STATISTICAL ANALYSIS PLAN

A PHASE 1/2A SINGLE DOSE-ESCALATING STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND PHARMACOKINETIC EFFECTS OF ARO-HBV IN NORMAL ADULT VOLUNTEERS AND MULTIPLE ESCALATING DOSES EVALUATING SAFETY, TOLERABILITY AND PHARMACODYNAMIC EFFECTS IN HBV PATIENTS

Protocol No.: AROHBV1001

Product Code: ARO-HBV, JNJ-56136379

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SAP APPROVAL

By my signature, I confirm that this SAP has been reviewed by Arrowhead Pharmaceuticals Inc., and has been approved for use on the AROHBV1001 study:

Name	Title / Company	Signature	Date
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1. INTRODUCTION

The following Statistical Analysis Plan (SAP) provides the outline for the statistical analysis of the data from AROHBV1001 study.

This Statistical Analysis Plan (SAP) is an adjunct to the Arrowhead Pharmaceuticals protocol number AROHBV1001 (Version 6.0, 28 February 2020). The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post hoc analyses not necessarily identified in this SAP may be performed to further examine study data. Any post hoc, or unplanned, exploratory analyses performed will be clearly identified as such in the final CSR.

2. PROJECT OVERVIEW

2.1 Study Design

This is a phase 1/2a single dose-escalating study to evaluate the safety, tolerability and pharmacokinetic effects of ARO-HBV in Normal Healthy Volunteers (NHV) and multiple escalating doses to evaluate safety, tolerability and pharmacodynamic effects in HBV patients. ARO-HBV is a drug candidate developed by Arrowhead Pharmaceuticals, Inc. to treat chronic HBV infection. ARO-HBV is administered through subcutaneous injection.

This study will include the following cohorts, with the dose escalation schedule plotted as below. Dose escalation and start of new cohort are subject to Data Safety Committee (DSC) approval based on the evaluation of all available safety data.

- Normal Healthy Volunteers (NHV): Cohorts 1, 2, 3, 4 and 5.

  Each NHV cohort will recruit 6 healthy volunteers, with subjects randomized to receive placebo (2 subjects) or active ARO-HBV (4 subjects) in a double blinded fashion. The first two subjects in each cohort serve as sentinel participants (one ARO-HBV and one placebo). NHV cohorts will be single dosed as follows:
  - Cohort 1: 35 mg ARO-HBV, at Day 1
  - Cohort 2: 100 mg ARO-HBV, at Day 1
  - Cohort 3: 200 mg ARO-HBV, at Day 1
  - Cohort 4: 300 mg ARO-HBV, at Day 1
  - Cohort 5: 400 mg ARO-HBV, at Day 1

- Chronic Hepatitis B (CHB) Patients: Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10, 11 and 12.

  CHB cohorts 1b, 1c, 2b, 3b, 4b and 5b will each enroll a minimum of 4 and a maximum of 8 subjects and the remaining CHB cohorts (except Cohort 12) will each recruit a maximum of 4 chronic hepatitis B patients, with all subjects receiving three doses of ARO-HBV at dose intervals ranging from once every week to once every 4 weeks in an open label fashion. All CHB cohorts except Cohorts 8 and 9 will include CHB patients regardless of NUC or HBeAg status. Cohort 8 will include HBeAg(+) and treatment naïve patients, and Cohort 9 will include HBeAg(+) and entecavir or tenofovir experienced patients. CHB patients on current nucleos(t)ide (NUC) therapy (entecavir or tenofovir) will stay on NUC therapy for the study duration. CHB patients not on NUC therapy (NUC naïve) will be started on either entecavir or tenofovir (selection between entecavir and tenofovir based on site Principal Investigator (PI) discretion) on Day 1. Cohort 12 will enroll 12 CHB patients who will either enter the study on NUCs or start NUCs on Day 1. Cohort 12 patients will also initiate daily JNJ-56136379 (JNJ-6379) 250 mg on Day 1 and continue through Day 84.

  CHB cohorts will be multi-dosed as follows:
  - Cohort 1b: 25 mg ARO-HBV, at Days 1, 29 and 57
  - Cohort 1c: 50 mg ARO-HBV, at Days 1, 29 and 57
  - Cohort 2b: 100 mg ARO-HBV, at Days 1, 29 and 57

- Cohort 3b: 200 mg ARO-HBV, at Days 1, 29 and 57
- Cohort 4b: 300 mg ARO-HBV, at Days 1, 29 and 57
- Cohort 5b: 400 mg ARO-HBV, at Days 1, 29 and 57
- Cohort 6: 100 mg ARO-HBV, at Days 1, 15 and 29
- Cohort 7: 100 mg ARO-HBV, at Days 1, 8 and 15
- Cohort 8 (HBeAg +, Treatment naïve): 300 mg ARO-HBV, at Days 1, 29 and 57
- Cohort 9 (HBeAg +, NUC (entecavir/tenofovir) experienced): 300 mg ARO-HBV, at Days 1, 29 and 57
- Cohort 10: 200 mg ARO-HBV, at Days 1, 8 and 15
- Cohort 11: 300 mg ARO-HBV, at Days 1, 8 and 15
- Cohort 12: 200 mg ARO-HBV, at Days 1, 29 and 57 + 250 mg daily JNJ-6379 + NUCs

Dose Escalation Schedule

Healthy Volunteers (double blind) *			CHB Patients (open label)	
Cohort	Dose (Day 1)	Day 8 safety evaluation	Cohort	Dose Regimen
Cohort 1	35 mg		Cohort 1b (all eligible CHB patients regardless of NUC or HBeAg status)	ARO-HBV 25 mg dosed on Day 1, 29, 57
			Cohort 1c (all eligible CHB patients regardless of NUC or HBeAg status)	ARO-HBV 50 mg dosed on Day 1, 29, 57
Cohort 2	100 mg		Cohort 2b (all eligible CHB patients regardless of NUC or HBeAg status)	ARO-HBV 100 mg dosed on Day 1, 29, 57
Cohort 3	200 mg		Cohort 3b (all eligible CHB patients regardless of NUC or HBeAg status)	ARO-HBV 200 mg dosed on Day 1, 29, 57
Cohort 4	300 mg		Cohort 4b (all eligible CHB patients regardless of NUC or HBeAg status)	ARO-HBV 300 mg dosed on Day 1, 29, 57
Cohort 5	400 mg		Cohort 5b (all eligible CHB patients regardless of NUC or HBeAg status)	ARO-HBV 400 mg dosed on Day 1, 29, 57
			Cohort 6 (all eligible CHB patients regardless of NUC or HBeAg status)	ARO-HBV 100 mg dosed on Day 1, 15, 29

		→	Cohort 7 (all eligible CHB patients regardless of NUC or HBeAg status)	ARO-HBV 100 mg dosed on Day 1, 8, 15
		→	Cohort 8 HBeAg+, treatment naïve	ARO-HBV 300 mg dosed on Day 1, 29, 57
		→	Cohort 9 HBeAg+, entecavir or tenofovir experienced	ARO-HBV 300 mg dosed on Day 1, 29, 57
		→	Cohort 10 (all eligible CHB patients regardless of NUC or HBeAg status)	ARO-HBV 200 mg dosed on Day 1, 8, 15
		→	Cohort 11 (all eligible CHB patients regardless of NUC or HBeAg status)	ARO-HBV 300 mg dosed on Day 1, 8, 15
		→	Cohort 12 (all eligible CHB patients regardless of NUC or HBeAg status)	JNJ-6379 daily 250mg + ARO-HBV 200 mg dosed on Day 1, 29, 57

* All NHV Cohorts use 2 sentinel subjects

NHV cohorts will be followed for a maximum of 13 weeks from the beginning of the screening to the Day 29 EOS examination. CHB cohorts will be followed for approximately 25 weeks from screening to the Day 113 EOS examination. During the study period, safety assessments, immunologic assessments (CHB cohorts in New Zealand only), HBV virology assessments (CHB cohorts), Immunogenicity (CHB cohorts), pharmacodynamics endpoints (NHV cohorts), cytokines, complement (NHV cohorts), excretion and metabolism will be conducted as per the Schedule of Assessments in the protocol. CHB patients consenting to participate in the additional follow-up period will be followed as per Additional Follow-Up Schedule of Assessments (refer to the study protocol), every 56 days (± 5 days) for 5 additional visits after Day 113. In addition, Cohort 12 patients will require follow-up until the Day 337 (± 5 days).

Pharmacokinetic (PK) intensive sampling will be conducted for NHV cohorts on Day 1 (dosing day) at the time of 0 (pre-dose), 15 minutes, 0.5, 1, 2, 3, 6, 24 and 48 hours post-dose. No PK data will be sampled for CHB cohorts, except in Cohort 12 where plasma will be collected two-hours post-ARO_HBV dose to measure plasma concentration of ARO-HBV, JNJ-6379, and NUC (ETV or TDF).

2.2 Objectives

2.2.1 Primary objective

- To determine the incidence and frequency of adverse events possibly or probably related to treatment as a measure of the safety and tolerability of ARO-HBV using escalating single doses in healthy volunteers (NHV) and escalating multiple doses in patients chronically infected with hepatitis B virus (CHB).

2.2.2 Secondary objective(s)

- To evaluate the single-dose pharmacokinetics of ARO-HBV in healthy volunteers
- To determine the reduction from Day 1 pre-dose baseline to post-dose nadir of HBsAg in response to ARO-HBV in CHB patients as a measure of activity

2.2.3 Exploratory objective

- To determine the reduction from Day 1 pre-dose baseline to post-dose nadir of HBcrAg, HBsAg, HBV DNA, HBV RNA (if scientifically feasible) and HBeAg (e+ only), in response to ARO-HBV (alone or in combination with JNJ-6379) in CHB patients as a measure of activity. The following categories will be considered for HBV DNA: >LLQ, <LLQ target detected and <LLQ target not detected.
- To evaluate the effect of single doses of ARO-HBV on cytokines (Cytokine panel A: interleukin-6 [IL-6], monocyte chemoattractant protein-1 [MCP-1], tumor necrosis factor-alpha [TNF-alpha], interleukin-8 [IL-8], interleukin-1beta [IL-1beta], interferon alpha [IFN-alpha], IL-10, IL-12 [p40], IL-12 [p70], macrophage inflammatory protein-1alpha [Mip-1alpha]) in healthy volunteers.
- To evaluate the effect of single escalating doses of ARO-HBV on complement factors Bb, CH50, C5a, C4a, and C3a in healthy volunteers.
- To collect plasma samples in healthy volunteers for subsequent metabolite identification (reported in a separate report outside of this study)
- To collect urine samples in healthy volunteers for subsequent determination of urinary excretion and metabolite identification (reported in a separate report outside of this study)
- To evaluate the effect of multiple doses of ARO-HBV (alone or in combination with JNJ-6379) on cytokines (Cytokine panel B: TNF-alpha, IFN-gamma, CXCL-9, and CXCL-10) in CHB patients
- To evaluate the effect of multiple doses of ARO-HBV (alone or in combination with JNJ-6379) on HBV patient immune cell profile including T-cells, NK cells, B cells and monocytes (if scientifically feasible)
- To evaluate the effect of multiple doses of ARO-HBV (alone or in combination with JNJ-6379) on HBV antigen specific T-cell response (if scientifically feasible).
- To evaluate the effect of interferon response gene single nucleotide polymorphisms (SNPs) including IL28B on response to ARO-HBV (alone or in combination with JNJ-6379).

- To determine the incidence and frequency of adverse events possibly or probably related to treatment as a measure of the safety and tolerability of ARO-HBV in combination with JNJ-6379 in patients chronically infected with hepatitis B virus (CHB) (Cohort 12 only).

- To determine plasma concentration of ARO-HBV, JNJ-6379, and NUCs at specified timepoints in HBV patients (Cohort 12 only).

2.3 Study Endpoints

Safety endpoints

- Monitoring of AEs/SAEs
- Physical examinations
- Vital signs
- ECG measurements
- Injection Site Reactions (Mild, Moderate or Severe)
- Clinical laboratory tests (hematology, biochemistry, coagulation, urinalysis)
- Concomitant medications/therapy, and
- Reasons for treatment discontinuation due to toxicity

Cellular Immunologic Endpoints (CHB Cohorts in New Zealand only)

- Patient immune cell profile: T cell subsets (activation and exhaustion state), NK cell subsets (activation and exhaustion state), B cell subset, monocyte subsets. To be conducted if scientifically feasible.
- HBV antigen specific T cell response (including HBcAg, HBsAg). To be conducted if scientifically feasible.

Virology Endpoints (CHB Cohorts only)

- Qualitative assessments: HBsAg, HBeAg, anti-HBsAg, anti-HBeAg
- Quantitative assessments: HBV DNA, qHBsAg, qHBeAg, qHBcrAg, qHBV RNA (if feasible), anti-HBsAg and ratio of bound/free anti-HBsAg
- HBV genotyping and HBV sequencing

Immunogenicity (CHB Cohorts only)

- Anti-drug antibodies

Pharmacokinetics (NHV Cohorts and limited PK in Cohort 12)

- Plasma PK blood samples will be collected at Day 1
- Plasma concentrations of ARO-HBV, NUC and JNJ-6379 will be measured at a single post-dose time point in Cohort 12 only

Cytokines

- Cytokine panel A (NHV Cohorts): interleukin-6 [IL-6], monocyte chemoattractant protein-1 [MCP-1], tumor necrosis factor-alpha [TNF-alpha], interleukin-8 [IL-8], interleukin-1beta [IL-1beta], interferon alpha [IFN alpha], IL-10, IL-12 [p40], IL-12 [p70], macrophage inflammatory protein-1alpha [Mip-1alpha]
- Cytokine panel B (CHB Cohorts): TNF-alpha, IFN gamma, CXCL-9, and CXCL-10

Complement (NHV Cohorts)

- Bb, CH50, C5a, C4a, and C3a

Genetic Testing (consenting CHB patients only)

- Interferon response gene SNP analysis testing

Excretion and Metabolism Parameters

- Samples for metabolic analyses will be stored and reported outside of this study
- Urine collections will be collected per the Schedule of Assessments.

2.4 Sample Size

No formal statistical calculation of sample size will be used for this Phase 1/2a study. The sample size is empirical. The small numbers per cohort in this study are not intended for statistical hypothesis inference analysis. Results from this study will be utilized in sample size calculations for subsequent studies.

This study will involve approximately 30 eligible normal healthy volunteers in NHV cohorts and a minimum of 60 and a maximum of 84 CHB patients in CHB cohorts. Each of the 5 NHV cohorts will recruit 6 healthy volunteers. CHB cohorts 1b, 1c, 2b, 3b, 4b and 5b will recruit a minimum of 4 and a maximum of 8 patients, and CHB cohorts 6, 7, 8, 9, 10, 11 will recruit a maximum of 4 CHB patients. Cohort 12 will recruit 12 CHB patients.

2.5 Randomisation

NHV Cohorts

The six (6) healthy volunteers in each of the five (5) NHV cohorts will be randomized at a ratio of 2:1 (active: placebo) to receive ARO-HBV or Placebo in a double-blind fashion. Therefore 4 subjects will be randomized to receive ARO-HBV and 2 subjects to receive placebo in each of the NHV cohorts.

CHB Cohorts

All CHB patients in each of the 13 CHB cohorts will receive ARO-HBV (alone or in combination with JNJ-6379) and daily NUC, and no randomization is applied.

3. STATISTICAL CONSIDERATIONS

Data will be handled and processed according to the sponsor's representative (Novotech (Australia) Pty Ltd) Standard Operating Procedures (SOPs), which are written based on the principles of GCP.

All data collected on the eCRFs will be presented in the data listings and will be listed and sorted by subject number and visit, where applicable. All summaries will present the data by ARO-HBV dose level/cohort and overall (total subjects), as applicable.

Data collected during the main study (up to the Day 29 or Day 113 EOS visits) and at the additional follow-up visits (CHB cohorts only) will be presented in the same summary table, as appropriate. The first part of each table will present the main study results for the specific analysis. The second part of each table will include all data collected during the study, including data collected during the follow-up period, for the subset of CHB patients that consented to participate in the follow-up. All data will be included in the listings, and data collected during the follow-up period will be flagged in all event/medication-based listings. Separate figures that include all data will be presented for the subset of patients that participated in the follow-up period.

Unless otherwise stated, the following statistical approaches will be taken:

- Continuous variables: Descriptive statistics will include the number of non-missing values (N), mean, standard deviation (SD), median, minimum, maximum.
- Categorical variables: Descriptive statistics will include frequency counts and percentages per category. Percentages will be rounded to one decimal place, with the denominator being the number of subjects in the relevant population with non-missing data, unless otherwise specified.
- Imputation: No missing data will be imputed generally.
- Confidence intervals (CIs): CIs will be two-sided and will use 95% confidence levels unless specified otherwise.
- Baseline: Baseline values will be defined as the last non-missing observation (pre-dose value closest to the first dose) for each subject prior to the dosing of study medication (i.e. start of injection on Day 1).
- Repeat assessments (Safety): If there is a repeat test, the repeat result will be used in the analysis table and the original result will only be listed in the data listing.
- Repeat assessments (Virology): Certain virologic assessments such as qHBsAg may be batch analyzed per patient at the end of study. In cases where both batch-analyzed and non-batch analyzed data are available, batch analyzed data with be used in the analysis table and all other results will be listed. In other instances, repeat tests may have been performed for other reasons than batch-analysis. If there is a repeat test, the repeat result will be used in the analysis table and the original result will only be listed in the data listing.

Continuous safety variables will be reported to the same precision as the source data. Derived variables will be reported using the same precision to the value(s) from which they were derived. For the reporting of descriptive statistics, the mean (95% CI) and median will be reported to 1 decimal place more than the source data; the minimum, and the maximum values will be presented to the same precision as the source data; and standard deviation will be

reported to 2 decimal places more than the source data. Rounding is not allowed in the middle of the calculation. It only takes place at the last step to report the final result. Post-dose time points/visits will be calculated relative to start time of injection on Day 1. Study day will be defined as assessment date minus dosing day +1.

The NHV cohorts (Cohorts 1, 2, 3, 4, and 5) will be summarized separately from the CHB cohorts (Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10,11 and 12). The dose levels (cohorts) will be referred to in the text, tables and listings as follows.

NHV Cohorts:

- Coh1: ARO-HBV (35 mg)
- Coh2: ARO-HBV (100 mg)
- Coh3: ARO-HBV (200 mg)
- Coh4: ARO-HBV (300 mg)
- Coh5: ARO-HBV (400 mg)
- Combined ARO-HBV
- Combined Placebo
- Total (including all ARO-HBV and Placebo)

CHB Cohorts:

- Coh1b: ARO-HBV (25 mg, Q28D)
- Coh1c: ARO-HBV (50 mg, Q28D)
- Coh2b: ARO-HBV (100 mg, Q28D)
- Coh3b: ARO-HBV (200 mg, Q28D)
- Coh4b: ARO-HBV (300 mg, Q28D)
- Coh5b: ARO-HBV (400 mg, Q28D)
- Coh6: ARO-HBV (100 mg, Q14D)
- Coh7: ARO-HBV (100 mg, Q7D)
- Coh8: ARO-HBV (300 mg, Q28D, HBeAg+/Trt Naive)
- Coh9: ARO-HBV (300 mg, Q28D, HBeAg+/NUC)
- Coh10: ARO-HBV (200 mg, Q7D)
- Coh11: ARO-HBV (300 mg, Q7D)
- Coh12: ARO-HBV (200 mg, Q28D) + JNJ-6379 250mg
- Combined ARO-HBV
- Pooled ARO-HBV (300 mg, Q28D)

where Q7D: dosing once every 7 days,
Q14D: dosing once every 14 days,
Q28D: dosing once every 28 days

Summary tables and listings will be produced separately for NHV cohorts (Cohorts 1, 2, 3, 4 and 5) and CHB cohorts (Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10,11 and 12). The Pooled ARO-HBV (300 mg, Q28D) group will only be presented for the safety outputs.

Due to the large number of treatment columns that will be displayed in the outputs, the results for a specific parameter/visit could span multiple pages. Summaries will be presented by groups of treatments, i.e., if only CHB Coh1b to Coh7 can be fit onto a page, all of the results for these cohorts will be presented on the subsequent pages before the results for the initial visits of the next group of cohorts are presented. Where appropriate, the outputs may also be

transposed to present the treatment information in rows instead of columns to facilitate the review process.

4. ANALYSIS POPULATIONS

In this study, three analysis populations are defined: Safety Population, Pharmacokinetic Population, and Pharmacodynamic population. Data for Screen Failures will not be included in any summary tables, figures, or data listings. Subjects included in the defined (various) analysis populations will be decided at the blinded data review meeting prior to unblinding of NHV cohorts. The same process will be applied to the CHB cohorts as well even if there is no blinding for these cohorts.

Furthermore, any additional analysis populations not identified in the SAP will be identified in the final CSR as post hoc analyses. This may include the addition of additional study populations or subgroups of interest.

The number and percentage of subjects in each analysis population will be summarized.

Safety Population
All subjects who receive at least one dose of study treatment (ARO-HBV or JNJ-6379) will be included in the Safety Population. Subjects will be summarized according to the treatment they received.

All safety, treatment exposure, demographic and baseline characteristic data will be listed and summarized using the Safety Population.

Pharmacokinetic (PK) Population
Subjects who have received the active treatment (ARO-HBV) and have adequate PK data to characterize PK profile will be included in the PK Population. This includes NHV Cohorts 1, 2, 3, 4 and 5 and CHB Cohort 12 subjects that received at least one dose of active study treatment (ARO-HBV).

Subjects who prematurely discontinue from the study will be included in the Safety Population but may not be included in the PK Population if they do not have PK data to contribute to the analyses. Subjects with missing sample concentrations will be included in the PK analyses provided their PK parameters can be adequately characterized based upon the remaining data. Subjects who received only placebo will be excluded from the PK population. The PK population will be used for the summaries of all PK data.

Subjects with protocol violations will be assessed on a subject-by-subject basis for inclusion in the PK Population. The determination of study populations will be made, prior to unblinding the PK data, at the blinded data review meeting before the final analyses for NHV Cohorts 1, 2, 3, 4, 5, and 12.

Pharmacodynamic (PD) Population
Subjects who received at least one dose of study treatment (ARO-HBV, JNJ-6379, or placebo) and had PD assessment from baseline and ≥1 assessment from post-baseline will be included in the PD population. Subjects will be summarized according to the treatment they received.

Subjects with protocol violations will be assessed on a subject-by-subject basis for inclusion in the PD Population. The determination of study populations will be made, prior to unblinding the PD data, at the blinded data review meeting before the final analyses. The PD population will be used for the summaries of all immunologic endpoints, virology endpoints, cytokines and complement.

5. SUBJECT DISPOSITION

All subjects who provide informed consent and are randomized (NHV Cohorts 1, 2, 3, 4 and 5)/enrolled (CHB Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10,11 and 12) will be accounted for in this study. Subject disposition will be summarized using the Safety Population.

By-subject data listings for subject disposition will be generated, including informed consent date, randomization date/number (NHV cohorts), completion status, date of withdrawal and reason for withdrawal from the study, if applicable. The listing will also include the date of informed consent for CHB subjects that consented to participate in the follow-up period and the date of consent to single nucleotide polymorphisms (SNP) genetic testing and optional sampling.

The number of subjects randomized (NHV cohorts)/enrolled (CHB cohorts), as well as the number and percentage of subjects completing the study and withdrawn from the study will be presented by dose level (cohort) and overall. The reason for withdrawal will also be summarized for all subjects who do not complete the study. The table will also show the number of CHB subjects that participated in the follow-up period. Patients who participated in the follow-up period will be deemed to have completed the main part of the study (up to Day 113).

6. PROTOCOL DEVIATIONS

In case protocol deviations are reported, protocol deviations will be presented for each subject in the by-subject data listings.

Prior to database lock, all protocol deviations will be reviewed by medical monitors and assigned a category (see below).

A protocol deviation is defined as any intentional or unintentional change to, or noncompliance with, the approved protocol procedures or requirements. Deviations may result from the action or inaction of the patient, investigator, or site staff. All deviations will be tracked and should be reported to IRBs in accordance with their reporting policy. Examples of deviations include, but are not limited to:

- Failure to adhere to study exclusion and inclusion criteria;
- Failure to comply with dispensing or dosing requirements;
- Use of medications, food, drink, herbal remedies, or supplements that are specifically prohibited in the protocol;
- Missed or out-of-window visits;
- Drug dosing not administered within the time frame specified in the protocol;
- Failure to adhere to test requirements, including vital signs, laboratory tests, physical examinations, blood draws, medical history, etc. – either tests not done, incorrect tests done, or not done within the time frame specified in the protocol;
- Procedural deviations such as incorrect storage of study drug, failure to update the ICF when new risks become known, failure to obtain IRB/EC approvals for the protocol and ICF revisions.

7. DEMOGRAPHIC AND BASELINE INFORMATION

Demographic and baseline body measurements will be summarized using the Safety Population.

7.1 Demographics

Demographic data, including age, gender, race, weight, height and BMI, will be summarized by dose level (cohort) and overall. The table will also be repeated for the subset of CHB subjects that participated in the Additional Follow-up period. A by-subject data listing for demographic characteristics will be generated.

Baseline disease characteristics including, baseline alanine aminotransferase (ALT), baseline Fibroscan score, prior nucleos(t)ide (NUC) treatment status and the type of prior treatments and the log-transformed quantitative HBV DNA, genotype (if available), qHBsAg, qHBeAg, qHBcrAg, qHBV RNA (if feasible), and anti-HBsAg values and the and ratio of bound/free anti-HBs (untransformed, subset of patients only) at baseline will be summarized for the CHB cohorts as well as for the subset of CHB subjects that participated in the follow-up period. The table will also be repeated for the PD Population. A by-subject data listing for baseline disease characteristics will be generated.

7.2 Medical history

Past medical history will be coded using the Medical Dictionary for Regulatory Activities, MedDRA® with the latest available version. Medical history data, including the MedDRA codes, will be presented in the by-subject data listings.

7.3 Informed Consent and Eligibility

Informed consent date, and inclusion/exclusion eligibility criteria information, including any criteria not met, will be listed for each subject.

7.4 Pregnancy Test (Urine)

Child-bearing potential (yes/no), and if No, the reason (post menopause, surgically sterile, and other), and pregnancy test results will be included in the by-subject data listings. This includes the urine dipstick pregnancy test results assessed regularly at the scheduled study visits. Screening Follicle-Stimulating Hormone (FSH) will also be listed.

7.5 Serology Screen (Hepatitis/HIV)

Data for Hepatitis B, Hepatitis C and HIV assessment at screening will be listed for each subject.

7.6 Urine Drug Screen

Urine Drug Screen results at Screening will be listed for each subject.

7.7 Hepatic Fibrosis Measure

The score of hepatic fibrosis at Screening will be listed for each subject.

8. TREATMENT EXPOSURE

Study drug administration results will be presented using the Safety Population. Study drugs include drug administration for ARO-HBV or placebo (Placebo is only applicable for NHV Cohorts 1, 2, 3, 4 and 5), NUC and JNJ-6379 (CHB Cohort 12 only).

Each single dose of either active drug (ARO-HBV) or Placebo will be administered by subcutaneous injection (either one or two subcutaneous injections per dose as required for each dose level). Injections will be made into the subcutaneous tissue at an appropriate site (e.g. abdomen, thigh, upper arm, etc.). The abdomen is the preferred site. Injection site is to be varied (no multiple injections into the same exact site). Alternating various locations on the abdomen is acceptable, and injection site location is to be recorded in the eCRF.

A by-subject data listing will be generated for study drug (ARO-HBV or Placebo) administrations. This listing will include study drug administration date, time, dose, and injection site. If study drug was not administered, the reason why the drug was not administered will be reported. Separate listings will be created for the NUC and JNJ-6379 treatment compliance and dosing deviation data.

9. PHARMACOKINETICS (PK)

PK analyses will be conducted with the PK Population. PK analysis of ARO-HBV concentration-time data will be performed using validated PK software (Phoenix WinNonlin version 6.3 or higher), by a standard non-compartmental model. The actual plasma sampling times from the CRF database, i.e., the elapsed time of the blood sampling time from the dosing time, will be used for PK analysis.

PK samples will be collected for NHV Cohorts 1, 2, 3 4 and 5 on Day 1 (dosing day) at the time of 0 (pre-dose), 15 minutes, 0.5, 1, 2, 3, 6, 24 and 48 hours post-dose.

Plasma concentrations of ARO-HBV, NUC and JNJ-6379 will be measured at 2 hours post-dose on Days 1, 29 and 57 in Cohort 12 only.

9.1 Definition of variables

Whenever possible, the PK parameters listed below will be calculated for each subject based on the plasma concentrations of ARO-HBV according to the model independent approach, at Day 1.

Parameter	Description
AUC_{0-24}	The area under the plasma concentration-time curve, from time 0 (time of dosing) to 24 hours post dose, i.e., partial AUC, calculated by the log-linear trapezoidal method. AUCs for other time period could also be calculated in the analysis time.
AUC_{0-inf}	The area under the plasma concentration-time curve from time 0 extrapolated to infinity. AUC_{0-inf} is calculated as the sum of AUC_{0-t} plus the ratio of the last measurable plasma concentration to the elimination rate constant (λz).
AUC_{0-t}	The area under the plasma concentration-time curve, from time 0 (time of dosing) to the last time point with measurable analyte concentration, calculated by the log-linear trapezoidal method.
C_{max}	Maximum observed concentration.
T_{max}	The first time when C_{max} is observed
$t_{½}$	Apparent terminal elimination half-life of medication, calculated as 0.693/λz.
λz:	The apparent first-order terminal elimination rate constant, calculated by linear least-squares regression analysis the terminal log-linear phase of the plasma concentration vs. time curves using at least 3 time points.
DN_AUC_{0-24}	Dose-normalized AUC_{0-14d}, calculated as AUC_{0-t} divided by dose

Parameter	Description
DN_$AUC_{0\text{-}inf}$	Dose-normalized $AUC_{0\text{-}inf}$, calculated as $AUC_{0\text{-}inf}$ divided by dose
DN_$AUC_{0\text{-}t}$	Dose-normalized $AUC_{0\text{-}t}$, calculated as $AUC_{0\text{-}t}$ divided by dose
DN_C_{max}	Dose-normalized C_{max}, calculated as C_{max} divided by dose

9.2 Biostatistical methods

The two ARO-HBV analytes, JNJ 73763976 (AD04872) and JNJ 73763924 (AD05070) will be analyzed and presented separately (as appropriate).

ARO-HBV plasma concentrations will be listed by subject, dose level/treatment, and nominal (scheduled) sampling time. ARO-HBV concentrations will be summarized by dose level/treatment and nominal sampling time for the PK Analysis Population. Plasma concentrations that are below the limit of quantitation (BLQ) will be set to 0 for calculation of summary statistics for concentration data at each time point, except geometric statistics (geometric mean and geometric CV%). For the calculation of the geometric statistics they will be treated as equal to the Lower Limit of Quantification (LLQ). Missing values will be omitted from the calculation of descriptive statistics.

The actual blood sampling dates and times relative to dosing time will be listed by study group (dose level/treatment), subject and nominal sampling time, with time deviation calculated, for all subjects with available plasma concentration data, including subjects receiving placebo or subjects excluded from the PK Analysis Population.

Figures of individual plasma concentration vs. actual time profiles for ARO-HBV will be produced on both linear and semi-log scales for the PK Analysis Population. Mean and median plasma blood concentration vs. nominal time curves for all dose levels/treatments in the PK Analysis Population will be plotted together on both linear and semi-log scales for ARO-HBV.

Pharmacokinetic parameters for each dose level will be calculated from the concentrations of ARO-HBV measured in pre-dose and post-dose plasma samples. For the calculation of the PK parameters, all plasma concentrations that are BLQ prior to the first measurable concentration will be set to zero. The BLQ values that are between measurable concentrations will be set to missing. The BLQ values that occur at the end of the profile (after the last quantifiable concentration) will be set to missing and will not be used for the estimation of parameter values. Dose normalized PK parameters (DN_$_{AUC0\text{-}24}$, DN_$AUC_{0\text{-}inf}$, DN_$AUC_{0\text{-}t}$, and DN_C_{max}) will be calculated as well.

For each dose level, descriptive statistics will be provided for the PK parameters. Summary tabulations will display the number of observations, mean, SD, CV%, median, minimum and maximum. Geometric means and geometric CV% will be calculated for AUCs and C_{max}. PK parameters will be displayed by treatment. $AUC_{0\text{-}24}$, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max} will also be presented in scatter plots by treatment.

The dose proportionality of ARO-HBV over the dose range 35–400 mg (NHV Cohorts 1-5) will be assessed by fitting a simple unweighted linear regression model with the natural log-transformed pharmacokinetic parameters ($AUC_{0\text{-}24}$, $AUC_{0\text{-}t}$, and C_{max}) and dependent and the natural log-transformed dose values as independent variables.

Dose proportionality will be declared if the 95% CI for the slope of the regression line (β_1) contains the value 1. AUC_{0-24}, AUC_{0-t}, and C_{max} will be assessed separately.

The CHB Cohort 12 ARO-HBV, NUC and JNJ-6379 concentrations data will be summarized and presented graphically. The data will also be listed. PK parameters will not be calculated for Cohort 12.

10. SAFETY

Statistical methods for the safety analyses will be primarily descriptive in nature. Each dose level (cohort) will be summarized separately.

Safety endpoints included in the analysis are AEs, concomitant medications, clinical laboratory assessments, vital signs, physical examination, and 12-lead ECG.

Safety endpoints will be analyzed separately for the main study (up to Day 113 EOS) and for the overall study duration, including the follow-up period, for the subset of CHB patients that consented to participate in the follow-up. Endpoints will be derived separately for each analysis taking into consideration all the applicable data for the specific period.

Safety endpoints will be analyzed using the Safety Population.

10.1 Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®, the latest available version), and data will be summarized by System Organ Class (SOC) and Preferred Term (PT). The number and percent of subjects reporting each AE will be summarized for each dose level (cohort) and overall. A subject with two or more AEs within the same level of summarization (i.e., SOC or PT) will be counted only once in that level. Percentages will be based on the number of subjects in the Safety Population within each dose level (cohort). The number of AEs reported will also be presented.

Treatment-emergent AEs (TEAEs) are defined as pre-treatment existing conditions that worsen after study drug administration, or events that occur during the course of the study during or after administration of study drug. Only TEAEs will be included in the AE summary tables which will present data by dose level (NHV/CHB cohorts) for active treatment versus pooled placebo subjects (NHV cohorts). In the case of a missing AE start date or stop date, the most conservative approach will be followed to classify AE into TEAE unless it is not possible that the AE could be treatment emergent. AEs that occurred during the follow-up period will only be included in the follow-up table.

A table providing an overall summary of AEs will be produced which will include the number of TEAEs; the number and % of subjects reporting at least one: TEAE, serious TEAE, grade 3 (severe) or higher TEAE, TEAE related to study treatment (related to ARO-HBV or JNJ-6379 [Cohort 12 only]: possibly/probably), serious TEAE related to study treatment, grade 3 or higher TEAE related to the study drug, TEAEs by severity and TEAEs by relationship, drug or study discontinuations due to TEAEs. The table will also be repeated for related (ARO-HBV or placebo) TEAEs.

Additional AE tables will be generated as follows:

- TEAEs by SOC and PT
- TEAEs by decreasing incidence of the PTs in the Combined ARO-HBV group
- Study Drug (ARO-HBV or placebo) Related TEAEs by SOC and PT
- Study Drug (ARO-HBV or placebo) Related TEAEs by decreasing incidence of the PTs in the Combined ARO-HBV group
- Study Drug (JNJ-6379) Related TEAEs by SOC and PT (Cohort 12 only)

- Study Drug (JNJ-6379) Related TEAEs by decreasing incidence of the PTs in the Combined ARO-HBV group (Cohort 12 only)
- TEAEs by Severity
- TEAEs by Relationship to Study Drug (ARO-HBV)
- Treatment Emergent SAEs
- Study Drug (ARO-HBV or placebo) Related SAEs by SOC and PT
- Study Drug (JNJ-6379) Related SAEs by SOC and PT (Cohort 12 only)
- TEAEs Leading to Study Drug or Study Withdrawn
- TEAEs occurring at the treatment injection site by SOC (General disorders and administration site conditions) and PT linked to High Level Term, "Injection Site Reaction"
- TEAEs fitting the definition of LISR by SOC and PT

A by-subject AE data listing, including verbatim term, MedDRA SOC and PT, severity, outcome and relationship to study treatment, will be provided. Separate listings will be generated for SAEs. AEs that started during the follow-up period will be flagged. Cohort 12 data will be listed separately.

Local Injection Site Reactions (LISR)

Local Injection Site Reactions will be reviewed based on description of symptoms, level of severity (mild, moderate or severe) and outcome of the reactions as well as other relevant data elements such as de/re-challenge, medical history, and possible confounding variables. Based on the review, the reactions will be specifically categorized and collated for the analysis.
The results will be summarised by cohort across all dose levels and percentages for the reported LISR by using the MedDRA coding system by System Organ Class (SOC), General disorders and administration site conditions and Preferred Terms that are associated with local injection site reactions.

The following MedDRA Preferred Terms determined by the Sponsor's pharmacovigilance personnel represent the local injection site reaction:

Injection site discomfort	Injection site abscess
Injection site discoloration	Injection site abscess sterile
Injection site erythema	Injection site atrophy
Injection site irritation	Injection site calcification
Injection site inflammation	Injection site cellulitis
Injection site induration	Injection site dermatitis
Injection site pain	Injection site erosion
Injection site oedema	Injection site fibrosis
Injection site pruritus	Injection site indentation
Injection site rash	Injection site necrosis
Injection site urticaria	Injection site nodule
Injection site reaction	Injection site ulcer
Injection site swelling	

Those summaries will only include events that start on the day of injection and persist for at least 2 days (48 hours) post injection (i.e., event onset date on the day of injection and

resolution date not on the day of injection or the day after the injection) will be included. Events with onset date on the day of injection and missing resolution date will also be included in the summary.

The percentage of injections leading to local injection site reactions will be summarized using descriptive statistics.

The following calculation will be utilized to determine the percentage of injections leading to local injection site reactions for each subject:

(A/B) *, where A = number of injections with a local injection site reaction, and B = total number of injections.

The results of local injections site reactions will be provided in summary tabulation.

10.2 Concomitant medication

Concomitant medications and non-drug therapies will be coded using World Health Organization Drug Dictionary (WHO-DD, the latest available version). Concomitant medications are medications taken at least once after the start of first study-drug administration. Medications stopped prior to the day of the start of first study-drug administration will not be considered concomitant medication. The prior medication will not be summarized, but they will be listed along with concomitant medications. Only concomitant medications will be summarized. Medications that started during the follow-up period will only be included in the follow-up concomitant summary table and will be flagged in the listing.

Individual data listings will be presented for each subject and summarized by WHO-DD Anatomical Therapeutic Chemical (ATC) anatomical group, and preferred term using frequency counts and percentages. Subjects who take the same medication more than once will be counted only once for that preferred term.

Dispensing of Nucleos(t)ide (NUC) will be listed for CHB cohorts, as appropriate.

10.3 Laboratory

10.3.1 Definition of variables

Hematology Parameters

- Hemoglobin
- Red Blood Cell Count
- Hematocrit
- Mean Cell Volume (MCV)
- Mean Cell Hemoglobin (MCH)
- Mean Cell Hemoglobin Concentration (MCHC)
- Platelets
- White Blood Cell Count
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils

Chemistry Parameters

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Glucose
- Urea
- Creatinine (including calculated creatinine clearance)
- Creatine kinase
- Uric acid
- Phosphate
- Total calcium
- Anion gap
- Cholesterol
- Albumin
- Globulins
- Protein
- Total bilirubin
- Conjugated bilirubin
- Gamma glutamyltransferase (GGT)
- Alkaline phosphatase (ALP)
- Alanine aminotransferase (ALT)
- Aspartate transaminase (AST)
- Lactate dehydrogenase (LD)
- Triglycerides
- Amylase
- Lipase
- C-reactive protein
- Troponin I

Coagulation Parameters

- Partial Thromboplastin Time (PTT)
- Prothrombin Time (PT)
- INR

Urinalysis Parameters

- Leukocytes
- Nitrites
- Urobilinogen
- Protein
- pH
- Blood
- Specific Gravity
- Ketone
- Bilirubin
- Glucose

Microscopic urinalysis will be performed if indicated: White blood cells, red blood cells, epithelial cells, and bacteria.

10.3.2 Biostatistical methods

All hematology, chemistry, coagulation and urinalysis parameters will be summarized using descriptive statistics for each dose level (cohort) for all time points assessed, including change from baseline (last pre-dose value) for all post-dose assessments. All continuous parameters will be summarized using the units reported from the laboratory.

Laboratory values will be compared to normal range of the single local laboratory and values that fall outside of the normal ranges will be flagged as: H (High) and L (Low) in the data listings. Results that were flagged as 'LP' will be reported as 'L' and results flagged as 'HP' will be reported 'H'. Shift tables from Day 1 (pre-dose) to all follow-up visits will also be generated for each hematology, chemistry and coagulation laboratory parameter with values of Within Normal Limits (WNL), High, and Low used for the shift categories.

To assess the liver function of CHB patients, number of subjects with ALT above the upper limit of normal over time will be summarized for CHB cohorts.

All laboratory data will be included in the by-subject data listings. Microscopic urinalysis will only be listed.

Time series of mean values for the following safety assessments will be plotted by NHV and CHB Cohorts.

- Creatinine
- Creatine Kinase
- AST
- ALT
- Total Bilirubin

10.4 Vital Signs

10.4.1 Definition of variables

- Systolic Blood Pressure (SBP) (mmHg)
- Diastolic Blood Pressure (DBP) (mmHg)
- Pulse Rate (beats/min)
- Body Temperature (°C)
- Respiratory rate (breaths/minute)

10.4.2 Biostatistical methods

All vital sign parameters will be summarized using descriptive statistics for each dose level (cohort) for all time points assessed, including change from baseline (last pre-dose value) for all post-dose assessments. Pre-dosing vital signs on Day 1 will be used as baseline data. If the baseline value is missing, then the data from screening will be used as baseline data as appropriate.

All vital sign parameters will be listed for each dose level (cohort) for all time points assessed.

10.5 Physical examination

10.5.1 Definition of variables

The following body systems will be assessed:

- General Appearance
- HEENT (Head, Eyes, Ears, Nose and Throat)
- Cardiovascular
- Lungs
- Abdomen
- Lymph nodes
- Genitourinary
- Extremities
- Neurological
- Skin
- Musculoskeletal
- Other

For abnormal result of physical examination:

- Abnormal NCS (Not Clinically Significant)
- Abnormal CS (Clinically Significant).

10.5.2 Biostatistical methods

Physical examination will be summarized by study visit and treatment cohort. The frequency counts and percentages of subjects with different physical examination results and their clinical significance (for abnormal) will be summarized.

According to the schedule of assessment, a complete physical exam will be performed at Screening. Symptom-directed physical examinations will only be conducted at other visits as necessary. Only complete exams (screening) will be summarized.

By-subject data listings will be generated for all the physical examination data, including the Investigator assessment of clinical significance for abnormal findings, for all time points assessed.

10.6 12-lead ECG

10.6.1 Definition of variables

- Heart Rate (beats/min)
- PR interval (msec)
- QRS interval (msec)
- QT interval (msec)
- QTcF interval (msec)
- Overall interpretation of 12-lead ECG:
  - Normal
  - Abnormal NCS (Not Clinically Significant)
  - Abnormal CS (Clinically Significant).

10.6.2 Biostatistical methods

Descriptive statistics will be calculated for heart rate, PR interval, QRS interval, QT interval, and QTcF interval, including change from baseline (last pre-dose value on Day 1) for each dose level (cohort) for all time points assessed.

12-lead ECG measurements will be obtained at the scheduled time points after the participant is semi-supine for at least 3 minutes. Any abnormal ECGs will be repeated in triplicate, with each measurement approximately 1 minute apart. If triplicate ECG parameters are available, the average of the triplicate ECG parameters will be used. Unscheduled visits will be excluded from summary tables. However, the findings from the unscheduled will be listed.

In addition, the overall interpretation of 12-lead ECG results will be classified using frequency counts and percentages for the categories of Normal, Abnormal - Not Clinically Significant (NCS) and Abnormal - Clinically Significant (CS) for each treatment group for all time points assessed.

All ECG data will be presented in the by-subject data listings.

11. VIROLOGY

Virology endpoints are only collected for CHB cohorts across the study period according to the protocol schedule of assessment. The analysis population for virology data is PD.

Virology endpoints will be analyzed separately for the main study (up to Day 113 EOS) and for the overall study duration, including the follow-up period, for the subset of patients that consented to participate in the follow-up. Endpoints will be derived separately for each analysis taking onto consideration all the applicable data for the specific period.

Data Handling Rules

The units and lower limit of quantitation (LLQ) cut-off and imputed values in the table below will be used in all derivations and outputs.

Parameter	Qualitative / Quantitative	LLQ	Unit	Values for Imputation		
				< LLQ	< LLQ Detected	< LLQ Not Detected
HBeAg	Qualitative	0.22	PEIU/mL	N/A	N/A	N/A
qHBeAg	Quantitative	0.11	PEIU/mL	0.055	0.055	0.055 [a)]
HBV DNA	Quantitative	20	IU/mL	N/A	15	5
HBV RNA	Quantitative	1.65	Log10 U/mL	N/A	0.825	0.4125
qHBcrAg	Quantitative	1	kU/mL	0.5	N/A	N/A
qHBsAg	Quantitative	0.05	IU/mL	0.025	N/A	N/A

[a)] Values below 0.11 PEIU/mL may have been reported as 'not detected'

All reported qHBsAg and qHBcrAg results below the LLQ cut-off values will be treated as below LLQ and included in the '< LLQ' category counts.

qHBeAg results will be imputed based on the reported HBeAg (qualitative) results provided by the analyzing laboratory:

- Positive: All reported qHBeAg results equal to or above the LLQ cut-off value (0.11 PEIU/mL)
- '< LLQ': All results below the LLQ cut-off value where the HBeAg result is any outcome other than 'Not Detected'
- Negative: All results below the LLQ cut-off value where the HBeAg result is 'Not Detected'

HBV DNA results reported as 'Not Detected' will be imputed as 5 IU/mL. Results reported as 'Detected' or results below the LLQ cut-off value where the status is not specified ('Detect' or 'Not Detected') will be imputed as 15 IU/mL.

The quantitative HBV RNA results will be imputed based on the HBV RNA interpretation provided by the analyzing laboratory. If the interpretation is reported as 'LLOQ' and the result is below the LLQ cut-off value, the result will be imputed as 0.825 Log10 U/mL. Interpretations

reported as 'Negative' or results below the LLQ cut-off value where the status is not specified ('LLOQ' or 'Negative') will be imputed as 0.4125 Log10 U/mL.

Screening and baseline results below LLQ will not be imputed for any of the parameters and patients with results below the LLQ value at baseline will not be included in any of the post-dose summaries or the figures for the specific parameter.

Results equal to or above the LLQ cut-off value will be analyzed as reported, except where the result has been reported as a range ('> x' or '< y') in which case the result will be imputed to one significant digit above or below the reported cut-off value (i.e., '<30' will be analyzed as 29 and '>30.0' will be analyzed as 30.1).

All results (except for HBV RNA) will be log transformed (base 10) for analysis purposes.

Imputed results will be identified in the data listings.

HBV genotyping and HBV sequencing

HBV genotyping and HBV sequencing will be summarised descriptively using frequency count and percentage by study cohort. Emergence of HBV mutations (sequencing of ARO-HBV target site, Core/pre-core, HBsAg epitope, NUC resistant mutations any other mutations by deep sequencing) will be summarized accordingly, depending on the available HBV mutation data. It should be noted that the HBV sequencing data could be missing for HBeAg negative subjects and subjects on NUCs, as they may have HBV DNA that is too low to sequence.

Quantitative assessments: HBV DNA, qHBsAg, qHBeAg, qHBcrAg, qHBV RNA, anti-HBsAg and ratio of bound/free anti-HBsAg (if available)

Quantitative HBV DNA, qHBsAg (overall and by IL28B genotype mutation [rs12979860 and rs8099917]), qHBeAg qHBcrAg and qHBV RNA will be logarithm (log 10) transformed, and the observed log transformed value and change from baseline of the log transformed value will be summarised descriptively for all time points assessed. In addition, for HBV DNA, qHBsAg, qHBeAg, qHBcrAg, and qHBV RNA, the change to the maximum post-dose decline (nadir) from baseline will be pooled for a nadir 'visit' and summarized by cohort as well. The nadir values will also be calculated based on the overall study period (including the follow-up visits). The ratio of bound/free anti-HBsAg will be summarized descriptively without log transformation. The change from baseline values at each post-baseline visit will also be categorized ('<0.5 log decline', '0.5-<1.5 log decline', '1.5-< 3 log decline', '> 3 log decline') and summarized. Only patients with a baseline result above the LLQ for the specific parameter will be included in the post-baseline summaries.

The summary table will also be repeated for the following subgroups (based on the categories described for the qualitative assessments below):

- Baseline HBV DNA:
    - Baseline HBV DNA Not Detected
    - Baseline HBV DNA Detected

- Baseline HBeAg:
    - Baseline qHBeAg Negative
    - Baseline qHBeAg Positive

The quantitative HBV DNA, qHBsAg, qHBeAg, qHBcrAg and qHBV RNA over time (up to Day 113) will be plotted for mean and individual subject values, based on log transformed data, by cohort. The log transformed results will be plotted on a linear scale (y-axis). The log transformed LLQ values will be added as a horizontal reference line. The change from baseline values will also be presented. The plots will also be presented for the subset of CHB patients that participated in the follow-up period and will include all available data. Only patients with a baseline result above the LLQ for the specific parameter will be included in the plots.

Qualitative assessments: HBV DNA, HBV RNA, HBsAg Loss, anti-HBsAg, HBeAg and anti-HBeAg

The quantitative HBV DNA results will be categorized as follows for the qualitative HBV DNA summary:

- Target Detected: All results that are equal to or above the LLQ cut-off value and results below the LLQ that have been classified as 'Detected' (for example, '<15 Detected', '< 20 Detected', etc.) by the analyzing laboratory.
- Target Not Detected: Results below the LLQ cut-off values that have been classified as 'Not Detected' by the analyzing laboratory.

The HBV RNA interpretation provided by the analyzing laboratory will be categorized as follows for the qualitative HBV RNA summary:

- Target Detected: All results where the interpretation provided by the analyzing laboratory is 'Positive' or 'LLOQ'.
- Target Not Detected: All results where the interpretation provided by the analyzing laboratory is 'Negative'.

Loss of HBsAg ('Not Detected') is defined as HBsAg of less than 0.05 IU/mL. Post-baseline qHBsAg results will be classified as follows for the qualitative HBsAg summary:

- Loss of HBsAg: Reported qHBsAg result is below the LLQ cut-off value.
- HBsAg Present: Reported qHBsAg result is equal to or above the LLQ cut-off value.

The qualitative HBeAg results will be categorized as follows for the qualitative HBeAg summary:

- Positive: Qualitative results reported as 'Detected' by the analyzing laboratory.
- Negative: Qualitative results reported as 'Not Detected' by the analyzing laboratory.

Anti-HBsAg and anti-HBeAg will be reported as 'Detected' or 'Not Detected' by the analyzing laboratory. Anti-HBsAg and anti-HBeAg will only be assessed if there was a HBsAg or HBeAg loss during the study and may not be available at all timepoints.

Virology Responses

The following virology responses are also defined based on the qualitative response data:

- Anti-HBsAg seroconversion is defined as the absence of HBsAg (i.e. a 'Not Detected' result for HBsAg which is defined as a value less than 0.05 IU/mL) and the presence of Anti-HBsAg (i.e. a 'Detected' result for Anti-HBsAg). Patients will be analyzed as non-responders (seroconversion = 'No') at a specific time point if the HBsAg result at that time point is reported as equal to or greater than 0.05 IU/mL ('Detected').
- Anti-HBeAg seroconversion is defined as the change from HBeAg 'Detected' to HBeAg 'Not Detected' and the presence of anti-HBeAg (i.e. a 'Detected' result for anti-HBeAg). Patients will be analyzed as non-responders (seroconversion = 'No') at a specific time point if the HBeAg result at that time point is reported as 'Detected'. Anti-HBeAg seroconversion is only applicable to HBeAg positive patients.

For each of the response endpoints, frequent count and percentage will be summarised for each category of qualitative HBsAg, anti-HBsAg, anti-HBsAg seroconversion, HBeAg, anti-HBeAg and anti-HBeAg seroconversion response by cohort for all the assessed study visits. The exact (Clopper-Pearson) 95% confidence interval for each category (response) will be reported as well.

Time to Event Endpoints

- Time to HBsAg Loss is defined as the duration from first dosing to the date of HBsAg 'Not Detected' (HBsAg loss defined as HBsAg < 0.05 IU/mL). Subjects without HBsAg loss will be censored at the end of study (or the end of follow-up period).

- Time to anti-HBsAg seroconversion is defined as the duration from first dosing to the date of anti-HBsAg seroconversion. Subjects without anti-HBsAg seroconversion will be censored at the end of study (or the end of follow-up period).

- Duration of Response (for HBV DNA, qHBsAg, qHBeAg, qHBcrAg, qHBV RNA): defined as the duration from post dose nadir back to within 20% of baseline value. The analysis will only be performed for the overall study period (including the follow-up period) and only patients with baseline values above the LLQ for the specific parameter will be included in the analysis. Subjects with the endpoint not returning to within 20% of baseline value will be censored at the end of the follow-up period.

The time to event endpoints will be analyzed by survival analysis method. Survival analysis will only be conducted if there are at least some responders within a cohort. The survival functions of the time to event endpoints will be summarized for 25th percentile, median, and 75th percentile and their 95% confidence intervals. The rates of HBsAg Loss and anti-HBsAg seroconversion at Day 60 and Day 113 post dosing (and also at Days 169, 225, 281, 337 and 393 for the subset of CHB subjects that participated in the follow-up), the response rates (for HBV DNA, qHBsAg, qHBeAg, qHBcrAg, qHBV RNA) at Day 30 and Day 60 (and additional time points at 30 days intervals as appropriate) post nadir, and their respective 95% confidence intervals will be derived based on their survival functions estimated by Kaplan-Meier method. In addition, the graphs of Kaplan-Meier estimates of survival functions (survival plots) will be presented. Histograms will also be presented showing the response rates for each cohort over 30-day intervals.

All the above analyses will be conducted by CHB cohorts. In addition, separate subgroup analyses might be completed for all CHB patients receiving at least one dose, all HBeAg negative patients and all HBeAg positive patients, all treatment naïve and all entecavir or tenofovir experienced patients. As the sample size is small for each CHB cohort, the subgroup analysis might be conducted as post hoc basis, after reviewing the data from the overall 'by CHB cohort' analyses.

All virology data will be presented in the by-subject data listings. Imputed values will be flagged. Separate listings that includes only patients that had results below LLQ at baseline and that had a post-dose results above LLQ (i.e., patients that 'worsened' during the study) will be presented for all the parameters with quantitative results.

12. CELLULAR IMMUNOLOGY

For CHB cohorts in New Zealand, if feasible, cellular immunology data will be collected at Days 1 (pre-dose), 43 and 113.

Cellular immunology data will be analyzed using the PD Population. Descriptive statistics will be used for the summary. For continuous antibody measurement data, the observed value and change from baseline (last pre-dose value on Day 1) for each dose level (cohort) for all time points assessed will be summarised descriptively. In addition to other descriptive statistics, the summary statistics will also include geometric mean in the table. If categorical data (negative/positive) are reported, these values will be summarised as well for frequent count and percentage. Post-hoc exploratory data analyses maybe conducted depending on the data available.

All cellular immunology data will be presented in the by-subject data listings.

13. IMMUNOGENICITY

For CHB cohorts (Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10,11 and 12) blood samples for anti-drug antibodies testing will be collected at pre-dose, day 57 and at the end of study visit (Day 113) or at early termination as per Schedule of Assessments. Anti-drug antibodies will be analyzed using the Safety Population.

Descriptive statistics will be summarised for anti-drug antibodies. For continuous antibody measurement data, the observed assay value and change from baseline (last pre-dose value on Day 1) for each dose level (cohort) for all time points assessed will be summarised descriptively. In addition to other descriptive statistics, the summary statistics will also include geometric mean in the table. If categorical data (negative/positive) are reported for antibody measurement data, these values will be summarised as well for frequent count and percentage.

All anti-drug antibodies measures will be presented in the by-subject data listings.

14. CYTOKINES AND COMPLEMENT

Cytokines Panel A (whole blood, NHV cohorts only) will be collected at the time of 0 (pre-dose), 15 min, 0.5, 1, 2, 3, 6, 24 and 48 hours post-dose. Cytokines Panel B (whole blood, CHB cohorts only) will be collected across the study period according the protocol schedule of assessment,

Complement (serum and plasma, NHV cohorts only) will be collected at the time of 0 (pre-dose), 0.5, 2, 6 and 24 hours post-dose.

Cytokines (Panels A/B) and complement data will be analyzed using the PD Population. Descriptive statistics will be summarised for cytokines and complement parameters, including the observed value, change from baseline (last pre-dose value on Day 1) and percentage change from baseline for each dose level (cohort) for all time points assessed. In addition to other descriptive statistics, the summary statistics will also include geometric mean in the table.

Mean and individual subject assessment values of cytokines and complement parameters over time will be plotted.

All cytokines and complement data will be presented in the by-subject data listings.

15. HANDLING OF MISSING DATA

Missing values will not be imputed.

16. CHANGES TO THE PLANNED ANALYSIS

Any changes to the analyses outlined in the approved SAP will be detailed in the Clinical Study Report (CSR).

17. INTERIM AND FINAL ANALYSIS

17.1 Dose Escalation, Data Safety Committee (DSC) Analyses

Dose escalation will require approval by the DSC based on a review of all cumulative available safety data for prior cohorts. Based on observations for all NHV subjects in a cohort through Day 8, and experience from any prior cohorts, dosing will begin for the next NHV cohort and as applicable the next CHB cohort at the discretion of the DSC.

Escalation to the next highest dose level will proceed in cohorts of 6 until the dose level of 400 mg is completed, or the trial is halted prematurely by the PI, DSC or Sponsor due to safety or other concerns. Blinding will be preserved to the extent possible for the NHVs; however, treatment un-blinding may occur, at the PI's discretion, where deemed necessary for treatment of an AE or for a decision to be made regarding trial continuation.

A formal charter will be in place prior to study start and will establish the rules, meeting frequency and scope of responsibilities of the DSC.

17.2 Interim Analyses

An interim analysis of the safety and PD data was planned and performed in May 2019 (data cut-off 27Mar2019). This interim analysis was conducted to assist with the planning of future studies and Health Authority interactions and did not impact the conduct of this study. The Sponsor was unblinded to selected summary data only.

A second interim analysis based on all study data up to Day 113 for all cohorts, was completed in February 2020 (data cut-off 14Nov2019).

17.3 Final Analysis (End of Study)

The final end of study analysis will be based on the final version of the SAP. If feasible, Clinical Study Report analysis of quantitative HBsAg through EOS (Day 113) and Additional Follow-Up (Day 393) will be based on a final batched analysis of samples. PD analyses will be completed at EOS (Day 113) and at the end of additional follow up period only in subjects entering into the additional follow up period.

18. SOFTWARE

The following software will be used to perform the statistical analyses: SAS® Version 9.4 or higher (SAS Institute, Cary, North Carolina, USA).

19. TABLES

Tables will be produced separately for NHV cohorts (Cohorts 1, 2, 3, 4 and 5), CHB cohorts (Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10, 11 and 12), and the subset of CHB patients that participated in the follow up period.

No.	Title	Analysis Population	Day 113: Interim Analysis
14.1.1.1	Summary of Disposition	Safety	X
14.1.1.2	Summary of Demographics	Safety	X
14.1.1.3.1	Summary of Baseline Disease Characteristics	Safety	X
14.1.1.3.2	Summary of Baseline Virology Characteristics	PD	X
14.2.1.1	Summary of Plasma Concentrations of ARO-HBV (ng/mL) by Dose *[NHV Cohorts 1, 2, 3, 4 and 5 only]*	PK	X
14.2.2.1	Summary of Plasma Pharmacokinetic Parameters of ARO-HBV by Dose *[NHV Cohorts 1, 2, 3, 4 and 5 only]*	PK	X
14.2.2.2	Analysis of Dose Proportionality for ARO-HBV *[NHV Cohorts 1, 2, 3, 4 and 5 only]*	PK	X
14.2.3.1	Summary of Plasma Concentrations of ARO-HBV (ng/mL), Nucleos(t)ide and JNJ-6397 Plasma Concentrations (Cohort 12) [CHB Cohort 12 only]	PK	
14.2.4.1	Summary of Anti-drug Antibodies *[CHB cohorts only]*	Safety	
14.2.4.2.1	Summary of Quantitative HBV Assessments and Change from Baseline *[CHB cohorts only]*	PD	X
14.2.4.2.1.1	Summary of Quantitative HBV Assessments and Change from Baseline by Baseline HBV DNA Group *[CHB cohorts only]*	PD	X
14.2.4.2.1.2	Summary of Quantitative HBV Assessments and Change from Baseline by Baseline HBeAg Group *[CHB cohorts only]*	PD	X
14.2.4.2.2	Summary of Quantitative HBsAg (IU/mL) by IL28B Genotype and Change from Baseline *[CHB cohorts only]*	PD	
14.2.4.2.3	Summary of Quantitative HBV Assessments Change from Baseline Categories *[CHB cohorts only]*	PD	X
14.2.4.2.4	Summary of Qualitative HBV Assessments *[CHB cohorts only]*	PD	X
14.2.4.3	Summary of HBV Virology Response *[CHB cohorts only]*	PD	X
14.2.4.4	Summary of Time to HBsAg Loss *[CHB cohorts only]*	PD	X
14.2.4.5	Summary of Time to Anti-HBsAg Seroconversion *[CHB cohorts only]*	PD	X
14.2.4.6	Summary of Duration of Response for HBV DNA *[CHB cohorts only]*	PD	X
14.2.4.7	Summary of Duration of Response for HBsAg	PD	X

No.	Title	Analysis Population	Day 113: Interim Analysis
	[CHB cohorts only]		
14.2.4.8	Summary of Duration of Response for HBeAg *[CHB cohorts only]*	PD	X
14.2.4.9	Summary of Duration of Response for HBcrAg *[CHB cohorts only]*	PD	X
14.2.4.10	Summary of Duration of Response for HBV RNA *[CHB cohorts only]*	PD	X
14.2.4.11	Summary of Cellular Immunology Parameters *[CHB cohorts in New Zealand only]*	PD	
14.2.5.1	Summary of Cytokine Parameters *[Panel A for NHV cohorts, Panel B for CHB cohorts]*	PD	X
14.2.6.1	Summary of Complement Parameters *[NHV cohorts]*	PD	X
14.3.1.1	Summary of Concomitant Medications and Non-Drug Therapies	Safety	X
14.3.3.1	Overall Summary of Treatment Emergent Adverse Events	Safety	X
14.3.3.2	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety	X
14.3.3.3	Summary of Treatment Emergent Adverse Events in Descending Order of Frequency by Preferred Term	Safety	X
14.3.3.4	Overall Summary of Related Treatment Emergent Adverse Events	Safety	X
14.3.3.5.1	Summary of Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety	X
14.3.3.5.2	Summary of JNJ-6379 Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Cohort 12) *[CHB Cohort 12 only]*	Safety	X
14.3.3.6.1	Summary of Related Treatment Emergent Adverse Events in Descending Order of Frequency by Preferred Term	Safety	X
14.3.3.6.2	Summary of JNJ-6379 Related Treatment Emergent Adverse Events in Descending Order of Frequency by Preferred Term (Cohort 12) [CHB Cohort 12 only]	Safety	X
14.3.3.7	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term and by Severity	Safety	X
14.3.3.8	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term and by Relationship to Study Drug	Safety	X
14.3.3.9	Summary of Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety	X
14.3.3.10.1	Summary of Serious Study Drug Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety	X

No.	Title	Analysis Population	Day 113: Interim Analysis
14.3.3.10.2	Summary of Serious JNJ-6379 Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Cohort 12) *[CHB Cohort 12 only]*	Safety	X
14.3.3.11	Summary of Treatment Emergent Adverse Events Leading to Study Drug or Study Withdrawn	Safety	X
14.3.3.12	Summary of Treatment Emergent Adverse Events Occurring at the Treatment Injection Site	Safety	X
14.3.3.13	Summary of Treatment Emergent Adverse Events Fitting the Definition of Local Injection Site Reactions (LISR) (See LISR definition in Section 10.1)	Safety	X
14.3.3.14	Summary of Treatment Emergent Adverse Events Fitting the Definition of Local Injection Site Reactions (LISR) by System Organ Class and Preferred Term and by Severity	Safety	X
14.3.4.1	Laboratory – Hematology: Summary and Change from Baseline	Safety	X
14.3.4.2	Laboratory - Chemistry: Summary and Change from Baseline	Safety	X
14.3.4.3	Laboratory – Coagulation: Summary and Change from Baseline	Safety	X
14.3.4.4	Laboratory - Urinalysis: Summary and Change from Baseline	Safety	X
14.3.4.5	Summary of Haematology Shifts from Baseline	Safety	X
14.3.4.6	Summary of Biochemistry Shifts from Baseline	Safety	X
14.3.4.7	Summary of Coagulation Shifts from Baseline	Safety	X
14.3.4.8	Summary of Subjects with ALT above Upper Limit of Normal Over Time *[CHB cohorts only]*	Safety	X
14.3.5.1	Summary of Vital Signs	Safety	X
14.3.6.1	Summary of Physical Examination	Safety	X
14.3.7.1	Summary of ECG Values	Safety	X
14.3.7.2	Summary of ECG Findings	Safety	X

20. LISTINGS

Listings will be produced separately for NHV cohorts (Cohorts 1, 2, 3, 4 and 5) and CHB cohorts (Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10,11 and 12).

No.	Title	Analysis Population	Day 113: Interim Analysis
16.2.1.1	Listing of Enrolment	Safety	X
16.2.1.2	Listing of Eligibility Criteria	Safety	X
16.2.2.1	Listing of Protocol Deviations	Safety	X
16.2.3.1.1	Listing of Disposition	Safety	X
16.2.3.1.2	Listing of Disposition (Follow-Up)	Safety	X
16.2.3.2	Listing of Randomization *[NHV Cohorts 1, 2, 3, 4 and 5 only]*	Safety	X
16.2.4.1	Listing of Demographics	Safety	X
16.2.4.2	Listing of Medical History	Safety	X
16.2.4.3	Listing of Child-bearing Potential, Follicle-Stimulating Hormone (FSH) Results and Pregnancy Test	Safety	X
16.2.4.4	Listing of Serology Screen	Safety	X
16.2.4.5	Listing of Drug Screen	Safety	X
16.2.4.6	Listing of Hepatic Fibrosis Measure	Safety	X
16.2.4.7	Listing of Baseline Disease Characteristics *[CHB cohorts only]*	Safety	X
16.2.5.1	Listing of Study Drug Administrations	Safety	X
16.2.5.2	Listing of Concomitant/Prior Medications and Non-Drug Therapies	Safety	X
16.2.5.3	Listing of Dispensing of Nucleos(t)ide *[CHB cohorts only]*	Safety	X
16.2.5.4	Listing of JNJ-6397 Compliance (Cohort 12) *[CHB Cohort 12 only]*	Safety	X
16.2.5.5	Listing of JNJ-6397 Dosing Deviations (Cohort 12) *[CHB Cohort 12 only]*	Safety	X
16.2.6.1.1	Listing of Individual ARO-HBV Plasma Concentration (ng/mL) *[NHV cohorts only]*	Safety	X
16.2.6.1.2	Listing of Individual ARO-HBV, Nucleos(t)ide and JNJ-6397 Plasma Concentrations (Cohort 12) *[CHB Cohort 12 only]*	PK	
16.2.6.2	Listing of Individual ARO-HBV Plasma Pharmacokinetic Parameters *[NHV cohorts only]*	PK	X
16.2.6.3	Listing of Anti-drug Antibodies *[CHB cohorts only]*	Safety	
16.2.6.4.1	Listing of HBV Genotyping and HBV Sequencing *[CHB cohorts only]*	PD	X
16.2.6.4.2.1.1	Listing of Quantitative HBV Serology: HBV DNA *[CHB cohorts only]*	PD	X

No.	Title	Analysis Population	Day 113: Interim Analysis
16.2.6.4.2.1.2	Listing of Quantitative HBV Serology: HBV DNA – Baseline Result Below LLQ *[CHB cohorts only]*	PD	X
16.2.6.4.2.2.1	Listing of Quantitative HBV Serology: HBsAg *[CHB cohorts only]*	PD	X
16.2.6.4.2.2.2	Listing of Quantitative HBV Serology: HBsAg – Baseline Result Below LLQ *[CHB cohorts only]*	PD	X
16.2.6.4.2.3.1	Listing of Quantitative HBV Serology: HBeAg *[CHB cohorts only]*	PD	X
16.2.6.4.2.3.2	Listing of Quantitative HBV Serology: HBeAg – Baseline Result Below LLQ *[CHB cohorts only]*	PD	X
16.2.6.4.2.4.1	Listing of Quantitative HBV Serology: HBcrAg *[CHB cohorts only]*	PD	X
16.2.6.4.2.4.2	Listing of Quantitative HBV Serology: HBcrAg – Baseline Result Below LLQ *[CHB cohorts only]*	PD	X
16.2.6.4.2.5.1	Listing of Quantitative HBV Serology: HBV RNA *[CHB cohorts only]*	PD	X
16.2.6.4.2.5.2	Listing of Quantitative HBV Serology: HBV RNA – Baseline Result Below LLQ *[CHB cohorts only]*	PD	X
16.2.6.4.2.6	Listing of Quantitative HBV Serology: Ratio of Bound/Free Anti-HBsAg *[CHB cohorts only]*	PD	X
16.2.6.4.3	Listing of HBV Virology Responses *[CHB cohorts only]*	PD	X
16.2.6.4.4	Listing of HBV Virology Time to Event Endpoints *[CHB cohorts only]*	PD	X
16.2.6.4.5	Listing of HBV Virology Time to Event Endpoints (Follow-Up) *[CHB cohorts only]*	PD	X
16.2.6.5	Listing of Cellular Immunology Parameters *[CHB cohorts in New Zealand]*	PD	
16.2.6.6	Listing of Cytokine Parameters *[Panel A for NHV cohorts, Panel B for CHB cohorts]*	PD	X
16.2.6.7	Listing of Complement Parameters *[NHV cohorts only]*	PD	X
16.2.7.1.1	Listing of Adverse Events	Safety	X
16.2.7.1.2	Listing of Adverse Events (Cohort 12) *[CHB Cohort 12 only]*	Safety	X
16.2.7.2	Listing of Serious Adverse Events	Safety	X
16.2.7.3	Listing of Adverse Events Leading to Study Drug Withdrawn or Study Withdrawn	Safety	X
16.2.7.4	Listing of Adverse Events Occurring at the Treatment Injection Site	Safety	X

No.	Title	Analysis Population	Day 113: Interim Analysis
16.2.7.5	Listing of Adverse Events Fitting the Definition of LISR	Safety	X
16.2.8.1	Listing of Haematology	Safety	X
16.2.8.2	Listing of Biochemistry	Safety	X
16.2.8.3	Listing of Coagulation	Safety	X
16.2.8.4	Listing of Urinalysis	Safety	X
16.2.8.5	Listing of Microscopic Urinalysis	Safety	X
16.2.9.1	Listing of Vital Signs	Safety	X
16.2.10.1	Listing of Physical Examination	Safety	X
16.2.11.1	Listing of ECG Values	Safety	X
16.2.11.2	Listing of ECG Findings	Safety	X
14.2.2.2	Analysis of Dose Proportionality for ARO-HBV	PK	X

21. FIGURES

PK Figures will be produced for NHV cohorts (Cohorts 1, 2, 3, 4 and 5). Others will be produced separately for NHV cohorts (Cohorts 1, 2, 3, 4 and 5), CHB cohorts (Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10,11 and 12)*, and the subset of CHB patients that participated in the follow up period*.

No.	Title	Analysis Population	Day 113: Interim Analysis
14.2.1.1.1a	Mean (+/-SD) Plasma Concentrations of ARO-HBV versus Time by Dose (Linear Scale)	PK	X
14.2.1.1.1b	Mean (+/-SD) Plasma Concentrations of ARO-HBV versus Time by Dose (Semilogarithmic Scale)	PK	X
14.2.1.2.1a	Median Plasma Concentrations of ARO-HBV versus Time by Dose (Linear Scale)	PK	X
14.2.1.2.1b	Median Plasma Concentrations of ARO-HBV versus Time by Dose (Semilogarithmic Scale)	PK	X
14.2.2.1.1a	Individual Plasma Concentrations of ARO-HBV versus Time (Linear Scale)	PK	X
14.2.2.1.1b	Individual Plasma Concentrations of ARO-HBV versus Time (Semilogarithmic Scale)	PK	X
14.2.1.1.2a	Mean (+/-SD) Plasma Concentrations of ARO-HBV, Nucleos(t)ide and JNJ-6397 versus Time by Dose (Linear Scale) (Cohort 12) [CHB Cohort 12 only]	PK	X
14.2.1.1.2b	Mean (+/-SD) Plasma Concentrations of ARO-HBV, Nucleos(t)ide and JNJ-6397 versus Time by Dose (Semilogarithmic Scale) (Cohort 12) [CHB Cohort 12 only]	PK	X
14.2.1.2.2a	Median Plasma Concentrations of ARO-HBV, Nucleos(t)ide and JNJ-6397 versus Time by Dose (Linear Scale) (Cohort 12) [CHB Cohort 12 only]	PK	X
14.2.1.2.2b	Median Plasma Concentrations of ARO-HBV, Nucleos(t)ide and JNJ-6397 versus Time by Dose (Semilogarithmic Scale) (Cohort 12) [CHB Cohort 12 only]	PK	X
14.2.2.1.2a	Individual Plasma Concentrations of ARO-HBV, Nucleos(t)ide and JNJ-6397 versus Time (Linear Scale)	PK	X
14.2.2.1.2b	Individual Plasma Concentrations of ARO-HBV, Nucleos(t)ide and JNJ-6397 versus Time (Semilogarithmic Scale) (Cohort 12) [CHB Cohort 12 only]	PK	X
14.2.3.1	Scatterplot of Individual and Mean Plasma AUC_{0-24} versus Dose for ARO-HBV	PK	X
14.2.3.2	Scatterplot of Individual and Mean Plasma AUC_{0-inf} versus Dose for ARO-HBV	PK	X
14.2.3.3	Scatterplot of Individual and Mean Plasma AUC_{0-t} versus Dose for ARO-HBV	PK	X
14.2.3.4	Scatterplot of Individual and Mean Plasma C_{max} versus Dose for ARO-HBV	PK	X

No.	Title	Analysis Population	Day 113: Interim Analysis
14.2.4.1	Scatterplot of Individual and Mean Plasma Dose Normalized AUC_{0-24} versus Dose for ARO-HBV	PK	X
14.2.4.2	Scatterplot of Individual and Mean Plasma Dose Normalized AUC_{0-inf} versus Dose for ARO-HBV	PK	X
14.2.4.3	Scatterplot of Individual and Mean Plasma Dose Normalized AUC_{0-t} versus Dose for ARO-HBV	PK	X
14.2.4.4	Scatterplot of Individual and Mean Plasma Dose Normalized C_{max} versus Dose for ARO-HBV	PK	X
14.2.5.1	Mean (+/-SD) of Creatinine versus Time by Cohort	Safety	X
14.2.5.2	Mean (+/-SD) of Creatine Kinase versus Time by Cohort	Safety	X
14.2.5.3	Mean (+/-SD) of AST versus Time by Cohort	Safety	X
14.2.5.4	Mean (+/-SD) of ALT versus Time by Cohort	Safety	X
14.2.5.5	Mean (+/-SD) of Total Bilirubin versus Time by Cohort	Safety	X
14.2.6.1.1	Mean (+/-SD) of Logarithm Transformed Quantitative HBV DNA versus Time by Cohort *[CHB cohorts only]*	PD	X
14.2.6.1.2	Mean (+/-SD) Change from Baseline in Logarithm Transformed Quantitative HBV DNA versus Time by Cohort *[CHB cohorts only]*	PD	X
14.2.6.2.1	Mean (+/-SD) of Logarithm Transformed Quantitative HBsAg versus Time by Cohort *[CHB cohorts only]*	PD	X
14.2.6.2.2	Mean (+/-SD) Change from Baseline in Logarithm Transformed Quantitative HBsAg versus Time by Cohort *[CHB cohorts only]*	PD	X
14.2.6.3.1	Mean (+/-SD) of Logarithm Transformed Quantitative HBeAg versus Time by Cohort *[CHB cohorts only]*	PD	X
14.2.6.3.2	Mean (+/-SD) Change from Baseline in Logarithm Transformed Quantitative HBeAg versus Time by Cohort *[CHB cohorts only]*	PD	X
14.2.6.4.1	Mean (+/-SD) of Logarithm Transformed Quantitative HBcrAg versus Time by Cohort *[CHB cohorts only]*	PD	X
14.2.6.4.2	Mean (+/-SD) Change from Baseline in Logarithm Transformed Quantitative HBcrAg versus Time by Cohort *[CHB cohorts only]*	PD	X
14.2.6.5.1	Mean (+/-SD) of Logarithm Transformed Quantitative HBV RNA versus Time by Cohort *[CHB cohorts only]*	PD	X

No.	Title	Analysis Population	Day 113: Interim Analysis
14.2.6.5.2	Mean (+/-SD) Change from Baseline in Logarithm Transformed Quantitative HBV RNA versus Time by Cohort *[CHB cohorts only]*	PD	X
14.2.7.1.1	Individual Logarithm Transformed Quantitative HBV DNA versus Time by Cohort *[CHB cohorts only]*	PD	X
14.2.7.1.2	Individual Change from Baseline in Logarithm Transformed Quantitative HBV DNA versus Time by Cohort *[CHB cohorts only]*	PD	X
14.2.7.2.1	Individual Logarithm Transformed Quantitative HBsAg versus Time by Cohort *[CHB cohorts only]*	PD	X
14.2.7.2.2	Individual Change from Baseline in Logarithm Transformed Quantitative HBsAg versus Time by Cohort *[CHB cohorts only]*	PD	X
14.2.7.3.1	Individual Logarithm Transformed Quantitative HBeAg versus Time by Cohort *[CHB cohorts only]*	PD	X
14.2.7.3.2	Individual Change from Baseline in Logarithm Transformed Quantitative HBeAg versus Time by Cohort *[CHB cohorts only]*	PD	X
14.2.7.4.1	Individual Logarithm Transformed Quantitative HBcrAg versus Time by Cohort *[CHB cohorts only]*	PD	X
14.2.7.4.2	Individual Change from Baseline in Logarithm Transformed Quantitative HBcrAg versus Time by Cohort *[CHB cohorts only]*	PD	X
14.2.7.5.1	Individual Logarithm Transformed Quantitative HBV RNA versus Time by Cohort *[CHB cohorts only]*	PD	X
14.2.7.5.2	Individual Change from Baseline in Logarithm Transformed Quantitative HBV RNA versus Time by Cohort *[CHB cohorts only]*	PD	X
14.2.8.1	Kaplan-Meier Plot of Time to HBsAg Loss by Cohort *[CHB cohorts only]*	PD	X
14.2.8.2	Kaplan-Meier Plot of Time to Anti-HBsAg Seroconversion by Cohort *[CHB cohorts only]*	PD	X
14.2.8.3	Kaplan-Meier Plot of Duration of Response for Quantitative HBV DNA by Cohort (Follow-Up) *[CHB cohorts only]*	PD	X
14.2.8.4	Kaplan-Meier Plot of Duration of Response for Quantitative HBsAg by Cohort (Follow-Up) *[CHB cohorts only]*	PD	X

No.	Title	Analysis Population	Day 113: Interim Analysis
14.2.8.5	Kaplan-Meier Plot of Duration of Response for Quantitative HBeAg by Cohort (Follow-Up) *[CHB cohorts only]*	PD	X
14.2.8.6	Kaplan-Meier Plot of Duration of Response for Quantitative HBcrAg by Cohort (Follow-Up) *[CHB cohorts only]*	PD	X
14.2.8.7	Kaplan-Meier Plot of Duration of Response for Quantitative HBV RNA by Cohort (Follow-Up) *[CHB cohorts only]*	PD	X
14.2.8.8	Histogram of Duration of Response for Quantitative HBV DNA by Cohort (Follow-Up) *[CHB cohorts only]*	PD	X
14.2.8.9	Histogram of Duration of Response for Quantitative HBsAg by Cohort (Follow-Up) *[CHB cohorts only]*	PD	X
14.2.8.10	Histogram of Duration of Response for Quantitative HBeAg by Cohort (Follow-Up) *[CHB cohorts only]*	PD	X
14.2.8.11	Histogram of Duration of Response for Quantitative HBcrAg by Cohort (Follow-Up) *[CHB cohorts only]*	PD	X
14.2.8.12	Histogram of Duration of Response for Quantitative HBV RNA by Cohort (Follow-Up) *[CHB cohorts only]*	PD	X
14.2.9.1	Mean (+/-SD) of Cytokine Parameter Levels versus Time by Dose	PD	X
14.2.9.2	Mean (+/-SD) of Cytokine Parameter Change from Baseline versus Time by Dose	PD	X
14.2.9.3	Mean (+/-SD) of Cytokine Parameter Percentage Change from Baseline versus Time by Dose	PD	X
14.2.10.1	Individual Cytokine Parameter Levels versus Time	PD	X
14.2.10.2	Individual Cytokine Parameter Change from Baseline versus Time	PD	X
14.2.10.3	Individual Cytokine Parameter Percentage Change from Baseline versus Time	PD	X
14.2.11.1	Mean (+/-SD) of Complement Parameter Levels versus Time by Dose	PD	X
14.2.11.2	Mean (+/-SD) of Complement Parameter Change from Baseline versus Time by Dose	PD	X
14.2.11.3	Mean (+/-SD) of Complement Parameter Percentage Change from Baseline versus Time by Dose	PD	X
14.2.12.1	Individual Complement Parameter Levels versus Time	PD	X
14.2.12.2	Individual Complement Parameter Change from Baseline versus Time	PD	X
14.2.12.3	Individual Complement Parameter Percentage Change from Baseline versus Time	PD	X

Notes: Each cytokine and complement parameter will be plotted separately. Therefore, each PD output above could have multiple plots.

22. REFERENCES

1) AROHBV1001 Clinical Study Protocol, Version 4.0, 01Oct2018
2) AROHBV1001 Clinical Study Protocol, Version 5.0, 04Jan2019
3) AROHBV1001 Clinical Study Protocol, Version 6.0, 28Feb2019