STATISTICAL ANALYSIS PLAN

Study Title:	A Multicenter, Open-label, Randomized Phase 2b Clinical Study to Assess Efficacy and Safety of Bulevirtide in Combination with Pegylated Interferon alfa-2a in Patients with Chronic Hepatitis Delta
Name of Test Drug:	Bulevirtide (BLV)
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BLV	bulevirtide
BMI	body mass index
CHD	chronic hepatitis delta
CI	confidence interval
CRF	case report form
CRP	c-reactive protein
CS	clinically significant
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced liver injury
ECG	electrocardiogram
EOT	end of treatment
EQ-5D-3L	EuroQol 5-dimentions 3-levels
ET	early termination
FAS	full analysis set
FSS	fatigue severity scale
GGT	gamma glutamyl transferase
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HQLQ	hepatitis quality of life questionnaire
HLT	high-level term
INR	International Normalized Ratio
LLOQ	lower limit of quantification
LOD	limit of detection
MedDRA	Medical Dictionary for Regulatory Activities
MEF	missing equals failure
NCS	not clinically significant
NOCB	next observation carried backward
OC	observed case
PEG-IFNα	pegylated interferon alfa-2a
PP	per-protocol

PT	preferred term
Q1, Q3	first quartile, third quartile
QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave representing time for ventricular depolarization
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
RR	electrocardiographic interval representing the time measurement between the R wave of one heartbeat and the R wave of the preceding heartbeat
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SVR24	sustained virological response at follow-up Week 24
SVR48	sustained virological response at follow-up Week 48
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TSH	thyroid stimulating hormone
ULN	upper limit of normal
ULOQ	upper limit of quantification
VAS	visual analogue scale
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentation to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study MYR204. This SAP is based on the study protocol dated 08 February 2022 and the electronic case report form (eCRF). The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objective of this study is to evaluate the efficacy of bulevirtide (BLV) administered subcutaneously at a dose of 2 mg/day or 10 mg/day in combination with pegylated interferon alfa-2a (PEG-IFNα) once weekly relative to 10 mg/day BLV monotherapy in participants with chronic hepatitis delta (CHD).

The secondary objective of this study is to assess the safety of BLV.

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1.2. Study Design

This is a randomized, open-label, active controlled, parallel group multicenter Phase 2b study investigating the efficacy and safety of BLV given alone or with PEG-IFNα in participants with CHD with or without compensated cirrhosis.

A total of 175 participants were randomized, with stratification by presence of liver cirrhosis to 4 treatment groups in the ratio of 1:2:2:2, of whom 174 participants were treated as follows:

- Arm A (n=24): PEG-IFNα for 48 weeks with additional 48 weeks follow-up
- Arm B (n=50): BLV 2 mg/day + PEG-IFNα for 48 weeks followed by BLV 2 mg/day for 48 weeks with an additional 48 weeks follow-up
- Arm C (n=50): BLV 10 mg/day + PEG-IFNα for 48 weeks followed by BLV 10 mg/day for 48 weeks with an additional 48 weeks follow-up
- Arm D (n=50): BLV 10 mg/day for 96 weeks with an additional 48 weeks follow-up

1.3. Sample Size and Power

The primary efficacy endpoint analysis is the difference in rates of sustained virological response at follow-up Week 24 (SVR24) between Arm C and Arm D, where SVR24 is defined as undetectable HDV RNA at follow-up Week 24. With 48 participants per treatment group, a two sided continuity corrected 95% confidence interval for the difference in the SVR24 rates between Arms D and C would extend less than 22.5% from the observed difference. The sample size was slightly increased to 50 participants per treatment group to account for a few potential early withdrawals. Arm B would be of the same size, and Arm A would include 25 participants; hence a total of 175 participants would be randomized.

2. TYPE OF PLANNED ANALYSIS

2.1. Week 24 Analysis

The analysis was conducted when all participants completed visit at Week 24 or discontinued the study. The details of the analysis methods were specified in the separate SAP.

2.2. Follow-up Week 24 Analysis (Primary Analysis)

The analysis was conducted when all participants completed visit at follow-up Week 24 or discontinued the study. The details of the analysis methods were specified in the separate SAP.

2.3. Final Analysis

The final analysis will be performed after all participants have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of participants in each category will be presented; for continuous variables, the number of participants (n), mean, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

All statistical tests will be 2-sided and performed at the 5% significance level unless otherwise specified.

By-participant listings will be presented for all participants in the All Randomized Analysis Set and sorted by participant identification number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order for each participant. The treatment group to which participants were randomized will be used in the listings. Age, sex at birth, and race will be included in the listings, as space permits.

3.1. Analysis Sets

Analysis sets define the participants to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle for each table, figure, and listing.

For each analysis set, the number and percentage of participants eligible for inclusion will be summarized by treatment. In addition, the number and percentage of participants who were excluded from the Per-Protocol (PP) Analysis Set and the reasons for their exclusion will be presented, and the corresponding listing will be provided.

3.1.1. All Randomized Analysis Set

All Randomized Analysis Set includes all participants who were enrolled (informed consent signed) and randomized in the study. This is the primary analysis set for listings.

3.1.2. All Enrolled Analysis Set

All Enrolled Analysis Set includes all participants who were screened and enrolled in the study. The All Enrolled Analysis Set will be used for listings if it differs from the All Randomized Analysis Set.

3.1.3. Full Analysis Set

The Full Analysis Set (FAS) includes all randomized participants who took at least 1 dose of study drug. This is the primary analysis set for efficacy analyses.

3.1.4. Per-Protocol Analysis Set

The Per-Protocol (PP) Analysis set includes participants in the FAS for whom no protocol deviations are judged to have an impact on the analysis of the primary efficacy endpoint of SVR24. The PP Analysis Set is the secondary analysis set for efficacy analyses.

The decision of whether a particular protocol deviation is considered as reason for exclusion from the PP Analysis Set should be made at the follow-up Week 24 data review meeting and documented in the data review meeting report.

3.1.5. Safety Analysis Set

The Safety Analysis Set includes all participants who took at least 1 dose of study drug. This is the primary analysis set for safety analyses.

3.1.6. Anti-drug Antibody Analysis Set

The Anti-drug antibody (ADA) Analysis Set includes all participants who took at least 1 dose of BLV (alone or with PEG-IFNα) and had at least 1 nonmissing ADA data. This is the primary analysis set for the immunogenicity analyses.

3.1.7. Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set will include all randomized participants who took at least 1 dose of BLV (alone or with PEG-IFNα) and had at least 1 nonmissing BLV concentration value reported by the PK laboratory. This is the primary analysis set for the PK analyses.

3.2. Participant Grouping

For analyses based on the FAS, participants will be grouped according to the treatment to which they were randomized. For analyses based on the PP Analysis Set, Safety Analysis Set, PK Analysis Set and ADA Analysis Set, participants will be grouped according to the actual treatment received. The actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration.

3.3. Strata and Covariates

Participants eligible for the study will be randomly assigned to treatment groups via the electronic randomization system in a 1:2:2:2 ratio using a stratified randomization schedule. Stratification will be based on the following variable:

- Cirrhosis status at randomization (presence vs. absence)

For efficacy endpoints, the stratification factor and region (France; Moldova/Romania; Russia) will be included as covariates in the efficacy analysis model as specified in Section 6.

3.4. Examination of Participant Subgroups

The efficacy endpoints will be examined using the following subgroups. Details will be specified in the corresponding sections.

- Cirrhosis status at randomization (presence vs. absence)
- Prior PEG-IFNα use (yes vs. no)
- Concomitant HBV medication (yes vs. no)

The safety endpoints will be examined using the following subgroups. Details will be specified in the corresponding sections.

- ADA incidence at Week 96 (positive vs. negative)
- ADA incidence at Week 48 (positive vs. negative)

3.5. Multiple Comparisons

All endpoint tests will be conducted at the significant level of 0.05 with no multiplicity adjustment in this Phase 2b study.

3.6. Missing Data and Outliers

3.6.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified.

The handling of missing or incomplete dates for AE is described in Section 7.1.5.2, and for prior and concomitant medications in Section 7.5. Imputation rules adopted in the efficacy analyses are specified in Section 6.

3.6.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

3.7. Data Handling Conventions and Transformations

In general, age in years at the time when informed consent was signed will be used for analyses and presented in listings.

For virology laboratory data and pharmacokinetics data the following rules will be applied:

- Values below the lower limit of quantification (< LLOQ) with specification of target not detected will be imputed as 0.
- Values < LLOQ without specification of target not detected will be imputed as half of the LLOQ value, if LLOQ does not equal the limit of detection (LOD).
- Values < LLOQ will be imputed as 0, if LLOQ equals LOD (ie, HBV DNA by MLM).
- Values above the upper limit of quantification (ULOQ) will be imputed as the ULOQ.
- Non-measurable data will be considered as missing data.

For $\log_{10}$ transformed data, the following rules will be applied:

- Untransformable value of 0 will be imputed as 0 if LOD > 1.
- Untransformable value of 0 will be imputed as $\log_{10}(LOD/2)$ if LOD < 1.

The LLOQ and LOD for virology parameters are specified in the Table 3-1.

Table 3-1. Virology LLOQ and LOD

Parameter	Lab Institute	LLOQ	LOD
HDV RNA	Frankfurt (transfered through MLM)	50 IU/mL	6 IU/mL
HBV DNA	Frankfurt (transfered through MLM)	10 IU/mL	10 IU/mL
HBV DNA	Invitro	100 IU/mL	20 IU/mL
HBsAg	Frankfurt (transfered through MLM)	not applicable	0.05 IU/mL

Safety laboratory data that are continuous in nature but less than the LLOQ or above the ULOQ (reported in the form of "< xx.xx" or "> xx.xx") will be imputed as one half of LLOQ, or as the same as ULOQ to calculate summary statistics.

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study day will be calculated from the first dose date of study drug and derived as follows:

1) For postdose study days: Assessment Date – First Dose Date + 1
2) For days prior to the first dose: Assessment Date – First Dose Date

Therefore, Study Day 1 is the day of first dose of study drug administration.

3.8.2. Analysis Visit Windows

The nominal visit as recorded on the CRF will be used when data are summarized by visit. However, when the nominal visit was made outside the analysis visit window (Table 3-2), the value will not be used in the analyses.

Table 3-2. Analysis Visit Windows for by Visit Assessments

Analysis Visit	Target Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 4	29	2	59
Week X	X×7+1	X×7+1-30	X×7+1+30
Follow-up Week X (Arm A)	(48+X)×7+1	(48+X)×7+1-30	(48+X)×7+1+30
Follow-up Week X (Arm B/C/D)	(96+X)×7+1	(96+X)×7+1-30	(96+X)×7+1+30

The measurement at end of treatment (EOT) are defined as records collected at the visit within (last dose date of bulevirtide ± 7 days) for Arms B, C and D, and (last dose of PEG-IFN + 6 days ± 7 days) for Arm A.

The data collected at unscheduled visits (including early termination [ET] visits) will be used in the following ways:

- An unscheduled visit on or prior to the first dose of study drug may be included in the calculation of the baseline value, if applicable.
- Unscheduled visits after the first dose of study drug will be included in determining the maximum postbaseline toxicity grade.
- Unscheduled visits after the first dose of study drug will be included in determination of the value at EOT.
- Record from unscheduled visit will be assigned to a visit when there is no available data in the corresponding analysis visit window. If multiple measurements from unscheduled visits exist, the selection rule specified in Section 3.8.3 will be followed.

3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window.

If multiple valid, nonmissing measurements from unscheduled visits exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last nonmissing value on or prior to the first dose of study drug will be selected, unless specified differently.
- For postbaseline, record from ET visit will be selected. If there is no available ET record, the data from unscheduled visits will be selected as below.
  - The record closest to the target day for that visit will be selected.
  - If there are 2 records that are equidistant from the target day, the later record will be selected.

4. PARTICIPANT DISPOSITION

4.1. Participant Enrollment and Disposition

A summary of participant enrollment will be provided by treatment group for each region. The summary will present the number and percentage of participants enrolled. For each column, the denominator for the percentage calculation will be the total number of participants analyzed for that column.

A similar enrollment table will be provided by randomization stratum. The denominator for the percentage of participants in the stratum will be the total number of enrolled participants.

A summary of participant disposition will be provided by treatment group. This summary will present the number of participants screened, the number of participants who met all eligibility criteria but were not randomized with reasons participants not randomized, the number of participants enrolled, the number of participants randomized, the number of participants randomized but not dosed, and the number of participants in each of the categories listed below:

- Safety Analysis Set
- Full Analysis Set
- Per-Protocol Analysis Set
- Completed Week 48
- Completed Week 96
- Completed Follow-up Week 24
- Completed study (ie, complete follow-up Week 48)
- Did not complete the study with reasons for premature discontinuation of study

For the status of study completion and reasons for premature discontinuation, the number and percentage of participants in each category will be provided. The denominator for the percentage calculation will be the total number of participants in the Safety Analysis Set corresponding to that column.

The following by-participant listings will be provided by participant identification (ID) number in ascending order to support the above summary tables:

- Reasons for premature study discontinuation
- Reasons for screen failure (will be provided by screening ID number in ascending order)

4.2. Extent of Study Drug Exposure and Compliance

The sponsor will capture, clean, and validate the missing doses that are not documented in the participant diary (hereafter referred to as "sponsor-identified missed doses") in an excel file (included in the clean file report as an appendix).

4.2.1. Study Drug Exposure

The total duration of BLV exposure in weeks will be computed as (last dose date of BLV – first dose date of BLV + 1)/7 regardless of any temporary interruptions and will keep 2 decimal places (ie, 4.56 weeks). Total duration of PEG-IFNα exposure in weeks will be computed as (last dose of PEG-IFNα + 6 – first dose date of PEG-IFNα + 1)/7 regardless of any temporary interruptions and will keep 2 decimal places.

The total dose (in mg or μg) administered will be computed as the sum of all doses administered (as reported in the participant diary, which takes participant reported missed doses into consideration) minus sponsor identified missed doses (the number of days without dosing times the planned daily dose for BLV).

The dose intensity (in mg/week or μg/week) will be computed as the total dose administered divided by the total duration of exposure.

4.2.2. Study Drug Compliance

The compliance rate of the full regimen will be computed as the ratio of the total dose administered to the expected full regimen dose and expressed as a percentage. The expected full regimen dose for BLV is defined as 96 weeks of planned daily dosage (2 mg or 10 mg) for participants in Arms B, C and D, and the expected full regimen dose for PEG-IFNα is defined as 48 weeks of physician-prescribed dosage for participants in Arms A, B, and C.

The total number of missed doses will be computed as the expected total number of doses minus the number of doses administered (as reported in the participant diary), plus the number of sponsor-identified missed doses. If this results in a negative number, the total number of missed doses will be set to the number of sponsor-identified missed doses, or zero if there were no sponsor identified missed doses.

The expected total number of BLV doses will be defined as (last on-treatment visit date [or ET date, whichever comes first] – first dose date + 1). The expected total number of PEG-IFNα doses will be defined as (last on-treatment visit date [or ET date, whichever comes first] – first dose date + 1)/7 and rounded to the least integer greater than or equal to the quotient using the ceiling function. If this results in expected total number of doses greater than 48 for PEG-IFNα, it will be set to 48.

The proportion of missed doses will be computed as the ratio of the total number of missed doses to the expected total number of doses and expressed as a percentage.

4.2.3. Summaries of Study Drug Exposure and Compliance

Descriptive statistics for following parameters will be presented by treatment group for BLV by Weeks 48 and 96, and for PEG-IFNα by Week 48.

- Total duration of exposure
- Total dose administered
- Dose intensity
- Compliance rate
- Participants with ≥ 1 missed dose
- Total number of missed doses
- Proportion of missed doses

In addition, the by-participant listings of study drug administration and accountability will be provided. No formal statistical testing is planned.

4.3. Protocol Deviations

Participants who did not meet the eligibility criteria for study entry but enrolled in the study, will be summarized regardless of whether they were exempted by the sponsor or not. The summary will present the number and percentage of participants who did not meet at least 1 eligibility criterion and the number of participants who did not meet specific criteria by treatment group based on the All Randomized Analysis Set. A by-participant listing will be provided for those participants who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that participants did not meet and related comments, if collected.

Protocol deviations occurring after participants entered the study are documented during routine monitoring. The number and percentage of participants with important protocol deviations by deviation reason will be summarized by treatment group for the All Randomized Analysis Set. A by-participant listing will be provided for those participants with important protocol deviation.

4.4. Assessment of COVID-19 Impact

This study was ongoing during the novel coronavirus (COVID-19) pandemic which has an impact on the study conduct. This section describes how special situations due to COVID-19 will be handled in the analysis.

4.4.1. Protocol Deviations Due to COVID-19

A summary of important protocol deviations due to COVID-19 will be provided, similar to the summary described in the protocol deviations section (Section 4.3).

The number and percentage of participants with non-important protocol deviations related to COVID-19 by deviation reason will be summarized by treatment group.

A by-participant listing will be provided for participants with important protocol deviations related to COVID-19 if applicable. A separate listing will be provided for participants with non-important protocol deviations related to COVID-19 if applicable.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Participant demographic and baseline characteristics variables will be summarized by treatment group and overall using descriptive statistics for continuous variables, and number and percentage of participants for categorical variables. The summary of demographic and baseline characteristics data will be provided for the FAS and PP Analysis Sets for the following:

- Age (years)
- Sex (male, female)
- Race (Asian, Black or African American, White, other)
- Height (cm)
- Body weight (kg)
- Body mass index (BMI, kg/m^2)
- BMI categories (<30 kg/m^2, ≥ 30 kg/m^2)

If Safety Analysis Set differs from Full Analysis Set, or there are participants whose actual treatment differs from randomized treatment for the whole treatment period, this summary will be provided for Safety Analysis Set as well.

A by-participant demographic and baseline characteristics listing, including the informed consent date, will be provided. No formal statistical testing is planned.

5.2. Other Baseline Characteristics

Participant's other baseline characteristics variables will be summarized by treatment group and overall using descriptive statistics for continuous variables, and number and percentage of participants for categorical variables. The summary of other baseline characteristics data will be provided for the FAS and PP Analysis Sets for the following:

- Cirrhosis status at randomization (presence, absence)
- Baseline Child–Pugh score for cirrhotic participants
- Baseline Child–Pugh class for cirrhotic participants
- Abdominal ultrasound (abnormal clinically significant [CS], abnormal not clinically significant [NCS], normal)

- Baseline serum alpha-fetoprotein (AFP; IU/mL)
- Baseline alanine aminotransferase (ALT; U/L)
- Baseline ALT (≤ upper limit of normal [ULN], > ULN to ≤ 1.5×ULN, > 1.5×ULN)
- Baseline creatinine clearance (mL/min)
- Baseline creatinine clearance (≥ 60 to < 90 mL/min vs. ≥ 90 mL/min)
- Baseline liver stiffness (kpa)
- Baseline liver stiffness (< 12 kPa, 12 to 20 kPa, > 20 kPa)
- Prior PEG-IFNα use (Prior medication preferred name contains the word 'interferon') (yes, no)
- HIV antibody (positive, negative, missing)
- HCV antibody (positive, negative, missing)
- HDV antibody (positive, negative, missing)
- HBeAg (positive, negative, missing)
- HBeAg antibody (positive, negative, missing)
- Qualitative HBV DNA at screening (positive, negative, missing)
- HDV genotype
- HBV genotype
- Baseline HDV RNA (log_{10} IU/mL)
- Baseline HBV DNA (log_{10} IU/mL)
- Baseline HBV DNA (< LLOQ target not detected, < LLOQ target detected, ≥ LLOQ)
- Baseline HBsAg (log_{10} IU/mL)
- Baseline aspartate aminotransferase (AST) (U/L)
- Baseline alkaline phosphatase (ALP) (U/L)
- Baseline gamma glutamyl transferase (GGT) (U/L)

- Baseline platelet count (×10^9/L)
- Baseline total bilirubin (µmol/L)
- Baseline total bile salts (µmol/L)
- Concomitant oral HBV medication (yes, no)

If the Safety Analysis Set differs from the Full Analysis Set, or there are participants whose actual treatment differs from randomized treatment for the whole treatment duration, this summary will be provided for Safety Analysis Set as well.

A by-participant listing of other baseline characteristics will be provided. No formal statistical testing is planned.

5.3. Substance Use

Participant substance use will be summarized by treatment group and overall using number and percentage of participants. The summary will be provided for the FAS and PP Analysis Sets for the following:

- Smoking status (current, former, never)
- Alcohol consumption status (current, former, never)
- Alcohol breath test at screening (positive, negative)
- Alcohol breath test at baseline (positive, negative)
- Urine drug test at screening (positive, negative)
- Drug abuse status (current, former, never)

5.4. Medical History

Medical history collected at screening will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) 26.0.

Medical history will be summarized for Safety Analysis Set by system organ class (SOC), preferred term (PT), treatment group, and overall. Participants who report 2 or more medical history items that are coded to the same SOC and/or PT will be counted only once by the unique coded term in the summary. No formal statistical testing is planned. A by-participant listing of medical history will be provided.

6. EFFICACY ANALYSES

6.1. General Considerations

The primary analysis set for efficacy analyses will be the FAS, defined in Section 3.1.3.

Derivation of Multi-component Endpoints

For the derivation of multi-component endpoints including combined response, virological response, and composite endpoint we will use the following steps unless otherwise specified:

- Step 1: assign individual components to analysis visit windows specified in Section 3.8.2
- Step 2: impute missing data for individual components
- Step 3: derive the compound endpoint with the corresponding imputed individual components

Missing Data Imputation

Below are the descriptions for the imputation methods that will be used in the efficacy analyses:

- Missing Equals Failure (MEF): For binary response endpoints, missing value will be imputed as nonresponder. For all analyses of the primary endpoint using FAS, MEF will be adopted when missing was not related to COVID-19. CCI [redacted]
- Next Observation Carried Backward (NOCB): Missing value will be imputed using the next observation (including observation from unscheduled visit). For all analyses (except the sensitivity analysis) of the primary efficacy endpoint using FAS, NOCB will be used when missing was related to COVID-19.
- Observed Case (OC): Missing values remain missing. The OC will be used for analyses of continuous endpoints, analyses using PP Analysis Set, and analyses for completers.

6.2. Primary Efficacy Endpoint

The primary efficacy endpoint is SVR24 defined as undetectable HDV RNA (HDV RNA value < LLOQ with target not detected) at follow-up Week 24.

6.2.1. Primary Analysis of the Primary Efficacy Endpoint

The primary analysis of SVR24 is the estimated rate difference between Arms C and D with 95% exact unconditional confidence interval (CI) based on the score statistic. The p-value from two-sided Fisher's exact test will also be provided. For each arm the response rate with Clopper-Pearson 95% CIs will be presented.

6.2.2. Sensitivity Analysis of the Primary Efficacy Endpoint

The same analysis as specified in Section 6.2.1 will be repeated using the data for which missing values were imputed as failure regardless of whether it was related to COVID-19 (Section 6.1).

6.2.3. Logistic Regression of the Primary Efficacy Endpoint

To evaluate the impact of covariates on the primary efficacy endpoint, the SVR24 response in Arms C and D will be analyzed using the logistic regression of the same data as the primary analysis. The covariates to be included are stratification factor and region. The treatment odds ratio with 95% CI and p-value will be presented. The p-value for each covariate will also be provided.

6.2.4. Per-protocol Analysis of the Primary Efficacy Endpoint

The same analysis as specified in Section 6.2.1 will be repeated using the PP Analysis Set.

6.2.5. Subgroup Analysis of the Primary Efficacy Endpoint

Descriptive statistics for SVR24 will be provided by treatment and subgroups for efficacy endpoints as defined in Section 3.4 using FAS and PP Analysis Set, respectively. The Clopper-Pearson 95% CIs of response rate in each arm will also be presented.

6.2.6. Other Analyses of the Primary Efficacy Endpoint

For SVR24 response in Arms A and B, and remaining pairwise comparisons of SVR24 (Arm B vs Arm A; Arm C vs Arm A; Arm D vs Arm A; Arm C vs. Arm B; Arm D vs. Arm B), the same analyses as described in Section 6.2.1, 6.2.2, 6.2.3, 6.2.4 and 6.2.5, respectively, will be performed. The logistic regression will include data from all arms instead of constructing separate models for each pair of arms.

6.3. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Undetectable HDV RNA at Weeks 48 and 96
- Combined response at follow-up Week 24 and 48, defined as the fulfilment of both conditions below:
  - Undetectable HDV RNA or HDV RNA decrease ≥ 2 $\log_{10}$ IU/mL from baseline
  - ALT normalization
- Sustained virological response 48 (SVR48), defined as undetectable HDV RNA at follow-up Week 48
- Change from baseline in liver stiffness as measured by elastography at Week 48 and 96, and follow-up Week 48

6.3.1. Analysis of Secondary Efficacy Endpoints

Undetectable HDV RNA at Weeks 48 and 96

Descriptive statistics will be provided by treatment group for undetectable HDV RNA at Week 48 and 96 using FAS, and the Clopper-Pearson 95% CIs of response rate in each arm will also be presented. The same summary will be repeated by subgroups for efficacy endpoints as defined in Section 3.4.

Combined Response at Follow-up Week 24 and 48

Descriptive statistics will be provided by treatment group for combined response at follow-up Week 24 and 48 using FAS, and the Clopper-Pearson 95% CIs of response rate in each arm will also be presented. The estimated rate differences between each pair of arms with 95% exact unconditional CI, and the p-value from Fisher's exact test will also be provided.

Descriptive statistics for combined response at follow-up Week 24 and 48 will be provided by treatment and subgroups for efficacy endpoints as defined in Section 3.4 using FAS. The Clopper-Pearson 95% CIs of response rate in each arm will also be presented.

Sustained Virological Response 48 (SVR48)

Descriptive statistics will be provided by treatment group for SVR48, and the Clopper-Pearson 95% CIs of response rate in each arm will also be presented. The estimated rate differences between each pair of arms with 95% exact unconditional CI, and the p-value from Fisher's exact test will also be provided.

The same analyses as described above will be repeated for completers (participants with observed case).

To evaluate the impact of covariates, SVR48 will be analyzed using the logistic regression. The logistic regression will include data from all arms, and the covariates to be included are stratification factor and region. The odds ratio of each pair of arms with 95% CI and p-value will be presented. The p-value for each covariate will also be provided.

Descriptive statistics for SVR48 will be provided by treatment and subgroups for efficacy endpoints as defined in Section 3.4 using FAS and for completers, respectively. The Clopper-Pearson 95% CIs of response rate in each arm will also be presented.

Change from Baseline in Liver Stiffness at Week 48 and 96, and Follow-up Week 48

The mixed-effects models for repeated measurements (MMRM) model will be used to evaluate treatment effect on change from baseline in liver stiffness using FAS with treatment, region, presence of cirrhosis, visit and treatment by visit interaction included as fixed effects, and baseline value as covariable. An unstructured variance-covariance matrix will be used. The Kenward-Roger method will be used to estimate the degrees of freedom. Restricted maximum likelihoods (REML) will be used to fit the model. Missing change values will not be otherwise

imputed using MMRM. For each treatment group at each postbaseline visit, the least squares (LS) mean with 95% CI will be presented. For each pair of arms at each postbaseline visit, the difference in LS means with 95% CI and the p-value will be provided.

Since the study schedule differs between Arm A and Arms B, C, D, 2 different models will be fitted:

- The first model will be used for pairwise comparisons among Arms B, C and D, and data from Arms B, C and D will be included.
- The second model will be used for comparisons between Arm A and each of the rest of the arms, and data from all arms at the Arm A scheduled visits will be included.

Descriptive statistics of liver stiffness at each visit as well as the change from baseline will be provided by treatment group. The summary will be repeated by subgroups for efficacy endpoints defined in Section 3.4 using FAS. The plots of mean ± SD of change from baseline in liver stiffness over time, as well as by subgroup of cirrhosis status, will be presented.

CCI [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
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- [redacted]
- [redacted]
- [redacted]
- CCI [redacted]
- [redacted]


CCI


CCI

6.5. Additional Efficacy Endpoint

The composite endpoint is defined as the fulfilment of both conditions below:

- Undetectable HDV RNA

- ALT normalization

The composite endpoint at follow-up Week 24 will be analyzed in the same way as SVR24. The composite endpoint at follow-up Week 48 will be analyzed in the same way as SVR48.

In addition, a by-participant listing will be provided for SVR24, SVR48, and composite endpoint at follow-up Week 24 and 48. This listing will also present HDV RNA (log_{10} IU/mL) and change from baseline, ALT normalization, ALT and change from baseline, HBV DNA (log_{10} IU/mL), HBsAg (log_{10} IU/mL) and liver stiffness at all visits. The same listing will be repeated for non-responders of SVR24, SVR48, or composite endpoint at follow-up Week 24 or 48.

CCI [redacted]

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the MedDRA 26.0. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

The severity of adverse events will be graded as Grade 1, 2, 3, 4, or 5 according to the Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0), and the highest observed severity grade for each event will be reported. Events for which a CTCAE term cannot be found will be assigned a severity grade according to the classification of AEs specified in study protocol. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

7.1.3. Relationship of Adverse Events to Study Drug

The related AEs for each study drug are those for which the investigator selected "Reasonable possibility" on the AE CRF to the question of causality. Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-participant data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAEs captured and stored in the Gilead global safety database before data finalization.

For SAEs with multiple reports (initial reports and one or more follow-up reports), only the last report will be included in the summary tables and listings.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug

- Any AEs leading to premature discontinuation of study drug

7.1.5.2. Incomplete Dates

If the onset or end date of an AE is fully or partially unknown, the incomplete date will be imputed before analysis according to the rules in the Table 7-1, Table 7-2, Table 7-3 and Table 7-4.

Table 7-1. Impute Partial AE Dates (year and month available but day missing)

Scenario	Imputed Onset Date	Imputed End Date
AE year/month same as first dose year/month	First dose date or AE end date whichever comes first	Last day of the month
AE year/month before first dose year/month	First day of the month	Last day of the month
AE year/month after first dose year/month	First day of the month	Last day of the month

Table 7-2. Impute Partial AE Dates (year available but month and day missing)

Scenario	Imputed Onset Date	Imputed End Date
AE year same as first dose year	First dose date or AE end date, whichever comes first	31 December
AE year before first dose year	01 January	31 December
AE year after first dose year	01 January	31 December

Table 7-3. Impute Completely Missing AE Onset Date

Scenario	Imputed Onset Date	Imputed End Date
AE end date before first dose date	AE end date	NA
AE end date after first dose date	First dose date	NA

Table 7-4. Impute Completely Missing AE End Date

Scenario	Imputed Onset Date	Imputed End Date
All	NA	Last visit date or AE onset date, whichever comes last

7.1.6. Summaries of Adverse Events and Deaths

Summaries of AEs will be provided for the Safety Analysis Set.

7.1.6.1. Summaries of AE incidence

A brief, high-level summary of the number and percentage of participants who experienced at least 1 TEAE in the categories described below will be provided by treatment group. All deaths observed in the study will also be included in this summary.

For the AE categories described below, summaries will be provided by SOC, PT, and treatment group.

- TEAEs
- TEAEs with Grade 3 or higher
- TEAEs with Grade 2 or higher
- TEAEs related to BLV
- TEAEs related to PEG-IFNα
- TEAEs related to BLV with Grade 3 or higher
- TEAEs related to PEG-IFNα with Grade 3 or higher
- TEAEs related to BLV with Grade 2 or higher
- TEAEs related to PEG-IFNα with Grade 2 or higher
- TE SAEs
- TE SAEs related to BLV
- TE SAEs related to PEG-IFNα
- TEAEs leading to premature discontinuation of BLV
- TEAEs leading to premature discontinuation of PEG-IFNα
- TEAEs leading to dose reduction of PEG-IFNα
- TEAEs leading to death (ie, outcome of death)

Multiple events will be counted only once per participant in each summary. Adverse events will be summarized and listed first in alphabetical order of SOC, and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual participant during the study.

In addition to the above summary tables, all TEAEs, TEAEs with Grade 3 or higher, TEAEs occurred in ≥ 10% participants of any arm, TE SAEs, TEAEs related to BLV, TEAEs related to PEG-IFNα, TE SAEs related to BLV, TE SAEs related to PEG-IFNα, TEAEs leading to premature discontinuation of BLV, and TEAEs leading to premature discontinuation of PEG-IFNα will be summarized by PT only, in descending order of total frequency.

The TEAEs summaries described above will also be provided for period by Week 48. In addition, the TEAEs during treatment and AEs in post-treatment period will be summarized by PT and treatment group, respectively.

In addition, data listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent
- All SAEs
- All Deaths
- All AEs with severity of Grade 3 or higher
- All AEs with severity of Grade 2 or higher
- All SAEs related to BLV
- All SAEs related to PEG-IFNα
- All AEs leading to premature discontinuation of BLV
- All AEs leading to premature discontinuation of PEG-IFNα
- All AEs leading to dose reduction of PEG-IFNα

7.1.7. Additional Analysis of Adverse Events

7.1.7.1. Hepatic Adverse Events

The hepatic AEs will be identified using MedDRA search terms. The number and percentage of participants who experienced any TE hepatic AE will be summarized by PT and treatment group. In addition, the hepatic AEs will be summarized for on-treatment period up to Week 48, on-treatment period up to Week 96 and follow-up period, respectively. The by-participant listing of hepatic AEs will also be provided.

7.1.7.2. Subgroup Analyses of Adverse Events

The following subgroup analyses will be provided by PT and treatment group:

- TEAEs by ADA incidence at Week 96
- TEAEs by Week 48 by ADA incidence at Week 48

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. When values are below the LOQ, they will be listed as such, and the imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

A by-participant listing for laboratory test results will be provided for hematology, coagulogram, serum chemistry, total bile salts, and urinalysis separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the CTCAE severity grade will be flagged in the data listings, as appropriate. No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics of baseline values, values at each postbaseline visit, change and percentage change from baseline at each postbaseline visit will be provided by treatment group for the following laboratory tests. White blood cell differential results from manual assay will not be included as they are not considered valid.

- Hematology
  - Haematocrit (%)
  - Haemoglobin (g/dL)
  - Platelet Count (×10^9/L)
  - Reticulocytes (‰)
  - Red Blood Cells (×10^12/L)
  - White Blood Cells (×10^9/L)
  - Absolute Neutrophils (×10^9/L)
  - Relative Neutrophils (%)
  - Absolute Eosinophils (×10^9/L)
  - Relative Eosinophils (%)
  - Absolute Basophils (×10^9/L)
  - Relative Basophils (%)
  - Absolute Monocytes (×10^9/L)

  - Relative Monocytes (%)
  - Absolute Lymphocytes (×10^9/L)
  - Relative Lymphocytes (%)
- Total Bile Salts (µmol/L)
- Coagulogram
  - Prothrombin Time (%)
  - Activated Partial Thromboplastin Time (aPTT) (sec)
  - International Normalized Ratio (INR)
- Chemistry
  - Total Protein (g/L)
  - Albumin (g/L)
  - AST (U/L)
  - GGT (U/L)
  - Total Amylase (U/L)
  - Pancreatic Amylase (U/L)
  - ALP (U/L)
  - Lipase (U/L)
  - Total Bilirubin (µmol/L)
  - Direct Bilirubin (µmol/L)
  - Total Cholesterol (mmol/L)
  - Creatinine (µmol/L)
  - Urea (mmol/L)
  - Glucose (mmol/L)

- Potassium (mmol/L)
- Sodium (mmol/L)
- Chloride (mmol/L)
- Phosphorus (mmol/L)
- C-Reactive Protein (CRP) (mg/L)
- Vitamin D (ng/mL)
- Thyroid stimulating hormone (TSH; mU/L)

- Urinalysis
  - pH
  - Specific Gravity (g/L)

The change and percentage change from EOT at each visit will be provided by treatment group for AST, total bilirubin and direct bilirubin.

A baseline laboratory value will be defined as the last measurement obtained on or prior to the first dose of study drug. Change from baseline to a postbaseline visit will be defined as the visit value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

Median (Q1, Q3) of the observed values for these laboratory tests will be plotted using a line plot by treatment group and visit.

7.2.2. Summaries of Qualitative Laboratory Results

The summary of clinical assessment of laboratory variables (abnormal high CS, abnormal high NCS, normal, abnormal low NCS, abnormal low CS) will be presented by visit and treatment group for laboratory tests listed in Section 7.2.1 as well as for urinalysis of protein, glucose, bilirubin, urobilinogen, ketones, erythrocytes, leukocytes, and nitrites.

7.2.3. Graded Laboratory Values

The CTCAE Version 5.0 will be used to assign toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

7.2.3.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of last dose of study drug plus 30 days. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.3.2. Summaries of Laboratory Abnormalities

The following summaries (number and percentage of participants) for treatment-emergent laboratory abnormalities will be provided by lab test and treatment group. Participants will be categorized according to the most severe postbaseline abnormality grade for a given lab test:

- Graded laboratory abnormalities
- Grade 3 or 4 laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of participants with nonmissing postbaseline values up to 30 days after last dosing date. The summaries will be repeated for period by Week 48.

A by-participant listing of treatment-emergent laboratory abnormalities will be provided. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades or abnormal flags displayed. In addition, the listing of treatment-emergent Grade 3 or 4 laboratory abnormalities will also be provided.

7.2.4. Liver-related Laboratory Evaluations

7.2.4.1. Potential Drug Induced Liver Injury (DILI)

The participants with potential drug induced liver injury (DILI) will be summarized for period up to Week 48 and Week 96 by treatment, and the corresponding listing will be provided. The potential DILI is defined as participants meeting any of the following criteria at on-treatment visits:

- Criteria 1: ALT and/or AST > 3×ULN and Total Bilirubin > 2×ULN
- Criteria 2: ALT > 5×ULN
- Criteria 3: Total Bilirubin > 2×ULN

7.2.5. Shifts Relative to the Baseline Value

Shift tables will be presented by showing changes in results from baseline value (abnormal high CS, abnormal high NCS, normal, abnormal low NCS, abnormal low CS) to Week 48 and 96 for laboratory tests listed in Section 7.2.1 and 7.2.2. The number and percentage of participants in each cross-classification group of the shift table will be presented. Participants with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation.

7.3. Body Weight and Vital Signs

Descriptive statistics will be provided by treatment group for body weight and vital signs (systolic and diastolic blood pressures [mmHg], respiratory rate [breaths/min] and body temperature [C]) as follows:

- Baseline value
- Values at each postbaseline visit
- Change from baseline at each postbaseline visit

A baseline value will be defined as the last available value collected on or prior to the first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3. No formal statistical testing is planned.

A by-participant listing of vital signs will be provided. Body weight will be included in the vital signs listing if space permits. If not, they will be provided separately.

7.4. Physical Examination

For each type of local reaction at injection site, the number and percentage of participants with at least one instance reported will be summarized by severity and treatment, and the maximum severity grade of the reaction type will be presented. In addition, a by-participant listing will be provided for local reaction at injection site.

7.5. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the World Health Organization (WHO) Drug dictionary.

7.5.1. Prior and Concomitant Medications

Prior medications are defined as medications stopped prior to the first dose date of study drug. Concomitant medications are defined as ongoing medications or medications stopped on or after the first dose date of study drug, excluding medications started after the last dose date of study drug. Post-treatment medications are defined as medications started after the last dose date of study drug. If the medication start or stop date is partially unknown, the incomplete date will be imputed according to the rules in the Table 7-5. If a medication cannot be classified using the reported and/or imputed start and end dates, it will be considered as concomitant medication. The original reported dates will be presented in data listings.

Table 7-5. Impute Partial Medication Dates

Scenario	Imputed Start Date	Imputed End Date
Unknown year	Missing	Missing
Unknown month	01 January	31 December
Unknown day	First day of month	Last day of month

Prior medications, concomitant medications and post-treatment medications will be summarized separately by preferred name and treatment group. A participant reporting the same medication more than once will be counted only once when calculating the number and percentage of participants who received that medication. The summary will be ordered by preferred term in order of descending overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned. In addition, by-participant listings will be provided.

7.5.2. HBV Medications

HBV medications are defined as oral medications with preferred names containing any of the following terms: tenofovir, tenofovir alafenamide, tenofovir disoproxil fumarate, tenofovir disoproxil, entecavir, adefovir, lamivudine, telbivudine, adefovir dipivoxil.

The following HBV medications summaries will be provided by preferred name and treatment group, and the corresponding listings as well as the listing of participants with all HBV medication started after last dose date of study drug will be generated.

- Participants with concomitant HBV medications
- Participants with HBV medications started before baseline and ongoing during treatment: participants with any HBV medication started before the first dose date of study drug, and any concomitant HBV medication (same as or different from the previous one[s]) ongoing on/after the first dose date of study drug
- Participants with prior HBV medications (stopped before baseline): participants with all HBV medications stopped before the first dose date of study drug
- Participants with HBV medications started on-treatment: participants with all HBV medications started on/after the first dose date of study drug and on/before the last dose date of study drug
- Participants with HBV medications started post-treatment: participants with all HBV medications started after the last dose date of study drug

Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

7.6. Electrocardiogram Results

7.6.1. Investigator Electrocardiogram Assessment

The investigators' assessment of electrocardiogram (ECG) results (normal, abnormal NCS, abnormal CS, or missing) will be tabulated at each visit by treatment group. In addition, a shift table of the ECG assessment at each visit compared with baseline values will be presented by treatment group. The number and percentage of participants in each cross-classification group of the shift table will be presented. Participants with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation.

A by-participant listing for ECG assessment results will be provided. No formal statistical testing is planned.

7.6.2. Other Electrocardiogram Assessment

Descriptive statistics will be provided by visit and treatment group for ECG measurements and change from baseline including RR interval (msec), PQ interval (msec), QRS interval (msec), QT interval (msec), QT interval corrected for heart rate (QTc, Bazett) (msec), and heart rate(beats/min).

In addition, the number and percentage of participants with QTc values in each category below will be summarized by visit and treatment group:

- < 451 msec
- 451 to 480 msec
- 481 to 500 msec
- > 500 msec

The number and percentage of participants with QTc change from baseline values in each category below will be summarized by visit and treatment group:

- > 30 msec
- > 60 msec

In addition, a by-participant listing for ECG measurements will be provided. No formal statistical testing is planned.

7.7. Other Safety Measures

A data listing will be provided for participants who become pregnant during the study.

8. IMMUNOGENICITY ANALYSES

8.1. ADA Incidence and Prevalence

The evaluable population for ADA prevalence is participants with at least one nonmissing ADA data at any visit, including the baseline. The evaluable population for ADA incidence is participants with at least one nonmissing ADA data at postbaseline visits.

- ADA prevalence: participants with positive ADA at any visit including the baseline will be considered as ADA positive. Otherwise, participants will be considered as ADA negative.
- ADA incidence is defined in the Table 8-1

Table 8-1. Definition of ADA Incidence

Baseline ADA	Postbaseline ADA	ADA Incidence
Negative/Missing	Positive (any visit)	Positive
Positive/Negative/Missing	Negative (all visits)	Negative
Positive	Positive (any visit)	Negative

The number and percentage of ADA prevalence and incidence at Week 48 and Week 96 will be summarized by treatment group. The corresponding listing will be provided.

9. PHARMACOKINETIC (PK) ANALYSES

9.1. PK Sample Collection

For participants in Arms B, C and D, blood samples for analysis of BLV concentration will be collected at all treatment visits. Sampling will be done 60 ±15 minutes after BLV injection.

9.2. PK Analyses

Descriptive statistics (including geometric mean, arithmetic coefficients of variation [%CV], and geometric %CV) of BLV plasma concentrations will be presented by treatment group and visit. In addition, the geometric mean of BLV plasma concentration will be plotted by treatment group and visit using a line plot. The by-participant listing of PK sampling details and PK concentrations will be provided.

10. OTHER EVALUATIONS

The analyses of variables from other evaluation will be conducted using the FAS.

10.1. HBeAg

HBeAg status and HBeAg antibody status will be summarized by visit and treatment group for participants who are positive for HBeAg at screening.

10.2. Liver Biopsy - Molecular Analysis and Gene Expression

Descriptive statistics will be presented by visit and treatment group on $\log_{10}$ transformed data for the following parameters (including the change from baseline). In addition, the by-participant listings will be provided.

Molecular analysis:

- Relative expression level of HDV RNA
- Relative expression level HBV RNA (S region)
- Relative expression level of total HBV RNA (X region)
- Relative expression level of pregenomic HBV RNA
- HBV DNA (S region; copies/cell)
- Total HBV DNA (X region; copies/cell)
- HBsAg

Molecular analysis using immunofluorescence staining:

- HDAg, % of positive hepatocytes

Gene expression:

- Relative expression level of NTCP mRNA
- Relative expression level of CYP7A1 mRNA
- Relative expression level of CXCL10 mRNA
- Relative expression level of ISG15 mRNA
- Relative expression level of MX1 mRNA

- Relative expression level of OAS mRNA
- Relative expression level of HLA-E mRNA
- Relative expression level of TAP1 mRNA
- Relative expression level of USP18 mRNA
- Relative expression level of CXCL11 mRNA
- Relative expression level of CXCL9 mRNA
- Relative expression level of CXCR3 mRNA
- Relative expression level of CCL5 mRNA
- Relative expression level of CXCL8 mRNA
- Relative expression level of IL18 mRNA
- Relative expression level of TGFB1 mRNA

For the following parameters only the by-participant listings will be provided:

- Molecular analysis: DNA content (ng/µL), RNA content (ng/µL), Beta globin (copies), cccDNA (copies/cell).
- Gene expression: GAPDH CT, RPL30CT, SERPINA1 mRNA CT

11. SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

12. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision
13 NOV 2023	Sections 6.4.2 and 10.2	Analysis methods of liver biopsy data were added in Sections 6.4.2 and 10.2.	The liver biopsy data became available, so the analysis methods were added.
16 NOV 2023	Cover page	Administrative change to correct a typo on the cover page.	The analysis plan date on the cover page should be 13 November 2023 instead of 13 December 2023.

13. APPENDICES

Appendix 1. Sample SAS Code

The following statement will be used to construct the confidence interval for the binomial proportions described in Section 6:

```
proc freq data=final;
     table trtp*aval/riskdiff(cl=exact) fisher;
     exact riskdiff;
     where trtp = "Arm X" | trtp = "Arm Y";
run;

proc freq data=final;
     by trtp;
     table aval/bnomial;
     exact binomial;
run;
```

The following statement will be used to construct logistic regression described in Section 6:

```
proc logistic data=final;
     class region strata trtp (ref=”Arm X” param=ref);
     model aval(event=’1’)=trtp region strata;
run;
```

The following statement will be used to construct MMRM model described in Section 6:

```
proc mixed data=final;
     class usubjid trtp avisit region strata;
     model chg=base region strata trtp avisit trtp*avisit/ddfm=kr;
     repeated avisit/subject=usubjid type=un;
     lsmeans trtp*avisit/diff cl;
run;
```

MYR204 W144 SAP V3.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	PPD