followed at least every 12 weeks as protocol defined and the data will be entered as the corresponding scheduled visit.

Study Endpoints/Assessments

Primary Endpoint

- The proportion of subjects with serum HBV DNA <20 IU/ml at week 144.

Secondary Endpoints

- The proportion of subjects with serum HBV DNA <20 IU/ml at week 48 and 96.
- The proportion of subjects in the subgroup with confirmed multi-drug resistance at baseline with serum HBV DNA <20 IU/ml at week 48, 96 and 144.
- The $\log_{10}$ reduction in serum HBV DNA at Week 48, 96 and144.
- For HBeAg positive subjects: the proportion of subjects achieving HBeAg loss, HBeAg seroconversion or HBsAg loss and HBsAg seroconversion at Week 48, 96, and 144.
- For HBeAg negative subjects: the proportion of subjects achieving HBsAg loss and HBsAg seroconversion at Week 48, 96, and 144.
- The proportion of subjects with ALT normalization at Week 48, 96, and 144 in subjects who have abnormal ALT at baseline.
- Incidence of subjects who experience viral breakthrough (defined as ≥ 1 log increase in HBV DNA from nadir determined by two sequential HBV DNA measurements) up to week 144.
- Subject safety as determined by adverse events and laboratory assessments.

Exploratory Endpoints

- Evaluate the impact of the baseline virological characteristics (viral titer, mutation patterns, etc.) and early HBV DNA suppression on response to TDF at week 144.

1. INTRODUCTION

1.1. Background

Chronic infection with hepatitis B virus (HBV) affects more than 350 million people worldwide and continues to be an important cause of morbidity and mortality, and source of potential new infections[Lai, 2003; Perz, 2006]. Chronic hepatitis B (CHB) has a broad clinical spectrum ranging from a severe, rapidly progressive illness to an asymptomatic, stable illness. Between one-quarter and one-third of people chronically infected with HBV are expected to develop progressive liver disease[Lee, 1997]. An estimated one million people die annually from the complications of hepatitis B, making CHB one of the top ten leading causes of death worldwide[Lai, 2003].

Effective suppression of viral replication amends the course of the disease and decreases morbidity. However, if viral replication resumes as a result of the development of resistance mutations, the clinical benefit is lost. Therefore, one aim of therapy for the treatment of CHB is to suppress viral replication in a potent and durable fashion to prevent the emergence of complications. Most CHB patients require long-term therapy, so oral antiviral drugs with potent antiviral activity, a low rate of HBV antiviral resistance and proven long-term safety are needed.

In the last two decades, revolutionary changes happened in the management of chronic hepatitis B virus (HBV) infection. Nucleos(t)ide analogues (NAs) target the reverse transcriptase of hepatitis B virus (HBV), and are potent inhibitors of viral replication. In China lamivudine (LAM) was approved for the treatment of chronic hepatitis B in 1999. Subsequently, adefovir (ADV) and entecavir (ETV) were launched at 2005 in China. Then telbivudine (LdT) was licensed by CFDA (China Food and Drug Administration) in 2008. According to the international guidelines [European Association For The Study Of The Liver, 2012; Liaw, 2012; Lok, 2009], ETV and TDF should be considered for initial therapy for naïve patients because of superior viral suppression low risk of resistance development. But in a resource-limited country such as China, LAM, ADV and LdT remain widely used. The major problem with LAM is the high incidence of resistance, with up to 70% of patients developing drug related mutations after 4 years of treatment [Lai, 2003]. This makes it unsuitable for use as the first line oral antiviral drug in most circumstances. But in China LAM is still accepted as a first line antiviral agent because of its relatively low daily cost and well-established safety profile. Thus, the number of LAM resistant patients is high and management of LAM resistance is becoming a challenge for Chinese physicians.

The treatment options for patients who develop LAM resistance have been limited. ETV is potent and proven to have a high genetic barrier to resistance in NA-naïve HBV patients. After five years of ETV mono-therapy, only 1.2% of treatment naïve patients developed genotypic resistance to ETV [Tenney, 2009]. However, ETV was less potent and the frequency of resistance was increased in LAM refractory chronic HBV patients [Sherman, 2008; Sherman, 2006]. After five years of treatment, 51% of LAM-refractory patients showed genotypic ETV-resistance and in 43% a virological breakthrough was also observed [Tenney, 2009]. Another option for LAM resistant patients is LAM plus ADV combination therapy. This approach can reduce the risk of multi-drug resistance,

but the HBV DNA suppression may not be adequate. Recent studies from Asia demonstrated that only 22.6% to 41.3% [Chung, 2011; Ryu, 2010; Sheng, 2011; Son, 2012] of LAM resistant patients achieved HBV DNA undetectable after 48 weeks of ADV+LAM treatment.

The prevalence of CHB patients with drug-resistance mutations has rapidly increased. A population-based cross-sectional investigation[Liu, 2011] showed drug-resistant mutations were detected in 560 of 1803 NA(s) treatment experienced patients, comprising 214 patients that had received LAM, 35 patients that had received ADV, 5 patients that had received LdT , and 306 patients that had received either sequential monotherapies or combination NA(s) therapies. Therefore, the number of patients who experience treatment failure to different NA-treatment regimens poses a growing problem in daily clinical practice in China.

1.2. Rationale

Tenofovir disoproxil fumarate (TDF), the oral pro-drug of tenofovir (TFV), is a nucleotide analogue that inhibits viral polymerases by direct binding and after incorporation into DNA, by termination of the DNA chain [Heijtink, 1994]. TDF is a highly potent treatment in treatment-naïve and LAM resistant CHB patients [Baran, 2013]. In vitro studies have shown that HBV strains expressing the ADV resistance-associated substitutions rtA181V and/or rtN236T showed reductions in susceptibility to TDF ranging from 2.9-fold to 10-fold that of wild-type virus[Brunelle, 2005; Villet, 2008], but clinical trials[Berg, 2010] showed TDF mono-therapy resulted in complete viral suppression in the majority of patients with partial response to ADV by week 48, suggesting that this drug may be an effective treatment for patients who have previously failed treatment with different NAs.

Until recently, data on the efficacy of TDF treatment following failure of multiple NAs were limited. Patterson and colleagues reported the results of a prospectively conducted study that evaluated TDF treatment in CHB patients who had previously failed with LAM and followed by at least 24 weeks of ADV treatment. Serum HBV DNA at study entry were $>10^5$ copies/ml and $>10^4$ copies/ml in HBeAg-positive (n=40) and HBeAg negative patients (n=20), respectively. Those receiving combination ADV and LAM were switched to TDF plus LAM, and those on ADV monotherapy were switched to TDF monotherapy. At week 48 and 96, 27/59 (46%) and 38/59 (64%) patients achieved a HBV DNA <15 IU/mL. HBV DNA response was independent of baseline LAM therapy or mutations conferring ADV resistance. In another study, van Bommel and colleagues also investigated efficacy of TDF in patients with prior failure or resistance to different NAs. Of the 131 eligible patients in this retrospective study, 121 patients (93%) were LAM-experienced and 110 (85%) were ADV-experienced. Most patients had previously received sequential therapy with LAM and ADV (56%) or combination therapy with LAM and ADV (22%) after HBV DNA breakthrough during monotherapy. Three patients showed no response to ETV treatment. Resistance analysis in 113 of the 131 patients revealed genotypic LAM and ADV resistance in 62% and 19% of patients, respectively. The overall cumulative proportion of patients achieving HBV DNA levels <400 copies/ml was 79% after a mean treatment duration of 23 months. Although LAM

resistance did not influence the antiviral efficacy of TDF, the presence of ADV resistance impaired TDF efficacy (100% versus 52% probability of HBV DNA <400 copies/ml, respectively). The apparent discrepancy between two studies may be explained by the different baseline HBV DNA titre. The mean baseline HBV DNA viral load in van Bommel's study was much higher compared to the baseline HBV DNA in the Patterson study (>8.0 $\log_{10}$ copies/mL and 6.0 $\log_{10}$ copies/ml, respectively). Due to the fact that both studies had relatively small numbers of patients, it is still yet to be determined how ADV-R impacts response rates to TDF.

Our phase IV study is a multi-centre, prospective study and is expected to enrol a number of subjects(up to 20%) with confirmed multi-drug resistance (although the exact proportion of total subjects is unknown). The purpose of our study is to evaluate the efficacy of TDF treatment in Chinese CHB patients following failure of multiple NAs. In addition, we will also explore the relationship of baseline factors and early HBV DNA suppression to long-term virological response. The efficacy of TDF in multi-drug resistant patients will be analysed separately. The data generated by this study could then be used to optimize the clinical application of TDF and provide new evidence for management of the HBV infections following failure of multiple NAs.

1.3. Benefit:Risk Assessment

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

1.3.1. Risk Assessment

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP)		
Renal toxicity	TDF is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of VIREAD	• Exclusion of CHB patients with creatinine clearance <70 ml/min • Monitor renal function every 12 weeks • Dosing interval adjustment of VIREAD is recommended in all patients with creatinine clearance below 50 ml/min. • All study drugs should be permanently discontinued in the event that repeat 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. (See section 6.3.9)
Bone events	Decreases in Bone mineral density (BMD) has been reported in adults and pediatric patients.	• Monitoring the serum calcium and phosphate every 12 weeks • In every regular visits, the information of bone related symptoms will be collected. • Assessment of BMD and related treatment should be considered by the investigator's judgement.
Lactic acidosis/severe hepatomegaly with steatosis and lipodystrophy	Lactic acidosis/ severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, in combination with other antiretrovirals.	• Guidelines for management of lactic acidosis are outlined in Appendix 1.
Drug-Drug Interaction Potential	Since tenofovir is primarily eliminated by the kidneys, coadministration of VIREAD with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir,aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs	• Estimated creatinine clearance will be assessed in all patients every 12 during treatment with TDF • TDF should be avoided with concurrent or recent use of a nephrotoxic agent according to the protocol(See section5.6.2)

Post-treatment hepatic flares	Discontinuation of anti-HBV therapy, including VIREAD, may be associated with severe acute exacerbations of hepatitis and must only take place under careful supervision.	• Patients who withdrawal from the investigational product during treatment period will be followed as per the original schedule. • No post-study medication is provided; the investigator is responsible for ensuring that consideration has been given to the post-study care of the patient's medical condition.

1.3.2. Benefit Assessment

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

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

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

TDF has been studied in an extensive clinical development program. The strength of evidence supporting the overall efficacy of TDF is provided by large-scale long term phase III clinical studies, which demonstrate effective reduction of HBV viral load and histologic improvement.

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

A total of one hundred fifty-two subjects initiating TDF therapy in published studies (i.e.global studies 0102, 0103, 0106, 0108, and 0121) harbored HBV with known resistance substitutions to HBV nucleos(t)ide analogue reverse transcriptase inhibitors: 14 with ADV resistance-associated substitutions (rtA181S/T/V and/or rtN236T), 135 with LAM resistance-associated substitutions (rtM204I/V), and 3 with both ADV and LAM resistance-associated substitutions. Following up to 240 weeks of TDF treatment, 11 of the 14 subjects with ADV-resistant HBV, 124 of the 135 subjects with LAM-resistant HBV, and 2 of the 3 subjects with both ADV- and LAM-resistant HBV achieved and maintained virologic suppression (HBV DNA less than 400 copies/mL). Three of the 5 subjects whose virus harbored both the rtA181T/V and rtN236T substitutions remained viremic.

1.3.3. Overall Benefit:Risk Conclusion

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

2. OBJECTIVE(S)

2.1. Primary Objective

- To assess the proportion of multiple NA treatment failure chronic hepatitis B patients that achieves HBV DNA<20 IU/mL at week 144 of TDF treatment

2.2. Secondary Objective

To assess the efficacy of TDF following failure of multiple NAs by evaluating serum HBV DNA, ALT and serological responses at week 48, 96 and 144.

- The proportion of subjects with serum HBV DNA <20 IU/ml at week 48 and 96.
- The $\log_{10}$ reduction in serum HBV DNA at Week 48, 96, and144.
- For HBeAg positive subjects: the proportion of subjects achieving HBeAg loss, HBeAg seroconversion or HBsAg loss and HBsAg seroconversion at Week 48, 96, and 144.
- For HBeAg negative subjects: the proportion of subjects achieving HBsAg loss and HBsAg seroconversion at Week 48, 96, and 144.
- The proportion of subjects with ALT normalization at Week 48, 96, and 144 in subjects who have abnormal ALT at baseline.
- Incidence of subjects who experience viral breakthrough (defined as ≥ 1 log increase in HBV DNA from nadir determined by two sequential HBV DNA measurements) up to week 144.

To assess the efficacy of TDF in a subgroup with confirmed multi-drug resistance.

- The proportion of subjects with multi-drug resistance mutations at baseline who achieve serum HBV DNA <20 IU/ml at week 48, 96, and 144.

To evaluate the safety of TDF following failure of multiple NAs.

To evaluate the impact of the baseline characteristics (viral titer, mutation patterns, etc.) and early HBV DNA suppression on response to TDF at week 144.

3. INVESTIGATIONAL PLAN

3.1. Study Design

This is a single-arm, open-label, multi-centre study to assess the efficacy of TDF in CHB patients following failure of multiple NAs.

The study will enrol 200 CHB patients following failure of multiple NAs. All the eligible study subjects will undergo safety and efficacy assessments every 12 weeks for a total of 14 visits.

Screen phase (Visit 1): About 230 subjects will be assessed for eligibility at a screening visit, with eligible patients returning for a baseline assessment after approximately 4 weeks. Multiple NAs treatment failure is defined as HBV DNA higher than 200 IU/ml after two or more different NA(s) treatments (i.e. initiate with mono-therapy followed by add-on/switch rescue therapy; at least 6 months continuous treatment for each regimen, total duration to be no less than 12 months). At visit 1 all the testing will be performed locally except for the HBV DNA quantification which will be measured by a central lab. The subjects will maintain their current treatment from screening visit to baseline visit. All subjects will provide written informed consent before screening.

Treatment phase (Visits 2 to 14): In the 144 weeks open label period, all enrolled subjects will receive open label TDF at a dose of 300mg orally once daily. At each visit, subjects will be questioned about adverse events, concurrent medications, and study drug accountability; take chemistry (liver function, blood glucose, creatine phosphokinase) test; take electrolytes (sodium, potassium, chloridum, phosphorus and calcium) test; take pregnancy test; take urinalysis test; take renal function(blood creatinine clearance, blood urea nitrogen and blood uric acid) test. Blood routine and International Normalized Ratio(INR) and HBV markers will be measured every 24 weeks. Abdominal ultrasound and serum alpha-fetoprotein test will be tested every 24 weeks. Serum samples will be collected and analyzed for HBV DNA levels in a central lab from visit 2 to 14.

At the visit 2, resistance surveillance of the HBV polymerase gene will be performed by direct sequencing for all subjects at baseline.

During the treatment phase, rescue therapy will be initiated in those study subjects that do not achieve satisfied response to TDF, defined as:

- Experiencing virological breakthrough (defined as HBV DNA level increase $\geqslant$1 $\log_{10}$ IU/ml above the treatment nadir, confirmed on an additional visit, OR
- Subjects have HBV DNA $\geqslant$200IU/ml at week 48 and afterwards have $\leq$ 1 $\log_{10}$ IU/ml decrease in HBV DNA at two consecutive tests, confirmed by a third visit(additional visit) at least one month apart.

Meanwhile, subjects to be received rescue therapy must have investigational product (IP) compliance > 80% in the last regular visits period (usually 12 weeks).

Another NA(s) without cross-resistance (eg. LAM, LdT, or ETV) will be added, the choice to be decided by the investigator.

Additional Visit: During the treatment phase, subjects who do not achieve satisfied response to TDF (eg.experience virological breakthrough or HBV DNA level does not continue to decline,) need to perform another HBV DNA test at an additional visit at least one month apart. Before rescue treatment initiation, serum sample should be collected for resistance testing.

During the treatment phase, patients that have evidence of HBsAg loss or seroconversion and HBeAg loss/seroconversion (for baseline HBeAg positive subjects) and HBV DNA < 20 IU/ml at any two consecutive visits at least 3 months apart will enter a non-treatment observational arm of the study, and will be followed up until the end of the study according to protocol-defined assessments and procedures. Study treatment should be stopped within 15 days of the result confirming that the subject meets the criteria.

If a patient in the non-treatment observational arm subsequently develops HBV DNA ≥20 IU/ml, HBsAg re-emerges, and ALT > 1.5 ULN, they will be eligible to be re-treated with TDF up to week 144 of the study. Once the treatment is restarted, the patients should be followed at least every 12 weeks as protocol defined and the data will be entered as the corresponding scheduled visit.

3.2. Discussion of Design

The study is designed to evaluate the efficacy of TDF treatment in CHB patients following failure of multiple NAs.

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

4.1. Number of Subjects

200 qualified subjects will be included in this study and receive the TDF 300mg QD.

	Subjects number
Screen	230
Enrolled	200
Completed/evaluable	170

4.2. Inclusion Criteria

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

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

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

1. Aged between 18–65years (inclusive).
2. Male or female; a female is eligible to enter and participate in this study if she is of:
   a. Non-childbearing potential (i.e., physiologically incapable of becoming pregnant, including any female who is post-menopausal); or,
   b. Child-bearing potential, has a negative urine pregnancy test at baseline, and agrees to one of the following methods for avoidance of pregnancy during the period of the study and until 30 days after last dose of study medication:
      - Oral contraceptive, either combined or progestogen alone.
      - Injectable progestogen.
      - Implants of levonorgestrel.
      - Oestrogenic vaginal ring.
      - Percutaneous contraceptive patches.
      - Intrauterine device (IUD) or intrauterine system (IUS) showing that the expected failure rate is less than 1% per year as stated in the IUD or IUS product label.
      - Has a male partner who is sterilised.
      - Double barrier method: condom and an occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/film /cream/suppository).
3. The ability to understand and sign a written informed consent prior to any study-related procedure and comply with the requirements of the study.
4. Positive HBsAg for more than 6 months, and anti-HBs negative.
5. Serum HBV DNA level ≥200 IU/ml at study screening (Use central lab results).
6. Experienced multiple NAs treatment failure which is defined as HBV DNA higher than 200 IU/ml after two or more different NA(s) treatments (i.e. initiate with mono-therapy, followed by add-on/switch rescue therapy; at least 6 months continuous treatment for each regimen, total duration to be no less than 12 months). In addition, subjects judged by the treating physician to have adhered to previous NA therapy.
7. Agreement not to participate in any other investigational trials or to undertake other HBV systemic antiviral or IFN regimens during participation in this study.

4.3. Exclusion Criteria

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

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

1. Hepatocellular carcinoma as evidenced by one of the following:
    - Suspicious foci on ultrasound or radiological examination.
    - Normal ultrasound but serum alpha-fetoprotein >20 ng/ml at screening.
2. Clinical signs of decompensated liver disease at baseline. These may include but are not limited to:
    - Total serum bilirubin >1.5 x ULN.
    - International Normalized Ratio >1.3
    - Serum albumin <32g/L.
    - History of clinical hepatic decompensation (e.g., ascites, variceal bleeding, or encephalopathy).
3. Creatinine clearance less than 70 ml/min.
4. Alanine aminotransferase >10 times ULN at screening or history of acute exacerbation leading to transient decompensation.
5. Haemoglobin <8g/dL, absolute neutrophil count <1.0 x 10^9/L, platelets <75 x 10^9/L.
6. Documented co-infection with hepatitis A (HAV), hepatitis C (HCV), hepatitis delta virus (HDV), hepatitis E virus (HEV) or HIV. For HCV co-infection, subjects who are anti-HCV positive and in whom HCV RNA is undetectable are considered to be not eligible for enrolment.
7. Evidence of active liver disease due to autoimmune hepatitis (antinuclear antibody titre >1:160)
8. Any serious or active medical or psychiatric illnesses other than hepatitis B which, in the opinion of the Investigator, would interfere with subject treatment, assessment or compliance with the protocol. This would include any uncontrolled clinically significant renal, cardiac, pulmonary, vascular, neurogenic, digestive, metabolic (diabetes, thyroid disorders, adrenal disease), immunodeficiency disorders, pathological fractures or cancer.
9. Active alcohol or drug abuse or history of alcohol or drug abuse considered by the Investigator to be sufficient to hinder compliance with treatment, participation in the study or interpretation of results.
10. A female who is breastfeeding or plan to breast.
11. Use of immunosuppressive therapy, immunomodulatory therapy (including PEG-IFN and short-acting interferon or thymosin α,), systemic cytotoxic agents within the previous 6 months prior to screening.
12. Planned for liver transplantation or previous liver transplantation.
13. Receipt of TDF within 6 months prior to screening.
14. Therapy with nephrotoxic drugs (e.g., aminoglycosides, amphotercin B, vancomycin, cidofovir, foscarnet, cis-platinum, pentamidine etc.) or competitors of renal excretion (e.g., probenecid) within 2 months prior to study screening or the expectation that subject will receive any of these during the course of the study.

15. History of hypersensitivity to nucleoside and/or nucleotide analogues and/or any component of study medication.
16. Inability to comply with study requirements as determined by the study Investigator.

4.4. Withdrawal Criteria

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

Subjects who temporarily interrupted treatment for <28 days were allowed to continue in the study. Subjects with treatment interruptions of ≥ 28 days were required to withdraw from the study.
A subject may voluntarily discontinue participation in this study at any time. The investigator also have the right to withdraw patients from treatment or the study in the event of intercurrent illness, adverse events, pregnancy, protocol violations, administrative reasons or other reasons at any time. The reason for withdrawal from the study must be recorded in the case report form (CRF). Subjects who have received at least one dose of study drug and permanently discontinue study drug for any reason, the investigator was required to perform the evaluations described in Table **1**.

4.5. Screening/ Run-in Failures

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

5. STUDY TREATMENTS

5.1. Investigational Product and Other Study Treatment

Tenofovir disoproxil fumarate (9-[(R)-2-[[bis[[(isopropoxy-carbonyl) oxy] methoxy] phosphinyl] methoxy] propyl] adenine fumarate (1:1)); GS4331-05) is an oral pro-drug

(bisPOC-PMPA) of TFV (PMPA), an acyclic nucleoside phosphonate (nucleotide) analogue of adenosine 5'-monophosphate. TDF has demonstrated antiviral activity against HBV and HIV and is indicated for use in combination with other antiretroviral agents in the treatment of HIV infection.

Tenofovir disoproxil fumarate tablets are white, almond-shaped, film-coated tablets containing 300 mg of TDF, debossed with "GILEAD" and "4331" on one side of the tablet. Each tablet contains the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, pregelatinised starch, croscarmellose sodium, and magnesium stearate. The tablets are film coated with Opadry II White 32K18425.

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

For subjects who do not achieve satisfied response to TDF will add another drug without cross resistant to TDF including LAM (Heptodin, GlaxoSmithKline, 100mg QD), ETV (Baraclude, Bristol-Myers Squibb,0.5mg QD) and LdT(Sebivo,Novartis,600mg QD). Investigator will make the decision for the drug selection.

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

5.1.1. Handling and Storage of Investigational Product

No preparation of investigational product is required at site.

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

Investigational product must be stored in a secure area under the appropriate physical conditions for the product at room temperature lower than 30° C. Access to and administration of the IP will be limited to the Investigator and authorised site staff. Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

5.1.2. Dosage and Administration

Subjects will be assigned to receive Tenofovir disoproxil fumarate (TDF) 300 mg once daily during the study period.

Subjects will be instructed to return unused study medication in the original container at each post-baseline study visit. The Investigator will be responsible for maintaining accurate records for all study drug and study drug bottles dispensed and returned. The inventory must be available for inspection by the study monitor. Study medication

supplies, including partially used or empty bottles, must be accounted for and the dispensing logs must be verified by the study monitor prior to destruction or return.

Dose reduction in the patients with renal insufficiency

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

Calculated Creatinine Clearance (ml/minute)[a]			Requiring Haemodialysis
≥ 50	30–49	10–29	
TDF 300 mg every 24 h	TDF 300 mg every 48 h	TDF 300 mg every 72 h	TDF 300 mg every 7 days or after a total of approximately 12 h of dialysis[b]
LAM tablets 100mg every 24h	Use of LAM tablets is prohibited		
ETV tablets 0.5mg every 24h	ETV tablets 0.5mg every 48h	ETV tablets 0.5mg every 72h	ETV tablets 0.5mg every 5 to 7 days[c]
LdT tablets 600mg every 24h	LdT tablets 600mg every 48h	LdT tablets 600mg every 72h	LdT tablets 600mg every 96h[d]

a. Calculated using ideal (lean) body weight.
b. Generally once weekly assuming three haemodialysis sessions a week of approximately 4 h duration. Medication should be administered following completion of dialysis.
c. If administered on a hemodialysis day, administer ETV after the hemodialysis session.
d. When administered on hemodialysis days, administer LdT after hemodialysis.

5.2. Treatment Assignment

This is an open label, single arm study.

5.3. Blinding

NA

5.4. Product Accountability

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

5.5. Treatment Compliance

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

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

5.6. Concomitant Medications and Non-Drug Therapies

5.6.1. Permitted Medications and Non-Drug Therapies

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

5.6.2. Prohibited Medications and Non-Drug Therapies

No other investigational drugs, immunosuppressive therapies, immunomodulatory therapies (including IFN or thymosin α), systemic cytotoxic agents, oral antiviral agents (e.g., didanosine, LAM, ADV, ETV, LdT, other medicinal products containing TDF, ganciclovir, famciclovir, FTC, DAPD, LFMAU, HBIg), agents containing glycyrrhizic acid(e.g., compound glycyrrhizin, compound ammonium glycyrhetate, diammonium glycyrrihizinate), agents containing bicyclol or bifendate will be permitted except for the drugs which are allowed in the protocol.

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

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

In the events mentioned in Section 6.3.1, medicines intended to improve/protect liver function will be allowed based on the Investigator's judgement after consulting with the GlaxoSmithKline medical monitor. All concomitant medication and reasons for their use must be entered into the eCRF. However, agents containing bicyclol, bifendate or schisandra will not be permitted in any situation.

5.7. Treatment after the End of the Study

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

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

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

5.8. Treatment of Study Drug Overdose

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

6. STUDY ASSESSMENTS AND PROCEDURES

Table 1 Time and Events Table

Procedures	Screening[1] (≤ 4 weeks prior to dosing)	Baseline (Day 0)	Treatment Period (Week)[2]												Additional Visit Subjects who do not achieve satisfied response to TDF	Early Withdrawal (Week off treatment)
			12w± 6days	24w± 6days	36w± 6days	48w± 6days	60w± 6days	72w± 6days	84w± 6days	96w± 6days	108w± 6days	120w± 6days	132w± 6days	144w± 6days		12w±6days
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14		
Written informed consent	√															
Subject demography[3]	√															
Medical history	√[4]	√[5]														
Inclusion/exclusion criteria	√															
Concomitant medication[6]		√	√	√	√	√	√	√	√	√	√	√	√	√		√
Physical examination[7]	√	√	√	√	√	√	√	√	√	√	√	√	√	√		√
Vital signs[8]	√	√	√	√	√	√	√	√	√	√	√	√	√	√		√
Adverse events		√	√	√	√	√	√	√	√	√	√	√	√	√		√
Serious adverse events		√	√	√	√	√	√	√	√	√	√	√	√	√		√
Laboratory assessments																
Haematology	√	√		√		√		√		√		√		√		√

Chemistry (liver function, blood glucose, creatine phosphokinase)	√	√	√	√	√	√	√	√	√	√	√	√	√	√		√
Pregnancy test[9]	√	√	√	√	√	√	√	√	√	√	√	√	√	√		√
HCV/HDV/HIV	√															
ANA	√															
B-ultrasound[11]	√			√		√		√		√		√		√		√
AFP	√			√		√		√		√		√		√		√
Urinalysis[12]	√	√	√	√	√	√	√	√	√	√	√	√	√	√		√
Electrolytes (Sodium, potassium, chloridum, phosphorus and calcium)	√	√	√	√	√	√	√	√	√	√	√	√	√	√		√
International Normalized Ratio(INR)	√	√		√		√		√		√		√		√		√
Renal function(Blood Creatinine clearance, blood urea nitrogen and blood uric acid)	√	√	√	√	√	√	√	√	√	√	√	√	√	√		√
HBV DNA[10,13]	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
HBeAg/Anti-HBe	√	√		√		√		√		√		√		√		√
HBsAg/Anti-HBs	√	√		√		√		√		√		√		√		√
Resistance surveillance[10,14]		√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Investigational product																
Study drug dispensed and reconciliation of drug dupply[15]		√	√	√	√	√	√	√	√	√	√	√	√	√		√
Serum and plasma storage	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

1 All results to be obtained before baseline visit.
2 No more than 6 days before or 6 days after the date scheduled based on the time from baseline visit not from the previous visit.
3 Demographic data includes birth date, gender and race
4 Medical history will include any acute and chronic medical conditions including prior surgery, information related to hepatitis B history, any current and prior HBV medications, and previous HBV-related procedures.
5 Update any new medical conditions and/or concomitant medications that have occurred since study screening.
6 Concomitant medications including traditional Chinese medicines and/or herbal remedies.
7 At screening, a complete physical examination will be performed. For all following indicated visits, a brief physical examination will be performed.
8 Including blood pressure, pulse, respiratory rate and temperature.
9 Urine pregnancy test will be performed at screening, baseline and every 3 months after dosing.
10 Tests will be performed at central lab.
11 B ultrasound examination include liver, pancreas, spleen, gall bladder and kidney.
12 Urinalysis: urine glucose, ketones, specific gravity, blood, pH and protein.
13 HBV DNA will be tested using Roche COBAS Taqman HBV test (LLD:20IU/ML).
14 Resistance surveillance will be performed at baseline or under the condition defined in protocol by direct sequencing of the polymerase gene. See Section 6.2.5
15 Each study visit: All study medication to be collected and reconciled.

6.1. Critical Baseline Assessments

Subjects will be screened within 4 weeks prior to enrolment to determine eligibility for participation in the study. The assessments to be performed are listed in Table **1**.

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

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

6.2. Efficacy

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

6.2.1. Serum/Plasma Storage

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

6.2.2. Virological Endpoint

To evaluate the proportion of subjects with HBV DNA< 20 IU/mL at week 48,96 ,144 and viral load change over time, HBV DNA level will be quantified using the sensitive HBV test in central lab at times outlined in Table **1**.

6.2.3. Biochemical Endpoint

To evaluate the ALT normalization at week 48, 96 and 144, ALT will be measured at times outlined in Table **1**.

6.2.4. Serological Endpoint

To evaluate the serological response at week 48, 96 and 144, HBeAg/anti-HBe and HBsAg/anti-HBs will be measured at times outlined in Table **1**.

6.2.5. Resistance Surveillance

Resistance surveillance including genotypic analysis of the HBV polymerase gene will be performed on stored serum by direct sequencing using a central laboratory in the following situations:

- All subjects at baseline.
- Subjects that do not achieve satisfied response to TDF(see section 3.1)
- Subjects remain HBV DNA detectable at week 48, 96, or their last visit in the study.

6.3. Safety

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

DEFINITIONS

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

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

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

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

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

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

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

Evidence of worsening HBV infection:

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

In the absence of evidence of worsening HBV infection:

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

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

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

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

6.3.1.2. Increased monitoring for On-Treatment ALT Elevation Alone

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

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

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

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

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

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

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

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

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

Please refer to Appendix 2 for the recommend method for managing lactic acidosis

6.3.2. Adverse Events

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

6.3.2.1. Definition of an AE

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Events meeting the definition of an AE include:

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

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

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

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

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

6.3.2.2. Definition of an SAE

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

a. Results in death

b. Is life-threatening

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

c. Requires hospitalisation or prolongation of existing hospitalisation

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

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

d. Results in disability/incapacity, or

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

e. Is a congenital anomaly/birth defect

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

6.3.2.3. Sentinel Events

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

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

6.3.3. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

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

6.3.4. Cardiovascular Events

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

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

This information should be recorded in the specific cardiovascular eCRF within one week of when the AE/SAE(s) are first reported.

6.3.5. Death Events

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

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

6.3.6. Pregnancy

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

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

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

6.3.7. Time Period and Frequency of Detecting AEs and SAEs

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

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

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to and including any follow up contact. All SAEs will be reported to GSK within 24 hours, as indicated in Section 6.3.8.

6.3.8. Method of Detecting AEs and SAEs

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

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

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

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

6.3.9. Prompt Reporting of Serious Adverse Events and Other Events to GlaxoSmithKline

Serious adverse events, pregnancies and liver function abnormalities meeting pre-defined criteria will be reported promptly by the Investigator to GlaxoSmithKline as described in the following table once the Investigator determines that the event meets the protocol definition for that event.

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

6.3.9.1. Regulatory Reporting Requirements for SAEs

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

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

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

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

6.3.10. Serum Creatinine Elevation

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

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

All study drugs should be permanently discontinued in the event that repeat testing of serum creatinine confirms >2.0 mg/dL. The subject should be followed weekly until the serum creatinine reaches within 0.3 mg/dL of the baseline value.

6.3.11. Other Safety Outcomes

Laboratory Assessments

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

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

7. DATA MANAGEMENT

For this study subject data will be collected using GlaxoSmithKline defined CRFs and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GlaxoSmithKline standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using MedDRA and an internal validated medication dictionary, GSK Drug. [An appropriate medical dictionary that covers all approved drugs in the region will be referenced.] Original CRFs will be retained by GlaxoSmithKline, while the Investigator will retain a copy. In all cases, subject initials

will not be collected or transmitted to GlaxoSmithKline, according to GlaxoSmithKline policy.

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

8.1. Hypotheses

No hypothesis is tested in this study.

8.2. Study Design Considerations

8.2.1. Sample Size Assumptions

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

The primary endpoint is the proportion of subjects with serum HBV DNA <20 IU/ml of TDF in multiple NAs treatment failure patients at Week 144.

To decide the number of subjects for analysis, some precision calculations have been performed. From our historical data, we hypothesize that the proportion of subjects with serum HBV DNA <20 IU/ml in multiple NAs treatment failure patients treated with TDF at Week 144 was 80%. A sample size of 170 patients will allow us to estimate the confidence interval of the incidence with a margin of error at ± 6% (range from 74-86%). Assuming a dropout rate of 15 per cent during a 144 week period, the number of patients required overall is estimated to be 200.

Formulae for the sample size estimation.

As Margin of error is: $\mathrm{E} = \mathrm{z}_c\sqrt{\frac{p(1-p)}{n}}$

So, the sample size required is: $\mathrm{N} = \mathrm{p}(1-p)\left(\frac{z_c}{e}\right)^2$

8.2.2. Sample Size Sensitivity

The sample size estimate is sensitive to the assumed proportions and the margin of error. The estimated sample size for several scenarios is presented in Table 2.

Table 2 Sample Size Sensitivity Table

Assumed proportion	Margin of error	95% confidence interval	Sample Size
75%	5%	(70%,80%)	288
75%	6%	(69%,81%)	200
75%	7%	(68%,82%)	147
80%	5%	(75%,85%)	246
80%	**6%**	**(74%,86%)**	**170**

80%	7%	(73%,87%)	125
85%	5%	(80%,90%)	196
85%	6%	(79%,91%)	136
85%	7%	(78%,92%)	100

8.2.3. Sample Size Re-estimation

No sample size re-estimation is planned.

8.3. Data Analysis Considerations

8.3.1. Analysis Populations

Three populations will be used in the analysis:

- modified Intent to Treat(mITT) Population

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

- Per Protocol (PP) population

The PP population will consist of subjects in the mITT population with the exception of major protocol violators.

- Safety Analysis (SA) population

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

All efficacy endpoints will be analysed using the mITT and PP population.

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

8.3.2. Analysis Data Sets

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

8.3.3. Treatment Comparisons

It is a single arm study and no comparison will be performed.

8.3.4. Interim Analysis

No interim analysis is planned for this study.

8.3.5. Key Elements of Analysis Plan

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

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

For the primary analysis of HBV DNA<20IU /ml at Week 144, data from non-completers will be considered to be “failures”.

8.3.5.1. Efficacy analyses

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

For the primary endpoint, descriptive analysis will be used to evaluate the efficacy of TDF in multiple NAs treatment failure patients.

Multiple-factor analysis will be used to assess the baseline variables that were significantly associated with HBV DNA negativity at week 144.

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

8.3.5.2. Safety analyses

Clinical safety observations will include: extent of exposure information, AEs, deaths, laboratory abnormalities and withdrawals from study.

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

Adverse events will be assigned preferred terms and categorized into body systems according to the MedDRA classification of the World Health Organisation terminology. The proportion of subjects who experienced AEs will be calculated by dividing the number of subjects who experienced the AE during the treatment period by the number of subjects evaluable for safety analysis. Adverse events will be summarised by treatment group, and by body system and event within each body system. The following summaries of AEs will be provided:

- All AEs.
- All treatment related AEs.
- All SAEs.
- All treatment related SAEs.
- All AEs leading to permanent discontinuation of study drug.
- All AEs leading to permanent discontinuation from the study.

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

9. STUDY CONDUCT CONSIDERATIONS

9.1. Posting of Information on Clinicaltrials.gov

Study information from this protocol will be posted on clinicaltrials.gov before enrolment of subjects begins.

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

Prior to initiation of a study site, GlaxoSmithKline will obtain approval from the appropriate regulatory agency to conduct the study in accordance with applicable country-specific regulatory requirements, including those required under a United States of America Investigational New Drug application.

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

- Ethics committee review and approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

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

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

9.3. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP and GlaxoSmithKline procedures, GlaxoSmithKline monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements and their responsibilities to satisfy regulatory, ethical and GlaxoSmithKline requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GlaxoSmithKline will monitor the study to ensure that the:

- Data are authentic, accurate and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP and all applicable regulatory requirements.

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

9.4. Quality Assurance

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

9.5. Study and Site Closure

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

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

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

9.6. Records Retention

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

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The Investigator must ensure that all reproductions are legible and are a true and accurate

copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The Investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

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

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

9.7. Provision of Study Results to Investigators, Posting to the Clinical Trials Register and Publication

Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the clinical study report. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GlaxoSmithKline site or other mutually agreeable location.

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

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

The results summary will be posted to the Clinical Study Register at the time of the first regulatory approval or within 12 months of any decision to terminate development. In addition, a manuscript will be submitted to a peer-reviewed journal for publication within 12 months of the first approval or within 12 months of any decision to terminate development. When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GlaxoSmithKline Clinical Study Register to supplement the results summary.

The results summary will be posted to the Clinical Study Register no later than 12 months after last subject last visit (LSLV) or sooner if required by legal agreement, local law or regulation. In addition, a manuscript will be submitted to a peer-reviewed journal for publication within 18 months of LSLV. When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GlaxoSmithKline Clinical Study Register to supplement the results summary.

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

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11. APPENDIX

11.1. Appendix 1: Estimated Creatinine Clearance Rate (CLcr) Formula and Estimated Glomerular Filtration Rate (GFR) Equation

Creatinine clearance rate(CLcr) using Cockcroft-Gault (CG) formula：

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

Scr=Serum Creatinine in mg/dl； for femal Multiplied by the coefficient of 0.85

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

Calculation Formula for IBW:

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

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

1Inch=2.54cm

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

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

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

11.2. Appendix 2: Lactic Acidosis Guidelines

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

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

Section A. Symptomatic Hyperlactatemia

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

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

AND

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

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

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

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

Section B. Asymptomatic Hyperlactatemia

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

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

Section C. Specimen Collection

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

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

Protocol Amendment Summary 1

Protocol Number:201215

Protocol Title：A multi-centre, single-arm, open-label study to evaluate the efficacy and safety of Tenofovir Disoproxil Fumarate(TDF) treatment in Chinese chronic hepatitis B (CHB) subjects following failure of multiple Nucleos(t)ide analogues(NAs)

Clinical Study Identifier: 201215

Sponsor Legal Registered Address:
GlaxoSmithKline (China) Investment Co., Ltd.

Protocol Amendment Summary 1

This protocol amendment summary applies to all sites in China.
Summary of amendment changes with rationale.

Section	Previous Text (Version: 1.0/16-May-2014)	Revised Text(Version: 2.0/27-May-2015)	Rationale
4.3. Exclusion Criteria Page 23	1.Hepatocellular carcinoma as evidenced by one of the following: • Suspicious foci on ultrasound or radiological examination. • Normal ultrasound but a history of rising serum alpha-fetoprotein and serum alpha-fetoprotein >20 ng/ml at screening.	1.Hepatocellular carcinoma as evidenced by one of the following: • Suspicious foci on ultrasound or radiological examination. • Normal ultrasound but ~~a history of rising serum alpha-fetoprotein and~~ serum alpha-fetoprotein >20 ng/ml at screening.	History of rising serum alpha-fetoprotein maybe due to chronic inflammation instead of carcinoma. And such history is not usually reliable but better to be regarded as only reference but not solid evidence for diagnosis.
Table 1 Time and Events Table Page 30		**Early Withdrawal** Add Pregnancy test, AFP, B ultrasound examination and reconciliation of drug supply	For safety reason.
6.2.5. Resistance Surveillance Page 32	• Subjects that do not achieve satisfied response to TDF(see section 3.2)	• Subjects that do not achieve satisfied response to TDF(see section 3.~~2~~1)	Correct the reference.
TABLE OF CONTENTS	11.1. Appendix 1: Estimated Glomerular Filtration Rate (GFR) Equation	11.1. Appendix 1: Estimated creatinine clearance rate (CLcr) using Cockcroft-Gault formula and Estimated Glomerular Filtration Rate (GFR) Equation	Consistence with the content of Appendix 11.1

11.1 Appendix 1 Page 49	**11.1 Appendix 1: Estimated Glomerular Filtration Rate (GFR) Equation** **GFR Equation:** Glomerular filtration rate is estimated by Chronic kidney disease (CKD)-Epidemiology Collaboration (EPI) equation: GFR(mL/min per 1.73 m2) = 141 × min(Scr/κ, 1)α × max(Scr/κ, 1)−1.209 × 0.993Age [× 1.018 if female] [× 1.159 if black], where Scr is serum creatinine (mg/dl), κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min is the minimum of Scr/κ or 1, and max is the maximum of Scr/κ or 1	**11.1 Appendix 1: Estimated Creatinine Clearance Rate (CLcr) Formula and Estimated Glomerular Filtration Rate (GFR) Equation** Creatinine clearance rate(CLcr) using Cockcroft-Gault (CG) formula： CLcr=[(140-Age)×Ideal Body Weight(kg)]/[72×Scr(mg/dl)] Scr=Serum Creatinine in mg/dl；for female Multiplied by the coefficient of 0.85 Note：If actual body weight(ABW) is lower than ideal body weight (IBW), ABW should be used. Calculation Formula for IBW: (Male)IBW=50kg+2.3kg×[Height(Inches)-60] (Female)IBW=45.5kg+2.3kg×[Height(Inches)-60] 1Inch=2.54cm **GFR Equation:** Glomerular filtration rate is estimated by Chronic kidney disease (CKD)-Epidemiology Collaboration (EPI) equation: GFR(mL/min per 1.73 m2) = 141 × min(Scr/κ, 1)α × max(Scr/κ, 1)−1.209 × 0.993Age [× 1.018 if female] [× 1.159 if black], where Scr is serum creatinine (mg/dl), κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min is the minimum of Scr/κ or 1, and max is the maximum of Scr/κ or 1	CLcr is a little different from GRF. In the protocol, the renal insufficiency was defined by serum creatinine clearance. So we provide the CLcr calculation (Cockcroft-Gault, CG) formula.

<table>
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<td>6.3.9. Prompt Reporting of Serious Adverse Events and Other Events to GlaxoSmithKline
Page 40</td>
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<table>
<tr><th></th><th colspan="2">Initial Reports</th><th colspan="2">Follow-up Information on a Previous Report</th></tr>
<tr><th>Type of Event</th><th>Time Frame</th><th>Documents</th><th>Time Frame</th><th>Documents</th></tr>
<tr><td>All SAEs</td><td>24 h</td><td>“SAE” data collection tool</td><td>24 h</td><td>Updated “SAE” data collection tool</td></tr>
<tr><td>Pregnancy</td><td>2 Weeks</td><td>Pregnancy Notification Form</td><td>2 Weeks</td><td>Pregnancy Follow-up Form</td></tr>
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</td>
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<tr><th></th><th colspan="2">Initial Reports</th><th colspan="2">Follow-up Information on a Previous Report</th></tr>
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<tr><td>Pregnancy</td><td>2 Weeks</td><td>Pregnancy Notification Form</td><td>2 Weeks</td><td>Pregnancy Follow-up Form</td></tr>
<tr><td>Adverse Drug Reaction (ADR)</td><td>5 calendar days</td><td>ADR Form</td><td>5 calendar days</td><td>ADR Follow-up Form</td></tr>
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<td>To align with new local pharmacovigilance requirements.</td>
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<td>SPONSOR INFORMATION PAGE
Page 3</td>
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PPD
Medical Affairs Physician
Medical Affairs, GlaxoSmithKline (China) Investment Co., Ltd.
Telephone: PPD
Cell phone:</td>
<td>Sponsor Medical Monitor Contact Information:

PPD
Medical Affairs Manager
Medical Affairs, GlaxoSmithKline (China) Investment Co., Ltd.
Telephone: PPD</td>
<td>Role transition.</td>
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Page 3</td>
<td>Sponsor Serious Adverse Events (SAE) Contact Information:
GSK China PV Department
Fax: PPD
Email: PPD</td>
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GSK China PV Department
Fax: PPD
Email: PPD
PPD</td>
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Protocol Amendment Summary 2

Protocol Number:201215

Protocol Title：A multi-centre, single-arm, open-label study to evaluate the efficacy and safety of Tenofovir Disoproxil Fumarate(TDF) treatment in Chinese chronic hepatitis B (CHB) subjects following failure of multiple Nucleos(t)ide analogues(NAs)

Clinical Study Identifier: 201215

Sponsor Legal Registered Address:
GlaxoSmithKline (China) Investment Co., Ltd.

Protocol Amendment Summary 2

This protocol amendment summary applies to all sites in China.
Summary of amendment changes with rationale.

Section	Previous Text (Version: 2.0/27-May-2015)	Revised Text(Version: 2.1/21-Oct-2015)	Rationale
3.1. Study Design Page 11	Abdominal ultrasound and serum alpha-fetoprotein test will be tested every 48 weeks.	Abdominal ultrasound and serum alpha-fetoprotein test will be tested every ~~48~~ 24 weeks.	According to the protocol, abdominal ultrasound and serum alpha-fetoprotein test will be tested every 48 weeks. But the guidelines for the treatment of persons with Chronic Hepatitis B recommend: Routine surveillance for HCC with abdominal ultrasound and alpha-fetoprotein testing every six months. For safety reason, we decided to adjust the abdominal ultrasound and alpha-fetoprotein testing every 24weeks.
3.1. Study Design Page 20	Abdominal ultrasound and serum alpha-fetoprotein test will be tested every 48 weeks.	Abdominal ultrasound and serum alpha-fetoprotein test will be tested every ~~48~~ 24 weeks.	
Table 1 Time and Events Table Page 30		Add AFP, B ultrasound examination at 24w, 72w and 120w.	