Statistical Analysis Plan

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)

Sponsor: GlaxoSmithKline (China) Investment Co., Ltd.

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LIST OF ABBREVIATIONS

Abbreviation	Description of Abbreviation
ADV	Adefovir
AE	Adverse event
ALT	Alanine aminotransferase
CFDA	China Food and Drug Administration
CHB	Chronic hepatitis B
95% CI	95% Confidence Interval
DNA	Deoxyribonucleic acid
ETV	Entecavir
eCRF	Electronic case report form
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B s antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
ICF	Informed consent form
INR	International Normalized Ratio
LAM	Lamivudine
LdT	Telbivudine
mITT	Modified Intent-to-treat (population)
NAs	Nucleos(t)ide analogues
OR	Odds Ratio
PP	Per protocol (population)

Abbreviation	Description of Abbreviation
PT	Prothrombin time
SA	Safety analysis (population)
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
TDF	Tenofovir disoproxil fumarate
TEAE	Treatment-emergent adverse events

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1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures to be used for analyzing and reporting the efficacy and safety for study 201215. It should be used in conjunction with the following documents: study protocol, case report form, and shells for tables, listings and graphs. This SAP is based on the final protocol (Version 2.1, OCT 21, 2015).

2. STUDY OBJECTIVE

2.1 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.

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.
- 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.

3. STUDY DESIGN

3.1 Overall 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 enroll 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, bloodurea 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.

No formal interim analysis was planned. Key analysis outputs will be provided annually with the 48-week and 96-week cutoff data for publication purpose. No adjustment for multiplicity will be made for the analysis in different period.

3.2 Sample size

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.

4. ANALYSIS SET

- 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 who have no major protocol deviations that impact the safety and efficacy evaluation.

- 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 analyzed using the mITT and PP population. All safety endpoints will be analyzed using the SA population according to the actual treatment they received.

5. STUDY ENDPONITS

5.1 Primary endpoint

The primary endpoint is the proportion of subjects with serum HBV DNA <20 IU/mL at week 144.

5.2 Secondary endpoints

- The proportion of subjects with virological response (serum HBV DNA <20 IU/mL and serum HBV DNA <69 IU/mL, respectively) at week 48 and 96.
- The proportion of subjects with virological response (serum HBV DNA <20 IU/mL and serum HBV DNA <69 IU/mL, respectively) at week 48, 96 and 144 in the subgroup with confirmed multi-drug resistance at baseline.
- The $\log_{10}$ reduction in serum HBV DNA at Week 48, 96 and 144.
- 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.

5.3 Exploratory endpoints

- Evaluate the impact of the baseline host and virological characteristics (HBV DNA level, resistance type, HBeAg status, prior treatment with ADV, prior treatment with ETV, prior treatment with IFN, overall duration of prior NA treatment, compliance, cirrhosis, ALT level, age, gender, BMI, AST, r-GT, platelets, INR, total bilirubin, albumin, etc.) and early HBV DNA suppression on response to TDF at week 144.
- Time to virological response to TDF (defined as HBV DNA <20 IU/mL) for overall and subjects with different patterns of mutation.

6. STATISTICAL CONSIDERATIONS

6.1 General rule

All analysis will be conducted using SAS® Version 9.2 or higher (SAS Institute, Cary, NC). For Continuous variables, descriptive statistics will be presented as the mean, standard deviation, minimum, median, maximum, and the number of observations. For categorical variables, the number and percentage for each of the categories will be presented. Counts that are zero will be displayed as “0”. Unless otherwise specified, the denominator for all percentages will be based on the number of subjects in the analysis set of that treatment group. Baseline is defined as the last assessment before administration of the study drug.

6.2 Data handling

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 (<20 IU/mL) or results of “not detected” will be analyzed as being the value of the lower limit of quantification, which is 20 IU/mL. For the primary endpoint analyses and other analyses of response (success, failure) at a particular time point, a discontinued subject was considered as "failure" for all efficacy responses post termination. And the missing values of categorical efficacy endpoints (success, failure) will be imputed as "failure" at the analysis visits.

7. STATISTICAL ANALYSIS

7.1 Subject screening, disposition and protocol deviations

The screening failure subjects and the reasons for screening failure will be summarized by the numbers and percentages. The percentages are based on the number of screening failure subjects.

The disposition of subjects will be summarized, including the numbers and percentages of subjects for the following categories: all enrolled subjects, subjects completed the study, subjects early discontinued from the study, subjects in the modified intent to treat population, subjects in the per-protocol population, and subjects in the safety analysis population. All percentages are based on the

number of all enrolled subjects.

The primary reason for subject premature discontinuation from study will also be summarized. The reasons for discontinuation will include voluntarily discontinue participation, lost to follow-up, lack of efficacy, subjects with treatment interruptions of ≥28 consecutive days, adverse event, intercurrent illness, protocol violations, pregnancy, and other reason. A listing will be provided.

Protocol deviations will be summarized and listed for mITT population. Subject counts and percentages will be displayed by the following deviation categories:

- Poor compliance, defined as taking < 80% or > 120% of the required number of tablets
- Take the prohibited medication specified in protocol during the treatment period
- With actual visit day being more than 14 days deviated from the schedule visit day
- Had other significant protocol violations that were thought to affect the efficacy evaluation

Major protocol deviations which results in the exclusion of the subject from PP population will be discussed, determined, and documented by study team before final database lock.

7.2 Subject Information

7.2.1 Demographics and baseline characteristics

Demographic and baseline characteristics for subjects include subject age, sex (Male/Female), race (Asian/Others), weight, height, BMI, systolic blood pressure, diastolic blood pressure, pulse, respiratory, body temperature, alcohol abuse, drug abuse, history of medication hypersensitivity, cirrhosis and resistance mutations. Percentages for categorical data will be calculated based on the number of subjects in the analysis set of that treatment group. Descriptive statistics will be used for continuous data. A listing of demographics and baseline characteristics will also be provided. Age will be calculated by

Age (Year) = Year of Informed Consent Date - Year of Birth + 1

7.2.2 Medical history

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.

Medical history will be listed by system organ class and preferred term coded in MedDRA 17.0.

The previous treatment of chronic hepatitis B will also be summarized by drug categories (LAM, LdT, ETV, ADV, IFN) with drug duration >6 months. Drugs with duration ≤6 months will not be counted.

7.2.3 Inclusion and exclusion criteria

Subjects must meet all specified inclusion and none of the exclusion criteria in order to be eligible to participate in the study. Inclusion and exclusion criteria information will be presented in the listing.

7.3 Treatments and medications

7.3.1 Prior and concomitant medication

Prior medication: all the drugs taken by the subjects prior to the first dose date of TDF.

Concomitant medication: all the drugs taken by the subjects from the first dose date of TDF to completion of the study.

If medication start date is on or after the first dose date of TDF, then medication will be summarized as concomitant medication regardless of whether medication end date is missing or not. If medication end date is before the first dose date of TDF, then medication will be summarized as prior medication regardless of whether medication start date is missing or not. Note that medication that started prior to the first dose date of TDF and continued after dosing will be summarized as

prior medication and separately as concomitant medication.

All medications will be coded according to WHO drug dictionary (Version: WHODDE 2016Q3) and Anatomical Therapeutic Chemical (ATC) coding.

Medication class, medication name, indications, total daily dose, unit, route, start date and end date will be presented in the listing.

7.3.2 Non-drug therapies

For subjects who receive any non-drug therapy will be recorded on eCRF. Non-drug therapy information including therapy details, start and end date, and the reason for use will be presented in the listing.

7.3.3 Treatment compliance

The duration in days of study drug exposure from first dose date to the last dose date will be summarized by descriptive statistics.

The duration of the drug exposure (day) = Last dose date - First dose date + 1

Treatment compliance, defined as actual taken amount divided by expected taken amount per protocol times 100, will be summarized by descriptive statistics for mITT. The formulas for calculating the treatment compliance are as follows:

Treatment Compliance (%) = Actual taken amount×100 / Expected taken amount

Drug accountability information including date (dispensed or returned), dispensed amount, returned amount, lost amount, expected taken amount, actual taken amount, missing amount, and treatment compliance will be presented in the listing.

7.4 Efficacy analysis

This analysis will be conducted in mITT and PP population.

7.4.1 Analysis of primary variable

The primary efficacy endpoint for this study is the proportion of subjects with serum HBV DNA <20 IU/mL at week 144. Primary efficacy endpoints are evaluated by count and percentage, and two-sided 95% CI will also be provided based on normal approximation and continuity correction.

7.4.2 Analysis of secondary variables

Analysis for secondary variable of the $\log_{10}$ reduction in serum HBV DNA by patterns of mutation and overall per visit will be summarized by descriptive statistics as the mean, standard deviation, two-sided 95%CI, minimum, median, maximum, and the number of observations. The patterns of mutation will be summarized by 2 categories. One includes wild-type, LAM-R, ADV-R and ETV-R. The other one includes wild-type, ADV-R single mutation (A181T/V; N236T), ADV-R double mutation (A181T/V+N236T)) and other mutation. Nominal P values between different patterns of mutation will be provided at week 24, 48, 96, 144. Individual HBV DNA levels of subjects with genotypic resistance to ADV (A181T/V+N236T) will be summarized over time by figure.

In addition, the number and percentage will be presented respectively for secondary variables including:

- The proportion of subjects with virological response (serum HBV DNA <20 IU/mL and serum HBV DNA <69 IU/mL, separately) by visit
- The proportion of subjects with virological response (serum HBV DNA <20 IU/mL and serum HBV DNA <69 IU/mL, separately) by visit in the subgroup with confirmed multi-drug resistance at baseline
- The proportion of subjects with virological response(serum HBV DNA <20 IU/mL and serum HBV DNA <69 IU/mL, separately) by visit in the subgroup with medical history (previously exposed to ADV >6 months or not, ETV >6 months or not) (Subjects with ETV >6 months will be separated as ETV-R and non ETV-R)
- The proportion of subjects achieving HBeAg loss, HBeAg seroconversion, HBsAg loss and

HBsAg seroconversion at Week 48, 96 and 144 for HBeAg positive subjects

- The proportion of subjects achieving HBsAg loss and HBsAg seroconversion at Week 48, 96 and 144 for HBeAg negative subjects
- The proportion of subjects with ALT normalization at week 48, 96 and 144 in subjects who have abnormal ALT at baseline
- The incidence of subjects who experience viral breakthrough (defined as 1 log increase in HBV DNA from nadir determined by two sequential HBV DNA measurements) overall and by each visit.
- The proportion of subject with unsatisfactory response, overall and by each visit. Unsatisfactory response is defined as subjects who have HBV DNA ≥200 IU/mL at week 48 and afterwards have ≤1 log10 IU/mL decrease in HBV DNA at two consecutive tests, confirmed by a third visit (additional visit) at least one month apart
- Mutation pattern change from baseline at week 48, 96, 144

Also, two-sided 95% CI will be calculated for each percentage.

7.4.3 Exploratory analysis

The exploratory analysis is to evaluate the impact of the baseline host and virological characteristics (viral titer, mutation patterns, etc.) and early HBV DNA suppression on response to TDF at week 144. Multiple-factor logistic regression analysis will be used to assess the baseline variables that were significantly associated with HBV DNA negativity at week 144. The factors includeHBV DNA level, resistance type, HBeAg status, prior treatment with ADV, prior treatment with ETV, overall duration of prior NA treatment, compliance, cirrhosis, ALT level, age, gender, BMI, AST, r-GT, platelets, INR, total bilirubin, albumin, etc. The OR and 95% CI of each factor will be provided in the table.

Time to virological response to TDF defined as HBV DNA <20 IU/mL, as a time-to-event variable, will be analyzed by Kaplan-Meier curve for overall and subjects with different patterns of mutation. Log-rank test will be performed separately for each of the following factors: HBV DNA level, HBeAg status, prior treatment with ADV, resistance type (ADV or not), cirrhosis, compliance and

patterns of mutation. Cox regression model will be conducted to include all above factors and additional factors: prior treatment with IFN, ALT level, age, and gender.

In addition, three listings will be provided for

- The ALT for patients with any HBeAg Loss, HBeAg Seroconversion, HBsAg Loss and HBsAg Seroconversion over time
- The relationship between HBV DNA and medical history for previously exposed to NAs >6 months
- The HBV DNA for patients with virological breakthrough (defined as 1 log increase in HBV DNA from nadir determined by two sequential HBV DNA measurements), and
- The HBV DNA for patients with unsatisfactory response (defined as subjects who have HBV DNA ≥200 IU/mL at week 48 and afterwards have ≤ 1 log10 IU/mL decrease in HBV DNA at two consecutive tests, confirmed by a third visit (additional visit) at least one month apart).

7.5 Safety analysis

Safety endpoints include adverse events, vital signs, laboratory assessments, physical examination, and B-ultrasound. This analysis will be conducted in SA population.

7.5.1 Adverse events

AEs will be classified into standardized medical terminology from the verbatim description (investigator term) using the Medical Dictionary for Regulatory Activities (MedDRA). Verbatim description and MedDRA level terms, including the system organ class, preferred term, and lower level term, for all AEs will be presented in the data listings. In table summaries, the denominator for percentages will be the number of subjects in the treatment group within the safety analysis population. AEs are coded according to (MedDRA) version 17.0.

TEAE is defined as AE occurred on or after the first dose date of study drug. TEAEs will be presented by system organ class and preferred term. The subject level incidence is only one occurrence of a preferred term/system organ class per subject. If a subject reports multiple AEs

under the same preferred term, then the count of subject level incidences for that preferred term will only be incremented by one. If a subject reports multiple AEs under the same system organ class, then the count of subject level incidences for that system organ class will also only be incremented by one. System organ classes will be presented in descending order of total frequency of subject level occurrences. Within each system organ class, preferred terms are presented in the same descending order of total frequency of subject level occurrences.

The following summaries of AEs will be provided:

- All AEs.
- All TEAEs.
- All treatment related TEAEs.
- All serious TEAEs.
- All non-serious TEAEs.
- All treatment related serious TEAEs.
- All TEAEs leading to permanent discontinuation of study drug.
- All TEAEs leading to permanent discontinuation from the study.
- All TEAEs that caused a change in dose or temporary interruption of study drug.

7.5.2 Vital sign

Vital signs including systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse (beats/minute), respiratory rate (breaths/minute), body temperature (℃) and weight (kg) will be descriptively summarized by clinic visit. Changes from Baseline to each individual post-Baseline visit will also be presented.

7.5.3 Laboratory assessments

Results for clinical laboratory evaluations including: hematology, blood chemistry, blood coagulation, hepatitis B five items, pregnancy test, urinalysis and alpha fetoprotein (AFP) will be conducted at various visits as specified in the Study Schedule of the protocol. Descriptive statistics will be used for quantitative variables. For qualitative variables, the number and percentage for each

parameter will be presented.

Treatment-emergent grade 3 or grade 4 laboratory abnormalities are defined as values that increase at least one grade from baseline and get Grade 3 (severe) or 4 (potentially life threatening) at any post-baseline value. If the relevant baseline laboratory data are missing, then the screening laboratory result is used; if it is missing then any Grade 3 or 4 post-baseline values are considered treatment emergent.

The following summaries (number and percentage of subjects) of treatment-emergent laboratory abnormalities will be provided:

- Treatment-emergent Grade 3 or Grade 4 laboratory abnormalities
- Incidence of on-treatment hepatitis exacerbation defined as bilirubin ≥ 2 times ULN or albumin ≤ 3 g/dL or ALT ≥ 20 times ULN (and ≥ 2 times baseline)
- Confirmed (defined as two consecutive visits) increase in serum creatinine of 0.5 mg/dL above baseline
- Calculated creatinine clearance < 50 mL/min

7.5.4 Physical examination

The result of physical examination will be categorized as “Not Done”, “Normal” or “Abnormal”. The detailed information including date of physical examination and the result of body system for each subject will be presented in the listing.

7.5.5 B-ultrasound

B-ultrasound examination include sliver, pancreas, spleen, gall bladder and kidney. It is assessed based on 3-level system (normal, abnormal not clinically significant, or abnormal clinically significant). All B-ultrasound data will be presented in the listing.

8. APPENDIX

8.1 Description of Inclusion/Exclusion Criteria

Seq No	Type	Description
1	Inclusion	Aged between 18–65years (inclusive).
2	Inclusion	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	Inclusion	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	Inclusion	Positive HBsAg for more than 6 months, and anti-HBs negative.
5	Inclusion	Serum HBV DNA level ≥200 IU/ml at study screening (Use central lab results).
6	Inclusion	Experienced multiple NAs treatment failure which is defined as HBV DNA greater than 200 IU/ml after at least two NAs treatment (at least 6 months continuous treatment for each NA(s), total duration is no less than 12 months). In addition, subjects judged by the treating physician to have adhered to previous NA therapy.
7	Inclusion	Agreement not to participate in any other investigational trials or to undertake other HBV systemic antiviral or IFN regimens during participation in this study.
1	Exclusion	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	Exclusion	Clinical signs of decompensated liver disease at baseline. These may include but are not limited to: 1) Total serum bilirubin >1.5 x ULN. 2) International Normalized Ratio >1.3 3) Serum albumin <32g/L. 4) History of clinical hepatic decompensation (e.g., ascites, variceal bleeding, or encephalopathy).

Seq No	Type	Description
3	Exclusion	Creatinine clearance less than 70 ml/min.
4	Exclusion	Alanine aminotransferase >10 times ULN at screening or history of acute exacerbation leading to transient decompensation.
5	Exclusion	Haemoglobin <8g/dL, absolute neutrophil count <1.0 x 109/L, platelets <75 x 109/L.
6	Exclusion	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	Exclusion	Evidence of active liver disease due to autoimmune hepatitis (antinuclear antibody titre >1:160)
8	Exclusion	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	Exclusion	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 clinical significance of results.
10	Exclusion	A female who is breastfeeding or plan to breast.
11	Exclusion	Use of immunosuppressive therapy, immunomodulatory therapy (including PEG-IFN and short-acting interferon or thymosin ,), systemic cytotoxic agents within the previous 6 months prior to screening.
12	Exclusion	Planned for liver transplantation or previous liver transplantation.
13	Exclusion	Receipt of TDF within 6 months prior to screening.
14	Exclusion	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	Exclusion	History of hypersensitivity to nucleoside and/or nucleotide analogues and/or any component of study medication.
16	Exclusion	Inability to comply with study requirements as determined by the study Investigator.

8.2 Treatment-emergent Laboratory Abnormalities Grading Scale

Hematology				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemogolobin	10.0 to 10.9 g/dL 100 to 109 g/L OR Any decrease from baseline 2.5 to < 3.5 g/dL 25 to < 35 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L OR Any decrease from baseline 3.5 to < 4.5 g/dL 35 to < 45 g/L	7.0 to < 9.0 g/dL 70 to < 90 g/L OR Any decrease from baseline ≥ 4.5 g/dL ≥ 45 g/L	< 7.0 g/dL < 70 g/L
Neutrophil (ANC)	1000 to 1300 /mm^3 1.00 to 1.30 GI/L	750 to < 1000 /mm^3 0.75 to < 1.00 GI/L	500 to < 750 /mm^3 0.50 to < 0.75 GI/L	< 500 /mm^3 < 0.50 GI/L
Lymphocyte	600 to 650 /mm^3 0.60 to 0.65 GI/L	500 to < 600 /mm^3 0.50 to < 0.60 GI/L	350 to < 500 /mm^3 0.35 to < 0.50 GI/L	< 350 /mm^3 < 0.35 GI/L
Platelets	100,000 to < 125,000 /mm^3 100 to < 125 GI/L	50,000 to < 100,000 /mm^3 50 to < 100 GI/L	25,000 to < 50,000 /mm^3 25 to < 50 GI/L	< 25,000 /mm^3 < 25 GI/L
White Blood Cell	2000 to 2500 /mm^3 2.00 to 2.50 GI/L	1500 to < 2000 /mm^3 1.50 to < 2.00 GI/L	1000 to < 1500 /mm^3 1.00 to < 1.50 GI/L	< 1000 /mm^3 < 1.00 GI/L
Blood Chemistry				
ALT (SGOT)	1.25 to 2.50×ULN	> 2.50 to 5.00×ULN	> 5.00 to 10.0×ULN	> 10.0×ULN
AST (SGPT)	1.25 to 2.50×ULN	> 2.50 to 5.00×ULN	> 5.00 to 10.0×ULN	> 10.0×ULN
Alkaline Phosphatase	1.25 to 2.50×ULN	> 2.50 to 5.00×ULN	> 5.00 to 10.0×ULN	> 10.0×ULN
Albumin	3.0 g/dL to < LLN 30 g/L to < LLN	2.0 to < 3.0 g/dL 20 to < 30 g/L	< 2.0 g/dL < 20 g/L	NA
Hyponatremia	130 to 135 mEq/L 130 to 135 mmol/L	125 to < 130 mEq/L 125 to < 130 mmol/L	121 to < 125 mEq/L 121 to < 125 mmol/L	< 121 mEq/L < 121 mmol/L
Hypernatremia	146 to 150 mEq/L 146 to 150 mmol/L	> 150 to 154 mEq/L > 150 to 154 mmol/L	> 154 to 159 mEq/L > 154 to 159 mmol/L	> 159 mEq/L > 159 mmol/L
Hypokalemia	3.0 to 3.4 mEq/L 3.0 to 3.4 mmol/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L	< 2.0 mEq/L < 2.0 mmol/L
Hyperkalemia	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Hypoglycemia (Fasting)	55 to 64 mg/dL 3.03 to 3.58 mmol/L	40 to < 55 mg/dL 2.20 to < 3.03 mmol/L	30 to < 40 mg/dL 1.64 to < 2.20 mmol/L	< 30 mg/dL < 1.64 mmol/L
Calcium (Increase)	2.65 – 2.88 mmol/L	2.89 – 3.13 mmol/L	3.14 – 3.38 mmol/L	> 3.38 mmol/L
Calcium (Decrease)	1.95 – 2.10 mmol/L	1.75 – 1.94 mmol/L	1.53 – 1.74 mmol/L	< 1.53 mmol/L
Phosphorus (Decrease)	NA	2.0 to < 2.5 mg/dL 0.63 to < 0.80 mmol/L	1.0 to < 2.0 mg/dL 0.31 to < 0.630 mmol/L	< 1.0 mg/dL < 0.31mmol/L
Hyperbilirubinemia	> 1.0 to 1.5×ULN	> 1.5 to 2.5×ULN	> 2.5 to 5.0×ULN	> 5.0×ULN

Blood Urea Nitrogen	1.25 to 2.50×ULN	> 2.50 to 5.00×ULN	> 5.00 to 10.0×ULN	> 10.0×ULN
Serum Creatinine	> 1.5 to 2.0 mg/dL > 133 to 177 µmol/L	> 2.0 to 3.0 mg/dL > 177 to 265 µmol/L	> 3.0 to 6.0 mg/dL > 265 to 530 µmol/L	> 6.0 mg/dL > 530 µmol/L
Creatinine Phosphokinase	3.0 to < 6.0×ULN	6.0 to < 10.0×ULN	10.0 to < 20.0×ULN	≥ 20.0×ULN
Blood Coagulation				
Prothrombin Time	> 1.00 to 1.25×ULN	> 1.25 to 1.50×ULN	> 1.50 to 3.00×ULN	> 3.00×ULN

8.3 Examples for Mutation Changes

#	Senario	Examples				Caregory Code ***
		Result		Comments		
		Baseline	**Week 48**	**Baseline**	**Week 48**	
1	No change for “Result” and “comments” at all visits	W	W			NCW
2	No change for “Result” and “comments” at all visits	W	W	A100C	A100C	
3	No change for “Result” and “comments” at all visits	Mutant A* + Mutant B*	Mutant A* + Mutant B*			NCC
4	No change for “Result” and “comments” at all visits	Mutant* A	Mutant* A	T200C, C300D	T200C, C300D	
5	“Result” no change, but with emerging “Comments”	W	W		A100C	CNCM
6	“Result” no change, but with “Comments” changed	W	W	A100C		
7	“Result” no change, but with emerging “Comments”	Mutant* A	Mutant* A		T200C/A	
8	“Result” no change, but with “Comments” changed	Mutant* A	Mutant* A	T200C	T200C, A201C	
9	“Result” changed to “Mutant”	W	Mutant*			CCM
10	“Result” changed to “Mutant” with emerging “Comments”	W	Mutant*		T200C	
11	“Result” changed to “Mutant” with “Comments” changed**	W	Mutant A* + Mutant B*	A100C	T200C	
12	“Result” changed to other types of “Mutant”	Mutant* A	Mutant* B			
13	“Result” changed with “Comments” changed**	Mutant* A	Mutant* B	T200C	T200C, A250C	
14	“Result” changed with “Comments” changed**	Mutant* A	W	T200C		

15	“Result” is “UN”	W	UN/IN			UN
16	“Result” is “UN”	UN	W/UN			
17	“Result” is “UN”	W	UN	L220I, A222T		
18	“Result” is “UN”	V214A/V	UN	L220I, A222T		

* Mutant: mutations other than ‘Wild Type’, ‘UN’ or ‘IN’

** if one subject has both “confirmed mutation” and “non-confirmed mutation”, “confirmed mutation” will be set as the “category”.

*** NCW: No changes from baseline – Wild type at baseline

NCC: No changes from baseline – Confirmed NA-related mutation at baseline

CCM: Mutation Changes from baseline – Change from baseline about confirmed NA-related mutation

CNCM: Mutation Changes from baseline – Change from baseline about non-confirmed mutation

UN: Invalid sequence or DNA sequence undetectable

9. MOCK TABLES, LISTINGS AND GRAPHS (TLGS)

Mock TLGs will be provided in a separate document.

Identifier	Output Title	Annual Report
Table 1.1	Disposition	X
Table 1.2	Major Protocol Deviations - mITT	X
Table 2.1.1	Demographics - mITT	
Table 2.1.2	Baseline Characteristics - mITT	
Table 2.1.3	Resistance Mutations at Baseline - mITT	
Table 2.2	Previous Treatment of Chronic Hepatitis B - mITT	
Table 3.1	Compliance and Duration of the Study Drug - mITT	X
Table 4.1.1	The Proportion of Subjects with Serum HBV DNA <20 IU/mL at Week 144 - mITT	
Table 4.1.2	The Proportion of Subjects with Serum HBV DNA <20 IU/mL at Week 144 - PP	
Table 4.2.1	The Proportion of Subjects with Virological Response (Serum HBV DNA <20 IU/mL and Serum HBV DNA <69 IU/mL) by Visit - mITT	X
Table 4.2.2	The Proportion of Subjects with Virological Response (Serum HBV DNA <20 IU/mL and Serum HBV DNA <69 IU/mL) by Visit - PP	X
Table 4.3.1	The Proportion of Subjects with Virological Response (Serum HBV DNA <20 IU/mL and Serum HBV DNA <69 IU/mL) by Visit in the Subgroup with Confirmed Multi-drug Resistance at Baseline - mITT	X
Table 4.3.2	The Proportion of Subjects with Virological Response (Serum HBV DNA <20 IU/mL and Serum HBV DNA <69 IU/mL) by Visit in the Subgroup with Confirmed Multi-drug Resistance at Baseline - PP	X
Table 4.4.1	The Proportion of Subjects with Virological Response (Serum HBV DNA <20 IU/mL and Serum HBV DNA <69 IU/mL) by Visit in the Subgroup with Medical History (Previously Exposed to ADV >6 Months or Not, ETV >6 Months (ETV-R and Non ETV-R) or Not) - mITT	
Table 4.4.2	The Proportion of Subjects with Virological Response (Serum HBV DNA <20 IU/mL and Serum HBV DNA <69 IU/mL) by Visit in the Subgroup with Medical History (Previously Exposed to ADV >6 Months or Not, ETV >6 Months (ETV-R and Non ETV-R) or Not) - PP	

Identifier	Output Title	Annual Report
Table 4.5.1	The Proportion of Subjects Achieving HBeAg Loss, HBeAg Seroconversion, HBsAg Loss and HBsAg Seroconversion at Week 48, 96 and 144 for Subjects with Positive HBeAg at Baseline - mITT	
Table 4.5.2	The Proportion of Subjects Achieving HBeAg Loss, HBeAg Seroconversion, HBsAg Loss and HBsAg Seroconversion at Week 48, 96 and 144 for Subjects with Positive HBeAg at Baseline - PP	
Table 4.5.3	The Proportion of Subjects Achieving HBsAg Loss and HBsAg Seroconversion at Week 48, 96 and 144 for Subjects with Negative HBeAg at Baseline - mITT	
Table 4.5.4	The Proportion of Subjects Achieving HBsAg Loss and HBsAg Seroconversion at Week 48, 96 and 144 for Subjects with Negative HBeAg at Baseline - PP	
Table 4.6.1	The Proportion of Subjects with ALT Normalization at Week 48, 96 and 144 in Subjects Who Have Abnormal ALT at Baseline - mITT	X
Table 4.6.2	The Proportion of Subjects with ALT Normalization at Week 48, 96 and 144 in Subjects Who Have Abnormal ALT at Baseline - PP	X
Table 4.7.1	Change from Baseline for the log10 Reduction in Serum HBV DNA by Visit - mITT	X
Table 4.7.1.1	Mean log10 IU/mL in Serum HBV DNA by Patterns of Mutation Category 1 Over Time - mITT	X
Table 4.7.1.2	Mean log10 IU/mL in Serum HBV DNA by Patterns of Mutation Category 2 Over Time - mITT	X
Table 4.7.2	Change from Baseline for the log10 Reduction in Serum HBV DNA by Visit- PP	X
Table 4.7.2.1	Mean log10 IU/mL in Serum HBV DNA by Patterns of Mutation Category 1 Over Time - PP	X
Table 4.7.2.2	Mean log10 IU/mL in Serum HBV DNA by Patterns of Mutation Category 2 Over Time - PP	X
Table 4.7.3	Incidence of Subjects Who Experience Viral Breakthrough by Visit - mITT	X (Week 96)
Table 4.7.4	Incidence of Subjects Who Experience Viral Breakthrough by Visit - PP	X (Week 96)
Table 4.8.1	Incidence of Subjects with Unsatisfactory Response by Visit - mITT	X (Week 96)
Table 4.8.2	Incidence of Subjects with Unsatisfactory Response by Visit - PP	X (Week 96)
Table 4.8.3	Mutation Pattern Change from Baseline at Week 48, 96, 144 - mITT	X

Identifier	Output Title	Annual Report
Table 4.8.4	Mutation Pattern Change from Baseline at Week 48, 96, 144 - PP	X
Table 4.9.1	The Relationship Between Baseline Variables and Virological Response (Serum HBV DNA <20 IU/mL) at Week 144 - mITT	
Table 4.9.2	The Relationship Between Baseline Variables and Virological Response (Serum HBV DNA <20 IU/mL) at Week 144 - PP	
Table 4.10.1	Time to Virological Response (Serum HBV DNA <20 IU/mL) - mITT	
Table 4.10.2	Time to Virological Response (Serum HBV DNA <20 IU/mL) - PP	
Table 4.11.1	Log-rank Test for Time to Virological Response (Serum HBV DNA <20 IU/mL) - mITT	
Table 4.11.2	Log-rank Test for Time to Virological Response (Serum HBV DNA <20 IU/mL) - PP	
Table 4.12.1	Cox Regression Analysis for Time to Virological Response (Serum HBV DNA <20 IU/mL) - mITT	
Table 4.12.2	Cox Regression Analysis for Time to Virological Response (Serum HBV DNA <20 IU/mL) - PP	
Table 5.1.1	Overall Summary of Adverse Events - SA	X
Table 5.1.2.1	All TEAEs by System Organ Class and Preferred Term - SA	X
Table 5.1.2.2	All Serious TEAEs by System Organ Class and Preferred Term - SA	X
Table 5.1.2.3	All Non-Serious TEAEs by System Organ Class and Preferred Term - SA	X
Table 5.1.3.1	All TEAEs by Relationship to Study Drug - SA	X
Table 5.1.3.2	All Serious TEAEs by Relationship to Study Drug - SA	X
Table 5.1.4.1	All TEAEs by Intensity - SA	X
Table 5.1.4.2	All Serious TEAEs by Intensity - SA	X
Table 5.2	Change from Baseline in Vital Signs - SA	X
Table 5.3.1	Change from Baseline in Hematology - SA	X
Table 5.3.2	Change from Baseline in Blood Chemistry - SA	X
Table 5.3.3	Subjects with Treatment-emergent Laboratory Abnormalities - SA	X
Listing 1.1	Disposition - mITT	X
Listing 1.2	Analysis Set - mITT	X
Listing 1.3	Major Protocol Deviations - mITT	X
Listing 2.1.1	Demographics - mITT	X
Listing 2.1.2	Baseline Characteristics - mITT	X
Listing 2.1.3.1	HBV Variant at Baseline - mITT	X
Listing 2.1.3.2	Level of Susceptibility at Baseline - mITT	X
Listing 2.2.1.1	Diagnosis of Chronic Hepatitis B (Section 1) - mITT	X
Listing 2.2.1.2	Diagnosis of Chronic Hepatitis B (Section 2) - mITT	X
Listing 2.2.2.1	Treatment History of Chronic Hepatitis B (Section 1) - mITT	X

Identifier	Output Title	Annual Report
Listing 2.2.2.2	Treatment History of Chronic Hepatitis B (Section 2) - mITT	X
Listing 2.2.2.3	Treatment History of Chronic Hepatitis B (Section 3) - mITT	X
Listing 2.3.1	Medical History - mITT	X
Listing 2.3.2	Past History of Treatment - mITT	X
Listing 2.3.3	Relevant Surgery - mITT	X
Listing 2.4	Inclusion and Exclusion Criteria - mITT	X
Listing 3.1.1	Prior Medications - mITT	X
Listing 3.1.2	Concomitant Medications - mITT	X
Listing 3.1.3	Non-Drug Therapies - mITT	X
Listing 3.2.1	Study Drug Exposure - mITT	X
Listing 3.2.2	Drug Accountability - mITT	X
Listing 4.1	HBV DNA - mITT	X
Listing 4.1.1	Relationship Between HBV DNA and Medical History - mITT	X
Listing 4.1.2	HBV DNA for Patients with Virological Breakthrough - mITT	X
Listing 4.1.3	HBV DNA for Patients with Unsatisfactory Response - mITT	X
Listing 4.2	Hepatitis B Five Item - mITT	X
Listing 4.3	ALT for patients with any HBeAg Loss, HBeAg Seroconversion, HBsAg Loss and HBsAg Seroconversion - mITT	X
Listing 5.1.1	Non-Serious Treatment-emergent Adverse Events - SA	X
Listing 5.1.2	Serious Treatment-emergent Adverse Events - SA	X
Listing 5.1.3	Treatment Related Treatment-emergent Adverse Events - SA	X
Listing 5.2	Vital Signs - SA	X
Listing 5.3.1	Hematology - SA	X
Listing 5.3.2	Blood Chemistry - SA	X
Listing 5.3.3	Blood Coagulation - SA	X
Listing 5.3.4	Urinalysis - SA	X
Listing 5.3.5	Pregnancy Test - SA	X
Listing 5.3.6	Alpha Fetoprotein (AFP) - SA	X
Listing 5.4	Physical Examination - SA	X
Listing 5.5	B-ULTRASOUND - SA	X
Listing 5.6	CV Event - SA	X
Figure 4.1.1	Proportion (95% CI) of Subjects with HBV DNA <20 IU/mL Over Time - mITT	X
Figure 4.1.2	Proportion (95% CI) of Subjects with HBV DNA <20 IU/mL Over Time - PP	X
Figure 4.1.3	Proportion (95% CI) of Subjects with HBV DNA <69 IU/mL Over Time - mITT	X
Figure 4.1.4	Proportion (95% CI) of Subjects with HBV DNA <69 IU/mL Over Time - PP	X
Figure 4.5.1	Mean Log10 Copies/mL Reduction from Baseline in HBV DNA Over Time - mITT	X

Identifier	Output Title	Annual Report
Figure 4.5.2	Mean Log10 Copies/mL Reduction from Baseline in HBV DNA Over Time - PP	X
Figure 4.5.3	Distribution of HBV DNA levels Over Time - mITT	X
Figure 4.7.1.1	Mean Log10 IU/mL in HBV DNA by Patterns of Mutation Category 1 Over Time - mITT	X
Figure 4.7.1.2	Mean Log10 IU/mL in HBV DNA by Patterns of Mutation Category 2 Over Time - mITT	X
Figure 4.7.2.1	Mean Log10 IU/mL in HBV DNA by Patterns of Mutation Category 1 Over Time - PP	X
Figure 4.7.2.2	Mean Log10 IU/mL in HBV DNA by Patterns of Mutation Category 2 Over Time - PP	X
Figure 4.7.3	Mean Log10 IU/mL in HBV DNA by Medical History (Previously Exposed to ADV >6 Months or Not) Over Time - mITT	X
Figure 4.7.4	Mean Log10 IU/mL in HBV DNA by Medical History (Previously Exposed to ADV >6 Months or Not) Over Time - PP	X
Figure 4.8.1	Individual Courses of HBV DNA Levels of Subjects with Genotypic Resistance to ADV (A181T/V+N236T) - mITT	X
Figure 4.10.1	Kaplan-Meier Curves for Virological Response (Serum HBV DNA <20 IU/mL) - mITT	
Figure 4.10.1.1	Kaplan-Meier Curves for Virological Response (Serum HBV DNA <20 IU/mL) by Patterns of Mutation Category 1 - mITT	
Figure 4.10.1.2	Kaplan-Meier Curves for Virological Response (Serum HBV DNA <20 IU/mL) by Patterns of Mutation Category 2 - mITT	
Figure 4.10.2	Kaplan-Meier Curves for Virological Response (Serum HBV DNA <20 IU/mL) - PP	
Figure 4.10.2.1	Kaplan-Meier Curves for Virological Response (Serum HBV DNA <20 IU/mL) by Patterns of Mutation Category 1 - PP	
Figure 4.10.2.2	Kaplan-Meier Curves for Virological Response (Serum HBV DNA <20 IU/mL) by Patterns of Mutation Category 2 - PP	
Figure 5.3.1	Mean Estimated Glomerular Filtration Rate Change from Baseline Over Time - mITT	
Figure 5.3.2	Mean Estimated Glomerular Filtration Rate Change from Baseline Over Time - PP	X
Figure 5.3.3	Mean Serum Phosphorus Change from Baseline Over Time - mITT	
Figure 5.3.4	Mean Serum Phosphorus Change from Baseline Over Time - PP	X