Statistical Analysis Plan

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

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

Version: 2.0

Date: Feb 26, 2021

Protocol Number: 201213

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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
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B s antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
INR	International Normalized Ratio
LAM	Lamivudine
LdT	Telbivudine
mITT	Modified Intent-to-treat (population)
NAs	Nucleos(t)ide analogues
PP	Per protocol (population)
PT	Prothrombin time
SA	Safety analysis (population)

Abbreviation	Description of Abbreviation
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
TDF	Tenofovir disoproxil fumarate
TEAE	Treatment-emergent adverse events
ULN	Upper limit of the normal range

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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 201213. 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 3.0, March 27, 2016).

2. STUDY OBJECTIVE

2.1 Primary objective

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

2.2 Secondary objective

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

3. STUDY DESIGN

3.1 Overall study design

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

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

Treatment phase: 186 subjects will be administered TDF 300 mg QD and undergo regular safety and efficacy assessments every 12 weeks for a total of up to 240 weeks (see Table 1). Subjects will be questioned about adverse events, concurrent medications, and study drug accountability; blood will be taken for hematology and biochemistry profiles; serum samples will be tested for HBV markers, and the prothrombin time will be measured. Serum samples will be collected at Week 12, 24, 36, 48, 60, 72, 84, and 96 and every 24 weeks thereafter and analyzed for HBV DNA levels at a central laboratory. Abdominal ultrasound, the prothrombin time and serum alpha-fetoprotein test will be performed every visit. If abdominal ultrasound reports a liver mass or nodule, CT or MRI will be performed. At baseline and Week 216, 100 of subjects will take liver biopsy to evaluate liver histological changes pre and post TDF treatment. All subjects will be followed through to Week 240.

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

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

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

treatment, serum sample should be collected for resistance testing.

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

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

3.2 Sample size

3.2.1 Sample size Assumptions

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

To decide the number of subjects for analysis, some precision calculations have been performed for the primary endpoint HCC incidence. In the retrospective analysis of GS-US-174-0102 and GS-US-174-0103 trials, HCC incidence over 7 years was approximately 4.5% among patients (23% of whom were Asian, 25 of whom were genotype B or C) with cirrhosis at baseline. Accordingly, we hypothesize that the accumulative incidence of HCC at 240 weeks will be 5% in Chinese compensated cirrhotic patients treated with TDF. The precision is calculated by the following:

$$Precision = Z_{1-\alpha/2}\sqrt{\frac{p(1-p)}{N}}$$

where Z is the critical value of normal distribution corresponding to the probability of 1-α/2 (corresponding to (1- α)*100% confidence interval), and p is the percentage of patients who were diagnosed HCC during 240 weeks. Precision is half of the width of 95% confidence interval for the

point estimate. A sample size of 158 patients will allow us to estimate the confidence interval of the incidence with a margin of error at 3.4 % (0.016-0.084). Assuming a 15% drop out rate, 186 patients are to be recruited.

3.2.2 Sample Size Sensitivity

The sample size estimates are dependent upon the assumed incidence.

Different sample sizes and corresponding precisions are provided in the table below. It assumes the percentage of patients HCC is 5%.

P	1-p	Width (half CI)	N
5%	0.95	0.04	115
5%	0.95	0.034	158
5%	0.95	0.033	168
5%	0.95	0.032	179
5%	0.95	0.03	203
5%	0.95	0.02	457

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 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 population and PP population will be used for primary endpoints. All safety endpoints will be analyzed using the SA population.

5. STUDY ENDPONITS

5.1 Primary endpoint

- The cumulative incidence of newly diagnosed hepatocellular carcinoma (HCC) at Week 240, the subject must meet one of the following criteria:
  - Without HCC before Week 24
  - A histological diagnosis of HCC (i.e. by biopsy or at post-mortem);
  - In patients with nodules > 2 cm, identification of typical HCC characteristics (hypervascular in the arterial phase with washout in the portal venous or delayed phases) by 4-phase multidetector CT scan or dynamic contrast-enhanced MRI;
  - In patients with nodules > 1 cm, identification of typical HCC characteristics by both techniques (4-phase multidetector CT and dynamic contrast-enhanced MRI).
- The cumulative incidence of disease progression at Week 240, defined as the first occurrence of any one of the following criteria:
  - An increase in Childs-Pugh score (as defined in Appendix 2) of 2 or more points from baseline;
  - An increase in Childs-Pugh score of 2 or more points, solely based on laboratory parameters (i.e. bilirubin, prothrombin time and/or albumin), confirmed between two consecutive visits at least one month apart;
  - Spontaneous bacterial peritonitis (with proven sepsis);
  - Renal insufficiency defined as a decrease in creatinine clearance to ≤50 mL/minute confirmed on two occasions at least one week apart (calculated from serum creatinine concentration);
  - Bleeding gastric/oesophageal varices;
  - Hepatocellular carcinoma;
  - Liver-related death.

5.2 Secondary endpoints

- Cumulative incidence of newly diagnosed HCC at Week 48, Week 96, Week 144, and Week 192.
- Cumulative incidence of disease progression at Week 48, Week 96, Week 144, and Week 192.
- The mean changes of liver stiffness measurement (LSM) at Week 12, Week 24, Week 36, Week 48, Week 96, Week 144, Week 192 and Week 240 for patients with baseline ALT > ULN,

baseline ALT ≤ ULN and overall.

- Change of fibrosis stage for subjects with baseline ALT > ULN and ALT ≤ ULN.
- Change of non-invasive liver fibrosis evaluation index (GPR, APRI and FIB-4, defined in Section 8.5, appendix 5) from baseline by visit.
- The proportion of subjects with serum HBV DNA < 20 IU/mL or serum HBV DNA < 69 IU/mL (Roche COBAS Taqman HBV Test) at Week 12, Week 24, Week 36, Week 48, Week 96, Week 144, Week 192 and Week 240
- The mean $\log_{10}$ IU/mL reduction in serum HBV DNA at Week 12, Week 24, Week 36, Week 48, Week 96, Week 144, Week 192 and Week 240 compared with baseline
- The proportion of subjects with ALT normalization at Week 48, Week 96, Week 144, Week 192 and Week 240 in subjects who have abnormal ALT at baseline
- For HBeAg positive subjects: the proportion of subjects achieving HBeAg loss, HBeAg seroconversion or HBsAg loss and HBsAg seroconversion at Week 24, Week 48, Week 96, Week 144, Week 192 and Week 240
- For HBeAg negative subjects: the proportion of subjects achieving HBsAg loss and HBsAg seroconversion at Week 48, Week 96, Week 144, Week 192 and Week 240
- Incidence of virological breakthrough as defined by 1 $\log_{10}$ IU/mL increase in HBV DNA from nadir (as determined by two sequential HBV DNA measurements at least 1 month apart, or the last on-treatment measurement) 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
- Subject safety as determined by adverse events and laboratory assessments

5.3 Exploratory endpoints

- Incidence of TDF resistance substitutions (if identified) at Week 48, Week 96, Week 144, Week 192 and Week 240
- Baseline or on-treatment risk factors for HCC/disease progression (e.g. gender, age, HBV DNA, genotype, HBeAg sero-status, ALT, platelets, treatment response, etc.)
- Impact of HBV DNA and virologic response on change of liver stiffness measurement (LSM).
- The mean changes of LSM by visit.

- Time to improvement of fibrosis.
- The Relationship between baseline variables or on-treatment variables and improvement of fibrosis.
- Proportion of LSM improvement and of fibrosis stage improvement.
- Analyses of correlation coefficients between LSM and ALT level.
- Correlation coefficients between variables change at Week 12 and 24 and LSM change at Week240.
- Predicted and observed HCC risks at week 240 by REACH-B model.
- Decline in LSM from baseline to Week 240.
- Mean estimated glomerular filtration rate (eGFR) over time by baseline eGFR, mean creatinine clearance rate (Ccr) over time by baseline Ccr, mean serum phosphorus over time.
- Change of average LSM/ALT by visit, change of average LSM by visit, change of median of LSM by visit, change of average GPR APRI FIB-4 by visit, change of median of GPR APRI FIB-4 by visit, change of fibrosis stage by visit.

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, unless otherwise specified. 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. For baseline value, if it is missing at baseline visit, then the latest non-missing value of screening will be used to replace.

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 patients whose week 240 visits were influenced by COVID-19, a safety follow-up were added for these subjects. The missing week 240 will be imputed from safety follow-up visit in the analysis of primary endpoints. Please refer to section 7.4 for details.

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.

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

- Eligibility criteria not met
- Excluded medication, vaccine or device
- Assessment or time point completion
- Wrong study treatment/administration/dose

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. A listing of subject disposition in analysis data sets will be provide.

7.2 Subject Information

7.2.1 Demographics and baseline characteristics

Demographic include subject age, sex (Male/Female), race (Asian/Others), and baseline characteristics for subjects include subject height, weight, BMI, systolic blood pressure, diastolic blood pressure, pulse, respiratory rate, body temperature, liver stiffness measurement, LSM for patient with ALT>ULN or ALT≤ULN, creatinine level, serum phosphorus, eGFR, creatinine clearance rate, HBV DNA , alcohol abuse, drug abuse, history of medication hypersensitivity, family history of hepatitis B and hepatoma, liver cirrhosis, hypertension, HBeAg, Childs-Pugh score, ALT, liver biopsy, and HBV genotype. Age will be calculated as the difference of the year of informed consent date and year of birth. Percentages for categorical data will be calculated based on the number of subjects in the analysis set of the corresponding population. Descriptive statistics will be used for continuous data. Listings of demographics and baseline characteristics will also be provided.

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

7.2.2 Medical history

Medical history will include any acute and chronic medical conditions including medication of

chronic hepatitis B, medical history/current medical conditions, history of treatment, relevant surgeries. Medical history will be listed by system organ class and preferred term coded in MedDRA 17.0.

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 is defined as all the drugs taken by the subjects prior to the first dose date of TDF.

Concomitant medication is defined as 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 date of first dose of study drug, 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 date of first dose of study drug, 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 date of first dose of study drug 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.

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

7.3.2 Exposure of TDF and treatment compliance

Exposure of TDF information including dose start date, end date, duration of study drug and dosing compliance will be presented in the listing.

The duration in days of study drug exposure from first dose date to the last dose date will be summarized by descriptive statistics, including n, mean, sd, Q1, median, Q3, range.

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.

7.3.3 Rescue Treatment

Rescue treatment information including rescue treatment name, frequency, reason taken, other reason taken, start date, end date will be presented in the listing. If no patient received rescue treatment, the listing will not be presented.

7.3.4 Non-drug therapies

Non-drug therapy information including therapy details, start and end date, and the reason for use will be presented in the listing. If no patient received rescue treatment, the listing will not be presented.

7.4 Efficacy analysis

All analysis will be conducted in mITT, unless otherwise specified.

7.4.1 Analysis of primary variables

The primary efficacy endpoints for this study are the 240-Week cumulative incidence of newly diagnosed HCC and 240-Week cumulative incidence of disease progression. The newly diagnosed HCC is defined as HCC cases from Week 24 to Week 240. The analysis will be performed in mITT and PP population.

- Nominal cumulative incidence of newly diagnosed HCC at week 240 is defined as the percentage of patient who are newly diagnosed as HCC from Week 24 visit to Week 240 visit in overall patients. Nominal cumulative incidence of HCC will be summarized by frequency, percentage and its 95% two-sided Wald CI. When the value of the newly diagnosed HCC at week 240 is missing due to the epidemic of COVID-19, the missing value may be imputed with the value at the safety follow-up visit. Different missing imputation scenarios will be assessed for the primary analysis and sensitivity analyses, details are provided in below table in which “Y” means the missing value will be imputed with the value at the safety follow-up visit.

Difference between planned Week 240 visit and actual safety follow up visit	**Medication taken after previous visit**	**Primary Endpoints**	**Sensitivity Analysis 1**	**Sensitivity Analysis2**
<=28 days	Any	Y	Y	Y
>28 days	GSK	Y	N	Y
	Domestic	Y	N	N
	Both GSK & domestic	Y	N	N
Lost to follow up	NA	N	N	N

- Nominal cumulative incidence of disease progression at week 240 is defined as the percentage of patient who have disease progression before Week 240 visit in overall

patients. Nominal cumulative incidence of disease progression will be summarized by frequency, percentage and its 95% two-sided Wald CI. When the value of the disease progression at week 240 is missing due to the epidemic of COVID-19, the missing value will be imputed with the value at the safety follow-up visit. No sensitive analysis is planned.

- Cumulative incidence of newly diagnosed HCC/disease progression at week 240 and its 95% CI will be estimated from the Kaplan–Meier analysis. Time to newly diagnosed HCC/disease progression is defined as the interval between the date of first treatment dose and the analysis date. The rules of analysis date are described in the following table:

Patient's Condition	Status	Analysis date
Diagnosed HCC/disease progression on visit	Event	Date of diagnosis
Reported SAE related with HCC/disease progression between visits	Event	Date of diagnosis
Complete study without HCC/disease progression	Censor	Date of study complete
Lost follow up/ Early withdraws	Censor	Date of last visit with the adequate diagnosis data

7.4.2 Analysis of secondary variables

7.4.2.1 Nominal Cumulative Incidence and Nominal Incidence by visit

As defined in previous, the nominal cumulative incidence of newly diagnosed HCC and the nominal cumulative incidence of disease progression at Week 48, Week 96, Week 144, and Week 192 will be summarized by frequency, percentage and its 95% two-sided Wald CI. The analysis will be performed in mITT. Figures of nominal cumulative incidence of HCC/disease progress by each visit will be product respectively.

The nominal incidence at visit is defined as the percentage of subjects who had event during the previous visit to the current visit. The nominal incidence of newly diagnosed HCC and disease progression at each visit from Week 36 (Week 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168,

180, 192, 204, 216 and 240) will be summarized by frequency, percentage and its 95% two-sided Wald CI.

7.4.2.2 Cumulative incidence by visit

The cumulative incidence of newly diagnosed HCC and the cumulative incidence of disease progression at week 48, week 96, week 144, and week 192 will be estimated from the Kaplan–Meier analysis. Event or censoring rules are the same with cumulative incidence of week 240, as described in section 7.4.1. Figures of nominal cumulative incidence of HCC/disease progress by each visit will be product respectively.

7.4.2.3 Other secondary variables

The number and percentage will be presented respectively for secondary variables including:

- The proportion of subjects with serum HBV DNA < 20 IU/mL or serum HBV DNA < 69 IU/mL (Roche COBAS Taqman HBV Test) at Week 12, Week 24, Week 36, Week 48, Week 96, Week 144, Week 192 and Week 240.
- The proportion of subjects with serum HBV DNA < 20 IU/mL (Roche COBAS Taqman HBV Test) by baseline HBeAg status (HBeAg Positive and HBeAg Negative) at Week 48, Week 96, Week 144, Week 192 and Week 240.
- The proportion of subjects with serum HBV DNA < 20 IU/mL (Roche COBAS Taqman HBV Test) by baseline HBV DNA level (≥6 Log_{10} IU/mL and <6 Log_{10} IU/mL) at Week 48, Week 96, Week 144, Week 192 and Week 240.
- The proportion of subjects with ALT normalization at Week 48, Week 96, Week 144, Week 192 and Week 240 in subjects who have abnormal ALT at baseline, based on the lab report.
- The proportion of subjects with ALT normalization at Week 48, Week 96, Week 144, Week 192 and Week 240 in subjects who have abnormal ALT at baseline, based on AASLD criteria. Abnormal ALT by AASLD criteria is ⩾19 U/L for women and ⩾30 U/L for men.
- For HBeAg positive subjects: the proportion of subjects achieving HBeAg loss, HBeAg

seroconversion or HBsAg loss and HBsAg seroconversion at Week 48, Week 96, Week 144, Week 192 and Week 240.

- For HBeAg negative subjects: the proportion of subjects achieving HBsAg loss and HBsAg seroconversion at Week 48, Week 96, Week 144, Week 192 and Week 240.
- Incidence of virological breakthrough as defined by 1 $\log_{10}$ IU/mL increase in HBV DNA from nadir (as determined by two sequential HBV DNA measurements at least 1 month apart, or the last on-treatment measurement) overall and by 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.
- The proportion of subjects with histological improvement (a reduction of two or more points in the Knodell necroinflammatory score with no increase in fibrosis) at Week 216 in the subset of subjects with paired baseline and Week 216 liver biopsies.
- The proportion of subjects with cirrhosis reversal (a reduction of one or more points in the Ishak score and no evidence of cirrhosis) at Week 216 in the subset of subjects with paired baseline and Week 216 liver biopsies and with a baseline Ishak score higher than or equal to five
- Change of fibrosis stage measured by LSM for subjects with baseline ALT > ULN and ALT ≤ ULN, by baseline fibrosis stage. The fibrosis stage is measured by LSM value, based on the following rules:
  - For patient with baseline ALT>ULN: F0/1: LSM<9.4 kPA, F2: 9.4 kPa≤LSM<12.4 kPa, F3: 12.4 kPa≤LSM<17.5 kpa, F4: LSM≥17.5 kpa
  - For patient with baseline ALT≤ULN: F0/1: LSM<6.0 kPA, F2: 6.0 kPa≤LSM<9.0 kPa, F3: 9.0 kPa≤LSM<12.0 kpa, F4: LSM≥12.0 kpa

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

Below endpoints will be summarized by descriptive statistics as the mean, standard deviation, minimum, median, maximum, and the number of observations.

- The mean changes of liver stiffness measurement (LSM) at Week 12, Week 24, Week 36, Week 48, Week 96, Week 144, Week 192 and Week 240 for patients with baseline ALT > ULN, baseline ALT ≤ ULN and overall.
- The mean log_{10} IU/mL reduction in serum HBV DNA at Week 12, Week 24, Week 36, Week 48, Week 96, Week 144, Week 192 and Week 240 compared with baseline. And the result of log_{10} HBV DNA at each visit will be summarized for whole period.

In addition, line plots of the proportion of subjects with HBV DNA< 20IU/mL and <69 IU/mL by visit, mean HBV DNA (log10) over time by baseline ALT significance and a bubble plot for distribution of HBV DNA levels overtime will be provide. Newly diagnosed HCC, disease progression events, hepatitis B five item, liver stiffness measurement (LSM) and Childs-Pugh score will be listed.

7.4.3 Exploratory analysis

Incidence of TDF resistance substitutions such as mutation change, drug resistance test results will be summarized in patients with unsatisfied virological response, viral breakthrough, or discontinued treatment with HBV DNA≥20 IU/mL.

Univariate and multivariate analysis by logistic regression model will be performed to identify baseline or on-treatment risk factors associated with HCC and disease progression, if applicable. The factors will include gender, age, genotype, baseline HBV DNA category (≥2000 or <2000, IU/mL), baseline HBeAg sero-status, baseline ALT value, baseline LSM value, Week 24 treatment response, Week 48 treatment response. Treatment response is defined as serum HBV DNA < 20 IU/mL. Multivariate analysis will include sex, age and the factors with P≤0.20 in univariate analysis.

Time to HCC/disease progression will be analyzed by cox model. Univariate will be conducted to include all above factors and the selection of multivariate analysis will follow the same rule.

Impact of HBV DNA and virologic response on change of LSM will be summarized by shift table

of descriptive statistics as the mean, standard deviation, minimum, median, maximum, and the number of observations.

The mean changes and percent of the changes of liver stiffness measurement in each visit will be summarized by descriptive statistics as the mean, standard deviation, minimum, median, maximum, and the number of observations for patients with advanced fibrosis and compensated cirrhosis. Compensated cirrhosis is defined as LSM ≥ 12.0 Kpa (ALT ≤ ULN) or LSM ≥ 17.5 Kpa (ALT>ULN); advanced fibrosis is defined as 9.0 Kpa ≤LSM < 12.0 Kpa (ALT≤ULN) or 12.4 Kpa ≤LSM < 17.5 Kpa (ALT>ULN).

Time to improvement of fibrosis will be analyzed by cox regression. Improvement of fibrosis is defined as at least 30% decrease of LSM compared with baseline. Univariate analysis will include gender, age, genotype, baseline HBV DNA category (≥2000 or <2000, IU/mL), baseline HBeAg sero-status, baseline ALT value, Week 24 treatment response, Week 48 treatment response. Treatment response is defined as serum HBV DNA < 20 IU/mL. Multivariate analysis will include sex, age and the factors with P≤0.20 in univariate analysis.

The relationship between baseline variables or on-treatment variables and improvement of fibrosis will be analysis by univariate and multivariate logistic model. Univariate analysis will include gender, age, BMI category (<25 or ≥25 kg/m^2), baseline HBV DNA (≥2000 or <2000, IU/mL), baseline HBeAg sero-status, baseline ALT value, baseline LSM value, baseline total bilirubin, HBeAg loss at Week 24, treatment response at Week 24 and Week 48, ALT normalized or not at Week 24 and Week 48, change from baseline of LSM at Week 12 and Week 24, change from baseline of GGT at Week 24. Multivariate analysis will include sex, age and the factors with P≤0.20 in univariate analysis.

Proportion of LSM improvement will be summarized at Week48, Week96, Week144, Week192 and Week240 for patients with baseline LSM result in following groups: LSM improved (LSM decreased from baseline≥30%), LSM stable (LSM decreased from baseline < 30% or no change from baseline), and LSM deteriorate (LSM increase from baseline).

Proportion of fibrosis stage improvement will be summarized at Week 48, Week 96, Week 144, Week 192 and Week 240 for patients of fibrosis stage measured by fibrosis improved from baseline, ≥2 stage fibrosis stage improved from baseline, ≥1 stage fibrosis stage, no change from baseline, fibrosis stage increase from baseline.

Analyses of correlation coefficients between LSM and ALT level will be analyzed by Pearson correlation coefficients and P-value during every 48 weeks by patients with ALT normal at baseline, patients with abnormal at baseline and overall.

Correlation coefficients between variables change at Week 12 and 24 and LSM change at Week240 will be analyzed by correlation coefficients and P-value. The change from baseline of Gamma-Glutamyltransferase (GGT), Total Bilirubin (TBIL), Albumin (ALB), International Normalized Ratio (INR) and LSM will be included in the analysis of correlation coefficients at Week 12, platelets (PLT), GPR, APRI, FIB-4 and all the variables included at Week 12 will be included in the analysis of correlation coefficients at Week 24.

A 5-years predicted HCC risks by REACH-B model (see Section 8.5) and observed HCC risks (cumulative incidence of HCC) at Week 240 will be presented in table. Decline in LSM from baseline to Week 240 by visit will be analyzed by a line plot.

In addition, a listing of HBV DNA result will be provided for the following patients:

- Patients with virological breakthrough (defined as 1 log increase in HBV DNA from nadir determined by two sequential HBV DNA measurements).
- Patients with unsatisfied virological response: defined as subjects have HBV DNA ≥ 200 IU/ml at week 48 and afterwards have ≤ 1 $\log_{10}$ IU/mL decrease in HBV DNA at two consecutive visits, confirmed by a third visit at least one month apart.

7.5 Safety analysis

Safety endpoints include adverse events, vital signs, laboratory assessments, physical examination,

and B-ultrasound. The 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.

An overall summary table of AE will be provided, including summaries of all AEs, all TEAEs, all treatment related TEAEs, all 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, and all TEAEs that caused a change in dose or temporary interruption of study drug. Listings will be provided correspondingly.

All TEAEs and all serious TEAEs will be summarized by SOC and PT, and by intensity. All TEAEs will also be summarized by relationship to 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 visit. Changes from baseline to each individual post-baseline visit will also be presented.

A listing of vital signs will be provided.

7.5.3 Laboratory assessments

Summary tables of hematology and blood chemistry by visit will be provided including the changes from baseline for each post-baseline visits. 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 (as defined in Appendix 3). If the relevant baseline laboratory data are missing, then the screening laboratory result will be 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 $\geq$ 2 times ULN or albumin $\leq$ 3 g/dL or ALT $\geq$ 20 times ULN (and $\geq$ 2 times baseline)
- Confirmed (defined as two consecutive visits) serum creatinine $\geq$ 0.5 mg/dL above baseline
- Confirmed (defined as two consecutive visits) serum phosphate < 2 mg/dL
- Calculated creatinine clearance < 50 mL/min

Mean estimated glomerular filtration rate (eGFR) over time by baseline eGFR, mean creatinine

clearance rate (Ccr) over time by baseline Ccr, mean serum phosphorus over time will be analyzed by line plots, respectively.

Change of average LSM/ALT by visit, change of average LSM by visit, change of median of LSM by visit, change of average GPR/APRI/FIB-4 by visit, change of median of GPR/APRI/FIB-4 by visit, change of fibrosis stage by visit will be analyzed by line plots, respectively.

In addition, listings of hematology, blood chemistry, blood coagulation, urinalysis, pregnancy test, and alpha fetoprotein (AFP) will be provided.

7.5.4 Physical examination

A listing of physical examination will be provided. The result of physical examination will be presented as “Not Done”, “Normal” or “Abnormal”.

7.5.5 B-ultrasound

B-ultrasound examination results will be recorded in 3-level (normal, abnormal not clinically significant, or abnormal clinically significant). All B-ultrasound data will be presented in the listing.

8. APPENDIX

8.1 Appendix 1: Description of Inclusion/Exclusion Criteria

Seq No	Type	Description
1	Inclusion	Age 18-60 years(inclusive)
2	Inclusion	Presence of HBsAg in serum at screening and for at least 6 months before screening assessment
3	Inclusion	Serum HBV DNA ≥ 2000 IU/mL if HBeAg positive at screening (with or without ALT elevation); or serum HBV DNA ≥ 200 IU/mL if HBeAg negative at screening (with or without ALT elevation)
4	Inclusion	Pathologically or clinically diagnosed as advanced fibrosis or compensated cirrhosis defined as one of following(a or b) : a. Liver biopsy showing advanced fibrosis or cirrhosis (Ishak score ≥ 4 or Fibrosis stage ≥ S3 by Scheuer Score, or within the previous 6 months before baseline and provided that no treatment likely to improve liver histology has been taken since). The slides must be available for review by an independent histopathologist. b. Clinical diagnosis: liver stiffness measure (LSM) > 12.4 kpa (ALT > ULN) or LSM > 9.0 kpa (ALT ≤ ULN), plus one of the following: • Endoscopy-proven gastroesophageal or gastric varices, non-cirrhotic portal hypertension excluded; • Abdominal ultrasound or CT found changes indicating cirrhosis, irregular liver surface or nodularity, with/without splenomegaly(depth of spleen > 4.0 cm or spleen length >13 cm); • Blood platelets <100 x109/L (and other causes of thrombocytopenia excluded);
5	Inclusion	Ability to give written informed consent
6	Inclusion	A female is eligible to enter and participate in this study if she is of: a. Non-childbearing potential (i.e., physiologically incapable of becoming pregnant, including any female who is post-menopausal), or b. Child-bearing potential, has a negative urine pregnancy test at screening, and agrees to one of the following methods for avoidance of pregnancy during the period of the study and until 30 days after last dose of study medication: • 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

Seq No	Type	Description
		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 orcervical/vault caps) with a vaginal spermicidal agent (foam/gel/film /cream/suppository).
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 >50 ng/ml at screening.
2	Exclusion	ALT >10 times ULN at screening or history of acute exacerbation leading to transient decompensation.
3	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.
4	Exclusion	Evidence of active liver disease due to autoimmune hepatitis (antinuclear antibody titre >1:160)
5	Exclusion	Decompensated liver disease as indicated by any of the following: a. serum bilirubin >1.5 x ULN. b. prothrombin time activity <60% or INR>1.5 c. Serum albumin <32g/L. d. History of previous clinical hepatic decompensation (e.g., ascites, variceal bleeding, or encephalopathy).
6	Exclusion	Planned for liver transplantation or previous liver transplantation.
7	Exclusion	Creatinine clearance less than 70 ml/min.
8	Exclusion	Haemoglobin < 10 g/dL, white blood cell (WBC) count <1.5 x 10^9/L, platelets < 50 x 10^9/L.
9	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.
10	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.
11	Exclusion	A female who is breastfeeding or plan to breastfeed.

Seq No	Type	Description
12	Exclusion	Use of immunosuppressive therapy, immunomodulatory therapy (including IFN or thymosin α,), systemic cytotoxic agents, chronic antiviral agents including Chinese herbal medicines known to have activity against HBV (e.g., LAM, adefovir, ETV LdT or hepatitis B immunoglobulin (HBIg)) within the previous 6 months prior to screening into this study
13	Exclusion	Have ever received TDF or any medicinal products containing the above mentioned antiviral agents or any investigative anti-HBV treatments (e.g., emtricitabine (FTC), (2R, 4R)-4-(2,6-Diaminopurin-9-yl)-1,3-dioxolan-2-yl]methanol (DAPD) and 1-(2-fluoro-5-methyl-beta, Larabinofuranosyl) uracil (L-FMAU)).
14	Exclusion	History of hypersensitivity to nucleoside and/or nucleotide analogues and/or any component of study medication.
15	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.
16	Exclusion	Inability to comply with study requirements as determined by the study Investigator.

8.2 Appendix 2: CHILDS-PUGH SCORE*

Component	Score Given
CCI	CCI

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

Childs-Pugh Classification

Childs-Pugh Class CCI = score CCI

Childs-Pugh Class CCI = score CCI

Childs-Pugh Class CCI = score CCI

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

8.3 Appendix 3: 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

8.4 Appendix 4: Formulas and Equations

Ccr:

Cockcroft-Gault (CG) formula：

$$\boldsymbol{Ccr} = \frac{(140 - \text{Age}) \times \text{Ideal Body Weight(kg)}}{72 \times \text{Scr(mg/dL)}}$$

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

Calculation Formula for IBW:

（Male）$IBW = 50kg + 2.3kg \times [Height(Inch) - 60]$

（Female）$IBW = 45.5kg + 2.3kg \times [Height(Inch) - 60]$

$$1\ Inch = 2.54cm$$

Scr:

(Male) $Scr = Serum\ Creatinine\ (mg/dL)$

(Female) $Scr = Serum\ Creatinine\ (mg/dL) * 0.85$

GFR:

Chronic kidney disease (CKD)-Epidemiology Collaboration (EPI) equation:

eGFR(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

Non-invasive liver fibrosis evaluation index:

GPR (gamma glutamyl transpeptidase to platelet ratio):

$$GPR = \frac{GGT(/ULN)}{PLT\ counts(10^9/L)} \times 100$$

APRI (aspartate aminotransferase to platelet ratio index):

$$APRI = \frac{AST(/ULN)}{PLT\ counts(10^9/L)} \times 100$$

FIB-4 (fibrosis 4 score):

$$FIB-4 = \frac{Age(Years) \times AST(IU/L)}{PLT\ counts(10^9/L) \times [ALT(IU/L)]^{1/2}}$$

8.5 Appendix 5: REACH-B Model

$$HCC\ risk = 1 - P_0^{\exp(F)}, where$$

F = (0.78798(if male) + 0.09859*(age) +
0.38823(if 15≤ALT <44) + 0.96311(if ALT ≥45) + 0.81308 (if HBeAg positive) +
0.11648(if 300≤HBV DNA≤9999) + 1.31467(if $10^4 \leq$HBV DNA $\leq 10^5 - 1$) +
2.27028(if $10^5 \leq$HBV DNA $\leq 10^6 - 1$) + 2.09258(if HBV DNA $\geq 10^6$) - 6.12796

$P_0 = 0.99650$ if 5 –year HCC risk is estimated.

9. MOCK TABLES, LISTINGS AND GRAPHS (TLGS)

Mock TLGs will be provided in a separate document.

TFL	Number	Title
Table	1.1	Disposition
Table	1.2	Major Protocol Deviations - mITT
Table	2.1.1	Demographics - mITT
Table	2.1.2	Baseline Characteristics - mITT
Table	3.1	Compliance and Duration of the Study Drug - mITT
Table	4.1.1	The Nominal Cumulative Incidence of Newly Diagnosed Hepatocellular Carcinoma (HCC) at Week 240 - mITT
Table	4.1.2	The Nominal Cumulative Incidence of Newly Diagnosed Hepatocellular Carcinoma (HCC) at Week 240 - PP
Table	4.1.3	The Cumulative Incidence of Newly Diagnosed Hepatocellular Carcinoma (HCC) - mITT
Table	4.1.4	The Cumulative Incidence of Newly Diagnosed Hepatocellular Carcinoma (HCC) - PP
Table	4.2.1	The Nominal Cumulative Incidence of Disease Progression at Week 240 - mITT
Table	4.2.2	The Nominal Cumulative Incidence of Disease Progression at Week 240 - PP
Table	4.2.3	The Cumulative Incidence of Disease Progression - mITT

Table	4.2.4	The Cumulative Incidence of Disease Progression - PP
Table	4.3.1	The Nominal Cumulative Incidence of Newly Diagnosed Hepatocellular Carcinoma (HCC) by Visit - mITT
Table	4.3.3	The Nominal Incidence of Newly Diagnosed Hepatocellular Carcinoma (HCC) by Visit - mITT
Table	4.4.1	The Nominal Cumulative Incidence of Disease Progression by Visit - mITT
Table	4.5.1	The Proportion of Subjects with Virological Response (Serum HBV DNA <20 IU/mL) by Visit - mITT
Table	4.5.1.1	The Proportion of Subjects with Virological Response (Serum HBV DNA <20 IU/mL) by Baseline HBeAg Status (HBeAg Positive and HBeAg Negative) by Visit - mITT
Table	4.5.1.2	The Proportion of Subjects with Virological Response (Serum HBV DNA <20 IU/mL) by Baseline HBV DNA Level (≥6 Log10 IU/mL and <6 Log10 IU/mL) by Visit – mITT
Table	4.5.3	The Proportion of Subjects with Virological Response (Serum HBV DNA <69 IU/mL) by Visit - mITT
Table	4.6.1	The Proportion of Subjects with ALT Normalization (Lab) at Week 48, 96, 144, 192 and 240 in Subjects Who Have Abnormal ALT at Baseline - mITT
Table	4.6.1.1	The Proportion of Subjects with ALT Normalization (AASLD Criteria) at Week 48, 96, 144, 192 and 240 in Subjects Who Have Abnormal ALT at Baseline - mITT
Table	4.7.1	The Proportion of Subjects Achieving HBeAg Loss, HBeAg Seroconversion, HBsAg Loss and HBsAg Seroconversion at Week 48, 96, 144, 192 and 240 for Subjects with Positive HBeAg at Baseline - mITT
Table	4.7.3	The Proportion of Subjects Achieving HBsAg Loss and HBsAg Seroconversion at Week 48, 96, 144, 192 and 240 for Subjects with Negative HBeAg at Baseline - mITT
Table	4.8.1	Change from Baseline for the log10 IU/mL in Serum HBV DNA by Visit - mITT
Table	4.9.1	Incidence of Subjects Who Experience Viral Breakthrough by Visit - mITT
Table	4.9.3	Incidence of Subjects With Unsatisfied Response by Visit - mITT
Table	4.10.1	The Proportion of Subjects with Histological Improvement - mITT
Table	4.11.1	The Proportion of Subjects with Cirrhosis Reversal - mITT

Table	4.12.1	The Mean Changes of Liver Stiffness Measurement by Visit - mITT
Table	4.12.3.1.1	Shift from Baseline in Fibrosis Stage for Patients with Baseline ALT > ULN - mITT
Table	4.12.3.2.1	Shift from Baseline in Fibrosis Stage for Patients with Baseline ALT ≤ ULN - mITT
Table	4.12.3.3	Shift from Baseline in Fibrosis Stage - mITT
Table	4.13.1	Incidence of TDF Resistance Substitutions - mITT
Table	4.14.1	The Relationship Between Baseline Variables or On-treatment Variables and Newly Diagnosed Hepatocellular Carcinoma (HCC) - mITT
Table	4.14.3	The Relationship Between Baseline Variables or On-treatment Variables and Disease Progression - mITT
Table	4.17.1	Cox Regression Analysis for Time to Newly Diagnosed Hepatocellular Carcinoma (HCC) - mITT
Table	4.17.3	Cox Regression Analysis for Time to Disease Progression - mITT
Table	4.18.1	Impact of HBV DNA and Virologic Response on Change of LSM - mITT
Table	4.18.3	The Mean Changes of Liver Stiffness Measurement by Visit for Patients with Advanced Fibrosis and Compensated Cirrhosis - mITT
Table	4.18.3.1	The % Changes of Liver Stiffness from baseline by Visit for Patients with Advanced Fibrosis and Compensated Cirrhosis - mITT
Table	4.19.7	Cox Regression Analysis for Time to Improvement of Fibrosis - mITT
Table	4.20.3	The Relationship Between Baseline Variables or On-treatment Variables and Improvement of Fibrosis - mITT
Table	4.21.1	Proportion of LSM Improvement - mITT
Table	4.21.3	Proportion of LSM Stage Improvement - mITT
Table	4.22.1	Analyses of correlation coefficients between LSM and ALT level - mITT
Table	4.23.1	Analyses of correlation coefficients between Variables Change at Week 12 and 24 and LSM Change at Week240 - mITT
Table	4.24.1	Predicted and Observed Risk of HCC at Week240 - mITT
Table	5.3.4	Mean values in Non-invasive fibrosis - SA
Table	5.1.1	Overall Summary of Adverse Events - SA
Table	5.1.2.1	All TEAEs by System Organ Class and Preferred Term - SA

Table	5.1.2.2	All Serious TEAEs by System Organ Class and Preferred Term - SA
Table	5.1.3.1	All TEAEs by Relationship to Study Drug – SA
Table	5.1.3.2	All Serious TEAEs by Relationship to Study Drug - SA
Table	5.1.4.1	All TEAEs by Intensity – SA
Table	5.1.4.2	All Serious TEAEs by Intensity - SA
Table	5.2	Change from Baseline in Vital Signs - SA
Table	5.3.1	Change from Baseline in Hematology - SA
Table	5.3.2	Change from Baseline in Blood Chemistry - SA
Table	5.3.3	Subjects with Treatment-emergent Laboratory Abnormalities - SA
Listing	1.1	Disposition – mITT
Listing	1.2	Analysis Set
Listing	1.3	Major Protocol Deviations - mITT
Listing	2.1.1	Demographics - mITT
Listing	2.1.2	Baseline Characteristics - mITT
Listing	2.2.1	Treatment History of Chronic Hepatitis B - mITT
Listing	2.3.1	Medical History - mITT
Listing	2.3.2	History of Treatment - mITT
Listing	2.3.3	Relevant Surgery - mITT
Listing	2.4	Inclusion and Exclusion Criteria - mITT
Listing	3.1.1	Prior Medications - mITT
Listing	3.1.2	Concomitant Medications - mITT
Listing	3.1.3	Non-Drug Therapies - mITT
Listing	3.2.2	Drug Accountability - mITT
Listing	3.3.1	Rescue Treatment - mITT
Listing	4.1	Newly Diagnosed Hepatocellular Carcinoma (HCC) and Disease Progression Events - mITT
Listing	4.2	HBV DNA - mITT
Listing	4.2.3	Listing of Subjects Mutation - mITT
Listing	4.3	Hepatitis B Five Item – mITT
Listing	4.4	Liver Stiffness Measurement – mITT
Listing	4.5	Childs-Pugh Score – mITT
Listing	5.1.1	Non-Serious Treatment-emergent Adverse Events - SA
Listing	5.1.2	Serious Treatment-emergent Adverse Events - SA
Listing	5.1.3	Treatment Related Treatment-emergent Adverse Events - SA
Listing	5.1.4	Treatment-emergent Adverse Events Leading to Permanent Discontinuation of Study Drug - SA
Listing	5.1.5	Treatment-emergent Adverse Events Leading to Permanent Discontinuation from the Study - SA

Listing	5.2	Vital Signs - SA
Listing	5.3.1	Hematology - SA
Listing	5.3.2	Blood Chemistry - SA
Listing	5.3.3	Blood Coagulation - SA
Listing	5.3.4	Urinalysis - SA
Listing	5.3.5	Pregnancy Test - SA
Listing	5.3.6	Alpha Fetoprotein (AFP) – SA
Listing	5.4	Physical Examination - SA
Listing	5.5	B-ULTRASOUND - SA
Figure	4.1.1	The Cumulative Incidence (95% CI) of Newly Diagnosed Hepatocellular Carcinoma (HCC) Over Time in Subjects - mITT
Figure	4.2.1	The Cumulative Incidence (95% CI) of Disease Progression Over Time - mITT
Figure	4.5.1	The Proportion (95% CI) of Subjects with HBV DNA <20 IU/mL Over Time - mITT
Figure	4.5.1.1	The Proportion (95% CI) of Subjects with HBV DNA <69 IU/mL Over Time - mITT
Figure	4.8.1.1	Mean HBV DNA Log10 IU/mL Over Time by Baseline ALT Significance - mITT
Figure	4.8.3	Distribution of HBV DNA levels Over Time - mITT
Figure	4.15.1	Kaplan-Meier Curves for Newly Diagnosed Hepatocellular Carcinoma (HCC) – mITT
Figure	4.15.1.1.1	Kaplan-Meier Curves for Newly Diagnosed Hepatocellular Carcinoma (HCC) in Subjects with Platelets <100 - mITT
Figure	4.15.1.1.2	Kaplan-Meier Curves for Newly Diagnosed Hepatocellular Carcinoma (HCC) in Subjects with Platelets >=100 - mITT
Figure	4.15.3	Kaplan-Meier Curves for Disease Progression – mITT
Figure	4.15.3.1.1	Kaplan-Meier Curves for Disease Progression in Subjects with Platelets <100 - mITT
Figure	4.15.3.1.2	Kaplan-Meier Curves for Disease Progression in Subjects with Platelets >=100 - mITT
Figure	4.18.3.1	Decline in LSM from baseline to Week 240 - mITT
Figure	5.3.1.1	Mean Estimated Glomerular Filtration Rate Over Time by Baseline eGFR - SA
Figure	5.3.1.2	Mean Creatinine Clearance Rate Over Time by Baseline Ccr - SA
Figure	5.3.2	Mean Serum Phosphorus Over Time - SA
Figure	6.1.1	Change of Average LSM/ALT By Visit - mITT
Figure	6.1.2	Change of Average LSM By Visit - mITT
Figure	6.1.3	Change of Median of LSM By Visit - mITT

Figure	6.3.1	Change of Average GPR APRI FIB-4 By Visit - mITT
Figure	6.3.2	Change of Median of GPR APRI FIB-4 By Visit - mITT
Figure	6.4.1	Change of Fibrosis Stage By Visit - mITT