STATISTICAL ANALYSIS PLAN

Study Title: A Phase 2, Randomized, Open-Label, Multicenter Study Investigating AB-729 (imdusiran), Nucleos(t)ide Analogue and Pegylated Interferon Alfa-2a Treatment in Subjects with Chronic Hepatitis B Infection

Protocol Number: AB-729-201

Protocol Version: Version 3.0: June 17, 2022

Study Drug: Imdusiran (AB-729)

Sponsor: Arbutus Biopharma Corporation

Analysis Plan Date: July 23, 2025

Analysis Plan Version: Final

Analysis Plan Author: Elina Medvedeva

SIGNATURE PAGE

This document has been reviewed and approved by:

Tilly Varughese, MD Medical Director, Clinical Development		23 July 2025
	Signature	Date
Elina Medvedeva, MS Director, Biostatistics		July 23, 2025
	Signature	Date

TABLE OF CONTENTS

1 INTRODUCTION

Imdusiran (AB-729) is a potent, selective, subcutaneously (SC) administered, *N*-Acetylgalactosamine (GalNAc) conjugated small interfering ribonucleic acid (siRNA) inhibitor of hepatitis B virus (HBV) that cleaves and degrades HBV RNA, resulting in downstream silencing of viral proteins, DNA replication and virion production.

This study will assess the safety and antiviral efficacy of the addition of imdusiran to ongoing SOC NA therapy in HBV DNA suppressed, hepatitis B virus e-antigen (HBeAg) negative, non-cirrhotic CHB subjects for 24 weeks to reduce HBsAg levels, followed by addition of Peg-IFNα-2a with or without continued imdusiran treatment for either 12 or 24 weeks as consolidation therapy to further decrease HBsAg levels and promote anti-HBV immune reawakening.

This SAP provides detailed descriptions of the endpoints and the planned statistical methods for the study AB-729-201. This SAP should be read in conjunction with the study protocol and electronic Case Report Form (eCRF). Any further changes to the protocol or eCRF may necessitate updates to the SAP.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

- To evaluate the safety and tolerability of imdusiran plus Peg-IFNα-2a in subjects with NA-suppressed CHB infection

2.1.2 Secondary Objectives

- To evaluate changes in HBsAg concentration and other virologic parameters during and following repeat doses of imdusiran plus Peg-IFNα-2a
- To evaluate the proportion of subjects with HBsAb seroconversion
- To evaluate the proportion of subjects who meet NA therapy discontinuation criteria
- To evaluate the proportion of subjects who discontinue NA therapy and subsequently restart NA therapy during the follow-up period
- To evaluate the proportion of subjects who experience clinical and/or viral relapse in the follow-up period after discontinuing NA therapy
- To evaluate plasma concentrations of imdusiran

2.1.3 Exploratory Objectives

- To evaluate potential viral resistance to imdusiran, as data permit

- To evaluate changes in the levels of HBsAg isoforms (small, middle, and large)
- To evaluate changes in the levels of immune biomarkers with imdusiran treatment in lead-in period with imdusiran + Peg-IFNα-2a in consolidation period, as data permit
- To evaluate changes in the levels of immune biomarkers during and after treatment with imdusiran + Peg-IFNα-2a and NA + Peg-IFNα-2a, as data permit
- To profile HBV-specific immune function with imdusiran treatment in lead-in period with imdusiran + Peg-IFNα-2a in consolidation period, as data permit
- To profile HBV-specific immune function following treatment with imdusiran + PegIFNα-2a and NA + Peg-IFNα-2a
- To characterize interleukin (IL)28B genotype and explore potential correlation to virologic response, as data permit
- To explore relationships between safety and/or pharmacodynamics (PD) with immune/inflammatory gene polymorphisms, as data permit
- To monitor imdusiran RNA interference (RNAi) activity and explore correlation to virologic response, as data permit
- To evaluate changes in levels of HBV related microRNAs (miRNAs) during and after treatment with Imdusiran, as data permit
- To assess the SCALE-B score in predicting post-treatment clinical relapse and HBsAg loss

2.2 Study Endpoints

2.2.1 Primary Endpoints

- The frequency and severity of treatment-emergent adverse events (TEAEs)
- Discontinuations due to adverse events (AEs)
- Laboratory abnormalities after dosing with imdusiran plus Peg-IFNα-2a

2.2.2 Secondary Endpoints

- Change from baseline in HBsAg, HBV DNA, HBV RNA, HBsAb, and HBcrAg concentration at each timepoint

- Proportion of subjects with a change in HBsAg from baseline meeting response criteria (≥0.5, 1, 2, or 3 $\log_{10}$ reduction; ≤lower limit of quantitation [LLOQ] or target not detected [TND]) at each timepoint

- Proportion of subjects with a change in HBV RNA from baseline meeting response criteria (≥0.5, 1, 2, or 3 $\log_{10}$ reduction; ≤LLOQ or TND) at each timepoint

- Proportion of subjects with a change in HBcrAg from baseline meeting response criteria (≥0.5, 1, 2, or 3 $\log_{10}$ reduction; ≤LLOQ or TND) at each timepoint

- Proportion of subjects with HBsAb seroconversion at each timepoint

- Proportion of subjects who are eligible to stop NA after Week 24 of follow up

- Proportion of subjects who discontinue NA and subsequently restart NA therapy after meeting criteria

- Proportion of subjects who discontinue NA and subsequently meet protocol-defined clinical relapse criteria

- Proportion of subjects who discontinue NA and subsequently meet protocol-defined viral relapse criteria

- Proportion of subjects who have HBV DNA <LLOQ at each timepoint after discontinuation of NA therapy

- Proportion of subjects who have HBsAg <100 IU/mL or <10 IU/mL at each timepoint after discontinuation of NA therapy

- Post-dose plasma concentrations of AB-729 anti-sense (AS), AB-729 AS(N-1)3′, and AB-729 AS(N-2)3′ at selected timepoints

2.2.3 Exploratory Endpoints

- Identification of imdusiran target site variants from sequencing of drug resistant HBV variants, if observed

- Change from baseline in small, middle, and large isoforms of HBsAg

- Change from baseline in immune-related protein levels (such as soluble programmed death-1 [sPD-1] and cytokines) and HBsAg immune complex levels

- Assessment of the relationship between immune-related protein levels, immune complex levels, and virologic responses

- Assessment of the relationship between immunologic activity of peripheral blood mononuclear cells (PBMCs) and virologic response
- Assessment of the relationship between IL28B genotype and virologic response
- Assessment of immune and inflammatory gene polymorphisms via allele-specific oligonucleotide array
- Detection of HBV RNA cleavage products in blood resulting from imdusiran RNAi activity
- Assessment of the relationship between detection of HBV RNA cleavage products and virologic responses
- Change from baseline in selected potentially HBV-related miRNA levels
- Assessment of the relationship between HBV-related miRNAs and virologic responses
- Assessment of SCALE-B score at end-of treatment (EOT)
- Proportion of subjects who experience clinical relapse with SCALE-B scores of <260, 260 – 320, and >320 points
- Proportion of subjects who experience HBsAg loss with SCALE-B scores of <260, 260-320, and >320 points

3 STUDY DESIGN

3.1 Overview

This is a randomized, open label, multicenter Phase 2 study investigating the safety and antiviral activity of imdusiran in combination with ongoing NA therapy and short courses of Peg-IFNα-2a in subjects with CHB.

The study will enroll 40 stably NA-suppressed, HBeAg negative, non-cirrhotic CHB subjects.

All subjects will have a 24-week lead-in period (Lead-In Treatment Period) of imdusiran 60 mg SC every 8 weeks (Q8W) added to ongoing standard of care (SOC) NA (either ETV, TDF or equivalent, or TAF).

After the lead-in period, the subjects will be randomized in a 3:3:2:2 ratio to one of the four cohorts (A1: A2: B1: B2). The randomization will be stratified by HBsAg level at Week 24 (HBsAg ≤100 IU/mL vs >100 IU/mL).

- **Cohort A1**: Imdusiran 60 mg SC (Q8W x 2 doses) + NA + weekly Peg-IFNα-2a 180 mcg SC for 24 weeks (N = 12)
- **Cohort A2**: NA + weekly Peg-IFNα-2a 180 mcg SC for 24 weeks (N = 12)

- **Cohort B1**: Imdusiran 60 mg SC (Q8W x 1 dose) + NA + weekly Peg-IFNα-2a 180 mcg SC for 12 weeks (N = 8)

- **Cohort B2**: NA + weekly Peg-IFNα-2a 180 mcg SC for 12 weeks (N = 8)

After completion of the assigned Peg-IFNα-2a Consolidation Treatment Period, all subjects will remain on NA therapy for the initial 24-week follow up period (Post-Treatment Follow-Up Period 1), and then will discontinue NA treatment if the following criteria are met:

- Alanine aminotransferase (ALT) <2 × upper limit normal (ULN), and

- Undetectable HBV DNA, and

- At least one of the following:

    - HBsAg undetectable (via conventional assay) for at least 24 weeks after the end of treatment
    - HBsAg <100 IU/mL at two consecutive visits at least 24 weeks after the end of treatment
    - HBsAb positive for at least 24 weeks after the end of treatment

Participants who remain on NA therapy will be followed for an additional 24 weeks (Post-Treatment Follow-Up Period 2, 48 weeks total post-end of treatment).

Participants who discontinue NA therapy will enter a more intensive follow-up period for 48 weeks (NA-Discontinuation Period) to monitor for potential rebound of viral markers and safety events as well as for sustained viral response and HBsAg loss, defined as follows:

- Clinical relapse: HBV DNA >2000 IU/mL AND ALT >2x baseline and ≥2 × ULN, confirmed by repeat 4 weeks apart

- Virologic relapse: HBV DNA > 2000 IU/ml confirmed by repeat 4 weeks apart

Resumption of NA therapy during the second follow-up period should be considered in the following situations and discussed with the Sponsor Medical Monitor:

- Persistent ALT elevations ≥2 × baseline, AND ≥2 – 5 × ULN, AND HBV DNA >2000 IU/mL for 12 weeks

- Persistent ALT elevations ≥2 × baseline, AND ≥5 – 10 × ULN, AND HBV DNA >2000 IU/mL for 4 weeks

- ALT > 10 x ULN confirmed by repeat
- HBV DNA > 20,000 IU/mL regardless of ALT level, confirmed by repeat
- ALT > baseline and > ULN, AND:
  - increased direct or total bilirubin ≥2 × ULN and ≥2 × baseline confirmed by repeat, OR
  - increased INR from ≥0.5 from baseline, confirmed by repeat.

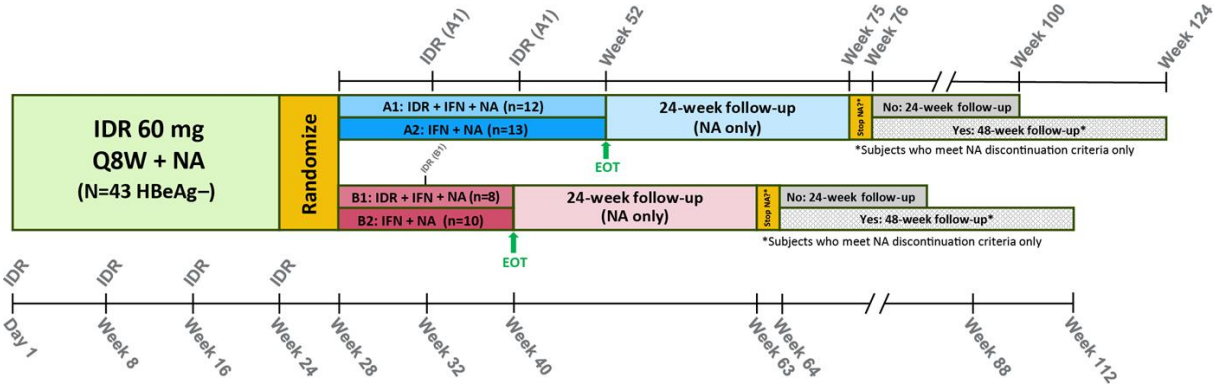
Participants who restart NA therapy will be assessed every 2 weeks until clinically stable (i.e. ALT and HBV DNA declining on 2 consecutive visits) and will be followed for 24 weeks total via unscheduled visits as needed prior to study discharge.

3.2 Statistical Hypothesis

No hypothesis will be formally tested in this study.

3.3 Schema

Figure 1. Schematic of Study AB-729-201



3.4 Sample Size Considerations

Approximately 80 subjects will be screened to achieve 40 dosed subjects. The sample size for this study is based on clinical rather than statistical rationale. The sample size is considered adequate to support the planning and design of future studies.

3.5 Study Visits and Duration

The study will be conducted for approximately 130 weeks as follows:

<u>Lead-in Treatment Period</u>

- The Screening Visit will occur within 45 days prior to the first dose of imdusiran.

- Dose 1 of imdusiran will be administered on Day 1 and subjects will be confined to the clinic for a minimum of 6 hours on Day 1 for PK assessments.

- All subjects will return to the clinic for monthly visits through Week 24 (6 visits) as shown in the Schedule of Activities. During the Week 24 visit subjects will be confined to the clinic for a minimum of 6 hours for PK assessments.

Consolidation Treatment Period and Post-Treatment Follow-Up:

- Participants randomized to Cohorts A1 and A2 will have between 19 (through Week 100) and 32 (through Week 124) visits depending on whether they qualify for NA discontinuation. Peg-IFN α -2a will be administered weekly for 24 weeks. Participants will record all self-administered Peg-IFN α -2a doses in a dosing diary, which will be reviewed at each study visit. The first Peg-IFN α -2a dose will be administered in the clinic at the Week 28 visit, and Peg-IFN α -2a administration will occur in the clinic on visit days (Weeks 30, 32, 34, 36, 38, 40, 44, 48). The remainder of Peg-IFN α -2a doses will be administered (Weeks 29, 31, 33, 35, 37, 39, 41, 42, 43, 45, 46, 47, 49, 50, 51). The last dose of Peg-IFN α -2a will be self-administered at Week 51.

- Participants randomized to Cohorts B1 and B2 will have between 16 (through Week 88) and 29 (through Week 112) visits depending on whether they qualify for NA discontinuation. Peg-IFN α -2a will be administered weekly for 12 weeks (Cohorts B1 and B2). Participants will record all self-administered Peg-IFN α -2a doses in a dosing diary, which will be reviewed at each study visit. The first Peg-IFN α -2a dose will be administered in the clinic at the Week 28 visit, and Peg-IFN α -2a administration will occur in the clinic on visit days (Weeks 30, 32, 34, 36, 38). The remainder of Peg-IFN α -2a doses will be self-administered (Weeks 29, 31, 33, 35, 37, 39). The last dose of Peg-IFN α -2a will be self-administered at Week 39.

- Participants who restart NA therapy will be followed for 24 weeks total via unscheduled visits as needed prior to study discharge. These subjects can have up to 12 additional visits that go through Week 144 in Cohorts A1 and A2 and Week 132 in Cohorts B1 and B2.

3.6 Baseline and end of study definitions

- **Baseline:** Baseline is the last assessment prior to the first dose of study drug

- **End of Study:** A subject is considered to have completed the study if s/he has completed all phases of the study including the final Post-Treatment Follow-up visit for the study Cohort in which the subject is enrolled. The end of the study is defined as the date of the last visit of the last subject in the study, globally.

3.7 Randomization and Blinding

This is an open label study where after completion of a 24-week lead-in period of imdusiran 60 mg SC Q8W added to ongoing SOC NA, subjects will be randomized into one of 4 cohorts (Cohort A1 or A2: Cohort B1 or B2). Treatment assignment will be stratified by HBsAg level at Week 24 (HBsAg ≤100 IU/mL vs >100 IU/mL).

Each subject will be issued a unique randomization number. The randomization schedule will be generated by the clinical contract research organization (CRO) and retained for the study. The randomization sequence along with the assigned study treatment for each number in the randomization sequence will be held confidentially. A manual randomization process will be followed. A Pharmacist will assign the subjects to randomization numbers to be assigned sequentially from a master randomization schedule.

This study is open-label, so no formal blinding will be performed. However, virology data or other laboratory/analyte results that could bias the conduct of the study will not be reported to investigative sites or other personnel until the subject reaches the end of the first 24 week follow up period to evaluate if NA discontinuation criteria have been met.

4 POPULATIONS FOR ANALYSES

All populations will be defined after database lock. For purposes of analysis, the following populations are defined:

- **Safety Lead-in:** All subjects who take at least 1 dose of study treatment in the Lead-in Treatment Period
- **Randomized (Intent-to-Treat, ITT):** All subjects randomly assigned to study treatment
- **Safety:** All subjects who were randomized and take at least 1 dose of study treatment in the Consolidation Treatment period. Participants' data will be analyzed according to the treatment they actually received.
- **Per Protocol (PP):** All subjects in the Safety Population who have no major protocol violations
- **Pharmacokinetics (PK):** All subjects in the Safety Population with PK samples adequate for the calculation of PK parameters.

5 PLANNED ANALYSIS

5.1 Interim Analyses

There are no formal interim analyses planned for this study; however, a Data Monitoring Committee will periodically review safety data from this study.

5.2 Final Analysis

Any data values requiring investigation or correction will be identified while programming the datasets and Tables, Figures, and Listings (TFLs). The database will not be locked until the identified issues are resolved.

The final statistical analysis will be conducted when the last subject has completed the study and will be based on the locked database.

6 GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

6.1 General Statistical Methodology

All statistical analyses will be prepared in accordance with the current International Conference on Harmonization (ICH) Guidelines, using SAS® (Version 9.4, SAS Institute Inc., Cary, NC, USA). Pharmacokinetic parameters will be calculated by the Sponsor using Phoenix® WinNonlin®8.0 or later versions (Certara USA, Inc., Princeton, NJ).

Continuous (quantitative) variables will be summarized using descriptive statistics including number of non-missing values, mean, standard deviation (SD), standard error (SE), median, minimum, and maximum. Where appropriate, estimates will be presented with 95% confidence intervals (CIs).

Categorical (qualitative) variables will be summarized using absolute frequency and percentage. When the absolute frequency is zero, the percentage will not be presented. Unless stated otherwise, the denominator for percentage calculations will be based upon the total number of subjects in the study populations for the treatment group, including subjects with missing data. For variables with missing values, the number and percentage of subjects with missing values will be presented. 95% CIs of proportions may also be presented for selected endpoints where applicable.

The PK parameters (except time of maximum observed plasma concentration [T_{max}]) will be summarized with geometric means, CV% and associated 95% confidence interval.

All statistical tests will be performed in the framework of explorative analysis and conducted at the 0.05 significance level using 2-tailed tests. When reporting the results of significance tests, p-values will be presented.

All final, planned analyses identified in the protocol and in this SAP will be performed after all relevant study data have been processed and integrated into the analysis database, analysis populations have been finalized, and the database has been locked. Any post-hoc, exploratory analysis completed to support planned study analyses, which were not identified in this SAP, will be documented, and reported in Section 9.8 of the Clinical Study Report (CSR). Any results from these unplanned analyses (post-hoc) will also be clearly identified as such in the text of the CSR.

Summary tables and listings will be prepared and numbered according to ICH Guideline E3. The convention to number tables and listings will be a decimal system to reflect main levels of unique

tables and listings and sub-levels of replicate tables and listings. Mock tables and graphs are presented in Data Display Plan (DDP), which is a supplementary document to this analysis plan.

6.2 Data Presentation Conventions

All collected data will be presented in listings, sorted by subject and scheduled time point.

Summaries will be presented by treatment group, and, where appropriate, by scheduled time point.

For continuous variables, all mean, median, geometric mean, first quartile (Q1), third quartile (Q3), confidence interval (95% CI), and % coefficient of variation (CV) values will be formatted to one more decimal place than the measured value. Standard deviation (SD) and standard error (SE) values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value.

For categorical variables, the number and percentage of responses will be presented in the form xx (xx.x) where the percentage is in the parentheses.

All PK parameters and PK summary statistics will be reported to 3 significant figures, except for T_{max}, which will be reported to 2 decimal places.

Confidence interval bounds will be presented with the same number of decimals as the corresponding point estimate, and p-values will be presented with 4 decimals or as '<.0001'.

All date values will be presented as yyyy-mm-dd (e.g., 2021-09-15) format. A 4-digit year is preferred for all dates.

The results from local labs will not be used for analysis.

Laboratory values reported with '<' or '≤' inequality symbols will be considered as below the limit of normal/detection limit. For tabulation of summary statistics, for values in the original units the ½ of the number associated with the inequality sign will be used for statistical calculations. For values in $\log_{10}$ units a value that is one significant unit below the number associated with the inequality sign will be used. For example, if the result of a continuous laboratory test is <3.0, a value of 2.9 will be assigned.

The following special imputation rules will be applied for the lab tests and reported values below the lower limits of quantitation in the table below.

Lab Test	Reported Value	Imputed Value
HBV DNA	<10 IU/mL and HBV DNA Interpretation (HBVDNAIN)="Not detected" <10 IU/mL and HBV DNA Interpretation (HBVDNAIN)="Detected, not quantifiable"	1 IU/mL 5 IU/mL
HBcrAg	<1.0 kU/mL	500 U/mL

HBeAg	<0.14 PEI U/mL	0.07 PEI U/mL
HBsAg	<0.05 IU/mL	0.025 IU/mL
HBV RNA	Not detected <0.49 $\log_{10}$ U/mL <0.80 $\log_{10}$ U/mL	0 0.48 $\log_{10}$ U/mL 0.79 $\log_{10}$ U/mL
HBsAb	<2 IU/L <3.5 IU/L	1 IU/L 1.75 IU/L

Laboratory values reported with '>' or '≥' inequality symbols will be considered as above the limit of normal/detection limit. For tabulation of summary statistics, the number associated with the inequality sign will be used for statistical calculations.

6.3 Data Management

Data handling and transfer will take place as described in the Data Management Plan (DMP) for the study.

SDTM datasets will be created based on the raw eCRF and laboratory data and adhere to CDISC SDTM Implementation Guide 3.2. Analysis datasets will be generated using SAS® version 9.4 software and adhere to ADaM Implementation Guide 1.1 structure.

6.4 Missing Data and Outliers

All attempts will be made to prevent missing data. For subjects who prematurely discontinue the study, all available data will be included in the analyses.

When data is not provided, it will be indicated using a 'blank' in subject listing displays. If all data for a specific visit is missing, the data will be excluded from the summaries. Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.

For subjects who prematurely discontinue the study, all available data will be included in the analyses. The planned safety and efficacy analyses will be based on the reported data.

An investigation will be made concerning the sensitivity of the results if extreme outliers are detected within the data.

No missing data will not be imputed, except for partial or missing dates.

For missing last dose date of study drug, imputation rules are described in Section 7.7. The handling of missing efficacy data is described in Section 9. The handling of missing or incomplete dates for adverse event (AE) onset is described in Section 8.1.1, and for prior and concomitant medications in Section 8.6.1.

6.4.1 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.

6.5 Handling of Dropouts

Participants who meet individual subject discontinuation rules for safety events assessed by the Investigator as related to imdusiran will not be replaced.

Participants who discontinue for other safety-related findings may be replaced after discussion with the DMC.

Participants may also be replaced if discontinuations occur for non-safety related reasons such as non-compliance with the protocol or an inability to complete all required study visits and procedures (e.g., withdrawal of consent). Any replacements should be made in a timely manner and only after discussion between the Investigator(s) and the Sponsor's Medical Monitor.

All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

6.6 Analysis visit windows

NA Restart Follow-up Visits will be based on CRF assigned visit. The visits occur at Weeks 2 and 4 after restart of NA, and then every 2 weeks until clinically stable, then every 4 weeks until Week 24/EOS.

The visits labeled "Restart NA Week 6-24" will be mapped to appropriate weeks, using the date of the "Restart NA Week 2" as the baseline.

Restart NA Week 2	As reported per CRF
Restart NA Week 4	As reported per CRF
Restart NA Week 6-24	Restart NA Week 6 Restart NA Week 8 Restart NA Week 10 Restart NA Week 12 Restart NA Week 14 Restart NA Week 16 Restart NA Week 18 Restart NA Week 20 Restart NA Week 22 Restart NA Week 24/EOS

6.6.1 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. If a single value is needed, but multiple valid, non-missing measurements exist in an analysis window, records will be chosen based on the following rules:

- For baseline, the last non-missing value on or prior to the first dose date of study drug will be selected, unless specified differently. If there are multiple records with the same time or no time recorded on the same day, the Baseline value will be the average of the measurements for continuous data, or the measurement with the lowest severity for categorical data (eg, normal will be selected over abnormal for safety ECG findings).

- For postbaseline values:

    - The record closest to the nominal day for that visit will be selected.

    - If there are 2 records that are equidistant from the nominal day, the later record will be selected.

6.7 Derived and Transformed Data

6.7.1 Study Day

If the date of interest occurs on or after the first dose date then study day will be calculated as:

- (date of interest – date of first dose) + 1.

If the date of interest occurs prior to the first dose date then study day will be calculated as:

- (date of interest – date of first dose).

There is no study day 0.

6.7.2 Change from Baseline

- Change from baseline is calculated as (post-baseline result – baseline result).
- Percent change from baseline is calculated as (change from baseline/baseline result * 100).
- Fold change from baseline is calculated as (change from baseline/baseline result).

6.7.3 Derived Endpoints

- HBcrAg will be converted from kU/mL units to U/mL by multiplying by 1000. The LLOQ for the HBcrAg assay is 3 $\log_{10}$ U/mL, which corresponds to 1.0 kU/mL or 1000 U/mL.

- Efficacy endpoints of HBsAg, HBsAb, HBcrAg, HBV DNA and HBV RNA will be converted to $\log_{10}$ scale. Listings will include the values in $\log_{10}$ scale and in the original scale.

- SCALE-B is a composite predictor calculated as (35*HBsAg($\log_{10}$ IU/mL) + 20*HBcrAg ($\log_{10}$ U/mL) + 2*age (years) + ALT (U/L) + 40 for tenofovir use. A low SCALE-B score (<260 points) may accurately predict a low risk of clinical flare and a higher chance of HBsAg seroclearance.

7 SUBJECT INFORMATION

7.1 Subject Disposition

The following will be presented by treatment group:

- Number of subjects in the Safety Lead-In Analysis Population
- Number of subjects in the All Randomized Analysis Population
- Number of subjects in the Safety Analysis Population
- Number and percentage of subjects in the Safety Analysis Population who completed the study
- Number and percentage of subjects in the Safety Analysis Population who discontinued the treatment
- Reason for treatment discontinuation
- Number and percentage of subjects in the Safety Analysis Population who discontinued the study
- Reason for study discontinuation

A by-subject listing with study duration and reason for withdrawal from the treatment/study will be provided. Randomization details will be provided in the listing.

7.2 Protocol Deviations

The number and percentage of randomized subjects with at least one major protocol deviation leading to exclusion from analysis population will be presented.

7.3 NA Discontinuation

The following will be summarized descriptively:

- Proportion of subjects who are eligible to stop NA after Week 24 of follow up

- Proportion of subjects who discontinue NA and subsequently restart NA therapy if the following criteria are met:
    - Persistent ALT elevations ≥2 × baseline, AND ≥2 – 5 × ULN, AND HBV DNA
    - >2000 IU/mL for 12 weeks
    - Persistent ALT elevations ≥2 × baseline, AND ≥5 – 10 × ULN, AND HBV DNA
    - >2000 IU/mL for 4 weeks
    - HBV DNA > 20,000 IU/mL regardless of ALT level, confirmed by repeat
    - ALT > 10 x ULN confirmed by repeat
    - ALT > baseline and > ULN, AND:
        - increased direct or total bilirubin ≥2 × ULN and ≥2 × baseline confirmed by repeat, OR
        - INR increase of ≥0.5 from baseline, confirmed by repeat.

- Proportion of subjects who discontinue NA and subsequently meet protocol-defined clinical relapse criteria

- Proportion of subjects who discontinue NA and subsequently meet protocol-defined viral relapse criteria

7.4 Demographic and Baseline Characteristics

Summary statistics and frequencies on demographic and baseline data will be presented for the Safety Analysis Population for each treatment group.

Height, Weight and BMI were measured at Screening.

The following variables will be summarized descriptively:

- Demographics: age (years), sex, race, and ethnicity;
- Baseline characteristics: height (cm), weight (kg), body mass index (BMI, kg/m^2)

If age is missing, age (years) will be calculated at Baseline as:

- the integer part of (Date of Baseline Visit - date of birth)/365.25. In case of incomplete dates, missing days will be set to 1st and missing months will be set to July.

7.5 Baseline Disease Characteristics

Summary statistics and frequencies on demographic and baseline data will be presented for the Safety Analysis Population for each treatment group.

The following variables will be summarized descriptively:

- Background Nucleos(t)ide analogue as a categorical variable

- IL28B Genotype as a categorical variable
- Baseline ALT (U/L) as a continuous variable
- Baseline HBsAg (IU/mL) as a continuous variable
- Baseline HBsAg (log_{10} IU/mL) as a continuous variable
- Baseline HBcrAg (U/mL) as a continuous variable
- Baseline HBcrAg (log_{10} U/mL) as a continuous variable
- Baseline HBV DNA (IU/mL) as a continuous variable
- Baseline HBsAb (IU/L) as a continuous variable

A by-subject listing of baseline characteristics will be provided by subject ID number in ascending order.

7.6 Medical History

Medical history was collected at screening and updated at baseline. Data will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0 or later. Medical history will be summarized for Safety Analysis Population by system organ classification (SOC) and preferred term (PT) for each treatment group. Participants who reported 2 or more medical history items that are coded to the same SOC, and PT will be counted only once. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency.

A by-subject listing of medical history and HBV treatment history will be provided.

7.7 Extent of Exposure to Study Drug

The number of injections will be summarized by treatment group separately for imdusiran and Peg-IFNα-2a.

- Exposure to Peg-IFNα-2a calculations

The database only provides the data for clinical visits at which Peg-IFNα-2a was administered. In order to calculate the full exposure to Peg-IFNα-2a, the available compliance data will be used. This includes the indicators on whether a dose was missed at home and the date it was missed, as well as whether or not the Peg-IFNα-2a was interrupted with dates of interruption and subsequent restart. For each subject, the number of Peg-IFNα-2a doses will be calculated by subtracting the number of doses missed in clinic and at home from the expected number of doses for each cohort.

Dosing records will be listed by cohort, subject, visit, treatment, actual dose received (mg or mcg), dosing date and time, as well as indicators and dates for Peg-IFNα-2a missed or interrupted doses.

8 SAFETY ANALYSES

All safety analyses will be performed on the Safety Lead-in Population. Safety will be assessed based on AEs, clinical laboratory data, vital signs, ECG parameters, and physical examinations.

8.1 Adverse Events

Adverse events will be coded using MedDRA (Medical Dictionary for Regulatory Activities) preferred term (PT), and system organ classification (SOC). Any events reported after the initiation of study treatment and through the end of study are defined as treatment-emergent AEs (TEAEs). The Investigator will provide an assessment of the intensity of each AE. Intensity will be assessed in terms of severity (mild, moderate, severe, potentially life-threatening or death). Participants will be counted once and summarized under their highest severity within a SOC and PT.

8.1.1 Missing Adverse Event (AE) Onset Dates

For adverse events with missing onset date, treatment-emergent flag will be assigned as follows:

- If the onset date is entirely missing, then the AE will be assigned as treatment-emergent .
- If the year of onset only is provided and the year is the same as the year of first dose of study drug, then this event would be treatment-emergent.
- If the year of onset only is provided and the year is not the same as the year of first dose, then the onset date will be imputed as the 1st of January of that year to determine if the event is treatment-emergent .
- If the month and year of onset are provided, and the month and year are equal to the month/year of first dose of any study drug, then this event would be treatment-emergent. In all other cases, the 1st day of the provided month/year of onset will be imputed for the onset date to determine if the AE is treatment-emergent .
- If the provided month/year of onset is prior to the month/year of first dose, an event will not be considered treatment-emergent.

8.1.2 Analysis of Treatment-Emergent Adverse Events

Adverse event summaries will summarize only TEAEs. A table with the number and percentage of subjects who experienced at least 1 treatment-emergent AE, as well as the number of events in the categories described below, will be provided by treatment group. In addition, separate tables for each AE category will present the number and percentage of subjects and the number of events by SOC, PT, and treatment group. In case of multiple events, subjects will be counted once and summarized under their highest severity within a SOC and PT.

The following TEAE summary tables will be prepared:

- Summary of Any TEAE
- Summary of TEAEs by SOC and PT
- Summary of TEAEs by SOC, PT, and maximum severity
- Summary of Grade 3 or Grade 4 TEAEs by SOC and PT
- Summary of TEAEs related to imdusiran by SOC and PT
- Summary of TEAEs related to Peg-IFNα by SOC and PT
- Summary of TEAEs by SOC, PT, and relationship to imdusiran
- Summary of TEAEs by SOC, PT, and relationship to Peg-IFNα
- Summary of TEAEs leading to imdusiran discontinuation by SOC and PT
- Summary of TEAEs related to imdusiran by PT occurring in 2 or more subjects with the same AE
- Summary of TEAEs related to Peg-IFNα by PT occurring in 2 or more subjects with the same AE
- Summary of TEAEs by System Organ Class and Preferred Term occurring in 2 or more subjects

1.1.1.1. Deaths and Serious Adverse Events

Listings for SAEs and death will be provided.

In addition, the following summary table will be prepared:

- Summary of Serious TEAE by SOC, PT
- Summary of Serious TEAE related to imdusiran by SOC, PT
- Summary of Serious TEAE related to Peg-IFNα by SOC, PT
- Summary of deaths

All AEs will be listed for individual subjects, showing both verbatim and preferred terms.

AEs with missing severity will be excluded from the severity summaries.

TEAEs with missing relationship to study drug will be considered as related to study drug in the summaries.
All AEs will be listed for individual subjects, showing both verbatim and preferred terms.

8.2 Pregnancies (as applicable)

A listing will be provided if any female subjects become pregnant during the study.

8.3 Clinical Laboratory Tests

Laboratory data collected during the study will be analyzed and summarized by treatment group using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis population and will include all available data.

Clinical Laboratory Tests will be performed at the timepoints indicated in **Appendix 3. Schedule of Activities.** The clinical laboratory assessments are listed in **Appendix 4.** .

8.3.1 Summaries of Laboratory Results

Continuous laboratory data will be summarized using descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum).

For each laboratory test specified in the protocol the following will be summarized by treatment group:

- Baseline values
- Values at each postbaseline visit
- Change from Baseline at each postbaseline visit

Categorical laboratory data will be summarized using the number and percentage of subjects in the study with the given response at baseline and each scheduled postbaseline visit. In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 6.6.1.

A by-subject listing for laboratory test results will be provided by subject ID number and timepoint in chronological order for hematology, serum chemistry, and urinalysis separately. Values outside of the relevant reference range will be flagged in the laboratory listings.

8.3.2 Treatment-emergent Laboratory Abnormalities

Laboratory abnormalities will be graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1. Any graded abnormality that occurs following the initiation of study treatment and represents at least a 1-grade increase from the baseline assessment, is defined as treatment-emergent.

The number and percentage of subjects experiencing treatment-emergent graded abnormalities in laboratory parameters (hematology, clinical chemistry, coagulation, urinalysis, urine chemistry, renal biomarkers) will be summarized by treatment group, laboratory test, and toxicity grade.

Separate summaries will be created for graded laboratory abnormalities and Grade 3 or 4 Laboratory abnormalities. Shift tables will be used to tabulate the grading observed at Baseline to the maximum post-Baseline result up to the end of study for each lab parameter, to highlight important grading differences noted during the study.

Graded laboratory abnormalities are obtained from the central laboratory; however, for total and direct bilirubin, DAIDS criteria are not followed for grading by the central laboratory. Total and direct bilirubin abnormalities will be graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1. Bilirubin lab abnormalities will be labeled as Grade 3 or 4 if the lab values are above the ULN and if the subject has the presence of clinical signs and symptoms of hepatoxicity, which will be assessed and confirmed by the Sponsor Medical Monitor. This will supersede toxicity grading performed by the central laboratory.

For all summaries of laboratory abnormalities, the denominator is the number of subjects with non-missing postbaseline values. Participants will be categorized according to the most severe postbaseline abnormality grade for a given laboratory test.

A by-subject listing of graded laboratory abnormalities will be provided by subject ID number and timepoint in chronological order. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades displayed.

8.3.3 Liver Function Tests

ALT Elevation Management

Participants with ALT ≥2 × baseline AND ≥5 × ULN should be monitored for changes in hepatic function every 1 – 2 weeks via testing of ALT, aspartate aminotransaminase (AST), total and direct bilirubin, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), serum albumin and international normalized ratio (INR).

Participants with persistent ALT ≥5 × baseline AND ≥10 × ULN for ≥2 weeks OR ALT ≥2 × baseline AND ≥5 × ULN accompanied by changes in direct bilirubin ≥2 × baseline without alternate cause, or symptoms of liver inflammation (such as jaundice, fatigue, nausea, vomiting, loss of appetite) should discontinue imdusiran treatment.

Participants on Peg-IFNα-2a therapy:

- Participants with confirmed ALT ≥2 × baseline AND ≥5 × ULN who are on Peg-IFNα2a therapy may be considered for Peg-IFNα-2a dose reduction to 135 mcg.

- If persistent ALT ≥2 × baseline AND ≥5 × ULN is observed after reduction of PegIFNα-2a dosage, Peg-IFNα-2a treatment should be interrupted.

- If at any time direct bilirubin ≥2 × baseline, treatment should be interrupted.

Participants in the Post-Treatment follow up period:

Participants who have confirmed ALT elevations ≥2 × baseline AND ≥2 × ULN should be monitored for changes in hepatic function every 2 weeks via testing of ALT, AST, total and direct bilirubin, ALP, GGT, serum albumin and INR. Additional testing for HBV DNA, HBsAg, and HBeAg should also be performed. Unscheduled visits should be added when necessary, since subjects may only have scheduled visits on a bi-weekly or monthly during this period.

For subjects who discontinued NA therapy per protocol (see Section 4.4 of the Protocol), resumption of NA therapy should be considered in the following situations and discussed with the Sponsor Medical Monitor:

- Persistent ALT elevations ≥2 × baseline, AND ≥2 – 5 × ULN, AND HBV DNA >2000 IU/mL for 12 weeks

- Persistent ALT elevations ≥2 × baseline, AND ≥5 – 10 × ULN, AND HBV DNA >2000 IU/mL for 4 weeks
- HBV DNA > 20,000 IU/mL regardless of ALT level, confirmed by repeat
- ALT > 10 x ULN, confirmed by repeat
  - ALT > baseline and > ULN, AND:
  - increased direct or total bilirubin ≥2 × ULN and ≥2 × baseline confirmed by repeat, OR
  - increased INR from ≥0.5 from baseline, confirmed by repeat.

Participants who restart NA therapy will be assessed every 2 weeks until clinically stable (i.e. ALT and HBV DNA declining on 2 consecutive visits) and will be followed for 24 weeks total via unscheduled visits as needed prior to study discharge (see Appendix 9 of the Protocol).

The number and proportion of subjects meeting the above criteria will be summarized by treatment group for each postbaseline point. Clinical signs or symptoms of liver inflammation will not be included in the summary. For individual laboratory tests, subjects will be counted once based on the most severe postbaseline values. For the composite criteria, subjects will be counted once when the criteria are met at the same visit. The denominator is the number of subjects in the Safety Analysis Population who have non-missing postbaseline values.

A listing of subjects who met at least 1 of the above criteria will be provided.

8.4 Physical Examinations

Complete physical examinations will be conducted at each timepoint indicated in Appendix 3. A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal, Dermatologic and Neurological systems. A targeted physical examination will be based on any changes to the subject's health since the last visit.

By-subject listing will be provided for physical examination results. The results will be labeled as normal, abnormal-not clinically significant (NCS), or abnormal-clinically significant (CS).

8.5 Vital Signs

The vital signs include systolic/diastolic blood pressure (BP), heart rate (HR), respiratory rate (RR), and temperature. The vital signs will be assessed at each study visit.

Vital signs will be summarized using descriptive statistics (n, mean, SD, median, min, and max) over time in terms of absolute values and changes from baseline at each scheduled time point. The results will be presented by treatment group for the Safety Analysis Population.

By-subject listings will be provided for vital sign results by subject ID number and timepoint.

8.6 Prior and Concomitant Medications

Medications received prior to, or concomitantly with study drug will be coded to the medicinal product name using the World Health Organization Drug Dictionary (WHO-DD Version March 2019).

- Prior medications are defined as medications with start and stop dates prior to the date of first dose of study drug.

- Concomitant medication is defined as any medication with a start date on or after date of first dose of study drug.

- Medications that are started prior to the date of first dose of study drug and are continuing after the date of first dose of study drug are considered to be both prior and concomitant medications.

Absolute counts (n) and percentages (%) will be presented for the number of patients with at least one prior or concomitant medication, and per WHO-ATC Drug Class 2 (ATC therapeutic main class) and per WHO-DD Drug Name (Preferred Term) within WHO-ATC Drug Class 2, for each treatment group and overall. Summaries will be based on the Safety Analysis Population. A subject reporting the same medication more than once will be counted only once within each ATC drug class.

All medications reported as part of HBV History will be considered as prior medications. The background nucleos(t)ide analogue therapy that met the Inclusion criterion and then transitioned to study-provided medication (stop dates on study Day -1 or Day 1) will be considered as concomitant medications (the nucleos(t)ide analogue co-administered with study drug).
Medications may appear under multiple ATC drug classes. The summary will be ordered alphabetically by ATC medical class and then by Preferred Term in descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

A by-subject listing of prior and concomitant medications will be provided, sorted by subject ID number and administration date in chronological order.

8.6.1 Missing Medication Dates

Missing and/or incomplete dates for prior and concomitant medications will be imputed for calculating relative start and stop days only. Dates will be listed as missing/incomplete [with "-"replacing missing information] but the Start/Stop Day listed between square brackets to denote it was calculated based on missing data (i.e. [-28], [1], [Ongoing]).

Missing and/or incomplete dates will be imputed in a manner that assumes the worst case scenario.

Incomplete stop dates will be imputed as follows:

- For a missing day (but month and year is available), it will be assumed that medication have been stopped on the last day of the respective month.

- For a missing month (but year is available), it will be assumed that medication has

stopped on 31st December of the respective year.

- For a completely missing stop date, the medication will be assumed to be ongoing.

Similarly, incomplete start dates will be imputed as follows:

- For a missing start day (but month and year is available), onset is assumed on the first day of the respective month.

- For a missing start month (but year is available), onset is assumed on 1st January of the respective year.

- For a completely missing start date, no imputation is performed. However, the medication will be considered as concomitant, unless indicated different by stop date.

8.7 ECG

The results will be presented by treatment group for the Safety Analysis Population.

By-subject listings will be provided for electrocardiogram results (including HR, PR interval, QRS duration, QT interval, RR interval, and QT interval corrected using Fridericia's formula [QTcF interval]) by subject ID number and time point. ECG results will be labeled as normal, abnormal-not clinically significant (NCS), or abnormal-clinically significant (CS).

The number and percentage of subjects with clinically significant abnormalities in ECGs will be reported.

Electrocardiogram results will be presented using descriptive statistics (n, mean, SD, median, min, and max) in terms of absolute values and changes from baseline for each measurement at each scheduled time point.

QTcF values will be summarized by category for ranges (≤ 450 msec, > 450 - ≤ 470 msec, > 470 - ≤ 500 msec, and > 500 msec) and increase from baseline ranges (≤ 30 msec, > 30 - ≤ 60 msec, > 60 msec) based on the max post dose QTcF value.

8.8 Other Observations Related to Safety

Results of other laboratory assessment will be summarized, including serum alpha fetoprotin (AFP), hemoglobin A1c (HbA1c), thyroid stimulating hormone (TSH), follicle stimulating hormone (FSH; females only), hCG pregnancy test, Fibroscan, HBcAb IgM, ANA, ASMA, anti-LKM1 serology.

9 EFFICACY ANALYSES

Measures of virologic responses will include quantitative assessments of HBV DNA, HBsAg, HBcrAg, HBV RNA, and HBsAb. Missing values will not be imputed. If either the

baseline or the post-baseline result is missing, the change from baseline and/or percentage change from baseline is set to missing as well.

9.1 Analysis Methods for Continuous Efficacy Endpoints

- The observed and mean change in $\log_{10}$ HBsAg, HBV DNA, HBV RNA, HBcrAg, and HBsAb (if applicable) from baseline will be summarized using descriptive statistics (sample size, mean, SD, standard error, median, Q1, Q3, minimum, and maximum) by treatment group and timepoint.

- Exploratory analysis will be performed to compare the mean changes from baseline of $\log_{10}$ HBsAg at selected timepoints between treatment groups. The primary comparison for mean change endpoints will be made using an analysis of covariance (ANCOVA) model, including baseline value of $\log_{10}$ HBsAg, the stratification factor (HBsAg level at week 24) and treatment group as predictors. The estimated least square means of treatment effects and estimated difference in treatment effects between treatment groups at selected timepoints will be presented along with the 95% CIs and p-values.

9.2 Analysis Methods for Categorical Efficacy Endpoints

The number and percentage of subjects will be tabulated by treatment group for the following endpoints:

- Participants with change in HBsAg from baseline meeting response criteria of $\geq$ 0.5, 1, 2, or 3 $\log_{10}$ reduction; $\leq$ LLOQ; <100 IU/mL, <10 IU/mL; at each post-baseline timepoint.

- Participants with change in HBV RNA from baseline meeting response criteria of $\geq$ 0.5, 1, 2, or 3 $\log_{10}$ reduction; $\leq$ LLOQ; at each post-baseline timepoint

- Participants with change in HBcrAg from baseline meeting response criteria of $\geq$ 0.5, 1, 2, or 3 $\log_{10}$ reduction; $\leq$ LLOQ; at each post-baseline timepoint

- Participants with HBsAb seroconversion; at each post-baseline timepoint

- Participants meeting NA treatment discontinuation criteria after Week 24 of follow up.

- Participants who discontinue NA and subsequently restart NA therapy; during the follow up period

- Participants who discontinue NA therapy and subsequently meet protocol-defined clinical relapse criteria; during the follow up period

- Participants who discontinue NA therapy and subsequently meet protocol-defined viral relapse criteria; during the follow up period

By-subject listings will be created for HBV DNA, HBV RNA, HBsAg, HBcrAg, HBeAb, and HBsAb sorted by subject ID number and timepoint.

Multivariable logistic regression will be employed for exploratory purposes for response criteria of HBsAg ≤ LLOQ at EOT and some other endpoints. The baseline log_{10} HBsAg, baseline weight, demographics and other variables will be included as predictors.

9.3 Efficacy Figures

The following figures will be prepared for HBsAg, HBV DNA, HBV RNA, and HBcrAg:

- Individual and individual log_{10} change from baseline over time
- Mean ± SE for the observed values and change from baseline over time

10 EXPLORATORY ANALYSES

10.1 Immune Biomarkers and Pharmacodynamic Exploratory Endpoints

The following exploratory endpoints as observed and change from baseline will be summarized by treatment group in tabular and graphic format using descriptive statistics.

The analysis may be reported separately from the clinical study report.

- Immune-related protein levels (such as soluble programmed death-1 [sPD-1] and cytokines)
- Immune activation / exhaustion markers on global and HBV-specific immune cells in PBMCs
- Potential polymorphisms in immune and inflammatory genes
- Small, middle, and large isoforms of HBsAg
- HBsAg immune complex levels
- RNAi PD marker levels
- HBV-related miRNAs

10.2 SCALE-B

The SCALE-B score will be summarized at end-of treatment (EOT). For SCALE-B scores of <260, 260 – 320, and >320 points the following will be presented:

- The number and proportion of subjects with who experience clinical relapse
- The number and proportion of subjects who experience HBsAg loss

11 PHARMACOKINETIC ANALYSES

Bioanalytical summary report(s) will include the analytical results, stability of the frozen samples, a summary of the standard curves and quality control samples, and results of the incurred sample reanalysis, if applicable. Residual plasma may be archived for exploratory metabolite analysis that would be reported separately from the clinical study report.

- All samples will be analyzed, and all concentrations listed.
- The listing of PK concentrations will be flagged for subjects who did not receive all doses and any other significant protocol deviations.
- Descriptive statistics will be performed on all PK concentrations for all time points available, with the exclusion of subjects who did not receive all doses or any other significant protocol deviations.
- Pharmacokinetic parameters will be derived where possible for all subjects. Data from subjects with incomplete profiles (missed blood draws, lost samples, samples unable to be quantified) may be used if PK parameters can be estimated using the remaining data points.
- Descriptive statistics will be performed on all parameters available, and any missing parameters will be flagged.

Estimation of PK Parameters

Plasma concentrations of imdusiran for each subject will be estimated over the sampling interval using non-compartmental analyses and summarized by treatment group using descriptive statistics.

Plasma PK parameters of AB-729 AS, AB-729 AS(N-1)3′, and AB-729 AS(N-2)3′ for each participant will be estimated over the sampling interval using non-compartmental analysis and summarized by treatment group using descriptive statistics. The plasma PK parameters that will be estimated, if feasible, are listed in the table below. Additional parameters may be analyzed, as appropriate.

Pharmacokinetic Parameters for Imdusiran

Pharmacokinetic Parameter	**Definition**
C_{max}	Maximum observed plasma concentration
T_{max}	Time of maximum observed plasma concentration
AUC_{0-t}	Area under the concentration time curve from the time of dosing to the last measurable concentration

Actual blood sampling times will be used for PK analysis. In all derivations of PK parameters, zero will be substituted for concentrations below the quantification limit (BQL) of the assay prior to the first quantifiable sample. Samples which are otherwise BQL will be treated as missing.

11.1 Statistical Analysis of Pharmacokinetic Data

11.1.1 Summaries

All analysis will be performed on the Pharmacokinetic Analysis Population and presented by treatment group.

Individual plasma concentrations will be summarized by treatment group for all time points available using the following descriptive statistics: sample size (N), arithmetic mean, standard deviation (SD), geometric mean, coefficient of variation (CV), median, minimum, and maximum. All plasma concentration values below the limit of quantification (BLQ) will be set to missing when calculating summary statistics.

The line charts where the mean (SD) plasma concentration is plotted against time will be created.

By-subject listings of individual PK parameters will be created.

PK parameters will be summarized by treatment group for all time points available using the following descriptive statistics: N, arithmetic mean, SD, geometric mean, CV, median, minimum, and maximum.

The following tables will be provided for imdusiran by treatment group:

- Individual subject concentration data and summary statistics
- Individual subject plasma PK parameters and summary statistics

The following figures may be provided for imdusiran by treatment group:

- Mean (+- SD) concentration data versus time (on linear and semilogarithmic scales
- Individual subject concentration data vs. time (on linear and semilogarithmic scales)

12 APPENDICES

APPENDIX 1. ABBREVIATIONS AND TRADEMARKS

Abbreviation	Definition
Arbutus	Arbutus Biopharma Corporation
AE	adverse event
AFP	alpha fetoprotein
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AS	anti-sense
AST	aspartate aminotransaminase
BMI	body mass index

BQL	below the quantification limit
CHB	chronic hepatitis B
CRF	case report form, electronic or paper
CRO	contract research organization
CYP	Cytochrome P450
DAIDS	Division of AIDS (acquired immunodeficiency syndrome)
ECG	electrocardiogram
ETV	entecavir
FSH	follicle stimulating hormone
GalNAc	*N*-Acetylgalactosamine
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBcrAg	hepatitis B virus core related antigen
HBeAb	hepatitis B virus e-antibody
HBeAg	hepatitis B virus e-antigen
HBsAb	hepatitis B virus surface antibody
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDV	hepatitis D virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	Institutional Ethics Committee
IgM	immunoglobulin M
IL	interleukin
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	microRNAs
NA	nucleos(t)ide analogue
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamic
Peg-IFNα	pegylated interferon alfa
PK	pharmacokinetic(s)
PT	prothrombin time
QTcF	QT interval corrected using Fridericia's formula
QW	every week
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
siRNA	small interfering ribonucleic acid
sPD-1	soluble programmed death-1
TAF	tenofovir alafenamide

TDF	tenofovir disoproxil fumarate
TEAE	treatment emergent adverse event
TND	target not detected
ULN	upper limit of normal
WOCBP	women of childbearing potential

APPENDIX 2. HBV SEROLOGY DEFINITIONS

- **Chronic HBV:** Chronic HBV infected patient was defined as having the following: positive HBsAg, HBV DNA, or HBeAg at least 6 months prior to the Screening Visit (historical documentation must be provided), and negative serum immunoglobulin M (IgM) anti-hepatitis B core-related antibody (HBcAb) at the Screening Visit.

- **HBsAg loss:** HBsAg changing from positive at baseline to ≤LLOQ at any post-baseline visit.

- **HBsAg seroclearance:** HBsAg seroclearance was defined as two consecutive serum HBsAg ≤LLOQ measurements.

- **HBsAb seroconversion:** HBsAg seroclearance plus HBsAb changing from <LLOQ or missing at baseline to positive and quantifiable at any post-baseline visit.

- **HBV functional cure:** HBV functional cure was defined as sustained HBV DNA suppression and HBsAg loss with or without hepatitis B surface antibody [HBsAb] seroconversion that is maintained for at least 24 weeks after discontinuation of antiviral therapy.

- **LLOQ:** HBV DNA: 10 IU/mL; HBsAg: 0.05 IU/mL; HBcrAg: 1 kU/mL or 3 $\log_{10}$ U/mL; HBV RNA: 0.49 $\log_{10}$ U/mL and 0.80 $\log_{10}$ U/mL

APPENDIX 3. SCHEDULE OF ACTIVITIES

Table 1 summarizes the schedule of study-related activities for the 24 Week Lead-In Treatment period for all subjects; Table 2 is the Cohort A Consolidation Treatment period and NA-only Post-Treatment follow up (Periods 1 and 2); Table 3 is the Cohort A NA-discontinuation period (for subjects who qualify). Table 4 is the Cohort B Consolidation Treatment period and NA-only Post-Treatment follow-up (Periods 1 and 2), and Table 5 is the Cohort B NA-discontinuation period (for subjects who qualify).

All laboratory assessments including clinical laboratory tests (safety assessments), virology, biomarker and PBMC collections should be drawn pre-dose (AB-729 or Peg-IFNα-2a) when applicable. Additional details of the various laboratory tests are found in Appendix 4.

Table 1. Schedule of Activities for 24 Week Lead-In Treatment Period (All Subjects)

Assessment	Screening Day -45 to Day -1[a]	Lead-In Treatment Period [b,d]								Notes
		Baseline Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Early Termination	
Written informed consent	X									
Review inclusion/exclusion criteria	X	X								
Demographics	X									
Height and BMI	X									
Weight	X									
Medical and medication history	X	X								
Concomitant medications	X	X	X	X	X	X	X	X	X	
Eye examination	X									Subjects must provide documentation of an eye examination including a retinal evaluation within 6 months prior to Day 1.
Physical examination	X	X	X	X	X	X	X	X	X	Complete PEs will be conducted at SCR> From Day 1, targeted PEs may be completed at any study visit based on any reported changes to the subject's health.
Vital signs	X	X	X	X	X	X	X	X	X	BP, HR, RR, and temp to be performed pre-dose, when applicable.

Assessment	Screening Day -45 to Day -1[a]	Lead-In Treatment Period [b,d]								Notes
		Baseline Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Early Termination	
ECG	X	X			X			X	X	Will be performed pre-dose, when applicable.
Clinical laboratory tests	X	X	X	X	X	X	X	X	X	Includes clinical chemistry (including fasting plasma glucose), hematology, coagulation tests, serology, and urine as specified in Appendix 4 of the Protocol, and are to be completed after an overnight fast of ≥8 hrs.
HbA1C	X									
TSH/Free T4	X									
AFP	X									
ANA, ASMA, anti-LKM1 serology	X									
Pregnancy test (females only)	X	X	X	X	X	X	X	X	X	Urine pregnancy test is required at SCR for all female subjects, and at subsequent study visits for WOCBP only. If the urine test is positive or not interpretable, a serum/plasma pregnancy test is to be conducted.
FSH (post-menopausal females only)	X									
Fibroscan®	X									Is only required if results from a previous study performed within 6 mos of Day 1 are not available. For subjects who do not have a Fibroscan® result, a prior liver biopsy (performed within 12 mos of Day 1) may be used to determine noncirrhotic status for the purposes of determining eligibility.
Liver ultrasound	X									Is only required if results from a previous study performed within 6 mos of Day 1 are not available.
HIV, HCV, HDV antibody	X									Positive antibody tests may reflex to a confirmatory PCR test.
Qualitative HBcAb IgM	X									
Qualitative HBeAg	X	X			X			X	X	
Quantitative HBsAg[c]	X	X	X	X	X	X	X	X	X	

Assessment	Screening Day -45 to Day -1[a]	Lead-In Treatment Period [b,d]								Notes
		Baseline Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Early Termination	
HBsAg Ultrasensitive[c]	X	X	X	X	X	X	X	X	X	To be assessed only if quantitative HBsAg result is <LLOQ
Quantitative HBsAb[c]		X			X			X	X	
Quantitative HBV DNA[c]	X	X	X	X	X	X	X	X	X	
Quantitative HBV RNA[c]		X	X	X	X	X	X	X	X	
Quantitative HBcrAg[c]		X	X	X	X	X	X	X	X	
Quantitative HBeAg[c]		X			X			X	X	To be assessed only if positive result obtained with HBeAg qualitative test
Qualitative HBeAb[c]		X			X			X	X	
HBsAg isoforms[c]		X	X	X	X	X	X	X	X	
HBsAg immune complex[c]		X			X			X	X	
Resistance Sample[c]	X	X	X	X	X	X	X	X	X	
HBV Genotype Sample		X								
IL28B GT		X								
Exploratory Immune genes SNP Sample		X								Will be stored and analyzed only if a non-response in HBsAg is observed.
miRNAs[c]		X			X			X	X	Will be stored and analyzed only if a HBsAg effect is observed
RNAi PD marker[c]		X	X	X	X	X	X	X	X	
Immune biomarker/cytokines sample[c]		X		X		X		X	X	Unscheduled samples will be collected in the event of any unexpected safety finding.
PBMCs[c]		X		X		X		X	X	Unscheduled samples will be collected in the event of any unexpected safety finding.
Randomization								X		Subjects will be randomized at the Week 24 visit into Cohort A (A1 or A2) or Cohort B (B1 or B1).
Drug dispensing/ accountability		X	X	X	X	X	X	X	X	Subjects will record all NA doses in a dosing diary, which will be reviewed at each study visit.
AB-729 dosing		X		X		X		X		Doses administered in the clinic only.

Assessment	Screening Day -45 to Day -1[a]	Lead-In Treatment Period [b,d]								Notes
		Baseline Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Early Termination	
Record AEs		X	X	X	X	X	X	X	X	Will be collected from the time of the start of study treatment through the last Post-Treatment F/U visit.
Record SAEs	X	X	X	X	X	X	X	X	X	Will be collected from the signing of the ICF through the last Post-Treatment F/U visit and followed until resolution of any event.
AB-729 PK sampling		X						X		Will be collected on Day 1 and at Week 24 according to the schedule provided in Appendix 7 of the Protocol On PK collection days, subjects will remain in the clinic a minimum of 6 hours post-dose.

Abbreviations: AEs = adverse events; AFP = alpha-fetoprotein; BMI = body mass index; ANA = antinuclear antibody; anti-LKM1 = liver/kidney microsomal antibody type 1; ASMA = anti-smooth muscle antibody; BP = blood pressure; ECG = electrocardiogram; FSH = follicle stimulating hormone; F/U = follow up; HBcAb = hepatitis B core-related antibody; HBcrAg = hepatitis B virus core-related antigen; HBeAb = hepatitis B virus e-antibody; HBeAg = hepatitis B virus e-antigen; HBsAb = hepatitis B virus surface antibody; HBsAg = hepatitis B virus surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis D virus; HbA1C = hemoglobin A1C; HIV = human immunodeficiency virus; HR = heart rate; hrs = hours; ICF = informed consent form; IgM = immunoglobulin M; IL28B GT = interleukin 28B genotype: LFTs = liver function tests; miRNAs = micro RNAs; mos = months; NA = nucleos(t)ide analogue; PBMCs = peripheral blood mononuclear cells; PCR = polymerase chain reaction; PD = pharmacodynamic; PE = physical exam; PK = pharmacokinetic; RNAi = RNA interference; RR = respiration rate; SAE = serious adverse event; SCR = screening; SNP = single nucleotide polymorphism; temp = temperature; TSH = thyroid stimulating hormone; T4 = thyroxine; WOCBP = women of childbearing potential.

a. If the Screening Visit is >45 days from Day 1 (up to a maximum of 60 days from Day 1), only the safety screening labs (hematology, chemistry including LFTs, and coagulation parameters) need be repeated for the subject to enroll.
b. Visit windows are ± 5 days.
c. Samples are to be drawn pre-dose where applicable.
d. If a subject discontinues on or before Week 28 (prior to peg-IFNα-2a treatment), they should complete an Early Termination visit. If they agree to remain in follow-up they should follow the schedule of activities for Early Termination (Lead-in Period only).

Table 2. Schedule of Activities for Cohort A: Consolidation Treatment Period and NA-only Post-Treatment Follow-Up Periods 1 and 2

Cohort A							
Assessment	**Consolidation Treatment Period**		**Post-Treatment Follow-Up (NA only) Period 1**		**Post-Treatment Follow-Up (NA only) Period 2[c]**	**Early Termination[e]**	**Notes**
	Weeks 28, 30, 32, 34, 36, 38[a]	**Weeks 40, 44, 48, 52[b]**	**Weeks 56, 60, 64, 68, 72[b]**	**Weeks 75 and 76[a]**	**Weeks 88 and 100 (EOS)**		
Concomitant medications	X	X	X	X	X	X	
Physical examination	X	X	X	X	X	X	Targeted PEs may be completed at any study visit based on any reported changes to the subject's health.
Vital signs	X	X	X	X	X	X	BP, HR, RR, and temp to be performed pre-dose, when applicable.
ECG	X	X	X	X	X	X	Will be performed pre-dose, when applicable.
Clinical laboratory tests[d]	X*	X*	X*	X	X	X	Includes clinical chemistry, hematology, coagulation tests, serology, and urine as specified in Appendix 4 of the Protocol be completed after an overnight fast of ≥8 hrs. *TSH to be drawn only at selected visits (Weeks 28, 40, 52 and 64).
Pregnancy test (WOCBP only)	X*	X	X	X**	X	X	Urine pregnancy tests will be collected as indicated. If the urine test is positive or not interpretable, a serum/plasma pregnancy test is to be conducted. *Samples to be collected at Weeks 28, 32, 36. **Sample to be collected at Week 76.
Quantitative HBsAg[d]	X	X	X	X	X	X	
HBsAg Ultrasensitive[d]	X	X	X	X	X	X	To be assessed only if quantitative HBsAg result is <LLOQ
Quantitative HBsAb[d]	X	X	X	X	X	X	Samples to be collected at Weeks 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 72, 76, 88, 100.
Quantitative HBV DNA[d]	X	X	X	X	X	X	
Quantitative HBV RNA[d]	X	X	X	X	X	X	
Quantitative HBcrAg[d]	X	X	X	X	X	X	
Qualitative HBeAg[d]	X	X	X	X	X	X	Samples to be collected at Weeks 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 72, 76, 88, 100.

Cohort A							
Assessment	**Consolidation Treatment Period**		**Post-Treatment Follow-Up (NA only) Period 1**		**Post-Treatment Follow-Up (NA only) Period 2[c]**	**Early Termination[e]**	**Notes**
	Weeks 28, 30, 32, 34, 36, 38[a]	**Weeks 40, 44, 48, 52[b]**	**Weeks 56, 60, 64, 68, 72[b]**	**Weeks 75 and 76[a]**	**Weeks 88 and 100 (EOS)**		
Quantitative HBeAg[d]	X	X	X	X	X	X	Samples to be collected at Weeks 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 72, 76, 88, 100. To be assessed only if positive result obtained with HBeAg qualitative test.
Qualitative HBeAb[d]	X	X	X	X	X	X	Samples to be collected at Weeks 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 72, 76, 88, 100.
HBsAg isoforms[d]	X	X	X	X	X	X	
HBsAg immune complex[d]	X	X	X	X	X	X	Samples to be collected at Weeks 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 72, 76, 88, 100.
Resistance Sample[d]	X	X	X	X	X	X	
miRNAs[d]	X	X	X	X	X	X	Will be stored and analyzed only if a HBsAg effect is observed. Samples to be collected at Weeks 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 72,76, 88, 100.
RNAi PD marker[d]	X	X	X	X	X	X	
Immune biomarker/cytokines sample[d]	X*	X	X**	X***	X	X	Unscheduled samples will be collected in the event of any unexpected safety finding. *Collected at Week 28, 32 and 36. **Collected at Week 56, 60, 64, and 72. ***Collected at Week 76 only.
PBMCs[d]	X*	X	X**	X***	X	X	. Unscheduled samples will be collected in the event of any unexpected safety finding. * Collected at Week 28, 32 and 36. ** Collected at Week 56, 60,64, and 72. ***Collected at Week 76 only.
Drug dispensing/ accountability	X	X	X	X	X	X	Subjects will record all doses in a dosing diary, which will be reviewed at each study visit.
AB-729 dosing in the clinic (Cohort A1 only)	X	X					Weeks 32 and 40 only.

Cohort A							
Assessment	**Consolidation Treatment Period**		**Post-Treatment Follow-Up (NA only) Period 1**		**Post-Treatment Follow-Up (NA only) Period 2[c]**	**Early Termination[e]**	**Notes**
	Weeks 28, 30, 32, 34, 36, 38[a]	**Weeks 40, 44, 48, 52[b]**	**Weeks 56, 60, 64, 68, 72[b]**	**Weeks 75 and 76[a]**	**Weeks 88 and 100 (EOS)**		
Peg-IFNα-2a dosing	X	X					First Peg-IFNα-2a dose to be administered in the clinic at Week 28 visit, and Peg-IFNα-2a administration will occur in the clinic on visit days. Remainder of Peg-IFNα-2a doses (odd numbered Weeks and Weeks 42, 46 and 50) to be self-administered with last dose at Week 51. Subjects will record all Peg-IFNα-2a doses in a dosing diary, which will be reviewed at each study visit.
Record AEs	X	X	X	X	X	X	Will be collected from the time of the start of study treatment through the last Post-Treatment F/U visit.
Record SAEs	X	X	X	X	X	X	Will be collected from the signing of the ICF through the last Post-Treatment F/U visit and followed until resolution of any event.
AB-729 PK sampling	X	X					Will be collected at Week 32 and Week 40 for Group A1 only according to the schedule provided in Appendix 7 of the Protocol On PK collection days, subjects will remain in the clinic a minimum of 6 hrs post-dose.

Abbreviations: AEs = adverse events; BP = blood pressure; ECG = electrocardiogram; EOS = end of study; ET = Early Termination; F/U = follow up; HBcrAg = hepatitis B virus core-related antigen; HBeAb = hepatitis B virus e-antibody; HBeAg = hepatitis B virus e-antigen; HBsAb = hepatitis B virus surface antibody; HBsAg = hepatitis B virus surface antigen; HBV = hepatitis B virus; HR = heart rate; hrs = hours; ICF = informed consent form; miRNAs = micro RNAs; NA = nucleos(t)ide analogue; RNAi = RNA interference; PBMCs = peripheral blood mononuclear cells; Peg-IFNα-2a = pegylated interferon α-2a; PD = pharmacodynamic; PE = physical exam; PK = pharmacokinetic; RR = respiration rate; SAE = serious adverse event; temp = temperature; WOCBP = women of childbearing potential.

a. Visit windows are ± 3 days.
b. Visit windows are ± 5 days.
c. Visit windows are ± 7 days.
d. Samples are to be drawn pre-dose where applicable.
e. If a subject discontinues between Week 28 and 52, they should complete an Early Termination visit. If they agree to remain in follow-up they should enter the Post-Treatment FU (NA only) Periods 1 and 2 within 4 weeks of the ET visit. The subject may skip the Week 75 visit as they will not be eligible for NA discontinuation.

Table 3. Schedule of Activities for Cohort A: NA-Discontinuation Period (For Subjects who Qualify)

Assessment	Cohort A NA-Discontinuation Period[a]		Notes
	Weeks 78, 80, 82, 84, 86, 88[0]	Weeks 92, 96, 100, 104, 108, 112, 116, 120, 124 (EOS)[c]	
Concomitant medications	X	X	
Physical examination	X	X	Targeted PEs may be completed at any study visit based on any reported changes to the subject's health.
Vital signs	X	X	BP, HR, RR, and temperature.
ECG	X	X	
Clinical laboratory tests	X	X	Includes clinical chemistry, hematology, coagulation tests, serology, and urine as specified in Appendix 4 of the Protocol, and are to be completed after an overnight fast of ≥8 hrs .
Pregnancy test (WOCBP only)	X*	X	Urine pregnancy tests will be collected as indicated. If the urine test is positive or not interpretable, a serum/plasma pregnancy test is to be conducted. *Samples to be collected at Weeks 80, 84, and 88.
Quantitative HBsAg	X	X	
HBsAg Ultrasensitive	X	X	To be assessed only if quantitative HBsAg result is <LLOQ
Quantitative HBsAb	X	X	Samples to be collected at Weeks 80, 84, 88, 92, 100, 112, 124.
Quantitative HBV DNA	X	X	
Quantitative HBV RNA	X	X	
Quantitative HBcrAg	X	X	
Qualitative HBeAg	X	X	
Quantitative HBeAg	X	X	To be assessed only if positive result obtained with HBeAg qualitative test.
Qualitative HBeAb	X	X	Samples to be collected at Weeks 80, 84, 88, 92, 100, 112, 124.
HBsAg isoforms	X	X	
HBsAg immune complex	X	X	Samples to be collected at Weeks 80, 84, 88, 92, 100, 112, 124.
Resistance Sample	X	X	
miRNAs	X	X	Will be stored and analyzed only if a HBsAg effect is observed. Samples to be collected at Weeks 80, 84, 88, 92, 100, 112, 124.

Assessment	Cohort A NA-Discontinuation Period[a]		Notes
	Weeks 78, 80, 82, 84, 86, 88[0]	Weeks 92, 96, 100, 104, 108, 112, 116, 120, 124 (EOS)[c]	
RNAi PD marker	X	X	
Immune biomarker/cytokines sample	X*	X**	Unscheduled samples will be collected in the event of any unexpected safety finding. *Collected at Weeks 80, 84, and 88. **Collected at Weeks 92,100, 112, and 124.
PBMCs	X*	X**	Unscheduled samples will be collected in the event of any unexpected safety finding. *Collected at Weeks 80, 84, and 88. **Collected at Weeks 92,100, 112, and 124.
Record AEs	X	X	Will be collected from the time of the start of study treatment through the last Post-Treatment F/U visit.
Record SAEs	X	X	Will be collected from the signing of the ICF through the last Post-Treatment F/U visit and followed until resolution of any event.

Abbreviations: AEs = adverse events; BP = blood pressure; ECG = electrocardiogram; EOS = end of study; F/U = follow up; HBcrAg = hepatitis B virus core-related antigen; HBeAb = hepatitis B virus e-antibody; HBeAg = hepatitis B virus e-antigen; HBsAb = hepatitis B virus surface antibody; HBsAg = hepatitis B virus surface antigen; HBV = hepatitis B virus; HR = heart rate; hrs = hours; ICF = informed consent form; miRNAs = micro RNAs; NA = nucleos(t)ide analogue; PBMCs = peripheral blood mononuclear cells; PD = pharmacodynamic; PE = physical exam; PK = pharmacokinetic; RNAi = RNA interference; RR = respiration rate; SAE = serious adverse event; temp = temperature.

a. Subjects who Early Terminate during this period should discuss restarting NA therapy and entering the NA Restart Follow-Up period or discuss alternative follow-up plans with the study Investigator.
b. Visit windows are ± 3 days.
c. Visit windows are ± 5 days.

Table 4. Schedule of Activities for Cohort B: Consolidation Treatment Period and NA-only Post-Treatment Follow-Up Periods 1 and 2

Cohort B						
	Consolidation Treatment Period[a]	**Post-Treatment Follow-Up (NA only) Period 1**		**Post-Treatment Follow-Up (NA only) Period 2[c]**	**Early Termination[e]**	
Assessment	**Weeks 28, 30, 32, 34, 36, 38, 40**	**Weeks 44, 48, 52, 56, 60[b]**	**Weeks 63 and 64[a]**	**Weeks 76 and 88 (EOS)**		**Notes**
Concomitant medications	X	X	X	X	X	
Physical examination	X	X	X	X	X	Targeted PEs may be completed at any study visit based on any reported changes to the subject's health.
Vital signs	X	X	X	X	X	BP, HR, RR, and temp to be performed pre-dose, when applicable.
ECG	X	X	X	X	X	Will be performed pre-dose, when applicable.
Clinical laboratory tests[d]	X*	X*	X	X	X	Includes clinical chemistry, hematology, coagulation tests, serology, and urine as specified in Appendix 4 of the Protocol and are to be completed after an overnight fast of ≥8 hrs. *TSH to be drawn only at selected visits (Weeks 28, 40, and 52)
Pregnancy test (WOCBP only)	X*	X	X**	X	X	Urine pregnancy tests will be collected as indicated. If the urine test is positive or not interpretable, a serum/plasma pregnancy test is to be conducted. * Samples to be collected at Weeks 28, 32, 36, and 40. **Sample to be collected at Week 64.
Quantitative HBsAg[d]	X	X	X	X	X	
HBsAg Ultrasensitive[d]	X	X	X	X	X	To be assessed only if quantitative HBsAg result is <LLOQ
Quantitative HBsAb[d]	X	X	X	X	X	Samples to be collected at Weeks 28, 32, 36, 40, 44, 48, 52, 60, 64, 76, and 88.
Quantitative HBV DNA[d]	X	X	X	X	X	

Cohort B						
Assessment	**Consolidation Treatment Period[a]**	**Post-Treatment Follow-Up (NA only) Period 1**		**Post-Treatment Follow-Up (NA only) Period 2[c]**	**Early Termination[e]**	**Notes**
	Weeks 28, 30, 32, 34, 36, 38, 40	**Weeks 44, 48, 52, 56, 60[b]**	**Weeks 63 and 64[a]**	**Weeks 76 and 88 (EOS)**		
Quantitative HBV RNA[d]	X	X	X	X	X	
Quantitative HBcrAg[d]	X	X	X	X	X	
Qualitative HBeAg[d]	X	X	X	X	X	
Quantitative HBeAg[d]	X	X	X	X	X	To be assessed only if positive result obtained with HBeAg qualitative test.
Qualitative HBeAb[d]	X	X	X	X	X	Samples to be collected at Weeks 28, 32, 36, 40, 44, 48, 52, 60, 64, 76, and 88.
HBsAg isoforms[d]	X	X	X	X	X	
HBsAg immune complex[d]	X	X	X	X	X	Samples to be collected at Weeks 28, 32, 36, 40, 44, 48, 52, 60, 64, 76, and 88.
Resistance Sample[d]	X	X	X	X	X	
miRNAs[d]	X	X	X	X	X	Will be stored and analyzed only if a HBsAg effect is observed. Samples to be collected at Weeks 28, 32, 36, 40, 44, 48, 52, 60, 64, 76, and 88.
RNAi PD marker [d]	X	X	X	X	X	
Immune biomarker/cytokines sample[d]	X*	X	X**	X	X	Unscheduled samples will be collected in the event of any unexpected safety finding. *Collected at Weeks 28, 32, 36 and 40. **Collected at Week 64 only.
PBMCs[d]	X*	X	X**	X	X	Unscheduled samples will be collected in the event of any unexpected safety finding. *Collected at Week 28, 32,36, and 40. ** Collected at Week 64 only.
Drug dispensing/ accountability	X	X	X	X	X	Subjects will record all NA doses in a dosing diary, which will be reviewed at each study visit.
AB-729 dosing in the clinic (Cohort B1 only)	X					Week 32 only.

Cohort B						
	Consolidation Treatment Period[a]	**Post-Treatment Follow-Up (NA only) Period 1**		**Post-Treatment Follow-Up (NA only) Period 2[c]**	**Early Termination[e]**	
Assessment	**Weeks 28, 30, 32, 34, 36, 38, 40**	**Weeks 44, 48, 52, 56, 60[b]**	**Weeks 63 and 64[a]**	**Weeks 76 and 88 (EOS)**		**Notes**
Peg-IFNα-2a dosing	X					First Peg-IFNα-2a dose to be administered in the clinic at Week 28 visit, and Peg-IFNα-2a administration will occur in the clinic on visit days. Remainder of Peg-IFNα-2a doses (odd numbered Weeks) to be self-administered with last dose at Week 39. Subjects will record all Peg-IFNα-2a doses in a dosing diary, which will be reviewed at each study visit.
Record AEs	X	X	X	X	X	Will be collected from the time of the start of study treatment through the last Post-Treatment F/U visit.
Record SAEs	X	X	X	X	X	Will be collected from the signing of the ICF through the last Post-Treatment F/U visit and followed until resolution of any event.
AB-729 PK sampling	X					Will be collected at Week 32 for Group B1 only according to the schedule provided in Appendix 7 of the Protocol . At this visit, subjects will remain in the clinic for a minimum of 6 hrs post-dose.

Abbreviations: AEs = adverse events; BP = blood pressure; ECG = electrocardiogram; EOS = end of study; ET = early termination; F/U = follow up; HBcrAg = hepatitis B virus core-related antigen; HBeAb = hepatitis B virus e-antibody; HBeAg = hepatitis B virus e-antigen; HBsAb = hepatitis B virus surface antibody; HBsAg = hepatitis B virus surface antigen; HBV = hepatitis B virus; HR = heart rate; hrs = hours; ICF = informed consent form; miRNAs = micro RNAs; RNAi = RNA interference; NA = nucleos(t)ide analogue; PBMCs = peripheral blood mononuclear cells; PD = pharmacodynamic; PE = physical examination; Peg-IFNα-2a = pegylated interferon α-2a; PK = pharmacokinetic; RR = respiration rate; SAE = serious adverse event; temp = temperature; TSH = thyroid stimulating hormone; WOCBP = women of childbearing potential.

a. Visit windows are ± 3 days.
b. Visit windows are ± 5 days.
c. Visit windows are ± 7 days.
d. Samples are to be drawn pre-dose where applicable.
e. If a subject discontinues between Week 28 and 40, they should complete an Early Termination visit. If they agree to remain in follow-up they should enter the Post-Treatment FU (NA only) Periods 1 and 2 within 4 weeks of the ET visit. The subject may skip the Week 63 visit as they will not be eligible for NA discontinuation.

Table 5. Schedule of Activities for Cohort B: NA-Discontinuation Period (For Subjects who Qualify)

Assessment	Cohort B NA-Discontinuation Period a		Notes
	Weeks 66, 68, 70, 72, 74, 76[b]	Weeks 80, 84, 88, 92, 96, 100, 104, 108, 112 (EOS)[c]	
Concomitant medications	X	X	
Physical examination	X	X	Targeted PEs may be completed at any study visit based on any reported changes to the subject's health.
Vital signs	X	X	BP, HR, RR, and temperature.
ECG	X	X	
Clinical laboratory tests	X	X	Includes clinical chemistry, hematology, coagulation tests, serology, and urine as specified in Appendix 4 of the Protocol and are to be completed after an overnight fast of ≥8 hrs and, during the treatment period, should be drawn prior to dosing, when applicable.
Pregnancy test (WOCBP only)	X*	X	Urine pregnancy tests will be collected as indicated. If the urine test is positive or not interpretable, a serum/plasma pregnancy test is to be conducted. *Samples to be collected at Weeks 68, 72, and 76
Quantitative HBsAg	X	X	
HBsAg Ultrasensitive	X	X	To be assessed only if quantitative HBsAg result is <LLOQ
Quantitative HBsAb	X	X	Samples to be collected at Weeks 68, 72, 76, 80, 88, 100, 112.
Quantitative HBV DNA	X	X	
Quantitative HBV RNA	X	X	
Quantitative HBcrAg	X	X	
Qualitative HBeAg	X	X	
Quantitative HBeAg	X	X	To be assessed only if positive result obtained with HBeAg qualitative test
Qualitative HBeAb	X	X	Samples to be collected at Weeks 68, 72, 76, 80, 88, 100, 112.
HBsAg isoforms	X	X	
HBsAg immune complex	X	X	Samples to be collected at Weeks 68, 72, 76, 80, 88, 100, 112.
Resistance Sample	X	X	
miRNAs	X	X	Will be stored and analyzed only if a HBsAg effect is observed. Samples to be collected at Weeks 68, 72, 76, 80, 88, 100, 112.
RNAi PD marker	X	X	

Assessment	Cohort B NA-Discontinuation Period a		Notes
	Weeks 66, 68, 70, 72, 74, 76[b]	Weeks 80, 84, 88, 92, 96, 100, 104, 108, 112 (EOS)[c]	
Immune biomarker/cytokines sample	X*	X**	Unscheduled samples will be collected in the event of any unexpected safety finding. *Collected at Weeks 68, 72, and 76. **Collected at Weeks 80,88, 100 and 112.
PBMCs	X*	X**	Unscheduled samples will be collected in the event of any unexpected safety finding. *Collected at Weeks 68, 72, and 76. **Collected at Weeks 80, 88, 100 and 112.
Record AEs	X	X	Will be collected from the time of the start of study treatment through the last Post-Treatment F/U visit.
Record SAEs	X	X	Will be collected from the signing of the ICF through the last Post-Treatment F/U visit and followed until resolution of any event.

Abbreviations: AEs = adverse events; BP = blood pressure; ECG = electrocardiogram; EOS= end of study; F/U = follow up; HBcrAg = hepatitis B virus core-related antigen; HBeAb = hepatitis B virus e-antibody; HBeAg = hepatitis B virus e-antigen; HBsAb = hepatitis B virus surface antibody; HBsAg = hepatitis B virus surface antigen; HBV = hepatitis B virus; HR = heart rate; hrs = hours; ICF = informed consent form; miRNAs = micro RNAs; RNAi = RNA interference; PBMCs = peripheral blood mononuclear cells; PD = pharmacodynamic; PE = physical exam; PK = pharmacokinetic; RR = respiration rate; SAE = serious adverse event; temp = temperature.

Subjects who Early Terminate during this period should discuss restarting NA therapy and entering the NA Restart Follow-Up period or discuss alternative follow-up plans with the study Investigator.

Visit windows are ± 3 days.

Visit windows are ± 5 days.

Table 6. Schedule of Activities for Subjects who Restart NA Therapy

Assessment	Visit 1[a] (Week 2)	Visit 2[a] (Week 4)	Remaining Visits[b] (every 2 weeks until clinically stable, then every 4 weeks until Week 24/EOS)	Notes
Concomitant medications	X	X	X	
Physical examination	X	X	X	Targeted PEs may be completed at any study visit based on any reported changes to the subject's health.
Vital signs	X	X	X	BP, HR, RR, and temperature.

Assessment	Visit 1[a] (Week 2)	Visit 2[a] (Week 4)	Remaining Visits[b] (every 2 weeks until clinically stable, then every 4 weeks until Week 24/EOS)	Notes
Clinical Laboratory tests	X	X	X	Includes clinical chemistry, hematology, coagulation tests, serology, and urinalysis as specified in Appendix 4, and are to be completed after an overnight fast of ≥8 hrs
Pregnancy test (WOCBP only)	X		X*	If the urine test is positive or not interpretable, a serum/plasma pregnancy test is to be conducted. *Every 8 weeks until study discharge
Quantitative HBV DNA	X	X	X	Local testing can be performed in addition to central lab testing to facilitate more rapid results.
Quantitative HBsAg	X	X	X	If HBsAg becomes <LLOQ an unscheduled HBsAb sample may be obtained
Quantitative HBV RNA	X	X	X	
Quantitative HBcrAg	X	X	X	
Record AEs	X	X	X	
Record sAEs	X	X	X	

Abbreviations: AEs = adverse events; BP = blood pressure; ECG = electrocardiogram; EOS = end of study; F/U = follow up; HBcrAg = hepatitis B virus core-related antigen; HBsAb = hepatitis B virus surface antibody; HBsAg = hepatitis B virus surface antigen; HBV = hepatitis B virus; HR = heart rate; hrs = hours; NA = nucleos(t)ide analogue; PE = physical exam; PK = pharmacokinetic; RR = respiration rate; SAE = serious adverse event; temp = temperature; WOCBP = women of childbearing potential.

a. Visit windows are ± 3 days.

b. Visit windows are ± 3 days of visits are every 2 weeks, ± 5 days if visits are every 4 weeks.

APPENDIX 4. CLINICAL LABORATORY TESTS

Laboratory Assessments	Parameters	
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	<u>WBC count with differential:</u> Neutrophil count Lymphocyte count Monocyte count Eosinophil count Basophil count
Clinical Chemistry	Sodium Potassium Glucose Chloride CO_2 BUN Creatinine Calcium Phosphorus Magnesium Uric acid Lactate dehydrogenase Lipase Albumin Total protein CPK	<u>Liver Function Tests</u>: AST ALT Alkaline phosphatase Bilirubin (total and direct) GGT
Coagulation	PT / INR aPTT	
Endocrine	TSH	
Urine Parameters	<u>Urinalysis</u>: Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick Microscopic examination (reflex if dipstick is abnormal)	
Virology Tests	HBV Genotype <u>Quantitative tests:</u> HBsAb HBsAg HBsAg isoforms HBcrAg	Resistance sample <u>Qualitative tests:</u> HBcAb IgM (screening only) HBeAg (screening only) HBeAb

Laboratory Assessments	Parameters
	HBeAg HBV DNA HBV RNA Ultrasensitive HBsAg
Biomarkers	HBV-related miRNAs Soluble immune biomarkers/immune complexes PBMCs
Genotype (24 Week Lead-In Period only)	IL28B Genotype
Pharmacogenomics (24 Week Lead-In Period only)	Exploratory immune genes SNP Sample
Other Screening Tests	FSH (as needed in postmenopausal females only) hCG pregnancy test (as needed for women of childbearing potential only)[a] Serology– HIV, HCV, and HDV antibody AFP, HbA_1C, and TSH/Free T4 ANA, ASMA, anti-LKM1 serology

Abbreviations: AFP = alpha fetoprotein; ALT = alanine aminotransferase; ANA = antinuclear antibody; anti-LKM1 = liver/kidney microsomal antibody type 1; aPTT = activated partial thromboplastin time; ASMA = anti-smooth muscle antibody; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CO_2 = carbon dioxide; CPK = creatine phosphokinase; DNA = deoxyribonucleic acid; FSH = follicle stimulating hormone; GGT = gamma glutamyl transpeptidase; HbA_1C = whole blood hemoglobin $A1_c$; HBcAb = hepatitis B core antibody; HBV = hepatitis B virus; HBeAb = HBV e-antibody; HBeAg = HBV e antigen; HBsAb = HBV surface antibody; HBsAg = HBV surface antigen; HBcrAg = HBV core antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HDV = hepatitis D virus; HIV = human immunodeficiency virus; IL28B = interleukin 28B; INR = international normalized ratio; miRNA = micro ribonucleic acid; PBMCs = peripheral blood mononuclear cells; PT = prothrombin time; RBC = red blood cells; RNA = ribonucleic acid; TSH = thyroid stimulating hormone; T4 = thyroxine; WBC = white blood cells.

a. Local hCG pregnancy urine testing will be standard for the protocol unless serum/plasma testing is required by local regulation or IRB/IEC. See Schedule of Activities for required pregnancy testing

13 REFERENCES

13.1 DMID Adult Toxicity Table

Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 July 2017.

https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

14 TABLE OF CONTENTS FOR DATA DISPLAY SPECIFICATIONS

The TOC will be provided in a separate document.