PROTOCOL NUMBER:	**AROHBV1001**
STUDY TITLE:	**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**
DRUG (Active):	**ARO-HBV**
ROUTE:	**Subcutaneous Injection**
STUDY DESIGN:	**Double blind, escalating single dose administrations to normal adult volunteers assessing safety, tolerability and pharmacokinetics and open label, escalating multiple dose administrations assessing safety, tolerability and pharmacodynamic effects in patients with chronic HBV infection**
SPONSOR:	**Arrowhead Pharmaceuticals, Inc.** **177 E. Colorado Blvd., Suite 700** **Pasadena, CA 91105** **Telephone: +1 626 304 3400 Facsimile: +1 626 304 3401**
	This amendment, specific to Hong Kong only, reduces the protocol required follow-up period to Day 337 (±5 days) for the open-label CHB Cohort 12 patients only. All previously enrolled CHB cohorts will continue with follow-up visits until Day 393 (±5 days).

1 PROTOCOL SYNOPSIS

Study Title: 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

Study Number: AROHBV1001

Phase: Phase 1 First-in-Human, Phase 2a First-in-Patient

Number of Sites: Healthy volunteers: Single site in New Zealand

Patients chronically infected with Hepatitis B: multiple sites in New Zealand, Australia and Hong Kong

Study Treatments:

There will be up to three study treatments (depending on the cohort); two active (Test Formulation) ARO-HBV and JNJ-56136379 (JNJ-6379) and one placebo (Reference Formulation).

Test Formulation:

The test formulation is active ARO-HBV Injection (also referred to as ARO-HBV). The active pharmaceutical ingredient (API) contained in ARO-HBV is composed of a 2:1 molar mixture of two synthetic, double-stranded, small interfering RNA (siRNA) duplexes each separately conjugated to a N-acetyl-galactosamine targeting ligand to facilitate hepatocyte delivery.

Cohort 12 only will add JNJ-56136379 (JNJ-6379) as a study treatment to be evaluated in CHB patients in combination with ARO-HBV. JNJ-6379 is a capsid assembly modulator (CAM) being developed for the treatment of hepatitis B infection. JNJ-6379 binds to the HBV core protein and interferes with the viral capsid assembly process and resulting in the formation of empty viral capsids devoid of HBV-DNA. JNJ-6379 also acts at an early stage of the viral life cycle by inhibiting the de novo formation of cccDNA.

Reference Formulation:

The reference formulation is placebo (PBO): normal saline (0.9%) administered subcutaneously, volume matched to the corresponding ARO-HBV dose volume.

Study Objectives:

Primary Objectives:

- 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).

Secondary Objectives:

- To evaluate the single-dose pharmacokinetics of ARO-HBV in NHVs
- To determine the reduction from Day 1 pre-dose baseline to post-dose nadir of HBsAg in response to ARO-HBV in patients chronically infected with HBV (CHB) as a measure of activity.

Exploratory Objectives

- To determine the reduction from Day 1 pre-dose baseline to post-dose nadir of HBcrAg, HBsAg, HBV RNA (if scientifically feasible) and HBeAg (e+ patients only), in response to ARO-HBV (alone or in combination with JNJ-6379) in CHB patients as a measure of activity.

- 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 NHVs.
- To evaluate the effect of single escalating doses of ARO-HBV on complement factors Bb, CH50, C5a, C4a, and C3a in NHVs.
- To collect plasma samples in NHVs for subsequent metabolite identification (reported in a separate report outside of this study)
- To collect urine samples in NHVs 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).

Study Population/Patient Number: This study will be conducted in NHVs, adult males and females, aged 18-55 years with BMI between 19.0 and 35.0 kg/m² (Cohorts 1 – 5) and in HBeAg negative or HBeAg positive CHB patients, aged 18-65 years with BMI between 19.0 and 38.0 kg/m² (Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10, 11and 12). Cohort 8 will enroll HBeAg positive treatment naïve patients (no prior chronic exposure to NUCs or Interferon) and Cohort 9 will enroll HBeAg positive NUC experienced patients (on entecavir or tenofovir for at least 12 months). Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 10, 11 and 12 will enroll either HBeAg positive or negative patients regardless of previous NUC or PEG IFN treatment experience. Only Cohort 12 patients will start JNJ-6379 on Day 1 and continue until Day 84. All patients will be started on entecavir or tenofovir on Day 1. Patients currently on PEG IFN will not be allowed.

Summary of Participant Profile by Cohort:

- Cohorts 1-5: NHVs, adult males and females, aged 18-55 years
- Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 10, 11 and 12: Any CHB patient regardless of HBeAg or prior therapy status (as long as other Inclusion and Exclusion criteria are met).
- Cohort 8: HBeAg positive treatment naïve patients (no prior chronic exposure to NUCs or Interferon).
- Cohort 9: HBeAg positive NUC experienced patients (on entecavir or tenofovir for at least 12 months).

NHV subjects will enroll sequentially into a total of 5 cohorts (comprised of 6 subjects each), randomized to receive ARO-HBV or placebo (4 active: 2 placebo) at single escalating doses of 35, 100, 200, 300 and 400 mg administered as a single subcutaneous injection.

CHB cohorts 1b, 1c, 2b, 3b, 4b and 5b will each enroll a minimum of 4 and a maximum of 8 subjects in an open

label fashion to receive escalating multiple doses of ARO-HBV. Cohorts 6, 7, 8, 9, 10 and 11 will each enroll a maximum of 4 subjects. Cohort 12 will enroll 12 CHB patients to each receive 250 mg daily oral JNJ-6379+NUCs+200mg ARO-HBV Q28 days X3 doses.

CHB patients regardless of HBeAg status or NUC/Interferon use history will enroll sequentially into a total of 11 open label cohorts (Cohorts 2b through 7, Cohorts 10, 11, 12, 1b and 1c). Cohorts 1b, and 1c through 5b will enroll at planned dose levels of 25 mg (Cohort 1b), 50 mg (Cohort 1c), 100 mg (Cohort 2b), 200 mg (Cohort 3b), 300 mg (Cohort 4b) and 400 mg (Cohort 5b) to receive three doses (Q28 days) of active treatment in an open label fashion. Cohort 6 will enroll CHB subjects (after Cohort 5b has completed enrollment) to receive three doses two weeks apart. Cohorts 7, 10 and 11 will enroll CHB patients sequentially (after Cohort 6 has completed enrollment) to receive three doses a week apart at increasing dose levels starting with a dose equal to Cohort 6. Cohorts 5b through 7 and Cohorts 10 and 11 will enroll sequentially (after being opened at the final planned DSC meeting) with enrollment and dosing in a later cohort not initiating until all subjects in the earlier cohort have received at least their first scheduled dose. Cohort 8 will enroll HBeAg positive treatment naïve CHB patients to receive three monthly doses of ARO-HBV. Cohort 9 will enroll HBeAg positive entecavir or tenofovir experienced CHB patients to receive three monthly doses of ARO-HBV. Cohorts 8 and 9 may enroll in parallel with Cohort 5b once opened by the DSC. Cohorts 6 through 12 will enroll at planned dose levels of 100 mg (Cohorts 6 and 7), 200 mg (Cohorts 10 and 12), and 300 mg (Cohorts 8, 9, and 11). CHB patient screening for all CHB cohorts may start when Cohort 1 opens for enrollment. However, no CHB patients may be dosed until their respective cohort is approved for dosing by the DSC (not including Cohorts 1b, 1c and 12). CHB dosing may begin and NHV dose escalation may occur based on DSC approval which can occur by vote after cumulative data through Day 8 from the current NHV cohort is available. See **Figure 1** for dose escalation schedule). CHB patients on current 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. Either tenofovir disoproxil fumarate (including generic) or tenofovir alafenamide are acceptable.

Cohort 12 will enroll 12 CHB patients to receive ARO-HBV 200 mg on Days 1, 29 and 57. Like all other CHB cohorts, patients enrolling in Cohort 12 will either enter the study on NUCs or start NUCs on Day 1. Cohort 12 patients will also initiate daily JNJ-6379 250 mg on Day 1 and continue through Day 84.

NHV subjects who withdraw from the study prior to collection of the final pharmacokinetic blood sample, for reasons other than an adverse event, may be replaced. CHB patients who are withdrawn or discontinue prior to the End-of-Study visit (EOS/Day 113) for reasons other than an adverse event, may be replaced.

A total of approximately 30 NHV and a minimum of 60 or a maximum of 84 CHB participants (not including potential replacements) may be enrolled in the study.

Number of Doses per Treatment: Single dose (Healthy Volunteer Cohorts 1 through 5) or three doses of ARO-HBV ranging in frequency from once weekly to once every 4 weeks (CHB patients).

Daily dose of JNJ-6379 250 mg from Day 1 through Day 84 (Cohort 12 CHB patients only).

Study Duration: For each NHV subject in the single dose cohorts, the duration of the study clinic visits is a maximum of 13 weeks from the beginning of the screening period to the Day 29 EOS examination.

For each CHB patient in the multi-dose Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10, 11 and 12 the duration of the study clinic visits is approximately 25 weeks from screening to the Day 113 EOS examination. With the exception of Cohort 12 patients, all other CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after Day 113. Only Cohort 12 patients will require follow-up until the Day 337 (±5 days) visit. Subjects consenting to additional follow up will continue on NUCs. Subjects not consenting to additional follow up will be followed per protocol based on Schedule of Assessment Tables 1.2, 1.3 and 1.4.

All CHB patients and NHV subjects will be contacted by phone 90 days after the EOS visit (post Day 29 for NHVs and post Day 113 for CHB patients) to confirm pregnancy status.

Study Confinement: For NHVs, clinical facility confinement will be approximately 2 days for single dose administration (Day -1 through 24-hour assessments). Subjects will return to the clinical facility for out-patient

visits.

For CHB patients, clinical facility confinement will be approximately 2 hours on dosing days unless additional monitoring at PI discretion is needed for safety reasons. Patients will return to the clinical facility for outpatient visits.

Study Design/Methods:

Healthy volunteers:

For NHVs, cohorts of 6 eligible subjects (2 placebo, 4 active ARO-HBV) will be evaluated at each dose level starting at dose level 1 (35 mg). Participants who have signed an HDEC (or local equivalent) approved informed consent form and have met all of the protocol eligibility criteria during screening, will be randomized at a ratio of 2:1 (active:PBO) to receive ARO-HBV or PBO in a double blind fashion. NHV cohorts will receive a single dose only.

Each cohort will begin with administration of ARO-HBV or PBO to two sentinel participants (one ARO-HBV, one PBO). Following the Day 3 evaluation in these participants, if there are no significant safety concerns based on PI's judgement, the remaining participants in the cohort will be treated. Dosing of participants will be staggered by at least 15 minutes such that no two participants will be dosed simultaneously.

Clinical facility confinement will be approximately 2 days for single dose administration (Day -1 through 24-hour assessments). Blood samples will be drawn pre-dose on Day 1 for baseline measurements. Height and weight will be measured at Screening only to calculate BMI.

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.

After all subjects in a cohort have completed an EOS visit (Day 29), Sponsor may be unblinded at Sponsor's request. PI and study participants will remain blinded.

CHB patients:

In Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10, 11 and 12, eligible CHB patients who have signed an HDEC (or local equivalent) approved informed consent form will receive three doses of ARO-HBV at dose intervals ranging from once every week to once every 4 weeks in an open label fashion. In addition, Cohort 12 patients will also initiate daily JNJ-6379 250 mg on Day 1 and continue through Day 84. Screening for the CHB cohorts can begin once Cohort 1 dosing has commenced. These cohorts (not including Cohorts 1b, 1c and 12) will be opened for accrual once the corresponding NHV cohort receiving the same single dose level has reached Day 8, based on agreement of the DSC that it is safe to proceed. Cohorts 6, 7, 8, 9, 10 and 11 can be opened for enrollment any time after Cohort 5 has reached Day 8 (and DSC has approved opening of such cohorts) and there is sufficient viral antigen response data from CHB patients to determine a dose level for these cohorts (at the discretion of the DSC). Dose levels for Cohorts 6-12 is between 100 and 300 mg. Cohorts 2b through Cohort 7 and Cohorts 10 and 11, will be enrolled in sequence (as shown in Figure 1). Cohorts 8 and 9 may be enrolled in parallel with other CHB cohorts after the DSC has voted post Cohort 5 to open the remaining CHB patient cohorts and the specified dose ($\leq$ 300 mg) has been identified. Cohort 12 is open for enrollment in Hong Kong only. Cohorts 1b and 1c are open for enrollment with the addition of a protocol amendment and may enroll in parallel. For clarity, after Cohort 5 is through Day 8, the DSC will review all available safety data and vote to open Cohorts 5b, 6, 7, 8, 9, 10 and 11. Cohorts 5b, 8 and 9 may enroll and dose patients in parallel. Cohorts 5b through 7 and Cohorts 10 and 11 must enroll sequentially, meaning that Cohort 5b must be fully enrolled with each subject receiving at least a first dose before Cohort 6 can enroll. Cohort 6 must be fully enrolled with each subject receiving at least a first dose before Cohort 7 can enroll. Cohort 7 must be fully enrolled with each subject receiving at least a first dose before Cohort 10 can enroll and Cohort 10 must be fully enrolled with each subject receiving at least a first dose before Cohort 11 can enroll. It is the intent that Cohorts 7, 10 and 11 will be treated at increasing dose levels starting with a dose equal to Cohort 6.

Enrollment in Cohort 12 can begin once enrollment is full in Cohorts 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10, 11. The ARO-HBV dose level for Cohort 12 is 200 mg Q28 days (Days 1, 29, 57). Cohort 12 patients will also initiate daily JNJ-6379 250 mg on Day 1 and continue through Day 84.

On dosing days, clinical facility confinement will be approximately 2 hours. Blood samples will be drawn pre-dose on Day 1 for baseline measurements. Height and weight will be measured at Screening only to calculate BMI. Participants will undergo evaluations at screening and at regular intervals during the study as described in the Schedule of Assessments.

With the exception of Cohort 12 patients, all other CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after Day 113. Only Cohort 12 patients will require follow-up until the Day 337 (±5 days) visit. Subjects consenting to additional follow up will continue on NUCs. Subjects not consenting to additional follow up will be followed per protocol based on Schedule of Assessment Tables 1.2, 1.3 and 1.4.

Single doses of ARO-HBV will be evaluated in normal healthy volunteers (NHVs) and multiple doses of ARO-HBV will be evaluated in patients with chronic hepatitis B (CHB) in a sequential manner as shown in **Figure 1.**

Figure 1: 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

Unblinding of NHV cohorts may occur at Sponsor discretion on a cohort by cohort basis after all subjects in a cohort have completed their last on-site study visit. Study participants as well as sites will remain blinded.

Open label anti-viral response data may be disclosed to investigators by the Sponsor at Sponsor's discretion. There is no requirement for Sponsor to disclose anti-viral response data while the study is ongoing unless required for safety reasons.

Adverse Event Monitoring

Safety assessments will include: AEs/SAEs, physical examinations, vital sign measurements (blood pressure, heart rate, temperature, and respiratory rate), ECGs, clinical laboratory tests, concomitant medications/therapy, and reasons for treatment discontinuation. Safety assessments will be performed at specified time points and prior to study completion.

The AE/SAE reporting period for an enrolled participant begins when the participant provides informed consent. Treatment-emergent AEs/SAEs are defined as those following study drug administration or pre-existing condition exacerbated by study drug. All AEs that occur during the AE reporting period specified in the protocol must be reported to Arrowhead via electronic case report forms within approximately 48 hours. All SAEs that occur during the reporting period, in addition to reporting via electronic case report forms, must also be reported to Arrowhead via the SAE report form within 24 hours of awareness. All AE/SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up. If the PI learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the PI will promptly notify the Sponsor. Laboratory abnormalities will be reported as AEs if considered clinically significant by the PI. Laboratory abnormalities not reported as AEs are not to be reported as Clinically Significant (CS) in the study database.

Treatment Stopping Rules:
Escalation to the next cohort will proceed according to the study design through the 400 mg dose level and until all subsequent cohorts are completed unless the trial is stopped early by the DSC or Sponsor. A decision to stop the trial early or discontinue drug in an individual subject or group of subjects **may** (following a case-by-case decision based on consultation between the sponsor, DSC and the PI) be indicated based on any of the following:

1. A single Serious Adverse Event (SAE, defined in Section 9.1) considered at least possibly related to ARO-HBV or JNJ-6379
2. One of the following abnormal results at least possibly related to ARO-HBV or JNJ-6379:
   - In NHVs, treatment emergent ALT or AST > 3X ULN, which must be confirmed by repeat blood draw within 48 hours of initial results.
   - In CHB patients, treatment emergent ALT or AST > 3X Day 1 pre-dose baseline, confirmed by repeat blood draw within 48 hours of initial results **AND** ALT > 10X ULN **AND** any one of the following:
     - Total Bilirubin newly elevated to 2X ULN **AND** 2X Day 1 pre-dose baseline (confirmed on repeat lab draw within 48 hours) or
     - Decrease in serum albumin of 0.5 g/dL or greater confirmed on repeat lab draw within 48 hours
   - Treatment emergent platelet count < 70,000 per microliter in NHVs or < 50,000 in CHB patients, confirmed on repeat measure within 48 hours of initial results
   - Treatment emergent serum creatinine > 180 μmol/L confirmed by repeat blood draw within 48 hours of initial results

Sponsor or PI can discontinue any subject at any time with or without DSC consultation. If such events (as described above) occur and the subject is not discontinued from the study the reason for not discontinuing the subject will be included in DSC meeting minutes. Including, but not limited to the events listed above, the DSC **may** pause the study to additional dosing or dose escalation to provide time to evaluate safety data and recommend the action to be taken, which may include, but is not limited to one of the following:

• Discontinuation of a subject or group of subjects from the study
• The study is stopped immediately with no further dosing
• The study will continue until the current cohort is completed
• The study will continue, but the next dose escalation will be to a level midway between the current level and the next level specified in Section 8.3
• The study will continue as planned

Study Assessments:

Safety Assessments:
Safety assessments will be performed at specified time points per the Schedule of Assessments and will include the following:

- Vital signs: Resting heart rate, semi-supine systolic/diastolic blood pressure, respiratory rate and temperature
- Clinical laboratory measurements (e.g., biochemistry, hematology, coagulation and urinalysis)
- Resting ECG measurements (measured after participant is semi-supine for at least 3 minutes).
- At each visit, participants will be asked about concomitant medications/therapy and will be instructed to volunteer any information regarding AEs and SAEs that he/she may have experienced. Any known untoward event that occurs beyond the AE reporting period that the PI considers an SAE possibly related to study treatment will be reported as an SAE.
- Injection site reactions: Injection site reactions will be defined and graded as mild, moderate or severe (based on clinical findings). ISRs will be photographed at time of reporting and at time of resolution.
- 90-day post-EOS pregnancy follow up call.

Immunologic Assessments (limited number of HBV patients 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 assessments (CHB patients only)
Virology assessments will be performed at specified time points per the Schedule of Assessments and will include the following:

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

Immunogenicity:
For Cohorts 1b, 1c, 2b, 3b, 4b, 5b, and 6-12 blood samples for the anti-drug antibodies test will be collected at screening, Day 57 and Day 113 or at the end of study visit.

Pharmacokinetics (NHVs only and limited PK in Cohort 12):
Blood samples will be collected from each subject for pharmacokinetic analysis after dose 1 (Cohorts 1-5) per the Schedule of Assessments and for Cohort 12 patients per the Schedule of Assessments.

Genetic Testing (CHBs only):
If subject consents to genetic testing while actively participating in the study, one whole blood sample will be

collected on Day 1 or any time thereafter for SNP analysis for IFN response genes.

Cytokines:
Blood samples will be collected from each NHV participant for cytokine analysis per the Schedule of Assessments. The resultant serum will be analyzed for the following cytokine panel A: IL-6, MCP-1, TNF-alpha, IL-8, IL-1beta, IFN alpha, IL-10, IL-12 (p40), IL-12 (p70), and Mip-1alpha. CHB patients will have cytokine panel B (TNF alpha, IFN gamma, CXCL-9, and CXCL-10) measured as per Schedule of Assessments. In Cohorts 1-5 (Panel A), initially the 0 (pre-) and 2-hour post-dose samples will be analyzed, with the remaining samples analyzed only if a change from pre-dose baseline is observed at 2 hours.

Complement:
Blood samples will be collected from each NHV (Cohorts 1-5) participant during the study for Complement analysis after dose 1 (all cohorts). Two blood samples will be collected at each collection time. One sample will be processed to produce serum for complement CH50 analysis, and one sample will be processed to produce plasma, which will be analyzed to determine the level of split products Bb, C5a, C4a, and C3a. Initially the 0 (pre-) and 2-hour post-dose samples will be analyzed, with the remaining samples analyzed only if a change from pre-dose baseline is observed at 2 hours.

Excretion and Metabolism:

Seven blood samples will be collected from each subject for metabolic analysis after dose 1 (Cohorts 2-5) per the Schedule of Assessments. Samples will be frozen at -80ºC for analysis outside of this study.

Urine collections will be performed after dosing per the Schedule of Assessments.

Data Analysis:

Two separate data analyses will be performed, one for all subjects through EOS (Day 29 for NHVs and Day 113 for CHB patients), and one additional and separate analysis for CHB patients who consent to the additional follow up through Day 337 (Cohort 12 only) or Day 393. Separate analyses including and excluding Cohort 12 may also be completed.

Screening, Compliance, Tolerability and Safety Data:
In general, safety analyses will be performed and the results summarized by cohort. Post-treatment safety assessments will be compared with measurements recorded at baseline. Treatment emergent AEs will be summarized using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) by System Organ Class (SOC) and Preferred Term (PT). The incidence and frequency of AEs, SAEs, related AEs, related SAEs, and AEs leading to discontinuation, will be summarized by cohort per SOC, PT, and severity. All Adverse Events will also be presented in listings. The duration of AEs will be determined and included in listings, along with the action taken and outcome. The incidence of laboratory abnormalities will be assessed using descriptive summary statistics and shift tables. Vital sign measurements will be summarized at each scheduled time point using descriptive statistics. Abnormal physical examination findings will be summarized by time point and presented in subject listings. ECG parameters, changes from baseline, and qualitative assessments will be summarized. Pregnancy and FSH test results will be listed separately by time point.

Safety population: All participants (NHV and CHB patients) that received at least one dose of ARO-HBV or JNJ-6379.

Unless otherwise specified, for data analysis purposes baseline will be defined as pre-dose on Day 1.

Immunology Assessments (limited number of CHB patients in New Zealand only)
Immunology parameters will be summarized by cohort for the following:

- Changes in profile from pre-dose to post-dose time points for: 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.
- Changes from pre-dose to post-dose time points for: HBV antigen specific T cell response (including

HBcAg, HBsAg). To be conducted if scientifically feasible.

Virology assessments (CHB patients only)
Virologic parameters will be summarized by cohort for the following:

- Quantitative HBsAg (qHBsAg: Log change from baseline to nadir and duration of response from nadir back to approximately 20% of baseline or EOS
- Percent of patients with loss of HBsAg (defined as HBsAg < 0.05 IU/mL) at EOS and time to occurrence (Kaplan Meier)
- Percent of patients with anti-HBS seroconversion at EOS and time to occurrence (Kaplan Meier).
- Change in Anti-HBs (quantitative) over time
- Quantitative HBV DNA (when quantifiable at baseline): Log change from baseline to EOS
- Quantitative HBV RNA: Log change from baseline to nadir and duration of response from baseline to EOS (if scientifically feasible)
- Quantitative HBcrAg: Log change from baseline to nadir and duration of response from baseline to EOS
- Quantitative HBeAg (where applicable): Log change from baseline to nadir and duration of response from baseline to EOS
- Emergence of HBV mutations (sequencing of ARO-HBV target site, Core/pre-core, HBsAg epitope, any other mutations by deep sequencing)

Descriptive statistics of virologic parameters will include mean, median, count, SD, minimum, and maximum. Additional details will be provided in the statistical analysis plan.

Separate analysis will 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.

Pharmacokinetics (NHV subjects and limited PK in Cohort 12):
Plasma concentrations of ARO-HBV product constituents will be used to calculate the following PK parameters: maximum observed plasma concentration (C_{max}), area under the plasma concentration time curve (AUC) from time 0 to 24 hours (AUC_{0-24}), AUC from time 0 extrapolated to infinity (AUC_{inf}), and terminal elimination half-life ($t_{½}$). Pharmacokinetic parameters will be determined using non-compartmental methods. Descriptive statistics of PK parameters will include mean, standard deviation (SD), coefficient of variation, median, minimum, and maximum. PK results will be analyzed for dose proportionality, and sex differences.

Plasma concentrations of ARO-HBV, NUC and JNJ-6379 will be measured at a single post-dose time point in Cohort 12 only.

PK population: All NHV subjects and Cohort 12 patients that received at least one dose of active study treatment (ARO-HBV).

Genetic Testing (CHB patients only):
Evaluate mean and maximum nadir HBsAg decline in relationship to patient variants in interferon response genes (e.g. IL28B).

Pharmacodynamics:
Pharmacodynamic results, percent change, and duration of response from baseline to 24 hours post-dose will be analyzed and summarized by cohort and number of doses administered.

Immunogenicity (Anti-Drug Antibodies):
Changes from assay negative to positive will be summarized by dose and number of doses administered. Descriptive statistics of immunogenicity parameters will include mean, SD, minimum, and maximum.

Additional details will be provided in the statistical analysis plan.

Table 1.1: Cohorts 1 through 5 (Healthy Volunteers):

Assessment	Screen (Days -60 to -1)	Day -1 Confine		Day 1	Day 2 Discharge	Day 3	Day 8	Day 15 (± 2)	Day 29 (± 2) EOS	Early Termination
Informed Consent	X		RANDOMIZE							
Eligibility Criteria	X	X								
Body Mass Index	X									
Demographics	X									
Medical History	X	X*								
Drug Screen	X									
Hepatitis/HIV Serology Screen	X									
Physical Exam[1]	X	X*			X[1]	X[1]	X[1]	X[1]	X	X[1]
FSH	X[11]									
Pregnancy test	X[8]			X[12]					X	X
ECG	X			X[2]	X		X		X	X
Vital Signs (BP, temp, RR, heart rate)	X			X[6]	X	X	X	X	X	X
Clinical Labs (heme, coag, chem, UA)	X			X[10]	X	X	X	X	X	X
PK[3]				X	X	X				
Metabolite ID [13]				X	X	X				
Urine collection for excretion and metabolite ID [14]				X	X		X	X	X	
Cytokines (Panel A)[4]				X	X					
Complement[5]				X	X					
Concomitant Meds/Therapies	X	X		X	X	X	X	X	X	X
Meals[7]				X	X					
Adverse Events[9]		X		X	X	X	X	X	X	X
Study Treatment				X						

* Repeat if > 2 weeks from Screening

1. Symptom-directed PEs to be performed by visit as necessary.
2. ECGs: Measured pre-dose and at 1 and 2 hours post-dose; more frequently per hour if necessary. Performed prior to other invasive procedures.
3. PK: (plasma) Blood samples collected 0 (pre-dose), 15 min, 0.5, 1, 2, 3, 6, 24 & 48 hours post-dose
4. Cytokines Panel A only in NHVs): (whole blood). Serial venous blood samples collected 0 (pre-dose) 0.5, 2, 6, & 24 hours after dosing.
5. Complement: (serum and plasma). 2 venous blood samples collected 0 (pre-dose), 0.5, 2, 6 & 24 hours after dosing.
6. Vitals: Measured pre-dose and at 5 min, 0.5, 1, 2, 3, and 6 hours post-dose.
7. Meals: Lunch, Dinner, and snack on Day 1 at approximately 2 hours, 6 hours and 8 hours post-dose. Breakfast optional on Day
8. Urine pregnancy test for females of childbearing potential only.
9. AE/SAE data capture begins from time of informed consent.
10. Clinical Chemistry, Hematology, Coagulation and Urinalysis pre-dose and at 6 hours post-dose.
11. Performed for females not of childbearing potential to confirm postmenopausal status
12. Pre-dose
13. **Cohorts 2-5 only** Metabolite ID: Blood samples collected 0 (pre-dose), 0.5, 1, 3, 6, 24 & 48 hours post-dose

14. **Cohorts 2-5 only:** Collect spot urine samples on days 1 (pre-dose), 8, 15, and 29 and aliquot into 3 aliquots and freeze and store at -80C. Collect all urine from 0-6 hours and 6-24 hours after dosing. Aliquot each collection into three aliquots and freeze and store at -80C. Discard the remainder of the collected urine.

Table 1.2: Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 8 and 9 (CHB patients, three Q28 day doses)

Assessment	Screen (Days -60 to -1)		Day 1	Day 2	Day 8	Day 15 (± 2)	Day 29, 57 (± 2)	Day 43, 71 (± 2)	Day 85 (± 2)	Day 113 (± 2) EOS	Early Termination
Informed Consent	X	RANDOMIZE									
Eligibility Criteria	X		X[9]								
Body Mass Index	X										
Demographics	X										
Medical History	X		X*								
Drug Screen	X										
Hepatitis/HIV Serology Screen	X										
Physical Exam[1]	X		X*	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X	X[1]
FSH	X[8]										
Pregnancy test	X[5]		X[5]				X[5]			X	X
ECG	X		X[2]				X[2]			X	X
Vital Signs (BP, temp, RR, heart rate)	X		X[4]	X	X	X	X[4]	X	X	X	X
Hepatic Fibrosis Measure (FibroScan®)	X										
Clinical Labs (heme, coag, chem, UA)	X		X[7]	X	X	X	X[7]	X	X	X	X
HBeAg qualitative	X										
Quantitative HBsAg, HBcrAg, HBeAg (e+ only) HBV DNA, HBV RNA	X		X		X	X	X	X	X	X	X
Quantitative anti-HBs, qualitative anti-HBe (e+ only)			X		X	X	X	X	X	X	X
HBV genotyping	X										
HBV sequencing	X									X	X
Cytokines (Panel B) TNF alpha, IFN gamma, CXCL-9, and CXCL-10[3]			X		X	X	X	X	X	X	X
Cellular Immunology[10]			X					X		X	
Concomitant Meds/Therapies	X		X	X	X	X	X	X	X	X	X
Adverse Events[6]			X	X	X	X	X	X	X	X	X

Study Treatment			X				X				
Anti-drug antibodies[9]	X						X[9]			X	X
Start NUCs (naïve patients only)			X								
SNP Analysis			X[11]								

* Repeat if > 2 weeks from Screening
1. Symptom-directed PEs to be performed by visit as necessary.
2. ECGs: Measured pre-dose and at 1 and 2 hours post-dose; more frequently per hour if necessary. Performed prior to other invasive procedures.
3. Cytokines Panel B: (whole blood). Venous blood samples collected pre-dose on dosing days then as indicated. Collected samples will only be analyzed at discretion of and with notification by Sponsor.
4. Vitals: Measured pre-dose and at 5 min, 0.5, 1, and 2 hours post-dose.
5. Urine pregnancy test for females of childbearing potential only. Complete pre-dose on dosing days.
6. AE/SAE data capture begins from time of informed consent.
7. Clinical Chemistry, Hematology, Coagulation and Urinalysis pre-dose only on dosing days.
8. Performed for females not of childbearing potential to confirm postmenopausal status.
9. Anti-drug antibodies collected pre-dose, Day 57 and on Day 113 or EOS.
10. 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. Cellular immunology studies to be conducted on **Days 1 (pre-dose), 43 and 113 in New Zealand only.**
11. If genetic testing consent is obtained, one-time whole blood sample collection will be on Day 1 or any time thereafter for SNP analysis for IFN response genes.

Table 1.3 Cohort 6 (CHB 3 doses Q14 days)

Assessment	**Screen (Days -60 to -1)**		**Day 1**	**Day 2**	**Day 8**	**Day 15 (± 2)**	**Day 29, (± 2)**	**Day 43, 57, 71, 85, 113 (EOS) (± 2)**	**Early Termination**
Informed Consent	X								
Eligibility Criteria	X		X[9]						
Body Mass Index	X								
Demographics	X								
Medical History	X		X*						
Drug Screen	X								
Hepatitis/HIV Serology Screen	X								
Physical Exam[1]	X	**RANDOMIZE**	X*	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
FSH	X[8]								
Pregnancy test	X[5]		X[5]			X[5]	X[5]	X[11]	X
ECG	X		X[2]			X[2]	X[2]		X
Vital Signs (BP, temp, RR, heart rate)	X		X[4]	X	X	X[4]	X[4]	X	X
Hepatic Fibrosis Measure (FibroScan®)	X								
Clinical Labs (heme, coag, chem, UA)	X		X[7]	X	X	X	X[7]	X	X
HBeAg qualitative	X								

Quantitative HbsAg, HbcrAg, HBV DNA, HBV RNA, HbeAg (e+ only	X		X		X	X	X	X	X
Quantitative anti-HBs, qualitative anti-Hbe (e+ only)			X		X	X	X	X	X
HBV genotyping	X								
HBV sequencing	X								X
Cytokines (Panel B) – TNF alpha, IFN gamma, CXCL-9, and CXCL-10[3]			X		X	X	X	X	X
Cellular Immunology[10]			X					X[10]	
Concomitant Meds/Therapies	X		X	X	X	X	X	X	X
Adverse Events[6]			X	X	X	X	X	X	X
Study Treatment			X			X	X		
Anti-drug antibodies[9]	X							X[9]	X
Start NUCs (naïve patients only)			X						
SNP Analysis			X[12]						

* Repeat if > 2 weeks from Screening

1. Symptom-directed PEs to be performed by visit as necessary.
2. ECGs: Measured pre-dose and at 1 and 2 hours post-dose; more frequently per hour if necessary. Performed prior to other invasive procedures.
3. Cytokines Panel B: (whole blood). Venous blood samples collected pre-dose on dosing days then as indicated. Collected samples will only be analyzed at discretion of and with notification by Sponsor.
4. Vitals: Measured pre-dose and at 5 min, 0.5, 1, and 2 hours post-dose.
5. Urine pregnancy test for females of childbearing potential only. Pre-dose on dosing days.
6. AE/SAE data capture begins from time of informed consent.
7. Clinical Chemistry, Hematology, Coagulation and Urinalysis pre-dose
8. Performed for females not of childbearing potential to confirm postmenopausal status
9. Anti-drug antibodies collected pre-dose, Day 57 and on Day 113 or EOS.
10. 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. Cellular immunology studies to be conducted on **Days 1 (pre-dose), 43 and 113 in New Zealand only.**
11. Pregnancy test on Day 113.
12. If genetic testing consent is obtained, one-time whole blood sample collection will be on Day 1 or any time thereafter for SNP analysis for IFN response genes.

Table 1.4 Cohort 7, 10 and 11 (CHB three weekly doses)

Assessment	Screen (Days -60 to -1)		Day 1	Day 2	Day 8	Day 15 (± 2)	Day 29 (± 2)	Day 43, 57 (± 2)	Day 71, 85 (± 2)	Day 113 (± 2) (EOS)	Early Termination
Informed Consent	X										
Eligibility Criteria	X		X								
Body Mass Index	X										
Demographics	X										
Medical History	X		X*								
Drug Screen	X										
Hepatitis/HIV Serology Screen	X										
Physical Exam[1]	X		X*	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
FSH	X[8]										
Pregnancy test	X[5]		X[5]		X[5]	X[5]				X	X
ECG	X		X[2]		X[2]	X[2]					X
Vital Signs (BP, temp, RR, heart rate)	X		X[4]	X	X[4]	X[4]	X	X	X	X	X
Hepatic Fibrosis Measure (FibroScan®)	X										
Clinical Labs (heme, coag, chem, UA)	X		X[7]	X	X[7]	X[7]	X	X	X	X	X
HBeAg qualitative	X										
Quantitative HbsAg, HbcrAg, HBV DNA, HBV RNA, HbeAg (e+ only)	X		X		X	X	X	X	X	X	X
Quantitative anti-HBs, qualitative anti-Hbe (e+ only)			X		X	X	X	X	X	X	X
HBV genotyping	X										
HBV sequencing	X									X	X
Cytokines (Panel B) – TNF alpha, IFN gamma, CXCL-9, and CXCL-10[3]			X		X	X	X	X	X	X	X
Cellular Immunology[10]			X					X		X	
Concomitant Meds/Therapies	X		X	X	X	X	X	X	X	X	X
Adverse Events[6]			X	X	X	X	X	X	X	X	X
Study Treatment			X		X	X					
Anti-drug antibodies[9]	X							X[9]		X	X
Start NUCs (naïve			X								

RANDOMIZE

patients only)											
SNP Analysis			X[11]								

* Repeat if > 2 weeks from Screening
1. Symptom-directed PEs to be performed by visit as necessary.
2. ECGs: Measured pre-dose and at 1 and 2 hours post-dose; more frequently per hour if necessary. Performed prior to other invasive procedures.
3. Cytokines Panel B: (whole blood). Venous blood samples collected pre-dose on dosing days then as indicated. Collected samples will only be analyzed at discretion of and with notification by Sponsor.
4. Vitals: Measured pre-dose and at 5 min, 0.5, 1, and 2hours post-dose.
5. Urine pregnancy test for females of childbearing potential only. Pre-dose on dosing days.
6. AE/SAE data capture begins from time of informed consent.
7. Clinical Chemistry, Hematology, Coagulation and Urinalysis pre-dose.
8. Performed for females not of childbearing potential to confirm postmenopausal status.
9. Anti-drug antibodies collected pre-dose, Day 57 and on Day 113 or EOS.
10. 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. Cellular immunology studies to be conducted on **Days 1 (pre-dose), 43 and 113 in New Zealand only.**
11. If genetic testing consent is obtained, one-time whole blood sample collection will be on Day 1 or any time thereafter for SNP analysis for IFN response genes.

Table 1.5: Additional Follow-Up Schedule of Assessments (All CHB Cohorts)

Assessment	Day 169 (±5)	Day 225 (±5)	Day 281 (±5)	Day 337 (±5)[2]	Day 393 (±5)	Early Termination
Physical Exam[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
Vital Signs (BP, temp, RR, heart rate)	X	X	X	X	X	X
Clinical Labs (heme, coag, chem, UA)	X	X	X	X	X	X
Quantitative HBsAg, HBcrAg, HBeAg (e+ only) HBV DNA, HBV RNA	X	X	X	X	X	X
Quantitative anti-HBs, qualitative anti-HBe (e+ only)	X	X	X	X	X	X
HBV genotyping (if technically feasible)	X	X	X	X	X	X
HBV sequencing (if technically feasible)	X	X	X	X	X	X
Concomitant Meds/Therapies	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X

1. Symptom-directed PEs to be performed by visit as necessary.
2. Only Cohort 12 patients will require follow-up until the Day 337 (±5 days) visit.

Table 1.6: Cohort 12 (CHB patients, ARO-HBV three Q28 day doses + JNJ-6379 daily)

Assessment	Screen (Days -60 to -1)		Day 1	Day 2	Day 8	Day 15 (± 2)	Day 29, 57 (± 2)	Day 43, 71 (± 2)	Day 85 (± 2)	Day 113 (± 2) EOS	Early Termination
Informed Consent	X	CONFIRM ELIGIBILITY									
Eligibility Criteria	X		X[9]								
Body Mass Index	X										
Demographics	X										
Medical History	X		X*								
Drug Screen	X										
Hepatitis/HIV Serology Screen	X										
Physical Exam[1]	X		X*	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X	X[1]
FSH	X[8]										
Pregnancy test	X[5]		X[5]				X[5]			X	X
ECG	X		X[2]				X[2]			X	X
Drug plasma concentrations (ARO-HBV, JNJ-6379, NUC)			X[13]				X[13]				
Vital Signs (BP, temp, RR, heart rate)	X		X[4]	X	X	X	X[4]	X	X	X	X
Hepatic Fibrosis Measure (FibroScan®)	X										
Clinical Labs (heme, coag, chem, UA, amylase, lipase)	X		X[7]	X	X	X	X[7]	X	X	X	X
HBeAg qualitative	X										
Quantitative HBsAg, HBcrAg, HBeAg (e+ only) HBV DNA, HBV RNA	X		X		X	X	X	X	X	X	X
Quantitative anti-HBs, qualitative anti-HBe (e+ only)			X		X	X	X	X	X	X	X
HBV genotyping	X										
HBV sequencing	X									X	X
Cytokines (Panel B) TNF alpha, IFN gamma, CXCL-9, and CXCL-10[3]			X		X	X	X	X	X	X	X
Concomitant Meds/Therapies	X		X	X	X	X	X	X	X	X	X
Adverse Events[6]			X	X	X	X	X	X	X	X	X

ARO-HBV Study Treatment			X				X				
Anti-drug antibodies[9]	X						X[9]			X	X
Start NUCs (naïve patients only)			X								
SNP Analysis			X[10]								
JNJ-6379 Study Treatment Begin			X								
JNJ-6379 Study Treatment End									X		
JNJ-6379 Treatment Dispensation[11]			X	X	X	X	X	X			
JNJ-6379 Treatment Reconciliation[12]				X	X	X	X	X	X		X

* Repeat if > 2 weeks from Screening
1. Symptom-directed PEs to be performed by visit as necessary.
2. ECGs: Measured pre-dose and at 1 and 2 hours post-dose; more frequently per hour if necessary. Performed prior to other invasive procedures.
3. Cytokines Panel B: (whole blood). Venous blood samples collected pre-dose on dosing days then as indicated. Collected samples will only be analyzed at discretion of and with notification by Sponsor.
4. Vitals: Measured pre-dose and at 5 min, 0.5, 1, and 2 hours post-dose.
5. Urine pregnancy test for females of childbearing potential only. Complete pre-dose on dosing days.
6. AE/SAE data capture begins from time of informed consent.
7. Clinical Chemistry, Hematology, Coagulation and Urinalysis pre-dose only on dosing days.
8. Performed for females not of childbearing potential to confirm postmenopausal status.
9. Anti-drug antibodies collected pre-dose, Day 57 and on Day 113 or EOS.
10. If genetic testing consent is obtained, one-time whole blood sample collection will be on Day 1 or any time thereafter for SNP analysis for IFN response genes.
11. JNJ-6379 bottles (both 25 and 100 mg) should be supplied to the patient for continuous daily dosing until the next scheduled visit. On Day 1 prior to JNJ-6379 initial treatment, subject should receive dosing administration training according to the Pharmacy Manual and will be provided a patient diary for daily dose recording.
12. Patients are instructed to bring all JNJ-6379 bottles at each visit to be reconciled against the patient diary.
13. Collect plasma two-hours post-ARO-HBV dose to measure plasma concentration of ARO-HBV, JNJ-6379 and NUC (ETV or TDF).

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2 STUDY INFORMATION AND SIGNATURES

Investigator's Statement:

I have read and understood the information in this protocol and agree to conduct the trial according to the protocol (subject to any amendments) and in accordance with the principles of Good Clinical Practice. I have read and agree to comply with the Investigator obligations stated in this protocol. Any changes in procedure will only be made if necessary to protect the safety, rights or welfare of participants.

I agree to conduct in person or to supervise the trial.

I agree to ensure that all that assist me in the conduct of the study are aware of their obligations.

Principal Investigator:

_____ _____
Signature Date

_____
Printed Name

3 LIST OF ABBREVIATIONS AND TERMS

AE	Adverse Event
ALT	Alanine aminotransferase
API	Active Pharmaceutical Ingredient
AST	aspartate transaminase
ARO-HBVAPI Solution for Injection	Vial containing sterile, liquid API
ARO-HBV	Clinical drug product solution ready for SC injection
AUC	Area Under Curve
B cell	Lymphocyte not processed by the thymus and producing antibodies
BMI	Body Mass Index
BP	Blood Pressure
cGMP	current Good Manufacturing Practice
CAM	Capsid Assembly Modulator
cccDNA	Covalently Closed Circular DNA
CDM	Carboxy Dimethyl Maleic anhydride
CHB	Chronic hepatitis B
C_{max}	Concentration maximum (peak)
CRF	Case Report Form
CRO	Contract Research Organization
CTN	Clinical Trial Notification
CVA	Cerebrovascular Accident
DSC	Data Safety Committee
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GLP	Good Laboratory Practice
HBcAg	HBV core antigen
HBcrAg	HBV core related antigen
HBeAg	HBV E (envelope) antigen
HBsAg	HBV S (surface) antigen
HBV	Hepatitis B virus
HDEC	Health and Disabilities Ethics Committee
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IFN	Interferon
IFNalpha	Interferon alpha
IL-6	Interleukin-6
IL-8	Interleukin-8
IL-1beta	Interleukin-1beta
IL-10	Interleukin-10
IL-12p40	Interleukin-12p40

IL-12p70	Interleukin-12p70
JNJ-6379	JNJ-56136379, a capsid assembly modulator (CAM)
MCP-1	Monocyte chemoattractant protein-1
MDMA	3,4-Methylenedioxymethamphetamine
MLP	Melittin-like peptide
MLP-(CDM-NAG)	MLP chemically modified with CDM-NAG
mmHg	millimeters of mercury
NAG	N-acetyl galactosamine
NHV	Normal healthy volunteer
NK cell	Natural Killer Cell
NUC	Nucleos(t)ide inhibitors
NYHA	New York Heart Association
OTC	Over-the-counter
PD	Pharmacodynamic
PBO	Placebo
PK	Pharmacokinetic
PR	PR interval - measured from the beginning of the P wave to the beginning of the QRS complex
PT	Prothrombin time
QRS	QRS duration (complex) - a structure on the ECG that corresponds to the depolarization of the ventricles
QT	QT interval - a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTc	QT interval corrected for heart rate
RNAi	RNA interference
SAD	Single Ascending Dose
SAE	Serious Adverse Event
siRNA	Short interfering RNA oligonucleotides
SNP	Single Nucleotide Polymorphism
T cell	Lymphocyte produced or processed by thymus gland
TIA	Transient Ischemic Attack
TNF alpha	Tumor Necrosis Factor
UA	Urinalysis
ULN	Upper Limit of Normal
UNA	Unlocked Nucleobase Analog containing RNAi trigger molecule

4 INTRODUCTION

4.1 Background Information

Globally, an estimated 360 million people are chronically infected with hepatitis B virus (HBV) and up to 1 million a year die because of hepatocellular carcinoma, cirrhosis of the liver, or liver failure caused by HBV. When drug treatment is deemed appropriate, the current treatment for chronic HBV infection is a daily oral dose of nucleotide/nucleoside analogs (NUC) (depending on renal function) or a regimen of interferon injections 1 to 7 times weekly for a year or longer. Nucleotide/nucleoside analogs effectively reduce viral deoxyribonucleic acid (DNA) production by inhibiting the viral polymerase, but patients can expect to take these antivirals for life because viral replication quickly rebounds upon cessation of treatment in more than half of patients who are HBeAg (+) at baseline and more than 80% in patients who are HBeAg (-) with Chronic Hepatitis B (CHB). A more desirable outcome would be HBV surface antigen (HBsAg) loss with or without S-antigen seroconversion, which is an effective antibody response to the envelope protein that is also called HBsAg. S-antigen loss (with or without seroconversion to Anti-HBsAg) represents immune mediated viral clearance and is considered a functional cure, if HBV DNA is also undetectable. Nucleotide/nucleoside analog treatment has very little effect, if any on the level of HBsAg that is produced, nor on production of the other viral proteins. The highly abundant HBsAg produced in the infected patient, as high as 10^{12} particles/mL of blood, is believed to counteract virus-neutralizing Anti-HBsAg antibodies, allowing the virus to spread cell to cell and to be maintained in the host. The large quantities of secreted HBsAg also lead to T-cell exhaustion and anergy. Thus, even on NUC therapy, the rate of HBsAg loss in CHB patients is only about 1% annually, even after many years of NUC treatment. The rate of HBsAg clearance is similarly low from interferon treatment, and these therapeutics cause significant side effects, including severe flu-like symptoms, bone marrow suppression, and autoimmune disorders. The lack of satisfactory therapeutics for treatment of chronic HBV infection highlights the need for a different approach to this disease.

Arrowhead Pharmaceuticals, Inc. has developed a product candidate, ARO-HBV to treat chronic HBV infection. ARO-HBV is designed to produce interference with HBV ribonucleic acid (RNA) translation into viral proteins, and also to knock down reverse transcription of HBV RNA into viral DNA, necessary for production of infectious viral particles. This novel product should allow testing of the hypothesis that significantly reducing circulating viral proteins, principally HBsAg, will allow for reconstitution of an effective host immune response and ultimately seroclearance. Seroclearance in

HBV patients, whether spontaneous or drug-induced, is associated with persistent absence of viremia and a reversal of hepatic inflammation off therapy.

ARO-HBV is a RNA interference (RNAi) based therapy. RNAi is a naturally-occurring phenomenon by which short interfering RNA oligonucleotides (siRNAs) trigger a sequence-specific down-modulation of gene expression. By delivering the siRNAs targeting HBV sequences to hepatocytes, it is possible to knock down expression of viral RNAs. This results in a reduction in viral load and viral proteins that result in disease and are believed to hinder the immune system's ability to eliminate the virus. Reawakening the immune system could allow a chronically infected patient to mount an effective antiviral response, resulting in a functional cure.

JNJ-6379 is a capsid assembly modulator (CAM) being developed for the treatment of hepatitis B infection. JNJ-6379 binds to the HBV core protein and interferes with the viral capsid assembly process and resulting in the formation of empty viral capsids devoid of HBV-DNA. JNJ-6379 also acts at an early stage of the viral life cycle by inhibiting the de novo formation of cccDNA. It is thought that by using an siRNA approach to silence production of viral antigen in combination with NUCs to inhibit viral replication and JNJ-6379 which inhibits capsid assembly and cccDNA formation the response to treatment and potentially the rate of functional cure could be enhanced.

4.2 ARO-HBV and JNJ-6379 Pre-clinical Pharmacology and Toxicology Studies

ARO-HBV has been studied in rats and in monkeys in single and multi-dose toxicity studies up to doses of 300 mg/kg. Further details regarding the nonclinical safety results are provided in the Investigator's Brochure. The human JNJ-6379 exposure at 28 days of 250 mg oral dose and the observed NOAEL in 6 month rat and 9 month dog exposure studies are described in Table 1. Details regarding nonclinical safety results using JNJ-6379 are provided in the JNJ-56136379 Investigator's Brochure.

Table 1.

	Sex	NOAEL (mg eq./kg/day)	C_{max} (ng/mL)	AUC_{0-24h} (ng.h/mL)	Ratio Total Concentration		Ratio Concentration Corrected for Plasma Protein Binding[b]	
					C_{max} A/H Ratio	AUC_{0-24h} A/H Ratio	C_{max} A/H Ratio	AUC_{0-24h} A/H Ratio
Human exposure[a]			13,798	265,384	-	-		
	M	30	7,540	93,100	0.6	0.4	0.9	0.6
6M rat	M	100[c]	13,600[d]	180,000[d]	1.0	0.7	1.7	1.1
	F	100	19,900	233,000	1.4	0.9	2.4	1.5
9M dog	M	25	30,000	606,000	2.2	2.3	3.3	3.5
	F	12.5	22,500	383,000	1.6	1.4	2.5	2.2

250 mg JNJ-56136379 once daily for 28 days (Study 56136379HPB1001).

[b] Ratio of the total C_{max} or AUC corrected for species difference in plasma unbound fraction. Calculation: [animal C_{max} or AUC_{0-24h} x animal free fraction] / [human C_{max} or AUC_{0-24h} x human free fraction].

[c] A dose of 100 mg eq./kg/day in male rats is considered to be above the NOAEL due to kidney findings in male rats, which are likely not relevant for human.

[d] The plasma C_{max} of 13,600 ng/mL and AUC_{0-24h} of 180,000 ng h/mL in male rats at 100 mg eq./kg/day corresponds to an unbound C_{max} of 1,754 ng/mL and AUC_{0-24h} of 23,220 ng h/mL (fraction unbound rat plasma=12.9%). This unbound plasma exposure will be achieved in humans at a total plasma C_{max} of 22,784 ng/ml and AUC_{0-24h} of 301,558 ng.h/mL (fraction unbound in human plasma=7.7%).

4.3 ARO-HBV Clinical Studies

Sponsor has conducted extensive clinical evaluation of other anti-HBV compounds using an siRNA mechanism including ARC-520 Injection and ARC-521 Injection. The critical difference between ARO-HBV and ARC-520/521 is that ARO-HBV is a conjugate of siRNA to a hepatocyte specific targeting ligand, N-acetyl-galactosamine which can be administered subcutaneously. ARC-520/521 used a separate delivery excipient (ARC-EX1) which was co-injected intravenously with the siRNA API. ARO-HBV requires no delivery excipient. ARC-EX1 is no longer being developed. In a Phase 1a/b study of ARC-521 conducted using escalating single doses in healthy volunteers up to a dose of 6 mg/kg and using a multiple escalating dose regimen in HBV patients, ARC-521 was well tolerated and demonstrated anti-viral activity (See Investigator Brochure for details). Thirty-six NHVs and 11 HBV patients received ARC-521 in this study.

Similarly, ARC-520 has been evaluated in a Phase 1, first in human, single ascending dose study in healthy subjects (Heparc-1001). Fifty-four subjects were successfully dosed in the Phase 1 study with 36 having received active drug. All dosing cohorts were completed without dose adjustment. There were no serious AEs or drug related AEs rated as severe, no discontinuations due to adverse events

(AEs) and a modest occurrence rate of AEs. A similar single dose healthy volunteer study (Heparc-1002 study) was conducted in 40 subjects using doses of either 4 mg/kg, 5 mg/kg or 6 mg/kg with similar favorable safety findings. Overall, it was concluded that a single IV administration of ARC-520 appeared to be safe and well-tolerated up to a single dose of 6.0 mg/kg in a healthy volunteer population. ARC-520 has also been evaluated in a Phase 2a, single ascending dose study in HBeAg negative and HBeAg positive, chronic hepatitis B patients to evaluate safety and tolerability as well as depth and duration of HBsAg knockdown (Heparc-2001) which was extended into a multi-dose study in select HBV patients. In the Heparc-2001 study, patients were randomized to receive a single dose of PBO (0.9% Normal Saline) or ARC-520 in cohorts of four escalating doses (1, 2, 3 and 4 mg/kg). A total of 58 patients were enrolled of which 48 received active treatment at doses between 1 and 4 mg/kg and 10 received PBO. In Heparc-2001 were no premature discontinuations, no serious or severe adverse events, no clinically relevant changes in physical exam, ECG or vital signs and no dose-limiting toxicities. An interim analysis of pharmacodynamic results showed that ARC-520 can produce deep (up to 1.9 log) and sustained reductions of multiple antigens (HBsAg, HBeAg, and HBcrAg) derived from cccDNA. Reductions in HBsAg in NUC experienced and HBeAg negative patients were less pronounced, consistent with lower levels of cccDNA derived mRNA transcripts in these patients. Additional multiple dose studies of ARC-520 including the Heparc-2002, 2003, 2004, 2007 and 2008 studies (which in aggregate exposed a total of 264 HBV patients to various doses of ARC-520) all demonstrated similar safety profiles. Across all clinical studies, both ARC-520 and ARC-521 were safe and well tolerated in a healthy volunteer and HBV patient populations.

The ARC-520 and ARC-521 programs were terminated early due to toxicity findings related to high doses of ARC-EX1 in a non-human primate study. Non-human primate toxicity findings were specific to the use of the ARC-EX1 excipient which is not used with ARO-HBV. Toxicity findings were not related to the siRNA API.

The potent reductions in viral antigens seen using ARC-520/521 and as described in the Investigator Brochure provides strong proof of concept for testing of next generation siRNA compounds like ARO-HBV in HBV patients. Additionally, the human safety profile seen with ARC-520/521 across several multi-dose clinical studies in HBV patients and two SAD healthy volunteer studies is encouraging. Updated interim clinical safety and pharmacologic activity data for ARO-HBV from the ongoing AROHBV1001 study are presented in the Investigator's Brochure 2nd Edition. These data indicate that ARO-HBV has been well tolerated and has demonstrated promising pharmacologic activity against the HBV virus based on reductions of viral antigens and HBV DNA. Pharmacodynamic data to date

justify the further clinical development of ARO-HBV with the goal of developing finite regimens aimed at HBsAg clearance in patients with chronic HBV.

4.4 JNJ-6379 Clinical Studies

Antiviral Activity

Interim data of the ongoing clinical study 56136379HPB1001 (Sessions 8 to 11), in CHB-infected subjects show that JNJ-6379 administration at doses of 25- to 250-mg leads to reduction in HBV DNA. A mean (±SD) reduction in plasma HBV DNA levels of 2.16 (0.49) log10 IU/mL (25 mg), 2.89 (0.48) log10 IU/mL (75 mg), 2.70 (0.53) log10 IU/mL (150 mg), and 2.70 (0.33) log10 IU/mL (250 mg) from baseline was observed at Day 29. In the 250-mg dosing group, 5 out of 12 subjects achieved HBV DNA levels below the LLOQ of the HBV DNA assay, while 3 out of 12 subjects in both the 75-mg and 150-mg dosing groups and none (out of 12) of the subjects in the 25-mg dosing group achieved this. A more pronounced and consistent decline in HBV DNA levels was observed across subjects in the 75-mg, 150-mg, and 250-mg group compared with the 25-mg group.

In line with HBV DNA levels, reductions in HBV RNA levels were observed with JNJ-56136379 treatment. Baseline levels of HBV RNA were generally low and sometimes undetectable, especially in the higher dose groups, limiting the HBV RNA decline observable in this study. No notable changes in HBsAg or HBeAg were observed.

Safety

Healthy Subjects

In a pooled analysis of 123 adult healthy subjects, 98 subjects received at least one dose of JNJ-6379. Eleven subjects did not complete their treatment: due to withdrawal by subject (such as withdrawal of consent or withdrawal due to personal reasons) (4 [3.3%] subjects), lost to follow-up (1 [0.8%] subject), other reasons (2 [1.6%] subjects) or due to adverse events (AEs) (4 [3.3%] subjects, see below).

There were no deaths and 2 subjects experienced a serious adverse event (SAE), both considered not related to JNJ-6379: one during the screening phase (spontaneous abortion; moderate) in study 5636379HPB1004, and the other (wrist fracture right; severe) in study 563679HPB1002, 24 days after the last single dose of JNJ-56136379. Apart from the severe wrist fracture, no severe AEs were reported. In most cases AEs were mild and not considered related to JNJ-56136379.

Two subjects in study 56136379HPB1001 Part 1, single dose escalation phase, discontinued from further dosing with JNJ-56136379 in subsequent sessions due to an AE. One subject in study 56136379HPB1001 Part 2, multiple dose phase, discontinued JNJ-6379 treatment after administration of JNJ-6379 150 mg bid for 2 days, followed by JNJ-6379 100 mg for 9 days due to the AEs abdominal pain lower and dizziness postural. These AEs were considered by the investigator of mild severity and possibly related to JNJ-6379 and resolved after discontinuation.

Overall, the most common treatment-emergent AEs, experienced by >10% of all subjects treated with JNJ-6379 was headache (27 [27.6%] subjects on JNJ-56136379 versus 3 [12.0%] subjects on placebo).

Most graded laboratory abnormalities were grade 1 or 2, except for a grade 3 amylase and grade 4 lipase elevation in 1 subject in study 56136379HPB1002 (both observed during follow-up), a grade 3 lipase elevation in another subject in study 56136379HPB1002 (observed when subject on treatment), and 2 grade 3 LDL cholesterol elevations in one subject each from study 56136379HPB1002 and study 56136379HPB1003 (both observed when subjects on treatment). Based on these cases, lipase and amylase have been identified as laboratory abnormalities of interest. The pooled data show that 5 (5.1%) and 6 (6.1%) subjects on JNJ-6379 had lipase and amylase elevations, respectively versus none on placebo.

CHB Infected Subjects

In the unblinded 25-250 mg sessions of Part 2 of study 56136379HPB1001 in CHB-infected subjects, no deaths were reported. No other SAEs, AEs leading to discontinuation or grade 4 AEs were observed in the 25, 75 and 250 mg treatment groups.

One subject in the JNJ-6379 150 mg treatment group experienced several grade 3 SAEs (idiopathic intracranial hypertension, headache, epilepsy, gliosis, brain edema, brain neoplasm, brain compression) 2 days after completing treatment with JNJ-6379. The subject was withdrawn from the study. All SAEs were considered not related to study drug with outcome unknown. Despite several attempts to reach the patient, the patient was lost to follow-up.

One subject experienced the grade 3 AE AST increased and grade 4 AE ALT increased during JNJ-6379 150 mg treatment. Both AEs were considered probably related to study drug, which was withdrawn, due to the protocol defined stopping criteria. The AEs were considered resolved after end of treatment. The subject also had the AEs liver tenderness (grade 1, possibly related, resolved before

end of treatment) and abdominal distension (grade 1, not related, resolved after end of treatment) for which study drug was withdrawn.

Other grade 3 AEs were reported for 1 subject during JNJ-56136379 25 mg treatment (amylase increased, possibly related, resolved before end of treatment), for 1 subject during JNJ-6379 75 mg treatment (ALT increased, possibly related, resolved after end of treatment) and 1 subject after JNJ-6379 150 mg treatment (AST increased, probably related, resolved).

The most frequently reported treatment-emergent AEs across all doses (>1 subject) on JNJ-6379 were headache (4 [11.8%] subjects on JNJ-6379 versus 6 [42.9%] subjects on placebo), nausea (2 [5.9%] subjects versus 0 subjects, respectively), dyspepsia (2 [5.9%] subjects versus 0 subjects, respectively), ALT increased (2 [5.9%] subjects versus 1 [7.1%] subject, respectively), amylase increased (2 [5.9%] subjects versus 0 subjects, respectively), and hypophosphatemia (2 [5.9%] subjects versus 0 subjects, respectively). All other AEs were reported in 1 subject at most. No dose-related trend in AEs was observed. The majority of AEs were grade 1.

The majority of laboratory abnormalities were grade 1 or 2. No grade 3 or 4 laboratory abnormalities were observed in the 250 mg treatment group. Grade 4 ALT elevations were observed in 1 subject each in the 75 and 150 mg treatment groups and were related to the AEs discussed above (for the subject in the 75 mg treatment group, this was observed during follow-up). Grade 3 pancreatic amylase (discussed above as AE) and grade 3 triglycerides (observed during follow-up) were observed in 1 subject each in the 25 mg treatment group. Grade 3 AST elevation was observed in 1 subject in the 75 mg treatment group (observed during follow-up) and in 2 subjects in the 150 mg group (for 1 subject observed during follow-up) (discussed as AE above). Grade 3 hyperkalemia was observed in 1 subject in the 150 mg treatment group.

No ECG-related or vital sign-related AEs were reported. No clinically relevant changes from baseline in ECG or vital signs values were observed.

Further details regarding clinical safety results using JNJ-6379 are provided in the JNJ-56136379 Investigator's Brochure.

4.5 ARO-HBV and JNJ-6379 Pre-Clinical Pharmacokinetic and Product Metabolism Studies

PK parameters for ARO-HBV have been evaluated in both rats and monkeys. Results of these studies can be found in the Investigator's Brochure. In general, ARO-HBV will be unmeasurable in the

circulation within 1-2 days following a single dose. In healthy subjects, JNJ-6379 is rapidly absorbed from the oral tablets, with a median t_{max} ranging between 1.26 and 3 hours in fasting conditions, and around 4 hours in fed conditions. Mean terminal half-life ($t_{1/2term}$) was comparable between studies 56136379HPB1001 and 56136379HPB1003, ranging between 93.3 and 116 hours across the dose levels in both studies, suggesting no significant difference in clearance between Asian and non-Asian subjects. In study 56136379HPB1003, approximately 18% of the administered dose was excreted via the kidney, resulting in a mean renal clearance of 0.161 L/h. No significant difference was observed in healthy volunteers when compared to patients with CHB. Details regarding pharmacokinetics and metabolism of JNJ-6379 are provided in the latest ARO-HBV and JNJ-56136379 Investigator's Brochure.

4.6 Rationale for the Study

Treatment with ARO-HBV is expected to reduce all HBV proteins and replicative intermediates via RNAi. The magnitude of the reduction and duration of effect will depend on the dose and dosing schedule. Since to date there has been no human clinical exposure to ARO-HBV, an effective therapeutic dose and optimal dosing schedule to administer to patients with chronic HBV infection is unknown. Accordingly, this single-ascending dose /multi-ascending-dose study has been designed to determine the tolerability of increasing doses in a healthy volunteer population as well as activity of ARO-HBV in patients with chronic HBV. Additionally, three separate dosing schedules from weekly to monthly dosing intervals will be evaluated. This strategy of evaluating monthly, bi-weekly and weekly dosing strategies is derived from published data in CHB patients receiving PEG-IFN alpha, where those patients experiencing a more rapid initial HBsAg response were more likely to eventually seroconvert for HBsAg. These studies imply that a faster HBsAg response (short time till HBsAg nadir) may be beneficial in driving future seroconversions. Additionally, it is likely that a longer period of lower viral antigen levels is more likely to prove clinically beneficial. For these reasons, two loading dose strategies (weekly and bi-weekly for three doses) will be tested in addition to monthly dosing. The purpose of these varied initial dosing regimens is to optimize for a rapid initial HBsAg decline.

CHB patients currently on entecavir or tenofovir for at least twelve months will be studied as well as CHB patients naive to NUCs or Interferon. These separate patient populations may respond differently to ARO-HBV. Safe and effective doses of ARO-HBV will then be studied in subsequent clinical trials aimed at producing HBsAg seroclearance (functional cure). Functional cure may allow patients to

discontinue their anti-viral medication in the future, and may prevent additional long-term liver damage or risk of developing hepatocellular carcinoma caused by chronic HBV infection.

The 25 and 50 mg dose levels (Cohorts 1b and 1c) are being added after the initial enrollment and dosing of Cohorts 2b through 5b (dose levels of 100 mg through 400 mg) have been completed to better understand dose response at lower doses.

Cohort 12 uses a combination of NUCs + ARO-HBV + JNJ-6379. Throughout the study all patients have been treated with the combination of NUCs + ARO-HBV in all other cohorts (Cohorts 1b through 11). It is thought that by using an siRNA approach to silence production of viral antigens in combination with NUCs to inhibit viral replication and JNJ-6379 which inhibits capsid assembly and cccDNA formation the response to treatment and potentially the rate of functional cure could be enhanced. ARO-HBV + NUCs has been well tolerated throughout the AROHBV1001 study. JNJ-6379 in combination with NUCs has also been well tolerated in CHB clinical studies. In vitro, JNJ-6379 does not inhibit phosphorylation of tenofovir or entecavir. Based on results from GLP toxicology studies and in vitro assessments of drug metabolism and transport for both JNJ-6379 and ARO-HBV, as well as safety and tolerability results from prior human studies in healthy volunteers and CHB, there is no indication that JNJ-6379 and ARO-HBV will have overlapping or additive toxicity. As such, the benefit of this combination "triple" therapy is expected to outweigh risk of toxicity.

4.7 Risk Assessment for Participants

4.7.1 ARO-HBV:

- *Embryo-fetal toxicity:* Limited GLP toxicology as well as preliminary non-GLP embryo-fetal studies have been conducted. Accordingly, eligible participants enrolled in this study, both male and female (including partners), must agree to use two effective methods of contraception (double barrier contraception or hormonal contraception along with a barrier contraceptive) during the study and for 3 months post-dose, or agree to abstinence (acceptable only if this method is in alignment with the normal life style of the patient).

- *Injection Site Reaction Risk:* Other subcutaneously administered modified siRNA drug candidates evaluated in clinical studies have been associated with mild to moderate injection site reactions (e.g. pain, erythema). This study includes a protocol for evaluation and grading of injection site reactions based on pre-defined criteria for mild, moderate and severe reactions. Injection site reactions will be photographed for tracking resolution and/or progression. Additionally, steps will be taken to minimize injection site reactions such as

rotating injection sites and allowing the ARO-HBV solution to come to room temperature prior to injecting.

- *Hepatic Toxicity (theoretical risk):* ARO-HBV targets the liver. Arrowhead has not seen meaningful drug induced transaminase changes with a previously studied liver targeted RNAi-based therapeutic (ARC-520/521) targeting HBV. However, another company (Alnylam Therapeutics) developing an siRNA for AATD has seen evidence of mild to moderate elevations in transaminases using hepatocyte targeted siRNA conjugates similar to those used by Arrowhead. Alnylam has described that these ALT changes were due to off- target effects of the siRNA seed region on microRNAs in the hepatocyte (Vaishnaw et al, 2017; Schlegel et al, 2017). The siRNA sequence of the ARO-HBV sense and antisense molecules have been screened for potential mRNA and microRNA off-target effects. No such off-target effects are anticipated. Multi-dose (3 weekly doses) GLP toxicity studies with ARO-HBV in rats and monkeys demonstrate no evidence of hepatic toxicity up to doses of 300 mg/kg. To mitigate this risk, the proposed study has built in stopping rules for ALT and AST elevation. Labs to evaluate liver injury and liver function will be drawn frequently. The Drug Safety Committee will include a hepatologist member with extensive clinical trial experience and significant experience in evaluation of liver targeted therapeutics, including siRNAs. Additionally, the planned starting dose of 35 mg is approximately 1/50th (assuming weight based conversion and a 60-kg subject) of the lowest dose of 30 mg/kg used in both the multi-dose rat and monkey GLP toxicity studies. This starting dose provides a safety margin of over 500-fold from the monkey NOAEL.

- *Host or viral induced ALT flares (theoretical risk):* Fluctuations in ALT are part of the natural history of CHB infection. In fact, many experts believe that ALT increase represents innate immune responses against infected hepatocytes and is required for HBsAg seroclearance. ALT elevation can also be seen in the setting of rebounding (such as with NUC discontinuation) HBV DNA levels or fluctuations of HBV DNA such as with NUC non-compliance. It is likely that host induced ALT flares will be seen in ARO-HBV studies as part of the normal sequelae associated with HBV. This risk will be mitigated by starting all patients NUCs (entecavir or tenofovir) upon entering the study, or kept on NUCs if NUC experienced. Measures of liver injury (ALT, AST) and of liver function (bilirubin, albumin and coagulation factors) will be measured frequently. Stopping rules for adverse changes in liver function are

included. Additionally, "ALT Flare Guidelines" are specified in Appendix 1 to help investigators evaluate ALT elevations during the study.

4.7.2. JNJ-6379:

- *Changes in amylase, lipase, cholesterol:* Based on data from Study 56136379HPB1002, lipase and amylase elevations were identified as laboratory abnormalities of interest. In addition, based on preclinical findings in rats and dogs, increased cholesterol was identified as laboratory abnormality of interest. Serum lipase, amylase and cholesterol will be monitored in patients.

- *Emergence of Resistance:* Treatment with JNJ-56136379 may lead to emergence of viral variants with reduced susceptibility or resistance to JNJ-56136379. Based on pre-clinical data, these variants remain susceptible to TDF and ETV but might affect treatment options with CAMs in the future.

4.7.3. ARO-HBV and JNJ-6379 combined

- *Overlapping drug toxicity (theoretical risk)*: Cohort 12 proposes the addition of JNJ-6379 to the treatment regimen of ARO-HBV+NUC which has been used throughout the study. Based on available clinical and pre-clinical experience with each compound as well as combination clinical studies of ARO-HBV with NUCs and JNJ-6379 with NUCs, clinically significant overlapping toxicity is not expected in Cohort 12.

4.8 Justification for Dose of ARO-HBV and JNJ-6379

Regulatory guidance for calculation of starting dose in healthy volunteer studies indicates that the No-Observed-Adverse-Effect-Level (NOAEL) in the most relevant animal species should be used (EMA, July 2017). FDA guidance also recommends calculation of human starting dose based on the NOAEL in the most relevant animal model (FDA Guidance, July 2005). The most pharmacologically relevant animal model for calculating the NOAEL is the monkey. This is supported by consensus statements regarding appropriate pharmacologically relevant animal models in toxicology studies of oligonucleotide therapeutics. (Marlowe et al, 2017).

Reported pharmacokinetic properties for several oligonucleotide subclasses across species, including humans (Geary et al, 2001, 2003; Yu et al, 2001), indicate that the most appropriate method for extrapolating animal doses to human equivalent doses is the comparison of dose per unit body weight (mg/kg), rather than dose per surface area (mg/m2) or plasma exposure (AUC or Cmax). The human equivalent dose for oligonucleotide therapeutics can be extrapolated directly from monkeys to humans with a scaling factor of 1.0 on mg/kg dose administrations (Yu et al, 2015). Arrowhead has historically

used 1:1 mg/kg scaling factor based on monkey NOAELs to determine starting dose in other siRNA first-in-human studies (ARC-520, ARC-521, both studied for hepatitis B, and ARC-AAT first in human studies).

Extrapolated based on body weight, the proposed starting dose of 35 mg will be administered to healthy volunteers in Cohort 1, the first dose level. The 35 mg starting dose is approximately 1/50th of the lowest dose of 30 mg/kg used in the monkey multi-dose GLP toxicity study (using a weight-based animal to human conversion and assuming a 60-kg human subject). The starting dose is equal to less than 1/500th of the 300 mg/kg NOAEL in monkeys. The maximum proposed dose in the study of 400 mg is 1/45th of the monkey NOAEL. After dose escalation through 400 mg, to better understand dose response at low doses, protocol amendment 4.0 added a 25 and 50 mg X3 Q28 days cohort (Cohorts 1b and 1c).

For cohort 12, the dose of ARO-HBV administered will be 200mg on Days 1, 29, and 57. ARO-HBV has been shown to be well tolerated and and effective at reducing viral antigens at doses up to 400mg dosed on Days 1, 29 and 57 (see Investigator's Brochure 2nd Edition). Since there was no obvious dose response observed between 100mg and 400mg ARO-HBV dosed on Days 1, 29, and 57, the second lowest dose level of 200 mg was chosen for cohort 12. The JNJ-6379 dose to be administered will be 250 mg given once daily. This dose is currently tested for up to 48 weeks in the ongoing Phase 2a study 56136379HPB2001 and has been selected based on all safety, PK, and antiviral activity data available following completion of the highest JNJ-6379 dose group (who received 250 mg once daily) in the Phase 1 study 56136379HPB1001 in treatment-naïve CHB-infected subjects treated for 28 days. No SAEs or AEs leading to treatment discontinuation were reported for CHB-infected subjects who received 250 mg JNJ-6379 once daily for 28 days, and all AEs were grade 1. In addition, no treatment-emergent laboratory abnormalities of >grade 2, ECG or vital signs abnormalities of ≥grade 2 were reported for these subjects, and no abnormalities were reported as AEs. The dose of 250 mg once daily has been selected to efficiently inhibit HBV DNA replication across a broad spectrum of patients and viral variants. In addition, 250 mg is expected to increase the potential to trigger the secondary mode of action (MoA) (i.e., inhibition of de novo cccDNA formation) which requires about 10-fold higher concentrations of JNJ-6379 than the primary MoA of inhibition, ie, interfering with capsid assembly (EC90 primary MoA=376 nM and EC90 secondary MoA=4019 nM).

5 OBJECTIVES

5.1 Primary Objectives

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 and escalating multiple doses in CHB patients.

5.2 Secondary Objectives

- To evaluate the single-dose pharmacokinetics of ARO-HBV in healthy volunteers
- To determine the reduction of HBsAg in response to ARO-HBV in CHB patients as a measure of activity

5.3 Exploratory Objectives

- To determine the reduction of HBcrAg, , HBsAg, 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
- 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 in a limited number of HBV patients in New Zealand only (if scientifically feasible).

- To evaluate the effect of multiple doses of ARO-HBV on HBV antigen specific T-cell response in a limited number of HBV patients in New Zealand only (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).

6 STUDY PLAN

6.1 Study Design

Healthy volunteers:

The study will be conducted in NHVs, adult males and females, aged 18-55 years with BMI between 19.0 and 35.0 kg/m² (Cohorts 1 – 5). For NHVs, cohorts of 6 eligible subjects (2 placebo, 4 active ARO-HBV) will be evaluated at each dose level starting at dose level 1 (35 mg). Participants who have signed an HDEC (or local equivalent) approved informed consent form and have met all of the protocol eligibility criteria during screening, will be randomized at a ratio of 2:1 (active:PBO) to receive ARO-HBV or PBO in a double-blind fashion. NHV cohorts will receive a single dose only.

Each cohort will begin with administration of ARO-HBV or PBO to two sentinel participants (one ARO-HBV, one PBO). Following the Day 3 evaluation in these participants, if there are no significant safety concerns based on PI's judgement, the remaining participants in the cohort will be treated. Dosing of participants will be staggered by at least 15 minutes such that no two participants will be dosed simultaneously.

Clinical facility confinement will be approximately 2 days for single dose administration (Day -1 through 24-hour assessments). Blood samples will be drawn pre-dose on Day 1 for baseline measurements. Height and weight will be measured at Screening only to calculate BMI.

Based on observations for all NHV subjects in a cohort through Day 8, 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 will occur, at the PI's discretion, where deemed necessary for treatment of an AE or for a decision to be made regarding trial continuation.

After all subjects in a cohort have completed an End-of-Study visit (Day 29), Sponsor may be unblinded at Sponsor's request. PI and study participants will remain blinded.

CHB patients:

HBeAg negative or HBeAg positive CHB patients, aged 18-65 years with BMI between 19.0 and 38.0 kg/m² (Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10, 11 and 12) will be enrolled. Cohort 8 will enroll HBeAg positive treatment naïve patients (no prior chronic exposure to NUCs or Interferon) and Cohort 9 will enroll HBeAg positive NUC experienced patients (on entecavir or tenofovir for at least 12 months). Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 10, 11 and 12 will enroll either HBeAg positive or negative patients regardless of previous NUC or PEG IFN treatment experience. All patients will be started on entecavir or tenofovir on Day 1. Cohort 12 will start on JNJ-6379 on Day 1 and continue oral 250 mg QD through Day 84. Patients currently on PEG IFN will not be allowed.

Summary of Participant Profile by Cohort and Cohort Size:

- Cohorts 1-5: NHVs, adult males and females, aged 18-55 years
    - 6 NHV subjects per cohort
- Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 10, 11 and 12: Any CHB patient regardless of HBeAg or prior therapy status (as long as other Inclusion and Exclusion criteria are met).
    - Cohorts 1b, 1c, 2b, 3b, 4b and 5b will enroll a minimum of 4 and a maximum of 8 patients per cohort.

- Cohorts 6, 7, 10 and 11 will enroll a maximum of 4 patients per cohort.
- Cohort 12 will enroll 12 patients.

- Cohort 8: HBeAg positive treatment naïve patients (no prior chronic exposure to NUCs or Interferon)
  - Cohort 8: Maximum of 4 patients per cohort
- Cohort 9: HBeAg positive NUC experienced patients (on entecavir or tenofovir for at least 12 months).
  - Cohort 9: Maximum of 4 patients per cohort

CHB patients regardless of HBeAg status or NUC/Interferon use history will enroll sequentially in Cohorts 2b through 7, Cohorts 10 and 11, and Cohorts 1b and 1c into a total of 10 open label cohorts. Cohorts 1b, and 1c through 5b will enroll at planned dose levels of 25 mg (Cohort 1b), 50 mg (Cohort 1c), 100 mg (Cohort 2b), 200 mg (Cohort 3b), 300 mg (Cohort 4b) and 400 mg (Cohort 5b) to receive three doses (Q28 days) of active treatment in an open label fashion. Cohorts 6 through 12 will enroll at planned dose levels of 100 mg (Cohorts 6 and 7), 200 mg (Cohort 10, 12), and 300 mg (Cohorts 8, 9, and 11). Cohort 6 will enroll CHB subjects (after Cohort 5b has completed enrollment) to receive three doses two weeks apart. Cohorts 7, 10 and 11 will enroll CHB patients sequentially (after Cohort 6 has completed enrollment) to receive three doses a week apart at increasing dose levels starting with a dose equal to Cohort 6. Cohorts 5b through 7 and Cohorts 10 and 11 will enroll sequentially (after being opened at the final planned DSC meeting) with enrollment and dosing in a later cohort not initiating until all subjects in the earlier cohort have received at least their first scheduled dose. Cohort 8 will enroll HBeAg positive treatment naïve CHB patients to receive three monthly doses of ARO-HBV. Cohort 9 will enroll HBeAg positive entecavir or tenofovir experienced CHB patients to receive three monthly doses of ARO-HBV. CHB patient screening for all CHB cohorts may start when Cohort 1 opens for enrollment. However, no CHB patients may be dosed until their respective cohort is approved for dosing by the DSC (not including Cohorts 1b,1c and 12). CHB dosing may begin and NHV dose escalation may occur based on DSC approval which can occur by vote after cumulative data through Day 8 from the current NHV cohort is available. (See **Figure 1** for dose escalation schedule).

CHB patients on current 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. Either tenofovir disoproxil fumarate (including generic) or tenofovir alafenamide are acceptable. During the extended follow up period after Day 113, NUCs may be discontinued at investigator discretion if subject becomes HBsAg undetectable (< 0.05 IU/mL).

Cohort 12 will enroll 12 CHB patients in an open label fashion to receive 200 mg ARO-HBV on Days 1, 29 and 57 as well as JNJ-6379 250 mg oral once daily starting on Day 1 and continuing through Day 84. Like all other cohorts, patients enrolling in Cohort 12 will either enter the study on NUCs or start NUCs on Day 1. Enrollment in Cohort 12 can begin once enrollment is full in Cohorts 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10, 11. The ARO-HBV dose level for Cohort 12 is 200 mg Q28 days (Days 1, 29, 57). Cohort 12 is open for enrollment in Hong Kong only.

In Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10, 11 and 12, eligible CHB patients who have signed an HDEC (or local equivalent) approved informed consent form will receive three doses of ARO-HBV at dose intervals ranging from once every week to once every 4 weeks in an open label fashion. Screening for the CHB cohorts can begin once Cohort 1 dosing has commenced. These cohorts (not including Cohorts 1b and 1c) will be opened for accrual once the corresponding NHV cohort receiving the same dose level has reached Day 8, based on agreement of the DSC that it is safe to proceed. Cohorts 6, 7, 8, 9, 10 and 11 can be opened for enrollment any time after Cohort 5 has reached Day 8 (and DSC has approved opening of such cohorts) and there is sufficient viral antigen response data from CHB patients to determine a dose level for these cohorts. Dose levels for Cohorts 6 through 11 is between 100 and 300 mg. Cohorts 2b through Cohort 7 and Cohorts 10 and 11 will be enrolled in sequence (as shown in Figure 1). Cohorts 8 and 9 may be enrolled in parallel with other CHB cohorts after the DSC has voted post Cohort 5 to open the remaining CHB patient cohorts and once a specified dose (≤ 400 mg) has been identified. Cohorts 1b, 1c and Cohort 12 are open for enrollment with the addition of applicable protocol amendments and may enroll in parallel.

For clarity, after Cohort 5 is through Day 8, the DSC will review all available safety data and vote to open Cohorts 5b, 6, 7, 8, 9, 10 and 11. Cohorts 5b, 8 and 9 may enroll and dose patients in parallel. Cohorts 5b through 7 and Cohorts 10 and 11 must enroll sequentially, meaning that Cohort 5b must be fully enrolled with each subject receiving at least a first dose before Cohort 6 can enroll. Cohort 6 must be fully enrolled with each subject receiving at least a first dose before Cohort 7 can enroll. Cohort 7 must be fully enrolled with each subject receiving at least a first dose before Cohort 10 can

enroll and Cohort 10 must be fully enrolled with each subject receiving at least a first dose before Cohort 11 can enroll. It is the intent that Cohorts 7, 10 and 11 will be treated at increasing dose levels starting with a dose equal to Cohort 6.

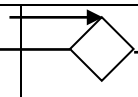
On dosing days, clinical facility confinement will be approximately 2 hours unless a longer period of post-dose observation is needed based on PI discretion. Blood samples will be drawn pre-dose on Day 1 for baseline measurements. Height and weight will be measured at Screening only to calculate BMI. Participants will undergo evaluations at screening and at regular intervals during the study as described in the Schedule of Assessments.

With the exception of Cohort 12 patients, all other CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after Day 113. Only Cohort 12 patients will require follow-up until the Day 337 (±5 days) visit. Subjects consenting to additional follow up will continue on NUCs and may have NUCs discontinued at the investigator's discretion if patients become HBsAg undetectable (< 0.05 IU/mL). Subjects not consenting to additional follow up will be followed per protocol based on Schedule of Assessment Tables 1.2, 1.3 and 1.4.

Single doses of ARO-HBV will be evaluated in normal healthy volunteers (NHVs) and multiple doses of ARO-HBV will be evaluated in patients with chronic hepatitis B (CHB) in a sequential manner as shown in **Figure 1**.

Figure 1. 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 250mg QD + ARO-HBV 200 mg dosed on Day 1, 29, 57

*All NHV cohorts will start with two sentinel subjects

Unblinding of NHV cohorts may occur at Sponsor discretion on a cohort by cohort basis after all subjects in a cohort have completed their last on-site study visit. Study participants (CHB patients and NHVs) as well as sites will remain blinded.

Open label anti-viral response data may be disclosed to investigators by the Sponsor at Sponsor's discretion. There is no requirement for Sponsor to disclose anti-viral response data while the study is ongoing.

6.2 Rationale for Study Design

This first-in-human study plans to investigate ARO-HBV in adult healthy volunteers (NHVs) and HBV patients to evaluate the drug's safety and tolerability as well as its pharmacokinetics in healthy volunteers and pharmacodynamics in HBV patients, following a single (or multiple subcutaneous doses in HBV patients). The study initiates in NHVs because the single dose risk is considered low. Additionally, this population will be otherwise healthy without co-morbidities that may increase risk

for toxicity. The siRNA triggers in ARO-HBV are targeted against the mRNA transcripts generated by HBV viral cccDNA and integrated DNA. Since NHVs will not have HBV infection the potential for toxicity due to pharmacodynamic (e.g. "on-target") effect is very low. After a period of post-dose safety evaluation in NHVs at each dose level, multi-dose (3 dose) cohorts in HBV patients at the same dose levels are planned (See Figure 1). Multiple doses of ARO-HBV are employed in the HBV patient cohorts as it is highly likely that prolonged reduction of viral antigens will be required to elicit functional cures. It is also important to note that this study excludes patients with excessive co-morbidities. HBV patients enrolled will not have other co-morbid conditions which could increase their risk of adverse effects to ARO-HBV. The anticipated safety profile in NHVs and HBV patients is likely to be very similar. This is supported by Sponsor's experience with ARC-521 Injection and ARC-520 Injection, which were siRNA therapeutics studied in single and multi-dose studies in NHV and CHB patient populations. Both ARC-521 Injection and ARC-520 Injection demonstrated a favorable safety profile in NHVs and HBV patients. Variation of dose frequency in the HBV patient cohorts (See Figure 1) is important to understand the dosing regimen that produces the deepest and most rapid reduction in viral antigen.

This study is similar to the ARC5211001 study which was executed successfully at the same site in New Zealand in NHVs and HBV patients.

The study is double-blind to limit the occurrence of conscious and unconscious bias in trial conduct and interpretation. Blinding will be achieved using a PBO product (0.9% normal saline). Inclusion of participants receiving PBO will reduce bias in the assessment of drug safety and tolerability. The study is randomized with a 2:1 (active:PBO) ratio to reduce bias.

Cohort 12 uses a combination of NUCs + ARO-HBV + JNJ-6379. Throughout the study all patients have been treated with the combination of NUCs + ARO-HBV. It is thought that by using an siRNA approach to silence production of viral antigen in combination with NUCs to inhibit viral replication and JNJ-6379 which inhibits capsid assembly and cccDNA formation the response to treatment and potentially the rate of functional cure could be enhanced. ARO-HBV + NUCs has been well tolerated throughout the AROHBV1001 study. JNJ-6379 in combination with NUCs has also been well tolerated in CHB clinical studies. In vitro, JNJ-6379 does not inhibit phosphorylation of tenofovir or entecavir. It is not expected that JNJ-6379 and ARO-HBV will have overlapping or additive toxicity. As such, the benefit of this combination "triple" therapy is expected to outweigh risk of toxicity.

6.3 Criteria for Dose-escalation and Stopping Rules

Escalation to the next cohort will proceed according to the study design until the 400 mg dose level and all subsequent cohorts are completed unless the trial is stopped early by the Data Safety Committee (DSC) or Sponsor. Dose escalation will require approval by the DSC based on all cumulative available safety data through Day 8 of the current cohort. Dose escalation will proceed until all cohorts are fully enrolled or until the study is stopped or the DSC votes to not escalate to the next dose.

A decision to stop the trial early or discontinue drug in an individual subject or group of subjects **may** (following a case-by-case decision based on consultation between the sponsor, DSC and the PI) be indicated based on any of the following:

1. A single Serious Adverse Event(SAE) (defined in Section 9.1) considered at least possibly related to ARO-HBV and/or JNJ-6379

2. One of the following abnormal results at least possibly related to ARO-HBV and/or JNJ-6379:

    - In NHVs, treatment emergent ALT or AST > 3X ULN which must be confirmed by repeat blood draw within 48 hours of initial results.

    - In CHB patients, treatment emergent ALT or AST > 3X Day 1 pre-dose baseline confirmed by repeat blood draw within 48 hours of initial results **AND** ALT > 10X ULN **AND** any one of the following:

        - Total Bilirubin newly elevated to 2X ULN AND 2X Day-1 pre-dose baseline (confirmed on repeat lab draw within 48 hours) or

        - Decrease in serum albumin of 0.5 g/dL or greater (confirmed on repeat lab draw within 48 hours)

    - Treatment emergent platelet count < 70,000 per microliter in NHVs or < 50,000 in CHB patients, confirmed on repeat measure within 48 hours of initial results

    - Treatment emergent serum creatinine > 180 μmol/L confirmed by repeat blood draw within 48 hours of initial results

Sponsor or PI can discontinue any subject at any time with or without DSC consultation. If such events (as described in #1, #2 above) occur and the subject is not discontinued from the study the reason for not discontinuing the subject will be included in DSC meeting minutes. Including, but not limited to the events listed above, the DSC may pause the study to additional dosing or dose escalation to provide time to evaluate safety data and recommend the action to be taken, which may include, but is not limited to one of the following:

- Discontinuation of a subject or group of subjects from the study
- The study is stopped immediately with no further dosing
- The study will continue until the current cohort is completed
- The study will continue, but the next dose escalation will be to a level midway between the current level and the next level specified in Section 8.3
- The study will continue as planned

If a serious adverse event (SAE) at least possibly related to study drug should occur for a single participant, subsequent dosing within that cohort **may** be put on hold pending a complete review of safety data by the DSC to determine if participant enrollment at the same dose may proceed, or if additional enrollment/dosing should stop. If following the DSC safety review it is deemed appropriate to restart dosing/enrollment, subject enrollment, dosing and dose escalation may proceed as planned.

6.4 Duration of the Study

For each NHV subject in the single dose cohorts, the duration of the study clinic visits is a maximum of 13 weeks from the beginning of the screening period to the Day 29 End-of-Study (EOS) examination.

For each CHB patient in the multi-dose cohorts the duration of the study clinic visits is approximately 25 weeks from screening to the Day 113 EOS examination. With the exception of Cohort 12 patients, all other CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after Day 113. Only Cohort 12 patients will require follow-up until the Day 337 (±5 days) visit. Subjects consenting to additional follow up will continue on NUCs. Subjects not consenting to additional follow up will be followed per protocol based on Schedule of Assessment Tables 1.2, 1.3 and 1.4.

All CHB subjects who complete the study until Day 113 EOS examination are considered to complete the study and may continue to attend the Additional Follow-Up visits per the Schedule of Assessments (Table 1.5) if re-consent is obtained. If a subject withdraws from the Additional Follow-Up visits before the Day 337 (Cohort 12 only) or 393 visit, he or she will still be considered as a completed subject and reason for not continuing with the Additional Follow-Up visits per protocol will be recorded.

All CHB patients and NHV subjects will be contacted by phone 90 days after the EOS visit (Day 29 for NHVs and Day 113 for CHB patients) to confirm pregnancy status.

7 SUBJECT SELECTION

7.1 Number of Subjects

A total of approximately 30 NHV and a minimum of 50 or a maximum of 84 CHB participants (not including potential replacements) may be enrolled in the study.

7.2 Inclusion Criteria

Inclusion Criteria for Healthy Volunteer Cohorts

To be eligible for enrollment, subjects must meet all the following inclusion criteria:

1. Male or female, 18 to 55 years of age inclusive, at the time of informed consent
2. Able to provide written informed consent prior to the performance of any study specific procedures
3. Body mass index (BMI) between 19.0 and 35.0 kg/m^2, inclusive

$$\text{BMI} = \text{weight (kg)}/(\text{height [m]})^2$$

4. A 12-lead ECG at Screening and pre-dose assessment that, in the opinion of the PI, has no abnormalities that compromise participant's safety in this study
5. Participants using two effective methods of contraception (double barrier contraception or hormonal contraception along with a barrier contraceptive, both male and female partners) during the study and for 3 months following the dose of ARO-HBV. Males must not donate sperm for at least 3 months after the last study treatment. Male partners of female subjects and female partners of male subjects must also use contraception, if they are of childbearing potential. Females of childbearing potential must have a negative urine pregnancy test at Screening and on Day 1, pre-dose. Females not of childbearing potential must be post-menopausal (defined as cessation of regular menstrual periods for at least 12 months), confirmed by follicle-stimulating hormone (FSH) level in the post-menopausal range.

- Using twice the normal protection of birth control by using a condom AND one other form of the following (abstinence is acceptable at PI's discretion):

  - Birth control pills (The Pill)
  - Depot or injectable birth control
  - IUD (Intrauterine Device)
  - Birth Control Patch (e.g., Ortho Evra)
  - NuvaRing®
  - Surgical sterilization. i.e., tubal ligation or hysterectomy for women or vasectomy for men or other forms of surgical sterilization

  Requirement for contraception can be waived in certain circumstances (i.e. same sex relationships) if approved by PI.

6. Willing and able to comply with all study assessments and adhere to the protocol schedule

7. Have suitable venous access for blood sampling

8. No abnormal finding of clinical relevance at the Screening evaluation

9. AST, ALT and Creatinine levels ≤ upper limit of normal at Screening

Inclusion Criteria for CHB Patient Cohorts

To be eligible for enrollment, patients must meet all the following inclusion criteria:

1. Male or female, 18 to 65 years of age, inclusive, at the time of informed consent

2. Able to provide written informed consent prior to the performance of any study specific procedures

3. Body mass index (BMI) between 19.0 and 38.0 kg/m^2, inclusive. Patients with BMI above or below the cutoff may be enrolled at the discretion of the PI based on risks and co-morbidities.

$$\text{BMI} = \text{weight (kg)}/(\text{height [m]})^2$$

4. A 12-lead ECG at Screening and pre-dose assessment that, in the opinion of the PI, has no abnormalities that compromise participant's safety in this study

5. Participants using two effective methods of contraception (double barrier contraception or hormonal contraception along with a barrier contraceptive, both male and female partners) during the study and for 3 months following the dose of ARO-HBV. Males must not donate sperm for at least 3 months after the last study treatment. Male partners of female patients and female partners of male patients must also use contraception, if they are of childbearing potential. Females of childbearing potential must have a negative urine pregnancy test at Screening and on Day 1, predose. Females not of childbearing potential must be post-menopausal (defined as cessation of regular menstrual periods for at least 12 months), confirmed by follicle-stimulating hormone (FSH) level in the post-menopausal range.

- Using twice the normal protection of birth control by using a condom AND one other form of the following (abstinence is acceptable at PI's discretion):

  - Birth control pills (The Pill)
    - *Cohort 12 Only: Female subjects of childbearing potential who are on a stable treatment regimen with hormonal contraceptives (i.e., same dose and not starting or stopping hormonal contraceptive use) for ≥3 months prior to screening should continue the same dose regimen until 12 weeks after EOT. Ethinylestradiol-containing contraceptives are only allowed if the ethinylestradiol content is ≤20 µg. For female subjects of childbearing potential who will start a hormonal contraceptive treatment during the study, ethinylestradiol-containing contraceptives are not allowed.*
  - Depot or injectable birth control
  - IUD (Intrauterine Device)
  - Birth Control Patch (e.g., Ortho Evra)
  - NuvaRing®
  - Surgical sterilization. i.e., tubal ligation or hysterectomy for women or vasectomy for men or other forms of surgical sterilization

  Requirement for contraception can be waived in certain circumstances (i.e. same sex relationships) if approved by PI.

6. Willing and able to comply with all study assessments and adhere to the protocol schedule

7. Have suitable venous access for blood sampling

8. Have a diagnosis of HBeAg positive or HBeAg negative chronic (> 6 months) HBV infection.

9. HBeAg positive at Screening and experienced to entecavir or tenofovir therapy defined as consistently on any entecavir or tenofovir for at least the most recent 12 months (Cohort 9 only).

10. HBeAg positive at Screening and naïve (has never received) any NUC or Interferon therapy (Cohort 8 only).

11. HBsAg at screening ≥ 5 IU/mL

12. Patients with liver Elastography (i.e. FibroScan®) score ≤ 10.5 at or within 3 months of Screening (for Cohort 12 patients must have FibroScan < 9.0 kPa).

13. No prior use of capsid assembly modulators

7.3 Exclusion Criteria

Exclusion Criteria for Healthy Volunteer Cohorts

A potential subject will be excluded from the study if *any* of the following criteria apply:

1. Female subjects have a positive pregnancy test or are lactating.

2. Acute signs of hepatitis/other infection (e.g., moderate fever, jaundice, nausea, vomiting, abdominal pain) at Screening or at baseline

3. Use within the last 14 days or an anticipated requirement for anticoagulants (aspirin is acceptable), systemic (oral, depot or intravenous) corticosteroids, immunomodulators, or immunosuppressants (other than those used in study treatment regimens)

4. Use of prescription medication within 14 days prior to administration of study treatment that in the opinion of the PI or the Sponsor would interfere with study conduct. Topical products without systemic absorption, statins, hypertensive medications, OTC and prescription pain medication or hormonal contraceptives (females) are acceptable.

5. A history of poorly controlled autoimmune disease or any history of autoimmune hepatitis

6. Human immunodeficiency virus infection, as shown by the presence of anti-HIV antibody (sero-positive)

7. Seropositive for HBV or HCV or a history of delta virus hepatitis

8. Has uncontrolled hypertension defined as blood pressure > 170/100 mmHg at screening confirmed by repeat

9. A history of torsades de pointes, ventricular rhythm disturbances (eg, ventricular tachycardia or fibrillation), pathologic symptomatic bradycardia (heart rate < 45 bpm), 2nd degree or 3rd degree heart block, congenital long QT syndrome, prolonged QT interval due to medications, or new elevation or depression in the part of an ECG immediately following the QRS complex and merging into the T wave (ST segment) or new pathologic inverted T waves, or new pathologic Q waves on ECG that are deemed clinically significant in the opinion of the PI. Subjects with a history of atrial arrhythmias should be discussed with the Sponsor Medical Monitor and CRO Medical Monitor.

10. A family history of congenital long QT syndrome, Brugada syndrome or unexplained sudden cardiac death

11. Is taking medications known to prolong the QTc interval (the length of washout from a medication know to prolong the QTc interval will be determined by the PI depending on the medication's half-life)

12. Symptomatic heart failure (per NYHA guidelines), unstable angina, myocardial infarction, severe cardiovascular disease (ejection fraction < 20%, transient ischemic attack (TIA) or cerebrovascular accident (CVA) within 6 months prior to study entry

13. History of malignancy within the last 5 years except for adequately treated basal cell carcinoma, squamous cell skin cancer, superficial bladder tumors, or in situ cervical cancer. Participants with other curatively treated malignancies who have no evidence of metastatic disease and >2 years disease-free may be entered following approval by the Sponsor Medical Monitor

14. History of major surgery within 3 months of Screening

15. Regular use of alcohol within one month prior to the Screening visit (i.e., more than fourteen units of alcohol per week [1 Unit = 150 mL of wine, 360 mL of beer, or 45 mL of 40% alcohol])

16. Has evidence of severe systemic acute inflammation, sepsis, or hemolysis

17. Recent (within 3 months) use of illicit drugs (such as cocaine, phencyclidine [PCP], MDMA,) or positive test for such drugs of abuse at screening. Subjects who are on prescription medications that cause a positive result on urine drug screen are eligible based on PI discretion. Subjects with a positive urine drug screen for opioids, cannabinoids or benzodiazepines may be eligible based on PI discretion.

18. Use of an investigational agent or device within 30 days prior to dosing or current participation in an investigational study

19. Has any clinically significant history or presence of poorly controlled or decompensated neurological, endocrine, cardiovascular, pulmonary, hematological, immunologic, psychiatric, metabolic, or other uncontrolled systemic disease, that may affect participation in the study

20. Blood donation (500 mL) within 7 days prior to study treatment administration.

21. Any concomitant medical or psychiatric condition or social situation that would make it difficult to comply with protocol requirements or put the participant at additional safety risk

22. Has a history of coagulopathy (including deep vein thrombosis and pulmonary embolism) or stroke within 6 months of baseline, and/or concurrent anticoagulant medication(s).

23. Subjects with any of the following laboratory abnormalities:

    a. International normalized ratio (INR) > 1.5 × ULN

    b. Platelets < 100,000 cells per microliter

24. Participants who are unable to return for all scheduled study visits

25. Has any other condition that, in the opinion of the PI, would render the subject unsuitable for enrolment, or could interfere with his/her participation in the study

    Note: The PI has the sole right to enroll a subject for the study. The Sponsor may discuss with the PI the suitability of enrolment based upon the subject's medical history or screening results, if it is felt that a subject's safety may be at risk.

Exclusion Criteria for CHB Patient Cohorts

A potential patient will be excluded from the study if *any* of the following criteria apply:

1. Female patients have a positive pregnancy test or are lactating.

2. Acute signs of hepatitis (e.g., combination of moderate fever, jaundice, nausea, vomiting, abdominal pain) within 4 weeks of Screening and/or at baseline

3. Use within the last 14 days or an anticipated requirement for anticoagulants (aspirin and other antiplatelet agents are acceptable), systemic (oral, depot or intravenous) corticosteroids, immunomodulators, or immunosuppressants (other than those used in study treatment regimens)

4. Use of prescription medication within 14 days prior to administration of study treatment that in the opinion of the PI or the Sponsor would interfere with study conduct. Topical products without systemic absorption, statins, hypertensive medications, OTC and prescription pain medication or hormonal contraceptives (females) are acceptable

5. A history of poorly controlled autoimmune disease or any history of autoimmune hepatitis

6. Human immunodeficiency virus infection, as shown by the presence of anti-HIV antibody (sero-positive)

7. Is sero-positive for HCV (defined by positive test for HCV RNA), or a history of delta virus hepatitis

8. A history of torsades de pointes, ventricular rhythm disturbances (eg, ventricular tachycardia or fibrillation), pathologic symptomatic bradycardia (heart rate < 45 bpm), 2nd degree or 3rd degree heart block, congenital long QT syndrome, prolonged QT interval due to medications, or new clinically significant elevation or depression in the part of an ECG immediately following the QRS complex and merging into the T wave (ST segment) or new clinically significant pathologic inverted T waves, or new pathologic Q waves on ECG that is deemed clinically significant in the opinion of the PI. Patients with a history of atrial arrhythmias should be discussed with the Sponsor Medical Monitor and CRO Medical Monitor

9. A family history of congenital long QT syndrome, Brugada syndrome or unexplained sudden cardiac death

10. Symptomatic heart failure (per NYHA guidelines), unstable angina, myocardial infarction, severe cardiovascular disease (ejection fraction < 20%, transient ischemic attack (TIA) or cerebrovascular accident (CVA) within 6 months prior to study entry

11. History of malignancy within the last 5 years except for adequately treated basal cell carcinoma, squamous cell skin cancer, superficial bladder tumors, or in situ cervical cancer. Participants with other curatively treated malignancies who have no evidence of metastatic disease and >1 year disease-free may be entered following approval by the Sponsor Medical Monitor

12. History of major surgery within 3 months of Screening

13. Regular use of alcohol within one month prior to the Screening visit (i.e., more than fourteen units of alcohol per week [1 Unit = 150 mL of wine, 360 mL of beer, or 45 mL of 40% alcohol])

14. Recent (within 3 months) use of illicit drugs (such as cocaine, phencyclidine [PCP], MDMA) or positive test for such drugs of abuse at screening. Subjects who are on prescription medications that cause a positive result on urine drug screen are eligible based on PI discretion. Subjects with a positive urine drug screen for opioids, cannabinoids or benzodiazepines may be eligible based on PI discretion.

15. Use of an investigational agent or device within 30 days prior to dosing or current participation in an investigational study

16. Has any clinically significant history or presence of poorly controlled or decompensated neurological, endocrine, cardiovascular, pulmonary, hematological, immunologic, psychiatric, metabolic, or other uncontrolled systemic disease, that may affect participation in the study

17. Any concomitant medical or psychiatric condition or social situation that would make it difficult to comply with protocol requirements or put the participant at additional safety risk

18. Has a history of coagulopathy (including deep vein thrombosis and pulmonary embolism) or stroke within 6 months of baseline, and/or concurrent anticoagulant medication(s).

19. Patients with any of the following laboratory abnormalities at screening:

    a. Serum creatinine > 1.5 mg/dL (132.6 µmol/L)

    b. International normalized ratio (INR) > 1.5 × ULN

    c. Platelets < 70,000 cells per microliter

    d. Hepatic transaminases (ALT or AST) > 5X ULN

20. Participants who are unable to return for all scheduled study visits

21. Has any other condition that, in the opinion of the PI, would render the patient unsuitable for enrolment, or could interfere with his/her participation in the study

Note: The PI has the sole right to enroll a patient for the study. The Sponsor may discuss with the PI the suitability of enrolment based upon the patient's medical history or screening results, if it is felt that a patient's safety may be at risk

7.4 Participant Withdrawal Criteria

Participants will be advised that they are free to withdraw from the study at any time for any reason or, if necessary, the PI, or medically trained designee, may withdraw a participant from the study, per the following criteria, to protect the participant's health:

- the need to take medication which may interfere with study measurements;
- intolerable/unacceptable adverse experiences;
- major violation of or deviation from study protocol procedures;
- non-compliance of participant with protocol;
- participant unwilling to proceed and/or consent is withdrawn; or
- withdrawal from the study if, in the PI's judgement, it is in the participant's best interest.

The reasons for withdrawal will be recorded on the case report form (CRF) and included in the final clinical study report, along with any adverse events and any necessary medical treatment.

If a participant is withdrawn from the study due to significant AE or SAE, the PI, or medically trained designee, will evaluate the urgency of the event. If the situation warrants, the PI, or medically trained designee, will take appropriate diagnostic and therapeutic measures. If the situation is not an immediate emergency, the PI, or medically trained designee, at the clinical study facility will attempt to contact the Arrowhead Pharmaceuticals, Inc. Medical Monitor or medically qualified designee for consultation. No medical help, diagnosis, or advice will be withheld from the participant due to an inability to contact the Medical Monitor. The participant will be encouraged to remain available for follow-up medical monitoring. The Sponsor will be notified as soon as possible of any participant withdrawals.

Participants who are withdrawn or discontinue prior to EOS visit for reasons other than an adverse event, may be replaced.

7.5 Restrictions and Concomitant Medications

1. ***Confinement:*** For each NHV participant, clinical facility confinement will be approximately 2 days, starting on Day -1, with discharge on Day 2 (after the 24-hour post-dose assessments) and dosing on Day 1. Participants will return to the clinical facility for out-patient visits as per Schedule of Assessments. For CHB patients confinement is limited to approximately 2 hours post-dose administration.

2. ***Fasting:*** On the day of dosing, patients will fast from food for at least 2 hours prior to study treatment administration and 2 hours post dose.

3. ***Recreational Drugs & Alcohol:*** Participants will be instructed to abstain from consuming alcohol for at least 48 hours prior to admission, and whilst confined to the clinical facility. In addition, participants will be instructed to refrain from regular use of alcohol (i.e., more than fourteen units of alcohol per week [1 Unit = 150 mL of wine, 360 mL of beer, or 45 mL of 40% alcohol]) for the study duration. Participants should abstain from use of recreational drugs throughout the study.

4. ***Concomitant Medications Healthy Volunteers:*** Subjects will be instructed not to take any prescription medication (other than medications used as part of the study) for 7 days prior to admission and for the duration of the study. Oral or other hormonal contraceptives are acceptable. Subjects will be instructed to inform the PI of the details (indication, dose and dates of administration) if they do take any medication, and these details will be recorded in the CRF. If necessary, paracetamol may be used during the study as necessary. Any other medication or therapy other than blood pressure medication must be approved by the Medical Monitor or PI prior to administration.

5. ***Concomitant Medications CHB Patients:*** Use of concomitant medications during the study is at the discretion of the PI unless otherwise specified. However, participants should not be on medications that would interfere with study evaluations. Topical or inhaled steroids, statins, hypertensive medications, and birth control (where appropriate), and oral analgesics are acceptable. Participants will be instructed not to take any anticoagulants (aspirin and antiplatelet agents are acceptable), systemic (oral, depo or intramuscular) corticosteroids, immunomodulators (other than those specified in the study), or immunosuppressants 14 days prior to dosing and for the duration of the study. Participants will be instructed to inform the PI of the details (indication, dose, and dates of administration) if they do take any medication, and these details will be recorded in the eCRF. CHB patients entering the study on entecavir or tenofovir will continue their NUC therapy at the prescribed dose and frequency throughout the study. All treatment naïve CHB patients entering the study will start on entecavir or tenofovir on Day 1.

   Based on results from drug-drug interaction study 56136379HPB1004 investigating the potential effect of co-administration of JNJ-6379 with oral contraceptives, it is not anticipated that the efficacy of oral contraceptives will be impacted during co-administration with JNJ-6379 since the exposure of a progestin sensitive to CYP3A4 induction was not significantly affected by co-administration of JNJ-56136379. In contrast, it is anticipated that co-administration with ethinyl-estradiol-containing contraceptives will result in an increased exposure to ethinyl-estradiol. In the current study, female subjects of childbearing potential who are on a stable treatment regimen with hormonal contraceptives (ie, same dose and not starting or stopping hormonal contraceptive use) for ≥3 months prior to screening, should continue the same dose regimen until 12 weeks after EOT. Ethinyl-estradiol-containing contraceptives are only allowed if the ethinyl-estradiol content is ≤20 µg. For female subjects of childbearing potential who will start a hormonal contraceptive treatment during the study, ethinyl-estradiol-containing contraceptives are not allowed, given the observed increase in ethinyl-estradiol in study 56136379HPB1004. Co-administration of JNJ-6379 170 mg qd with oral midazolam as a CYP3A4 probe showed a reduction of 41.7% in Cmax and 53.9% in AUC (study 56136379HPB1004), implying that JNJ-6379 may induce the metabolism of CYP3A4 sensitive substrates. Questions regarding use of ARO-HBV or JNJ-6379 concomitantly with other medications should be discussed with Sponsor medical monitor.

8 INVESTIGATIONAL PRODUCT

Arrowhead Pharmaceuticals, Inc. is responsible for the supply to the clinical site of active drug supplies together with detailed instructions (in a pharmacy manual) describing preparation and administration of ARO-HBV and of JNJ-6379. The PBO (normal saline 0.9%) will be supplied by the clinical site.

8.1 ARO-HBV Description, Identification and Dosage

ARO-HBV will be supplied as single sterile 2-mL vials containing ARO-HBV, with the correct dose of ARO-HBV prepared by the Pharmacy prior to dosing participants.

The placebo (PBO) will be 0.9% normal saline administered subcutaneously.

Doses administered per Dose Level:

Each single dose of either active drug (ARO-HBV) or PBO (normal saline 0.9%), 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.) using a 25-30 Gauge, ½ inch needle. 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. Prior to dose administration, the ARO-HBV vial must be allowed sufficient time to come to room temperature. Do not inject into areas of active skin disease or injury such as ecchymosis, sunburns, skin rashes, inflammation or skin infections.

8.2 Supply, Preparation, Storage and Labelling of ARO-HBV

ARO-HBV Injection is an aqueous solution in a sterile, 2-mL type I glass vial with a fluorocarbon-lined butyl stopper and a blue flip-off seal. Each vial contains a nominal volume of 1.15 mL to provide a full 1 mL withdrawable volume.

Strength: 200 mg/mL

Volume: 1.15 mL

Appearance: Clear, colorless to light yellow solution

Inactive ingredients: 0.5 mM sodium phosphate monobasic, 0.5 mM sodium phosphate dibasic in water for injection

Shipment and storage: Refrigerated, 2-8 ºC

ARO-HBV Injection syringes will be prepared, per the Pharmacy Manual, by a pharmacist or qualified staff at the clinical sites. Aseptic technique will be used to ensure sterility of the solution to be injected. The time of preparation for active drug must be documented and tracked. Please refer to the pharmacy manual for more detailed instructions

The final study doses will be labeled per Good Manufacturing Practice (cGMP)/Good Clinical Practice (cGCP).

Study drug supplies will be stored at clinical sites securely under the appropriate conditions.

8.3 JNJ-6379 Physical Description of Study Drug(s)

JNJ-56136379 supplied for this study is formulated as oral tablets containing 25 mg and 100 mg JNJ-56136379-AAA. Refer to the IB for a list of excipients.

8.4 Packaging and Storage

JNJ-56136379 will be packaged in bottles. All study drugs will be dispensed in child-resistant packaging. No study drugs can be repacked without prior approval from the sponsor.

JNJ-56136379 must be stored on site in the original package at controlled temperatures ranging from 15°C to 30°C. The NUCs ETV (Baraclude®) and TDF (Viread®) must be stored on site in the original package at controlled temperatures ranging from 15°C to 25°C. Refer to the pharmacy manual/study site investigational product and procedures manual for additional guidance on study drug preparation, handling, and storage.

8.5 Study Drug Handling

The Sponsor will provide the PI with a sufficient quantity of clinical drug supplies. The PI must ensure that deliveries of investigational product from the Sponsor are correctly received by a responsible person, that all receipts of drug shipments are recorded on the appropriate Drug Accountability forms prepared by the pharmacy at the clinical site and that the products are stored in a secure area under recommended storage conditions. It is also the responsibility of the PI to ensure that the integrity of packaged study product not be jeopardized prior to dispensing.

Only participants enrolled in the study may receive study drug, in accordance with all applicable regulatory requirements. Only authorized site staff may supply or administer study drug. The study drug must be stored in a secure area with access limited to the PI and authorized staff and under the physical conditions that are consistent with the study drug-specific requirements.

An authorized and trained staff member at each clinical trial site will dispense the study drug per pre-defined drug dispensing requirements. The dispensing and administration will be verified by a second member of site staff.

ARO-HBV and JNJ-6379 will be supplied by Arrowhead Pharmaceuticals, Inc. and labeled with the drug name, batch number, expiration date (as applicable) and storage conditions. Individual doses will

be dispensed by clinical trial site staff members at the time of dosing and recorded in the drug accountability records. A Pharmacy Manual will be prepared to define the procedures for dispensing.

Instructions provided in the Pharmacy Manual will be followed for the receipt, handling and accountability of the study formulations.

8.6 Accountability of Study Supplies

All material supplied is for use only in this clinical study and should not be used for any other purpose.

The PI is responsible for the investigational product accountability, reconciliation and record maintenance at the investigational site. In accordance with all applicable regulatory requirements, the PI or designated site staff must maintain investigational product accountability records throughout the course of the study. This person will document the amount of investigational product received from Arrowhead Pharmaceuticals, Inc., the amount supplied and/or administered to and returned by participants, if applicable. A non-blinded Clinical Research Associate (CRA) will perform initial and ongoing study drug kit and placebo accountability. The non-blinded CRA will protect the integrity of the assignment blind and will not participate in data review for study participants. Used vials of ARO-HBV will be retained sequestered per participant and cohort and made available to the non-blinded CRA during study drug and placebo reconciliation, where allowable by local policy. Used bottles of JNJ-6379 will be retained sequestered per participant and made available to the CRA for study drug reconciliation.

A Drug Dispensing Log must be kept current and will contain the following information:

- the identification of the participant to whom the drug was dispensed; and
- the date(s) and quantity of the drug dispensed to the participant.

The date and time of ARO-HBV/placebo dose preparation and release will be maintained to support administration of study drug/PBO. The authorized pharmacist or qualified staff will be un-blinded to the doses. The pharmacy will dispense ARO-HBV/placebo and the study center will administer ARO-HBV only to participants included in this study following the procedures set out in the study protocol. The pharmacy will dispense JNJ-6379 to the site staff who will provide it to the patients who will take their daily dose of 250 mg (oral) at home. Patients will record taking their daily dose of JNJ-6379 on a diary provided to the clinical site. Patients will bring their used bottles of JNJ-6379 and diaries with them to each subsequent visit so that the study staff may count the remaining tablets, compare the count to the patient's recorded diary and ascertain the level of patient compliance with study treatment. Patients will be provided with additional JNJ-6379 at each visit to cover the period of time

until their next clinic visit. The pharmacy/clinical site will dispense JNJ-6379 only to participants included in this study following the procedures set out in the study protocol.

Each participant will be given only the study medication carrying his/her study number. Study drug administration will be documented on the CRFs and/or other study drug record.

The study drug inventory must be available for inspection by the non-blinded monitor during the study. Drug supplies, excluding partially used or empty containers, will either be collected at the end of the study by the study monitor or returned by the PI or designee to Arrowhead Pharmaceuticals Inc. or its designee. When requested in writing by the Sponsor, following drug accountability and reconciliation, unused drug supplies may be destroyed by the PI or designee provided such disposition does not expose humans to risks from the drug and is permitted per the site's Standard Operating Procedures. Records shall be maintained by the PI of any such alternate disposition of the test drug. These records must show the identification and quantity of each unit disposed of, the method of destruction (considering the requirements of local law), and the person who disposed of the test substance. Such records must be submitted to the Sponsor.

8.7 Retention of Investigational Product Vials

For this study, used and partially used drug vials and bottles will be retained for an adequate period to allow accountability by the non-blinded CRA. No additional study drug samples will be retained.

8.8 Allocation to Treatment

All potential participants who sign an informed consent at Screening will receive a unique 6-digit number (i.e., a Screening Number). The first 3 digits will be the assigned site number and will be the same for each participant that screens at an individual site. The next 3 digits will be assigned sequentially (starting with 001). For patients who are deemed eligible, this 6-digit screening number will become the subject's permanent study ID number.

Once screened, eligible participants will be allocated to a sequentially numbered treatment and assigned a unique randomization number in accordance with the randomization schedule. Each participant will be assigned to either active (ARO-HBV) or PBO treatment. The allocation of active treatment or PBO will be performed using a block randomization algorithm. Randomization assignment can be requested up to 5 days prior to a scheduled Day -1 visit. Final confirmation of eligibility will be checked prior to dosing on Day 1.

Participants who drop out or are removed from the study prior to their final onsite study visit for reasons other than AEs may be replaced.

Only patients enrolled into Cohort 12 will received JNJ-6379.

8.9 Blinding and Code-break

Blinding of study drug (ARO-HBV)/PBO assignment is critical to the integrity of this clinical trial. It is expected that in most cases, AEs can be properly managed without the need for unblinding. However, in the event of a medical emergency in which knowledge of an individual participant's assignment is considered critical to the participant's well-being and management, the PI or documented designated treating physician may request permission to unblind the treatment assignment from the Sponsor Medical Monitor. If the situation is not an immediate emergency, the PI should contact the responsible Medical Monitor to discuss the participant and circumstances requiring the unblinding. The blind will be broken only for the specific participant under discussion. Unblinding in situations that are not an immediate emergency may only take place with the notification and agreement of the responsible Sponsor Medical Monitor. The randomization schedules will be maintained under controlled access. The personnel involved in the dispensing of investigational products will be accountable for ensuring compliance to randomization schedules. The non-blinded CRA will review the randomization schedule in comparison to the dispensing log to verify correct randomization.

As the NHV component of the study is double-blinded, sealed subject -specific code break envelopes will be produced by the Sponsor or Sponsor designee and will be retained at the clinical study site in a secure, accessible location. If the PI considers an adverse event to be of such severity as to require immediate specific knowledge of the identity and dose of the relevant product, the PI may break the study code for that participant only. A record, including date, time, name and signature of person opening the envelope and reason, must be made both on the opened envelope and in the participant's medical records. The study monitor should be informed promptly.

After the completion of the final study visit (not including 90-day follow up phone call) for each NHV cohort, unblinding for Sponsor analysis will occur at Sponsor discretion. However, the site will remain blinded to treatment assignment.

9 STUDY METHODS AND SCHEDULES

9.1 Overview of Procedures

For NHVs, cohorts of 6 eligible subjects (2 placebo, 4 active ARO-HBV) will be evaluated at each dose level starting at dose level 1 (35 mg). Participants who have signed an HDEC (or local equivalent) approved informed consent form and have met all of the protocol eligibility criteria during screening, will be randomized at a ratio of 2:1 (active:PBO) to receive ARO-HBV or PBO in a double blind fashion. NHV cohorts will receive a single dose only.

Each cohort will begin with administration of ARO-HBV or PBO to two sentinel participants (one ARO-HBV, one PBO). Following the Day 3 evaluation in these participants, if there are no significant safety concerns based on PI's judgement, the remaining participants in the cohort will be treated. Dosing of participants will be staggered by at least 15 minutes such that no two participants will be dosed simultaneously.

Clinical facility confinement for NHVs will be approximately 2 days for single dose administration (Day -1 through 24 hour assessments). Blood samples will be drawn pre-dose on Day 1 for baseline measurements. Height and weight will be measured at Screening only to calculate BMI.

Based on observations for all NHV subjects in a cohort through Day 8, dosing will begin for the next NHV cohort and as applicable the next CHB cohort at the discretion of the DSC (not including Cohorts 1b and 1c). 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 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.

After all subjects in a cohort have completed an End-of-Study (EOS) visit, Sponsor may be unblinded at Sponsors request. PI and study participants will remain blinded.

For CHB patients in Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10, 11 and 12, eligible CHB patients who have signed an HDEC (or local equivalent) approved informed consent form will receive three doses of ARO-HBV at dose intervals ranging from once every week to once every 4 weeks in an open label fashion. Screening for the CHB cohorts can begin once Cohort 1 dosing has commenced. These cohorts (not including Cohorts 1b and 1c) will be opened for accrual once the corresponding NHV cohort receiving the same dose level has reached Day 8, based on agreement of the DSC that it is safe

to proceed. Cohorts 6, 7, 8, 9, 10 and 11 can be opened for enrollment any time after Cohort 5 has reached Day 8 (and DSC has approved opening of such cohorts) and there is sufficient safety and viral antigen response data from CHB patients to determine a dose level for these cohorts. It is the intent that Cohorts 7, 10 and 11 will be treated at increasing dose levels starting with a dose equal to Cohort 6. Dose levels for Cohorts 6-11 is ≤ 300 mg. Cohorts 2b through Cohort 7 and Cohorts 10 and 11 will be enrolled in sequence (as shown in **Figure 1**). Cohorts 8 and 9 may be enrolled in parallel with other CHB cohorts after the DSC has voted post Cohort 5 to open the remaining CHB patient cohorts and once a specified dose (≤ 400 mg) has been identified. Cohorts 1b and 1c are open for enrollment with the addition of this protocol amendment and may enroll in parallel.

On dosing days, clinical facility confinement for CHB patients will be approximately 2 hours unless a prolonged period of post-dose observation is needed based on PI discretion. Blood samples will be drawn pre-dose on Day 1 for baseline measurements. Height and weight will be measured at Screening only to calculate BMI. Participants will undergo evaluations at screening and at regular intervals during the study as described in the Schedule of Assessments.

With the exception of Cohort 12 patients, all other CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after Day 113. Only Cohort 12 patients will require follow-up until the Day 337 (±5 days) visit. Subjects consenting to additional follow up will continue on NUCs. Subjects not consenting to additional follow up will be followed per protocol based on Schedule of Assessment Tables 1.2, 1.3 and 1.4.

Single doses of ARO-HBV will be evaluated in NHVs and multiple doses of ARO-HBV will be evaluated in CHB patients in a sequential manner as shown in **Figure 1**.

Cohort 12 will enroll 12 CHB patients in an open label fashion to receive 200 mg ARO-HBV on Days 1, 29 and 57 as well as JNJ-6379 250 mg oral once daily starting on Day 1 and continuing through Day 84. Like all other cohorts, patients enrolling in Cohort 12 will either enter the study on NUCs or start NUCs on Day 1. Enrollment in Cohort 12 can begin once enrollment is full in Cohorts 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10, 11.

9.2 Selection and Screening

Prior to commencement of any screening procedures, the PI, or designee, will inform the participant about the nature and purpose of the study, including the risks and benefits involved, possible AEs, the

fact that their participation is voluntary and provide a copy of the HDEC (or local equivalent)-approved Informed Consent Form for review. Each participant will acknowledge receipt of this information by giving written informed consent for their involvement in the study in the presence of the PI, or qualified designee, who will also sign and date the Informed Consent Form. Time of consent will be recorded on the Informed Consent Form. The original signed consent form will be retained by the PI and a copy of the original will be given to the participant. Informed consent will be performed per the Principles of the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) procedures.

Having given Informed Consent, potential participants will undergo procedures outlined in the Schedule of Assessments, to be performed within 60 days of the scheduled dosing date, to determine that he/she meets the inclusion/exclusion criteria specified in Sections 7.2 and 7.3.

9.3 On-Study Procedures/Assessments

9.3.1 *Study Procedures: Clinical Facility Confinement*

Eligible participants will present at the Clinical Facility on Day -1, the day prior to dosing. Note that study dose administration is on Day 1, which must occur within 60 days of screening. NHV participants only will be confined to the clinical facility until after the 24-hour post-dose (Day 2) assessments.

On arrival at the clinical facility on Day -1, the PI, or appropriately trained designee, will meet with participants to reiterate all study procedures and encourage participants to ask any questions. All participants shall undergo a check-in procedure during which questions will be asked regarding protocol compliance and safety monitoring.

Documentation of the participant's fulfillment of the entry criteria, for all participants considered for the study and subsequently included or excluded, is to be completed by the PI, or medically qualified designee. Documentation of screening failure details will be recorded using eligibility screening forms or a participant screen failure log. Procedures outlined in the Schedule of Assessments will be performed. Meals and water will be provided while participants are confined at the clinical facility. Timing will abide by fasting restrictions outlined in Section 7.5.

9.3.2 *Demographics/Medical History*

Medical History will include medication use over the previous 30 days, including vitamins, over-the-counter, prescription drugs, recreational drugs or supplements and alcohol and tobacco use.

9.3.3 *Physical Exam*

A complete physical exam will be performed at Screening and as per Schedule of Assessments.

At Screening, height (centimetres, without shoes) and weight (kilograms, without shoes) will be obtained to determine BMI.

At all other time points outlined in the Schedule of Assessments, a symptom-directed physical exam will be performed if indicated.

9.3.4 *Electrocardiogram*

A single 12-lead ECG measurement will be obtained at time points outlined in the Schedule of Assessments after the participant is supine for at least 3 minutes. Any abnormal ECGs will be repeated in triplicate, with each measurement approximately 1 minute apart. ECGs will be performed prior to venipuncture and other invasive procedures.

9.3.5 *Vital Sign Assessments*

Systolic/diastolic blood pressure, temperature, heart rate, respiratory rate (breaths/min) will be obtained at time points outlined in the Schedule of Assessments after the participant is seated or semi-supine for at least 3 minutes. Vitals signs will be obtained prior to venipuncture and other invasive procedures.

9.3.6 *Clinical Laboratory Tests & Pharmacodynamic Values*

Blood and urine samples will be collected to perform clinical laboratory tests run at a central laboratory. Participants will be required to fast for the Screening sample collections.

At the Screening visit, up to 60 days prior to the first dose of study medication, a blood and urine sample will be collected for the laboratory tests detailed below, to establish eligibility for enrolment. Baseline values will be the values from Day 1 pre-dose labs. If this sample is not available Screening values will be considered baseline. The results will be assessed by the PI, or medically qualified designee, before study enrolment. Any abnormality in laboratory values (that are confirmed on repeat) deemed clinically significant by the PI, or medically qualified designee (i.e., those that would jeopardize the safety of the participant or impact on the validity of the study results), will result in exclusion of that participant. Up to two retests for inclusionary or exclusionary labs are allowed. Clinical laboratory tests will be performed on participants' blood and urine at specified time-points listed in the Schedule of Assessments.

***Biochemistry*:** 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 and Troponin l.

Hematology: Hemoglobin, red blood cell count (RBC), hematocrit, mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), platelets, white cell count, neutrophils, lymphocytes, monocytes, eosinophils and basophils.

Coagulation: Partial thromboplastin time (PTT), Prothrombin time (PT) with INR.

Urinalysis: Leucocytes, nitrites, urobilinogen, protein, pH, blood, specific gravity, ketone, bilirubin and glucose.

Reflex microscopic urinalysis will be performed if indicated: White Blood Cells, Red Blood Cells, Epithelial cells, Bacteria.

Serology: HBV genotyping, HBV-RNA (if scientifically feasible), HBV-DNA, HBsAg (qualitative and quantitative), Anti-HBsAg (qualitative and quantitative), HBeAg (qualitative and quantitative), Anti-HBeAg (qualitative and quantitative), HBcrAg (quantitative), Hepatitis C antibody and HIV antibody screen. If necessary, participants will be counseled by the PI, or medically trained designee, concerning the blood tests for Hepatitis B surface antigen, Hepatitis C and HIV antibodies, and their subsequent results.

HBV DNA sequencing: To be analyzed only if HBV DNA serum levels are above 60 IU/mL for ARO-HBV target site, HBsAg epitope shift, and core/pre-core mutation tests, and above 1,900 IU/mL for HBV deep sequencing. An additional sample will be collected if resistance is suspected (defined as a > 1.0 log IU/mL increase in HBV DNA from NADIR from Day 1 through day 71, confirmed by repeat test).

FSH: Post-menopausal status will be confirmed by follicle-stimulating hormone (FSH) level consistent with post-menopausal state.

Drugs Screen: Urine drug screen for Benzodiazepines, Amphetamines, Barbiturates, Methamphetamines, Methadone, Opiates, Phencyclidine, Cannabinoids, Ecstasy and Cocaine.

Pregnancy: Females of childbearing potential will have a urine pregnancy test. If urine pregnancy test is positive, patient will be referred to their primary care provider for follow up.

Cytokines & Complement: Samples for analysis of Cytokine Panel A: IL-6, MCP-1, TNFalpha, IL-8, IL-1beta, IFNalpha, IL-10, IL-12 (p40), IL-12 (p70), Mip-1alpha) and Complement factors (Bb and CH50, C5a, C4a, C3a) and Cytokine Panel B: TNF alpha, IFN gamma, CXCL-9, and CXCL-10 will be obtained as indicated at time points outlined in the Schedule of Assessments. Collected cytokine Panel B samples will only be analyzed at discretion of and with notification by Sponsor.

Anti-Drug Antibodies: For Cohorts 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10 and11 blood samples for the anti-drug antibodies test will be collected at Screening, Day 57 and Day 113 or at EOS.

Cellular Immunology Studies: For all CHB patient cohorts, blood samples to evaluate changes in anti-viral host immunologist profile will be collected on Day 1 (pre-dose), 43 and 113. This will include T cell subsets (activation and exhaustion state), NK cell subsets (activation and exhaustion state), B cell subset, monocyte subsets and HBV antigen specific T cell response (including HBcAg,

HBsAg). Cellular immunology studies will be conducted if scientifically feasible in New Zealand only.

Interferon Response Gene SNP testing: Patient's interferon response gene SNPs will be evaluated (if patient consents to limited genetic testing). A blood sample for pharmacogenomics (DNA) research is optional and will only be collected from subjects who consent separately to this component of the study. Subjects who are enrolled in the study at the time of this amendment will be contacted to ask for their consent for this component of the study. Sample can be collected any time after the consent has been signed. This sample can be used to assess impact of IL28B polymorphism on efficacy of ARO-HBV treatment. In addition, samples can be used to investigate the potential association of genetic factors with efficacy, safety, or pharmacokinetics of ARO-HBV, CHB infection, or HBV-related disease or may be used to develop tests/assays related to ARO-HBV or HBV. These analyses will be performed at the sponsor's discretion, will always be under the sponsor's supervision, and may be reported separately.

9.3.7 *Pharmacokinetics*

Samples for analysis of circulating AD04872 and AD05070 will be obtained at time points following the end of injection outlined in the Schedule of Assessments.

Plasma concentrations of ARO-HBV, NUC and JNJ-6379 will be measured at a single post-dose time point in Cohort 12 only.

9.3.8 *Concomitant Medications/Therapies*

Participants will be instructed to inform the PI of the details (indication, dose and dates of administration) if they do take any medication, and these details will be recorded in the eCRF. If necessary, paracetamol may be used during the study as necessary. Any other medication or therapy other than blood pressure medication must be approved by the Medical Monitor or PI prior to administration.

9.3.9 *Follow-Up Procedures*

Day 90 (± 5 days) Telephone Call

Documented telephone contact with each participant to verify compliance with contraceptive measures and absence of any known pregnancy at 90 days post EOS (Day 29 for NHVs and Day 113 for CHB patients).

Additional CHB Follow-up

With the exception of Cohort 12 patients, all other CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after Day 113. Only Cohort 12 patients will require follow-up until the Day 337 (±5 days) visit. Subjects consenting to additional follow up will continue on NUCs. Subjects not consenting to additional follow up will be followed per protocol based on Schedule of Assessment Tables 1.2, 1.3 and 1.4.

9.3.10 *Early Termination Procedures*

The reason for Early Termination will be documented in source documents and eCRF. Procedures as outlined in the Schedule of Assessments will be completed.

9.4 Allocation of Formulations

Four NHV participants will receive active treatment and 2 participants will receive PBO in each dose level. Treatments will be administered per the randomized sequence kept by the pharmacy or in a secure place at the clinical site, under control of the un-blinded staff member. All CHB patients will receive active treatment. CHB patients in Cohort 12 will receive daily oral JNJ-6379 + ARO-HBV Q28 x 3.

9.5 Study Formulation Administration

Appropriately trained employees of the clinical site will administer ARO-HBV/PBO. Each dose will be administered as a subcutaneous injection. Doses of 400 mg will be administered as two injections per dose with each injection administered into separate a site. The date, time and location of administration will be recorded in the source notes and witnessed by a second person from the clinical facility. The preferred site of injection is the abdomen. Optional additional sites are the upper arms and thighs or other sites based on PI clinical judgement.

Table 2: Injection number and volume per cohort

Cohort	Dose	Concentration	Total Injection Volume	# Injections per planned dose
1	35 mg	200 mg/mL	0.175 mL	Single
1b	25 mg	200 mg/mL	0.125 mL	Single
1c	50 mg	200 mg/mL	0.25 mL	Single
2, 2b, 6, 7	100 mg	200 mg/mL	0.5 mL	Single
3, 3b, 10, 12	200 mg	200 mg/mL	1.0 mL	Single
4, 4b, 8, 9, 11	300 mg	200 mg/mL	1.5 mL	Single
5, 5b	400 mg	200 mg/mL	2.0 mL	Two (at separate sites)

JNJ-6379 will be dispensed to patients in Cohort 12 only who will take their daily dose (250 mg oral) at home. Patients will bring all remaining tablets to their subsequent visits for compliance assessment, and receive additional tablets to cover their daily doses until the next subsequent visit.

9.6 Timing of Treatments and Procedures

Actual times of procedures for each participant will vary depending on scheduling and will be recorded in the eCRF.

Post-dose time points will be determined based on time of injection.

In the event of multiple procedures scheduled at the same time, non-invasive procedures (i.e. ECGs, AE assessment) will be conducted prior to invasive procedures (i.e., blood sample collection). Timing of activities may be adjusted slightly to accommodate all procedures.

The following windows are allowed for study assessments/visits:

Pre-dose:	Within 60 minutes prior to dosing
PK/PD through 6 hours:	± 2 minutes
All other procedures through 6 hours:	± 10 minutes
PK/PD from 8 to 48 hours:	± 5 minutes
All other procedures from 8 to 48 hours:	± 15 minutes
Day 8:	± as per SOA
Day 15 to Day 29:	± as per SOA
Visits beyond Day 29:	± as per SOA

9.7 Safety Endpoints

The safety of ARO-HBV (alone or in combination with JNJ-6379) will be evaluated by collection of the following measurements performed at specified time points:

- Monitoring of AEs/ SAEs
- Physical examinations
- Vital signs
- ECG measurements
- Injection Site Reactions (Mild, Moderate or Severe): Photographic images will be taken of all injection site reactions at the time of reporting and at the time of resolution.
- Clinical laboratory tests (hematology, biochemistry, coagulation, urinalysis)
- Concomitant medications/therapy, and
- Reasons for treatment discontinuation due to toxicity

The AE/SAE reporting period for an enrolled participant will begin when the participant provides informed consent. Treatment-Emergent AEs/SAEs will be those defined as following dose administration. All AEs/SAEs that occur during the AE reporting period specified in the protocol must be reported to Arrowhead Pharmaceuticals, Inc., regardless of the relationship of the AE to study

treatment. Any known untoward event that occurs beyond the AE reporting period that the PI considers an SAE and possibly related to study treatment will be reported to Arrowhead.

9.8 Blood Sampling for Pharmacokinetic and Pharmacodynamic Analysis

Blood samples will be collected from participants through an indwelling cannula or through a fresh vein puncture. The actual blood collection time will be recorded in the source documents. All deviations outside the range allowed above will be documented as protocol deviations. In all such cases, appropriate time corrections, for the actual time of sample collection will be incorporated at the time of data analysis. Blood samples for pharmacokinetic and pharmacodynamic analyses will be collected at time points outlined in the Schedule of Assessments.

The target sample times will be printed in the eCRF. The actual sample times (times samples taken) will be recorded alongside the nominal times in the eCRF and will be entered at the time of or as soon as possible after sampling. All times must be recorded in the 24-hour format. An explanation must be given for any blood sample taken outside of the set sampling times.

9.8.1 Sample Processing and Analysis for Pharmacokinetic Samples

Blood samples will be collected and processed per the Laboratory Manual.

Plasma samples will be assayed by a validated hybridization-ligation method. The criteria for repeat analysis, as defined in the respective in-house procedure, will be followed.

The validation study conducted by the appointed bioanalytical laboratory to establish validity including accuracy, precision, reproducibility, specificity, recovery and frozen stability of the analytical method will be appended to the final report.

9.8.2 Sample Processing and Analysis for Pharmacodynamic, Cytokine and Complement Samples

Whole blood will be collected at specified time points for analysis of cytokines and complement.

Cytokines: Whole blood samples will be collected and processed per the Laboratory Manual. Initially the pre-dose and 2-hour post-dose samples will be analyzed, with the remaining samples analyzed if a change from baseline is observed at 2 hours.

Complement: Venous blood samples will be collected and processed per the Laboratory Manual at each time point. Initially the 0 (pre-) and 2-hour post-dose samples will be analyzed, with the remaining samples analyzed if a change from baseline is observed at 2 hours.

Results, percent change, and duration of response from baseline to 4 weeks (or longer as necessary) will be analyzed and summarized by dose cohort and treatment group**.**

10 ADVERSE EVENTS

The PI and clinical facility staff are responsible for detection, recording and reporting of events that meet the criteria and definition of various adverse events as listed below. Adverse events will be recorded from time of signed consent through to end of study; only AEs that occur post-dose will be considered treatment-emergent. The PI and clinical facility staff are responsible for detection, recording and reporting of pregnancy and appropriate follow up.

10.1 Definitions

An **Adverse Event (AE)** is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding or diagnostic test), symptom, or disease temporally associated with the use of a medicinal (investigational/experimental) product, whether related to this product or not. (Refer to International Conference on Harmonisation [ICH] E2a: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, 27 October 1994).

Treatment emergent AEs will be defined as AEs with onset after administration of the study drug, or when a preexisting medical condition increases in severity or frequency after study drug administration.

AEs will not include:

- A medical or surgical procedure such as surgery, endoscopy, tooth extraction, or transfusion (although the condition that leads to the procedure may be an AE)
- A pre-existing disease or condition present at the start of the study that does not worsen during the study
- Any situation where an untoward medical occurrence has not occurred (for example, hospitalizations for cosmetic elective surgery or “social” admissions)

- An overdose of either the investigational product or a concurrent medication without any resulting signs or symptoms.

A **Serious Adverse Event (SAE)** is an AE that:

- Results in death,
- Is life-threatening, (NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event/reaction in which the participant was at immediate risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death, if it were more severe)
- Requires inpatient hospitalization or prolongation of an existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect,
- Is a medically important event or reaction.

Medical and scientific judgment should be exercised in deciding whether other situations, should be considered serious such as important medical events that may not be immediately life-threatening or result in death or hospitalization but might jeopardize the participant or might require medical or surgical intervention to prevent one of the other serious outcomes listed in the above definition. These should also be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.2 Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs

Abnormal assessments (e.g. ECGs and vital signs) that are judged by the PI as clinically significant or result in clinical sequelae will be recorded as AEs. Laboratory abnormalities will be reported by the PI as AEs if the abnormality is considered clinically significant or results in clinical sequelae. Laboratory abnormalities not reported as AEs are not to be reported as Clinically Significant (CS) in the study database.

Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs.

The PI (or medically qualified designee) will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

10.3 Timing, Frequency, and Method of Detecting AEs

Any pre-existing conditions or signs and/or symptoms present in a participant prior to the start of the study (i.e., before informed consent) should be recorded as Medical/Surgical History.

All AEs occurring after informed consent and on or before the final visit must be reported as AEs; only AEs that occur post-dose will be considered treatment-emergent. All AEs must be recorded irrespective of whether they are considered drug-related.

At each visit/assessment in the period defined above, AEs will be evaluated by the PI (or medically qualified designee) and recorded.

10.4 Recording of AEs

When an AE occurs, it is the responsibility of the PI or medically qualified designee to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The PI or medically qualified designee will then record the AE on the AE CRF. Additional reporting requirements for an AE meeting serious criteria are discussed in Section 10.7 below.

The PI or medically qualified designee will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In all cases, when available, the diagnosis should be reported as the event and not the individual signs/symptoms. It is not acceptable for the PI to send photocopies of the subject's medical records to the Sponsor in lieu of completion of the appropriate AE CRF pages.

10.5 Evaluating AEs

10.5.1 Assessment of Intensity

The PI or medically qualified designee will assess intensity for each AE reported during the study. The assessment will be based on the PI's (or medically qualified designee's) clinical judgment. The intensity should be assigned to one of the following categories:

Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: An event that prevents normal everyday activities.

An AE that is assessed as severe should not be confused with a SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 10.1.

10.5.2 Injection site reactions

Injection site reactions will be graded as either Mild, Moderate or Severe. An injection site reaction is defined as an adverse reaction (usually immunologic) developing at the site of injection. Injection site reactions are graded Mild, Moderate or Severe based on symptoms. Photographs of local reactions around injection site should be obtained at the time of reporting and at the approximate time of resolution.

- Mild: Tenderness with or without associated symptoms (e.g., warmth, erythema, itching), mild pain or mild edema.
- Moderate: Pain with associated phlebitis or lipodystrophy
- Severe: Tissue ulceration or necrosis with associated severe tissue damage or if operative intervention is indicated

10.5.2 Assessment of Causality

The PI (or medically qualified designee) is obligated to assess the relationship between investigational product and the occurrence of each AE. The PI (or medically qualified designee) will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated. The PI (or medically qualified designee) will also consult the Investigator's Brochure in the determination of his/her assessment.

There may be situations when an SAE has occurred and the PI has minimal information to include in the initial SAE report. However, it is very important that the PI (or medically qualified designee)

always assess causality for every event prior to transmission of the SAE report form. The PI (or medically qualified designee) may change his/her opinion of causality considering follow-up information, amending the SAE report form accordingly. The causality assessment is one of the criteria used when determining global regulatory reporting requirements.

The PI (or medically qualified designee) will provide the assessment of causality utilizing three possible categories: Not Related, Possibly Related and Probably Related.

An AE will be considered "not related" to the use of the product if any of the following tests are met:

An unreasonable temporal relationship between administration of the product and the onset of the AE (e.g., the event occurred either before, or too long after administration of the product for it to be considered product-related);

A causal relationship between the product and the AE is biologically implausible (e.g., death as a passenger in an automobile accident)

A clearly more likely alternative explanation for the AE is present (e.g., typical adverse reaction to a concomitant drug and/or typical disease-related event)

An AE will be considered "Possibly related" when there is a reasonable possibility that the incident, experience, or outcome may have been caused by the product under investigation.

An AE will be considered "Probably related" when there are facts, evidence, or arguments to suggest that the event is related to the product under investigation.

10.6 Follow-up of AEs

After the initial AE, the PI is required to proactively follow each participant and provide further information on the participant's condition as deemed appropriate.

All AEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up. Once resolved, the appropriate AE CRF page and SAE report form (if event is serious) will be updated. The PI, or medically qualified designee, will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. In

the event of a fatal outcome in an SAE, the PI, or medically qualified designee, will attempt to obtain postmortem findings, including histopathology, and provide all additional information in a follow up SAE report.

New or updated information regarding an SAE will be recorded on a new SAE report form marked as follow-up with the appropriate follow-up number added to the report. The follow-up report will be signed and dated by the PI.

10.7 Prompt Reporting of SAEs

AEs meeting serious criteria MUST be reported promptly to the designated Pharmacovigilance CRO, and the HDEC or local equivalent.

10.7.1 Completion and Transmission of the SAE reports

Once the PI becomes aware that an SAE has occurred in a study participant, she/he will report the information on an SAE report form to the designated Pharmacovigilance CRO within 24 hours. The SAE report form will always be completed as thoroughly as possible with all available details of the event and signed by the PI or medically qualified designee. If the PI, or medically qualified designee, does not have all information regarding an SAE, he/she will not wait to receive additional information before reporting the event. The SAE report form will be updated when additional information is received.

The PI (or medically qualified designee) will always provide an assessment of causality at the time of the initial report as described in Section 10.5.2.

Facsimile or email transmission of the SAE report form are the preferred methods to transmit this information to the designated Pharmacovigilance CRO. In rare circumstances, notification by telephone is acceptable, with a copy of the SAE CRF sent by overnight mail. Initial notification via the telephone does not replace the need for the PI, or medically qualified designee, to complete and sign the SAE report form within the outlined time frames.

The Sponsor will provide a list of project contacts for SAE receipt, fax numbers, telephone numbers, and mailing addresses. Any event that in the opinion of the PI, or medically qualified designee, may be of immediate or potential concern for the participant's health or well-being will be reported to the Sponsor emergency contact listed below.

Sponsor Emergency Contact
[redacted]

10.7.2 Serious Adverse Event Reports to the HDEC (or local equivalent)

The PI, or responsible person per local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the HDEC or local equivalent.

10.8 Regulatory Requirements for Reporting of SAEs

The PI (or medically qualified designee) will promptly report all SAEs in accordance with the procedures detailed in Section 10.7. Prompt notification of SAEs by the PI **is essential** so that the Sponsor may comply with its regulatory obligations.

10.9 Post-study AEs

A post-study AE is defined as any event that occurs outside of the AE detection period defined in Section 10.3.

The PI is not obligated to actively seek AEs in former study participants. However, if the PI learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event at least possibly related to the investigational product, the PI will promptly notify Arrowhead.

10.10 SAEs Related to Study Participation

An SAE considered related to study participation (e.g., procedures, invasive tests, a change in existing therapy), even if it occurs during the pre- or post-treatment period, will be reported promptly (refer Section 10.7).

11 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

11.1 Data analysis through EOS and Additional follow-up

Two separate data analyses will be performed, one for all subjects through EOS (Day 29 for NHVs and Day 113 for CHB patients), and one additional and separate analysis for CHB patients who consent to the additional follow up.

11.2 Sample Size Considerations

This study represents a proof of principle study, and as such no formal sample size calculation was performed. Results from this study will be utilized in sample size calculations for subsequent studies.

11.3 Screening Data

Demographics will be tabulated by participant and summarized by cohort and treatment group. Eligibility assessments at baseline, including medical/surgical history data and physical examination data (including height and weight), will be listed for each participant.

11.4 Safety/Tolerability Data

In general, safety analyses will be performed and the results summarized by-cohort and treatment group.

Treatment-emergent AEs will be summarized using the latest version of MedDRA by System Organ Class (SOC) and Preferred Term (PT), classified from verbatim terms. The incidence and percentage of participants with at least 1 occurrence of a PT will be included, per the most severe grade using a 3-point scale (mild, moderate, severe). The number of events per Preferred Term will also be summarized. Causality (relationship to study treatment) will be summarized separately.

The incidence and frequency of AEs, SAEs, related AEs, related SAEs and AEs leading to withdrawal, dose modification, or treatment discontinuation will be summarized by dose and treatment group per SOC and Preferred Terms. AEs will also be summarized in listings. The duration of AEs will be determined and included in listings, along with the action taken and outcome.

The incidence of laboratory abnormalities will be summarized. Results for variables that are not coded will be presented in the listings as “below, within, and above” the normal limits of the laboratory. Pregnancy test results will be summarized separately by time point.

Vital sign measurements will be summarized at each scheduled time point using descriptive statistics. Physical examination findings will be summarized by time point and presented in subject listings.

ECG parameter changes overall, changes from baseline and qualitative assessments will be summarized.

The whole blood collected for analysis following a single dose of ARO-HBV at different dose levels will undergo analysis for cytokines (Panel A) and complement changes. Results, percent change, and duration of response from baseline to 24 hours (or 48 hours, as necessary) will be analyzed where indicated by initial testing at pre-dose and at 2-hours post-administration. If cytokine or complement levels are elevated from pre-dose to 2-hours post-dose then all other specified timepoints (See Schedule of Assessments) will also be analyzed. Whole blood collected following multiple doses of ARO-HBV for cytokine Panel B samples will only be analyzed at discretion of and with notification by Sponsor. Results, percent change, and duration of response from baseline will be analyzed where indicated. Results for cytokines and complement will be summarized by dose cohort and treatment group.

11.5 Pharmacokinetic Data

Plasma concentrations of ARO-HBV collected at specified time points post-dose from all participants at different dose levels will be used to calculate the following single dose pharmacokinetic parameters:

$AUC_{0–24}$: The area under the plasma concentration versus time curve from the zero to 24 hours.

AUC_{inf}: The area under the plasma concentration versus time curve from zero to infinity.

C_{max}: The maximum plasma concentration will be obtained directly from the plasma concentration time profile.

t_{max}: The time to maximum plasma concentration will be obtained by inspection.

$t_{½}$: The half-life will be calculated by the equation $t_{½} = \ln(2)/k_{el}$.

The pharmacokinetic parameters will be determined using non-compartmental method(s). Descriptive statistics of pharmacokinetic parameters will include mean, standard deviation (SD), and coefficient of variation (CV), minimum and maximum. Dose-related trends in pharmacokinetic parameters will be assessed.

Plasma concentrations of ARO-HBV, NUC and JNJ-6379 will be measured at a single 2 hour post-dose time point in Cohort 12 only.

Pharmacokinetic parameters will be tabulated and summarized by dose level where applicable. The concentration-time profiles for each participant and the mean concentration-time profiles by dose level will be plotted with concentration presented on both linear and logarithmic scales. Cohort 12 CHB patient limited PK data will be evaluated separately from NHV PK data.

Statistical analysis will be performed on the pharmacokinetic parameters using validated statistical software.

11.6 Pharmacodynamic Data

The whole blood collected for pharmacodynamic analysis following multiple doses of ARO-HBV at different dose levels will undergo analysis for changes in HBV-DNA, HBV-RNA (if scientifically feasible) and viral antigens based on reference laboratory (VIDRL) generated values. Cellular immunologic assessments will also be conducted (if scientifically feasible) at University of Auckland.

Immunology assessments (CHB patients in New Zealand only)

- Changes in profile from pre-dose to post-dose time points for: 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.

- Changes from pre-dose to post-dose time points for: HBV antigen specific T cell response (including HBcAg, HBsAg). To be conducted if scientifically feasible.

Virology assessments (CHB patients only)

- Virologic parameters will be summarized by cohort for the following:

- Quantitative HBsAg (qHBsAg): Log change from baseline to nadir and duration of response from nadir back to approximately 20% of baseline or EOS. In CHB patients who consent to additional follow up, HBsAg will be followed until the end of the additional follow-up period or early termination and summarized separately.

- Percent of patients with loss of HBsAg (defined as quantitative HBsAg < 0.05 IU/mL) at EOS and time to occurrence (Kaplan Meier). In CHB patients who consent to additional follow up,

HBsAg loss will be monitored until the end of the additional follow-up period or early termination and summarized separately.

- Percent of patients with anti-HBS seroconversion at EOS and time to occurrence (Kaplan Meier). In CHB patients who consent to additional follow up, anti-HBS seroconversion will be monitored until the end of the additional follow-up period or early termination and summarized separately.

- Change in Anti-HBs (quantitative) to EOS. In CHB patients who consent to additional follow up, change in Anti-HBs (quantitative) will be monitored until the end of the additional follow-up period or early termination and summarized separately.

- Quantitative HBV DNA (when quantifiable at baseline): Log change from baseline to EOS. In CHB patients who consent to additional follow up, HBV DNA will be monitored until the end of the additional follow-up period or early termination and summarized separately.

- Quantitative HBV RNA: Log change from baseline to nadir and duration of response from baseline to EOS (if scientifically feasible). In CHB patients who consent to additional follow up, HBV RNA will be monitored until the end of the additional follow-up period or early termination and summarized separately.

- Quantitative HBcrAg: Log change from baseline to nadir and duration of response from baseline to EOS. In CHB patients who consent to additional follow up, HBcrAg will be monitored until the end of the additional follow-up period or early termination and summarized separately.

- Quantitative HBeAg (HBeAg positive only): Log change from baseline to nadir and duration of response from baseline to EOS. In CHB patients who consent to additional follow up, HBeAg will be monitored until the end of the additional follow-up period or early termination and summarized separately.

- Emergence of HBV mutations (sequencing of ARO-HBV target site, Core/pre-core, HBsAg epitope, any other mutations by deep sequencing) to EOS. In CHB patients who consent to additional follow up, HBV mutations will be monitored until the end of the additional follow-up period or early termination and summarized separately.

- Virologic response parameters may be summarized based on presence of interferon response gene SNPs (e.g. IL28B).

Descriptive statistics of virologic parameters will include mean, median, count, SD, minimum, and maximum. Additional details will be provided in the statistical analysis plan. If feasible, Clinical Study Report analysis of, quantitative HBsAg through EOS will be based on a final batched analysis of samples.

Separate analysis will 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.

11.7 Data Recording and Quality Control

Source documents must be maintained for each participant in the study, consisting of all demographic and medical information, including clinical laboratory data, etc. A copy of the signed informed consent form must be retained. All information on the e-CRFs must be traceable to these source documents in the participant's file. Data recorded in all participants' eCRFs will be subjected to a quality control review.

12 STUDY APPROVAL AND CONDUCT

The following conditions will be met.

12.1 Regulatory Approval

The requirements for the conduct of clinical trials in accordance with local applicable regulations will be met before commencement of this study.

12.2 Institutional Review Board/Ethics Committee (HDEC or local equivalent) Approval

Prior to initiation of the study, written HDEC (or local equivalent) approval of the Protocol and Informed Consent Forms, based on the principles of ICH GCP procedures, will be received. A copy of the signed and dated letter of approval will be provided to the clinical site and Arrowhead Pharmaceuticals, Inc. prior to study commencement. Any written information and/or advertisements to be used for volunteer recruitment will be approved by the HDEC (or local equivalent) prior to use. A

list of the HDEC (or local equivalent) voting members, their titles or occupations, FWA number (where applicable) and their institutional affiliations will be requested before study initiation.

Protocol modifications that may impact subject safety or the validity of the study will be approved by the HDEC (or local equivalent), following written agreement from the Sponsor.

12.3 Ethical Considerations

This study will be carried out per the Declaration of Helsinki 1964, as modified by the 64th World Medical Assembly, Fortaleza, Brazil, October 2013, the Notes for Guidance on Good Clinical Practice (GCP) (2000) (CPMP/ICH/135/95), and the Principles of the ICH GCP. The protocol will be submitted for approval to the appropriate HDEC (or local equivalent), and written approval obtained before patients are enrolled. The composition of the HDEC (or local equivalent) will also be provided to the Sponsor. If approval is suspended or terminated by an HDEC (or local equivalent), the PI will notify the Sponsor immediately

Where applicable, the clinical site and Arrowhead Pharmaceuticals, Inc. agree to abide by the local compensation guidelines for injury resulting from participating in a company-sponsored research project. Compensation will only be provided on the understanding that the provision of compensation does not amount to an admission of legal liability, and is subject to the proposed recipient signing a full and complete release of the company from all claims, damages and costs.

12.4 Written Informed Consent

Informed consent will be obtained before the volunteer can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements. Study participation includes all screening procedures, as well as any wash-out of excluded medications.

It is the responsibility of the PI (or medically qualified designee) to obtain a written informed consent from everyone participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. The PI (or medically qualified designee) must also explain to the volunteers that they are completely free to refuse to enter the study or to withdraw from it at any time. Appropriate forms for documenting a written consent will be provided by the PI or by Arrowhead Pharmaceuticals, Inc.

For this study, each eligible participant will be required to provide written informed consent before participation in the study.

All eligible participants will have the study explained by the PI or designee. They will receive a full explanation, in lay terms, of the aims of the study, the discomforts, risks and benefits in taking part as well as of insurance and other procedures for compensation in case of injury. It will be explained that the study is for research purposes only and is not expected to provide any therapeutic benefit to the individual. It will be pointed out that they can withdraw from the study at any time without prejudice. Each participant will acknowledge receipt of this information by giving written informed consent for participation in the study. The volunteer will be given a copy of the signed Informed Consent Form to retain.

12.5 Emergency Contact with Principal Investigator

Suitable arrangements will be made for participants to contact the PI or medically trained designee in the event of an emergency.

12.6 Notification of General Practitioner

It is the responsibility of the PI or designee, to notify, where applicable, with the consent of the participant, the general practitioner of the subject's participation in the trial, by sending a letter stating the nature of the trial, treatments, expected benefits or adverse events and concomitant drugs to be avoided.

12.7 Clinical Laboratory Certification and Reference Ranges

Before the initiation of this study, the PI, or designee, will obtain a copy of the certification form, with certification number and expiration date for all clinical laboratories (excluding central laboratories) used in the study. Reference ranges for each clinical laboratory test used in this study will be obtained from the appropriate laboratory, which will perform the test for the study.

12.8 Protocol Deviations

A protocol deviation is defined as any intentional or unintentional change to, or noncompliance with, the approved protocol procedures or requirements. The PI will conduct the study in compliance with the approved protocol and will not implement any deviation from or changes to the protocol without prior agreement by the Sponsor and review and documented approval from the HDEC (or local

equivalent) of an amendment, except where necessary to eliminate an immediate hazard to study subjects.

Deviations may result from the action or inaction of the participant, PI, or site staff. 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, PK 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

Protocol deviations impacting subject safety or eligibility will be reported to the Sponsor or CRO within 2 business days of occurrence and to the HDEC (or local equivalent) /competent regulatory authority per local regulatory requirements.

The PI is responsible for ensuring that any known protocol deviations are recorded and reported as agreed. The nature and reasons for protocol deviations will be recorded in each participant's CRF.

12.9 Termination of the Study

The Sponsor reserves the right to discontinue the trial at any time. Reasons will be provided in the event of this happening. The PI reserves the right to discontinue the study for safety reasons at any time in collaboration with the Sponsor.

13 STUDY ADMINISTRATION

13.1 Study Monitoring

Arrowhead Pharmaceuticals, Inc. is responsible for assuring the proper conduct of the study about protocol adherence and validity of the data recorded on the CRFs. Participant confidentiality will be maintained.

In accordance with applicable regulations, GCP, and Arrowhead Pharmaceuticals, Inc. procedures, Arrowhead Pharmaceuticals, Inc. or its designee will be responsible for assigning a study monitor (CRA) who will contact the site to organize a visit prior to participant enrolment to review the protocol and data collection procedures with site staff. In addition, the assigned study monitor will periodically contact the site, including conducting on-site visits. The extent, nature and frequency of on-site visits will be based on such considerations as the study objective and/or endpoints, the purpose of the study, study design complexity, and enrolment rate.

During these site visits, the study monitor will:

- Check the progress of the study.
- Review study data collected.
- Conduct source document verification.
- Identify any issues and address their resolution.
- Check investigational product accountability
- Review blood and urine samples and ensure they are labeled and stored correctly.

This will be done to verify that the:

- Data are authentic, accurate and complete.
- Safety and rights of participants are being protected.
- Study is conducted in accordance with the currently approved protocol (and any amendments), GCP and all applicable regulatory requirements.

The PI agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant issues.

At study closure, a study monitor will conduct the following activities in conjunction with the PI or site staff as appropriate:

- Return of all study data to Arrowhead Pharmaceuticals, Inc.
- Data queries.
- Accountability, reconciliation and arrangements for unused investigational product(s).
- Inventory and final disposition (e.g., destruction, shipping to repository, etc.).
- Review of site study records for completeness.

Because the study is blinded, an unblinded study monitor will be assigned to visit the site pharmacy during, and at study completion to review the randomization schedule in comparison to the dispensing log to verify correct randomization of study drug.

13.2 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, Arrowhead Pharmaceuticals, Inc. may conduct a quality assurance audit of the study site. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the PI and clinical site agree to notify Sponsor as soon as possible following awareness of an impending regulatory inspection. The PI and clinical site agree to allow the auditor/inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

13.3 Records Retention

Following closure of the study, the PI must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection) and whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems and staff. When permitted by local laws/regulations or institutional policy, some or these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The PI must assure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the PI must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

Arrowhead Pharmaceuticals, Inc. will inform the PI of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or Arrowhead Pharmaceuticals, Inc. standards/procedures; otherwise, the retention period will default to 15 years.

The material to be stored shall include, but is not limited to, the following:

- Signed and dated copy of the final study protocol and any amendments.
- Signed and dated letter of IRB/EC approval, letter of constitution of the HDEC (or local equivalent) and copies of any other correspondence relevant to the study with the HDEC (or local equivalent) or regulatory authorities.
- The HDEC (or local equivalent) approved Informed Consent Form.
- Current *curriculum vitae* (signed and dated) of the PI and co-workers with major responsibilities in the trial.
- Site Signature and Delegation of Responsibility Log
- FDA Form 1572 (where applicable)
- Financial Disclosure Form(s)
- Blank CRF/eCRF.
- Signed participant informed consent forms.
- Laboratory reference ranges (signed and dated).
- The completed CTN Application Form (where applicable).
- The Final Study Report.
- Clinical raw data including the Source Data Forms, all clinical laboratory report forms, subject CRFs, drug accountability forms, and dispensing records, etc.

14 INFORMATION DISCLOSURE AND INVENTIONS

14.1 Ownership

[redacted]

[redacted]

14.2 Confidentiality

[redacted]

14.3 Publication

[redacted]

[redacted]

15 REFERENCES

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16 APPENDIX 1: ALT FLARE GUIDELINES

Fluctuations and elevations above ULN in ALT and AST are a normal part of CHB natural history. In fact, it is commonly believed that an elevation in ALT in the setting of undetectable or falling HBV-DNA, or in the setting of a decline in HBsAg may be a favorable prognosticator, representing immune system reconstitution against HBV. This is often referred to as an host induced flare. Similarly, elevated ALT in the setting of rising HBV-DNA may be a virus induced flare. In a first in human/first in patient clinical trial involving subjects infected with HBV, it is critically important to differentiate such causes of elevated ALT from drug induced liver injury which should inform the decision of whether to continue a subject with elevated ALT in the study. To facilitate this interpretation of ALT elevations the following guideline is provided.

Close monitoring and intercurrent diagnostic evaluations for any patient on study treatment (or placebo in blinded studies) who fits the following "ALT flare" definition:

- A rise in a patient's serum ALT to a value that is > 3-fold above the patient's Baseline ALT value (confirmed on repeat), and ALT value that is at least 10x ULN (confirmed on repeat)
- patient management should include a prompt clinic visit (and further follow-up visits when needed)
    - Drawn serum chemistry, hematology and cytokine Panel B and serially monitor if indicated. Immediately check and serially monitor albumin and direct bilirubin levels, to determine if liver functions are stable or deteriorating.
    - evaluate patient for potential causes of the ALT elevation, e.g.: intercurrent HAV, HEV, HCV or other infection; toxin exposures including acetaminophen, alcohol use, hepatotoxic herbal supplements or concomitant medicines.
    - patient's recent HBV DNA levels should be checked for pattern of change. If HBV DNA is declining the ALT flare is presumptively not due to viral breakthrough (resistance) and could be a `beneficial' (host immune system induced) flare if no intervening causes are found.

Study treatment interruption (pending diagnostic tests) or discontinuation for an ALT flare with biochemical evidence of hepatic decompensation should be considered as per protocol stopping rules.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

PROTOCOL NUMBER:	**AROHBV1001**
STUDY TITLE:	**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**
VERSION/DATE:	**Version 2.0, 13 June 2018**

OVERVIEW/RATIONALE:

This amendment:

1. Adds two additional CHB cohorts with all subjects in each cohort scheduled to receive three weekly doses.
2. Adds Immunologic Assessments to be performed in CHB patients in New Zealand
3. Clarifies that any patient volunteering for inclusion in cohort ***5b*** (in addition to 8 or 9) that has signed an informed consent at the time that the fourth patient in that cohort is enrolled, may also be enrolled if enrolment can be accomplished within 14 days of the fourth patient being dosed
4. Incorporates the following administrative changes submitted by Note to File dated 24May2018:
   - A ±2 day window applied to assessments performed on Days 71 & 85 in Cohort 7
   - A symptom directed physical exam added on Day 113/EOS for Cohort 7
   - A pregnancy test for females of child bearing potential added at Day 113/EOS for Cohort 6
5. Corrects any administrative, grammatical, formatting errors and inconsistencies; rewording for clarity.

SUMMARY OF CHANGES:

1. **Section/page:** Title Page, page 1

   Added:

   This amendment adds two additional CHB cohorts with all subjects in each cohort scheduled to receive three weekly doses.

   This amendment also adds Immunologic Assessments to be performed in CHB patients in New Zealand only.

2. **Section/page:** 1 Protocol Synopsis, Exploratory Objectives, p. 3

   Added:

   - ***To evaluate the effect of multiple doses of ARO-HBV 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 on HBV antigen specific T-cell response (if scientifically feasible).***

3. **Section/page:** 1 Protocol Synopsis, Study Population/Patient Number, p. 3

   From:

   This study will be conducted in NHVs, adult males and females, aged 18-55 years with BMI between 19.0 and 35.0 kg/m² (Cohorts 1 – 5) and in HBeAg negative or HBeAg positive CHB patients, aged 18-65 years with BMI between 19.0 and 38.0 kg/m² (Cohorts 2b, 3b, 4b, 5b, 6, 7, 8, and 9). Cohort 8 will enroll HBeAg positive treatment naïve patients (no prior chronic exposure to NUCs or Interferon) and Cohort 9 will enroll HBeAg positive NUC experienced patients (on entecavir or tenofovir for at least 12 months). Cohorts 2b, 3b, 4b, 5b, 6 and 7 will enroll either HBeAg positive or negative patients regardless of previous NUC or PEG IFN treatment experience. All patients will be started on entecavir or tenofovir on Day 1. Patients currently on PEG IFN will not be allowed.

   To:

   This study will be conducted in NHVs, adult males and females, aged 18-55 years with BMI between 19.0 and 35.0 kg/m² (Cohorts 1 – 5) and in HBeAg negative or HBeAg positive CHB patients, aged 18-65 years with BMI between 19.0 and 38.0 kg/m² (Cohorts 2b, 3b, 4b, 5b, 6, 7, 8, 9, ***10 and 11***). Cohort 8 will enroll HBeAg positive treatment naïve patients (no prior chronic exposure to NUCs or Interferon) and Cohort 9 will enroll HBeAg positive NUC experienced patients (on entecavir or tenofovir for at least 12 months). Cohorts 2b, 3b, 4b, 5b, 6, 7, ***10 and 11*** will enroll either HBeAg positive or negative patients regardless of previous NUC or PEG IFN treatment experience. All patients will be started on entecavir or tenofovir on Day 1. Patients currently on PEG IFN will not be allowed.

   From:

   Summary of Participant Profile by Cohort:

   - Cohorts 2b, 3b, 4b, 5b, 6, 7: Any CHB patient regardless of HBeAg or prior therapy status (as long as other Inclusion and Exclusion criteria are met.

To:

Summary of Participant Profile by Cohort:

- Cohorts 2b, 3b, 4b, 5b, 6, 7, ***10 and 11***: Any CHB patient regardless of HBeAg or prior therapy status (as long as other Inclusion and Exclusion criteria are met).

From:

CHB cohorts will each enroll 4 subjects in an open label fashion to receive escalating multiple doses of ARO-HBV. In addition, any patient volunteering for inclusion in cohort 8 or 9 that has signed an informed consent at the time that the fourth patient in that cohort is enrolled, may also be enrolled if enrolment can be accomplished within 14 days of the fourth patient being dosed.

To:

CHB cohorts will each enroll 4 subjects in an open label fashion to receive escalating multiple doses of ARO-HBV. In addition, any patient volunteering for inclusion in ***Cohort 5b***, 8 or 9 that has signed an informed consent at the time that the fourth patient in that cohort is enrolled, may also be enrolled if enrolment can be accomplished within 14 days of the fourth patient being dosed.

4. **Section/page:** 1 Protocol Synopsis, Study Population/Patient Number, pp. 3-4

From:

CHB patients regardless of HBeAg status or NUC/Interferon use history will enroll sequentially in cohorts 2b through 7) into a total of 6 open label cohorts (4 patients per cohort) at planned dose levels of 100 mg (Cohort 2b), 200 mg (Cohort 3b), 300 mg (Cohort 4B) and 400 mg (Cohort 5b) to receive three doses (Q28 days) of active treatment in an open label fashion. Cohort 6 will enroll 4 CHB subjects (after cohort 5b has completed enrollment) to receive three doses two weeks apart. Cohort 7 will enroll 4 CHB patients (after Cohort 6 has completed enrollment) to receive three doses a week apart. Cohort 8 will enroll 4 HBeAg positive treatment naïve CHB patients to receive three monthly doses of ARO-HBV. Cohort 9 will enroll 4 HBeAg positive entecavir or tenofovir experienced CHB patients to receive three monthly doses of ARO-HBV. The dose used for Cohorts 6, 7, 8 and 9 will be ≤ 400 mg with an expected dose level of 400 mg.

To:

CHB patients regardless of HBeAg status or NUC/Interferon use history will enroll sequentially into a total of ***8*** open label cohorts ***(Cohorts 2b through 7 and Cohorts 10 and 11***, 4 patients per cohort) at planned dose levels of 100 mg (Cohort 2b), 200 mg (Cohort 3b), 300 mg (Cohort 4b) and 400 mg (Cohort 5b) to receive three doses (Q28 days) of active treatment in an open label fashion. Cohort 6 will enroll 4 CHB subjects (after Cohort 5b has completed enrollment) to receive three doses two weeks apart. Cohorts 7, ***10 and 11*** will enroll 4 CHB patients ***sequentially*** (after Cohort 6 has completed enrollment) to receive three doses a week apart ***at increasing dose levels starting with a dose equal to Cohort 6. Cohorts 5b through 7 and Cohorts 10 and 11 will enroll sequentially (after being opened at the final planned DSC meeting) with enrollment and dosing in a later cohort not initiating until all subjects in the earlier cohort have received at least their first scheduled dose.*** Cohort 8 will enroll 4 HBeAg positive treatment naïve CHB patients to receive three monthly doses of ARO-HBV. Cohort 9 will enroll 4 HBeAg positive entecavir or tenofovir experienced CHB patients to receive three monthly doses of ARO-HBV. ***Cohorts 8 and 9 may enroll in parallel with Cohort 5b once opened by the DSC.*** The dose used for Cohorts 6, 7, 8, ***9, 10 and 11*** will be ≤ 400 mg with an expected dose level of *between 100 mg* to 400 mg.

5. **Section/page:** 1 Protocol Synopsis, Study Population/Patient Number, p. 4

From:

A total of approximately 30 NHV and 32 CHB participants (not including potential replacements) may be enrolled in the study.

To:

A total of approximately 30 NHV and **40** CHB participants (not including potential replacements) may be enrolled in the study.

6. **Section/page:** 1 Protocol Synopsis, Study Duration, p. 4

From:

For each CHB patient in the multi-dose cohorts 2b, 3b, 4b, 5b, 6, 7, 8 and 9 the duration of the study clinic visits is approximately 25 weeks from screening to the Day 113 EOS examination.

To:

For each CHB patient in the multi-dose Cohorts 2b, 3b, 4b, 5b, 6, 7, 8, 9, ***10 and 11*** the duration of the study clinic visits is approximately 25 weeks from screening to the Day 113 EOS examination.

7. **Section/page:** 1 Protocol Synopsis, Study Design/Methods, p. 5

From:

CHB patients:

In Cohorts 2b, 3b, 4b, 5b, 6, 7, 8 and 9, 4 eligible CHB patients per cohort who have signed an HDEC (or local equivalent) approved informed consent form will receive three doses of ARO-HBV at dose intervals ranging from once every week to once every 4 weeks in an open label fashion. Screening for the CHB cohorts can begin once cohort 1 dosing has commenced. These cohorts will be opened for accrual once the corresponding NHV cohort receiving the same dose level has reached Day 8, based on agreement of the DSC that it is safe to proceed. Cohorts 6, 7, 8 and 9 can be opened for enrollment concurrently with or any time after Cohort 5 has reached Day 8 (and DSC has approved opening of such cohorts) and there is sufficient viral antigen response data from CHB patients to determine a dose level for these cohorts (at the discretion of the DSC). The planned dose level for Cohorts 6-9 is ≤ 400 mg. Cohorts 2b through Cohort 7 will be enrolled in sequence (as shown in Figure 1). Cohorts 8 and 9 may be enrolled in parallel with other CHB cohorts after the DSC has voted post cohort 5 to open the remaining CHB patient cohorts and once a specified dose (≤ 400 mg) has been identified.

To:

CHB patients:

In Cohorts 2b, 3b, 4b, 5b, 6, 7, 8, 9, ***10 and 11***, 4 eligible CHB patients per cohort who have signed an HDEC (or local equivalent) approved informed consent form will receive three doses of ARO-HBV at dose intervals ranging from once every week to once every 4 weeks in an open label fashion. Screening for the CHB cohorts can begin once Cohort 1 dosing has commenced. These cohorts will be opened for accrual once the corresponding NHV cohort receiving the same ***single*** dose level has reached Day 8, based on agreement of the DSC that it is safe to proceed. Cohorts 6, 7, 8, 9, ***10 and 11*** can be opened for enrollment any time after Cohort 5 has reached Day 8 (and DSC has approved opening of such cohorts) and there is sufficient viral antigen response data from CHB patients to determine a dose level for these cohorts (at the discretion of the DSC). The planned dose level for Cohorts 6-***11*** is ***between 100 and 400 mg***. Cohorts 2b through Cohort 7 ***and Cohorts 10 and 11***, will be enrolled in sequence (as shown in Figure 1). Cohorts 8 and 9 may be enrolled in parallel with other CHB cohorts after the DSC has voted post Cohort 5 to open the remaining CHB patient cohorts and once a specified dose (≤ 400 mg) has been identified. ***For clarity, after Cohort 5 is through Day 8, the DSC will review all available safety data and vote to open Cohorts 5b, 6, 7, 8, 9, 10 and 11. Cohorts 5b, 8 and 9 may enroll and dose patients in parallel. Cohorts 5b through 7 and Cohorts 10 and 11 must enroll sequentially, meaning that Cohort 5b must be fully enrolled with each subject receiving at least a first dose before Cohort 6 can enroll. Cohort 6 must be fully enrolled with each subject receiving at least a first dose before Cohort 7 can enroll. Cohort 7 must be fully enrolled with each subject receiving at least a first dose before Cohort 10 can enroll and Cohort 10 must be fully enrolled with each subject receiving at least a first dose before Cohort 11 can enroll. It is the intent that Cohorts 7, 10 and 11 will be treated at increasing dose levels starting with a dose equal to Cohort 6.***

8. **Section/page:** 1 Protocol Synopsis, Figure 1, p. 6, pp. 34-35

From:

Figure 1: 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		N/A	N/A
Cohort 2	100 mg		Cohort 2b (all eligible CHB patients regardless of NUC or HBeAg status)	100 mg dosed on Day 1, 29, 57
Cohort 3	200 mg		Cohort 3b (all eligible CHB patients regardless of NUC or HBeAg status)	200 mg dosed on Day 1, 29, 57
Cohort 4	300 mg		Cohort 4b (all eligible CHB patients regardless of NUC or HBeAg status)	300 mg dosed on Day 1, 29, 57
Cohort 5	400 mg		Cohort 5b (all eligible CHB patients regardless of NUC or HBeAg status)	400 mg dosed on Day 1, 29, 57
			Cohort 6 (all eligible CHB patients regardless of NUC or HBeAg status)	Dose TBD** Day 1, 15, 29
			Cohort 7 (all eligible CHB patients regardless of NUC or HBeAg status)	Dose TBD** Day 1, 8, 15
			Cohort 8 HBeAg+, treatment naïve	Dose TBD** Day 1, 29, 57
			Cohort 9 HBeAg+, entecavir or tenofovir experienced	Dose TBD** Day 1, 29, 57

* All Cohorts use 2 sentinel subjects

**Dose for Cohort 6, 7, 8 and 9 to be determined based on safety and viral antigen response seen in Cohorts 2b, 3b, 4b and 5b. The planned dose level for Cohorts 6-9 is ≤ 400 mg. Cohorts 6-9 may be opened for enrollment any time after Cohort 5 Day 8 safety evaluation with a vote from the DSC. Cohorts 2b through Cohort 7 will be enrolled in sequence (as shown in Figure 1). Cohorts 8 and 9 may be enrolled in parallel with other CHB cohorts after the DSC has voted post cohort 5 to open the remaining CHB patient cohorts and once a specified dose (≤ 400 mg) has been identified.

To:

Figure 1: 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		N/A	N/A
Cohort 2	100 mg		Cohort 2b (all eligible CHB patients regardless of NUC or HBeAg status)	100 mg dosed on Day 1, 29, 57
Cohort 3	200 mg		Cohort 3b (all eligible CHB patients regardless of NUC or HBeAg status)	200 mg dosed on Day 1, 29, 57
Cohort 4	300 mg		Cohort 4b (all eligible CHB patients regardless of NUC or HBeAg status)	300 mg dosed on Day 1, 29, 57
Cohort 5	400 mg		Cohort 5b (all eligible CHB patients regardless of NUC or HBeAg status)	400 mg dosed on Day 1, 29, 57
			Cohort 6 (all eligible CHB patients regardless of NUC or HBeAg status)	Dose TBD** Day 1, 15, 29
			Cohort 7 (all eligible CHB patients regardless of NUC or HBeAg status)	Dose TBD** Day 1, 8, 15
			Cohort 8 HBeAg+, treatment naïve	Dose TBD** Day 1, 29, 57
			Cohort 9 HBeAg+, entecavir or tenofovir experienced	Dose TBD** Day 1, 29, 57
			Cohort 10 (all eligible CHB patients regardless of NUC or HBeAg status)	***Dose TBD** Day 1, 8, 15***
			Cohort 11 (all eligible CHB patients regardless of NUC or HBeAg status)	***Dose TBD** Day 1, 8, 15***

* All Cohorts use 2 sentinel subjects

** Dose for Cohort 6, 7, 8, 9, ***10 and 11*** to be determined based on safety and viral antigen response seen in Cohorts 2b, 3b, 4b, and 5b. The planned dose level for Cohorts 6-***11*** is ≤ 400 mg. Cohorts 6-***11*** may be opened for enrollment any time after Cohort 5 Day 8 safety evaluation with a vote from the DSC. Cohorts 2b through Cohort 7 ***and Cohorts 10 and 11*** will be enrolled in sequence (as shown in Figure 1). Cohorts 8 and 9 may be enrolled in parallel with other CHB cohorts after the DSC has voted post Cohort 5 to open the remaining CHB patient cohorts and once a specified dose (≤ 400 mg) has been identified.

9. **Section/page:** 1 Protocol Synopsis, Study Assessments, p. 8

   Added:

   Immunologic Assessments (limited number of HBV patients 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.***

10. **Section/page:** 1 Protocol Synopsis, Study Assessments, p. 8

    From:

    Immunogenicity:

    For Cohorts 2b, 3b, 4b, 5b, and 6-9 blood samples for the anti-drug antibodies test will be collected at screening, Day 57 and Day 113 or at the end of study visit.

    To:

    Immunogenicity:

    For Cohorts 2b, 3b, 4b, 5b, and 6-***11*** blood samples for the anti-drug antibodies test will be collected at screening, Day 57 and Day 113 or at the end of study visit.

11. **Section/page:** 1 Protocol Synopsis, Data Analysis, p. 9

    Added:

    Immunology Assessments (limited number of CHB patients in New Zealand only)
    Immunology parameters will be summarized by cohort for the following:
    - ***Changes in profile from pre-dose to post-dose time points for: 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.***
    - ***Changes from pre-dose to post-dose time points for: HBV antigen specific T cell response (including HBcAg, HBsAg). To be conducted if scientifically feasible.***

12. **Section/page:** Schedule of Assessments, Table 1.2, pp. 12-13

    From:

Table 1.2: Cohorts 2b, 3b, 4b, 5b, 8 and 9 (CHB patients, three Q28 day doses)

Assessment	**Screen (Days -60 to -1)**		**Day 1**	**Day 2**	**Day 8**	**Day 15 (± 2)**	**Day 29, 57 (± 2)**	**Day 43, 71 (± 2)**	**Day 85 (± 2)**	**Day 113 (± 2) EOS**	**Early Termination**
Informed Consent	X										
Eligibility Criteria	X		X[9]								
Body Mass Index	X										
Demographics	X										
Medical History	X		X*								
Drug Screen	X										
Hepatitis/HIV Serology Screen	X										
Physical Exam[1]	X		X*	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X	X[1]
FSH	X[8]										
Pregnancy test	X[5]		X[5]				X[5]			X	X
ECG	X		X[2]				X[2]			X	X
Vital Signs (BP, temp, RR, heart rate)	X		X[4]	X	X	X	X[4]	X	X	X	X
Hepatic Fibrosis Measure (FibroScan®)	X	**RANDOMIZE**									
Clinical Labs (heme, coag, chem, UA)	X		X[7]	X	X	X	X[7]	X	X	X	X
HBeAg qualitative	X										
Quantitative HBsAg, HBcrAg, HBeAg (e+ only) HBV DNA, HBV RNA	X		X		X	X	X	X	X	X	X
Quantitative anti-HBs, qualitative anti-HBe (e+ only)			X		X	X	X	X	X	X	X
HBV genotyping	X										
HBV sequencing	X									X	X
Cytokines (Panel B) TNF alpha, IFN gamma, CXCL-9, and CXCL-10[3]			X		X	X	X	X	X	X	X
Concomitant Meds/Therapies	X		X	X	X	X	X	X	X	X	X
Adverse Events[6]			X	X	X	X	X	X	X	X	X
Study Treatment			X				X				
Anti-drug antibodies[9]	X						X[9]			X	X
Start NUCs (naïve patients only)			X								

* Repeat if > 2 weeks from Screening

1. Symptom-directed PEs to be performed by visit as necessary.

2. ECGs: Measured pre-dose and at 1 and 2 hours post-dose; more frequently per hour if necessary. Performed prior to other invasive procedures.
3. Cytokines Panel B: (whole blood). Venous blood samples collected pre-dose on dosing days then as indicated. Collected samples will only be analyzed at discretion of and with notification by Sponsor.
4. Vitals: Measured pre-dose and at 5 min, 0.5, 1, and 2 hours post-dose.
5. Urine pregnancy test for females of childbearing potential only. Complete pre-dose on dosing days.
6. AE/SAE data capture begins from time of informed consent.
7. Clinical Chemistry, Hematology, Coagulation and Urinalysis pre-dose only on dosing days.
8. Performed for females not of childbearing potential to confirm postmenopausal status.
9. Anti-drug antibodies collected pre-dose, Day 57 and on Day 113 or EOS.

To:

Table 1.2: Cohorts 2b, 3b, 4b, 5b, 8 and 9 (CHB patients, three Q28 day doses)

Assessment	**Screen (Days -60 to -1)**		**Day 1**	**Day 2**	**Day 8**	**Day 15 (± 2)**	**Day 29, 57 (± 2)**	**Day 43, 71 (± 2)**	**Day 85 (± 2)**	**Day 113 (± 2) EOS**	**Early Termination**
Informed Consent	X										
Eligibility Criteria	X		X[9]								
Body Mass Index	X										
Demographics	X										
Medical History	X		X*								
Drug Screen	X										
Hepatitis/HIV Serology Screen	X										
Physical Exam[1]	X		X*	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X	X[1]
FSH	X[8]										
Pregnancy test	X[5]		X[5]				X[5]			X	X
ECG	X		X[2]				X[2]			X	X
Vital Signs (BP, temp, RR, heart rate)	X		X[4]	X	X	X	X[4]	X	X	X	X
Hepatic Fibrosis Measure (FibroScan®)	X										
Clinical Labs (heme, coag, chem, UA)	X		X[7]	X	X	X	X[7]	X	X	X	X
HBeAg qualitative	X										
Quantitative HBsAg, HBcrAg, HBeAg (e+ only) HBV DNA, HBV RNA	X		X		X	X	X	X	X	X	X
Quantitative anti-HBs, qualitative anti-HBe (e+ only)			X		X	X	X	X	X	X	X
HBV genotyping	X										
HBV sequencing	X									X	X

RANDOMIZE

Cytokines (Panel B) TNF alpha, IFN gamma, CXCL-9, and CXCL-10[3]			X		X	X	X	X	X	X	X
Cellular Immunology[10]			***X***					***X***		***X***	
Concomitant Meds/Therapies	X		X	X	X	X	X	X	X	X	X
Adverse Events[6]			X	X	X	X	X	X	X	X	X
Study Treatment			X				X				
Anti-drug antibodies[9]	X						X[9]			X	X
Start NUCs (naïve patients only)			X								

* Repeat if > 2 weeks from Screening
1. Symptom-directed PEs to be performed by visit as necessary.
2. ECGs: Measured pre-dose and at 1 and 2 hours post-dose; more frequently per hour if necessary. Performed prior to other invasive procedures.
3. Cytokines Panel B: (whole blood). Venous blood samples collected pre-dose on dosing days then as indicated. Collected samples will only be analyzed at discretion of and with notification by Sponsor.
4. Vitals: Measured pre-dose and at 5 min, 0.5, 1, and 2 hours post-dose.
5. Urine pregnancy test for females of childbearing potential only. Complete pre-dose on dosing days.
6. AE/SAE data capture begins from time of informed consent.
7. Clinical Chemistry, Hematology, Coagulation and Urinalysis pre-dose only on dosing days.
8. Performed for females not of childbearing potential to confirm postmenopausal status.
9. Anti-drug antibodies collected pre-dose, Day 57 and on Day 113 or EOS.
10. 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. Cellular immunology studies to be conducted on Days 1 (pre-dose), 43 and 113 in New Zealand only.

13. **Section/page:** Schedule of Assessments, Table 1.3, pp. 13-14

From:

Table 1.3 Cohort 6 (CHB 3 doses Q14 days)

Assessment	**Screen (Days -60 to -1)**		**Day 1**	**Day 2**	**Day 8**	**Day 15 (± 2)**	**Day 29, (± 2)**	**Day 43, 57, 71, 85, 113 (EOS) (± 2)**	**Early Termination**
Informed Consent	X	**RANDOMIZE**							
Eligibility Criteria	X		X[9]						
Body Mass Index	X								
Demographics	X								
Medical History	X		X*						
Drug Screen	X								
Hepatitis/HIV Serology Screen	X								
Physical Exam[1]	X		X*	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
FSH	X[8]								

Pregnancy test	X[5]		X[5]			X[5]	X[5]		X
ECG	X		X[2]			X[2]	X[2]		X
Vital Signs (BP, temp, RR, heart rate)	X		X[4]	X	X	X[4]	X[4]	X	X
Hepatic Fibrosis Measure (FibroScan®)	X								
Clinical Labs (heme, coag, chem, UA)	X		X[7]	X	X	X	X[7]	X	X
HBeAg qualitative	X								
Quantitative HBsAg, HBcrAg, HBV DNA, HBV RNA, HBeAg (e+ only	X		X		X	X	X	X	X
Quantitative anti-HBs, qualitative anti-HBe (e+ only)			X		X	X	X	X	X
HBV genotyping	X								
HBV sequencing	X								X
Cytokines (Panel B) – TNF alpha, IFN gamma, CXCL-9, and CXCL-10[3]			X		X	X	X	X	X
Concomitant Meds/Therapies	X		X	X	X	X	X	X	X
Adverse Events[6]			X	X	X	X	X	X	X
Study Treatment			X			X	X		
Anti-drug antibodies[9]	X							X[9]	X
Start NUCs (naïve patients only)			X						

* Repeat if > 2 weeks from Screening
1. Symptom-directed PEs to be performed by visit as necessary.
2. ECGs: Measured pre-dose and at 1 and 2 hours post-dose; more frequently per hour if necessary. Performed prior to other invasive procedures.
3. Cytokines Panel B: (whole blood). Venous blood samples collected pre-dose on dosing days then as indicated. Collected samples will only be analyzed at discretion of and with notification by Sponsor.
4. Vitals: Measured pre-dose and at 5 min, 0.5, 1, and 2 hours post-dose.
5. Urine pregnancy test for females of childbearing potential only. Pre-dose on dosing days.
6. AE/SAE data capture begins from time of informed consent.
7. Clinical Chemistry, Hematology, Coagulation and Urinalysis pre-dose
8. Performed for females not of childbearing potential to confirm postmenopausal status
9. Anti-drug antibodies collected pre-dose, Day 57 and on Day 113 or EOS.

To:

Table 1.3 Cohort 6 (CHB 3 doses Q14 days)

Assessment	**Screen (Days -60 to -1)**		**Day 1**	**Day 2**	**Day 8**	**Day 15 (± 2)**	**Day 29, (± 2)**	**Day 43, 57, 71, 85, 113 (EOS) (± 2)**	**Early Termination**
Informed Consent	X								
Eligibility Criteria	X		X[9]						
Body Mass Index	X								
Demographics	X								
Medical History	X		X*						
Drug Screen	X								
Hepatitis/HIV Serology Screen	X								
Physical Exam[1]	X		X*	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
FSH	X[8]								
Pregnancy test	X[5]		X[5]			X[5]	X[5]	***X[11]***	X
ECG	X		X[2]			X[2]	X[2]		X
Vital Signs (BP, temp, RR, heart rate)	X		X[4]	X	X	X[4]	X[4]	X	X
Hepatic Fibrosis Measure (FibroScan®)	X	**RANDOMIZE**							
Clinical Labs (heme, coag, chem, UA)	X		X[7]	X	X	X	X[7]	X	X
HBeAg qualitative	X								
Quantitative HBsAg, HBcrAg, HBV DNA, HBV RNA, HBeAg (e+ only	X		X		X	X	X	X	X
Quantitative anti-HBs, qualitative anti-HBe (e+ only)			X		X	X	X	X	X
HBV genotyping	X								
HBV sequencing	X								X
Cytokines (Panel B) – TNF alpha, IFN gamma, CXCL-9, and CXCL-10[3]			X		X	X	X	X	X
Cellular Immunology[10]			***X***					***X[10]***	
Concomitant Meds/Therapies	X		X	X	X	X	X	X	X
Adverse Events[6]			X	X	X	X	X	X	X

Study Treatment			X			X	X		
Anti-drug antibodies[9]	X							X[9]	X
Start NUCs (naïve patients only)			X						

* Repeat if > 2 weeks from Screening
1. Symptom-directed PEs to be performed by visit as necessary.
2. ECGs: Measured pre-dose and at 1 and 2 hours post-dose; more frequently per hour if necessary. Performed prior to other invasive procedures.
3. Cytokines Panel B: (whole blood). Venous blood samples collected pre-dose on dosing days then as indicated. Collected samples will only be analyzed at discretion of and with notification by Sponsor.
4. Vitals: Measured pre-dose and at 5 min, 0.5, 1, and 2 hours post-dose.
5. Urine pregnancy test for females of childbearing potential only. Pre-dose on dosing days.
6. AE/SAE data capture begins from time of informed consent.
7. Clinical Chemistry, Hematology, Coagulation and Urinalysis pre-dose
8. Performed for females not of childbearing potential to confirm postmenopausal status
9. Anti-drug antibodies collected pre-dose, Day 57 and on Day 113 or EOS.
10. 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. Cellular immunology studies to be conducted on Days 1 (pre-dose), 43 and 113 in New Zealand only.
11. Pregnancy test on Day 113

14. **Section/page:** Schedule of Assessments, Table 1.4, pp. 15-16

From:

Table 1.4 Cohort 7 (CHB three weekly doses)

Assessment	**Screen (Days -60 to -1)**		**Day 1**	**Day 2**	**Day 8**	**Day 15 (± 2)**	**Day 29 (± 2)**	**Day 43, 57 (± 2)**	**Day 71, 85**	**Day 113 (± 2) (EOS)**	**Early Termination**
Informed Consent	X	**RANDOMIZE**									
Eligibility Criteria	X		X								
Body Mass Index	X										
Demographics	X										
Medical History	X		X*								
Drug Screen	X										
Hepatitis/HIV Serology Screen	X										
Physical Exam[1]	X		X*	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]		X[1]
FSH	X[8]										
Pregnancy test	X[5]		X[5]		X[5]	X[5]				X	X
ECG	X		X[2]		X[2]	X[2]					X
Vital Signs (BP, temp, RR, heart rate)	X		X[4]	X	X[4]	X[4]	X	X	X	X	X
Hepatic Fibrosis Measure (FibroScan®)	X										

Clinical Labs (heme, coag, chem, UA)	X		X[7]	X	X[7]	X[7]	X	X	X	X	X
HBeAg qualitative	X										
Quantitative HBsAg, HBcrAg, HBV DNA, HBV RNA, HBeAg (e+ only)	X		X		X	X	X	X	X	X	X
Quantitative anti-HBs, qualitative anti-HBe (e+ only)			X		X	X	X	X	X	X	X
HBV genotyping	X										
HBV sequencing	X									X	X
Cytokines (Panel B) – TNF alpha, IFN gamma, CXCL-9, and CXCL-10[3]			X		X	X	X	X	X	X	X
Concomitant Meds/Therapies	X		X	X	X	X	X	X	X	X	X
Adverse Events[6]			X	X	X	X	X	X	X	X	X
Study Treatment			X		X	X					
Anti-drug antibodies[9]	X							X[9]		X	X
Start NUCs (naïve patients only)			X								

* Repeat if > 2 weeks from Screening
1. Symptom-directed PEs to be performed by visit as necessary.
2. ECGs: Measured pre-dose and at 1 and 2 hours post-dose; more frequently per hour if necessary. Performed prior to other invasive procedures.
3. Cytokines Panel B: (whole blood). Venous blood samples collected pre-dose on dosing days then as indicated. Collected samples will only be analyzed at discretion of and with notification by Sponsor.
4. Vitals: Measured pre-dose and at 5 min, 0.5, 1, and 2hours post-dose.
5. Urine pregnancy test for females of childbearing potential only. Pre-dose on dosing days.
6. AE/SAE data capture begins from time of informed consent.
7. Clinical Chemistry, Hematology, Coagulation and Urinalysis pre-dose.
8. Performed for females not of childbearing potential to confirm postmenopausal status.
9. Anti-drug antibodies collected pre-dose, Day 57 and on Day 113 or EOS.

To:

Table 1.4 Cohort 7, *10 and 11* (CHB three weekly doses)

Assessment	**Screen (Days -60 to -1)**		**Day 1**	**Day 2**	**Day 8**	**Day 15 (± 2)**	**Day 29 (± 2)**	**Day 43, 57 (± 2)**	**Day 71, 85 *(±2)***	**Day 113 (± 2) (EOS)**	**Early Termination**
Informed Consent	X	**RANDOMIZE**									
Eligibility Criteria	X		X								
Body Mass Index	X										
Demographics	X										
Medical History	X		X*								
Drug Screen	X										

Hepatitis/HIV Serology Screen	X										
Physical Exam[1]	X		X*	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	***X[1]***	X[1]
FSH	X[8]										
Pregnancy test	X[5]		X[5]		X[5]	X[5]				X	X
ECG	X		X[2]		X[2]	X[2]					X
Vital Signs (BP, temp, RR, heart rate)	X		X[4]	X	X[4]	X[4]	X	X	X	X	X
Hepatic Fibrosis Measure (FibroScan®)	X										
Clinical Labs (heme, coag, chem, UA)	X		X[7]	X	X[7]	X[7]	X	X	X	X	X
HBeAg qualitative	X										
Quantitative HBsAg, HBcrAg, HBV DNA, HBV RNA, HBeAg (e+ only)	X		X		X	X	X	X	X	X	X
Quantitative anti-HBs, qualitative anti-HBe (e+ only)			X		X	X	X	X	X	X	X
HBV genotyping	X										
HBV sequencing	X									X	X
Cytokines (Panel B) – TNF alpha, IFN gamma, CXCL-9, and CXCL-10[3]			X		X	X	X	X	X	X	X
Cellular Immunology[10]			***X***					***X***		***X***	
Concomitant Meds/Therapies	X		X	X	X	X	X	X	X	X	X
Adverse Events[6]			X	X	X	X	X	X	X	X	X
Study Treatment			X		X	X					
Anti-drug antibodies[9]	X							X[9]		X	X
Start NUCs (naïve patients only)			X								

* Repeat if > 2 weeks from Screening

1. Symptom-directed PEs to be performed by visit as necessary.
2. ECGs: Measured pre-dose and at 1 and 2 hours post-dose; more frequently per hour if necessary. Performed prior to other invasive procedures.
3. Cytokines Panel B: (whole blood). Venous blood samples collected pre-dose on dosing days then as indicated. Collected samples will only be analyzed at discretion of and with notification by Sponsor.
4. Vitals: Measured pre-dose and at 5 min, 0.5, 1, and 2hours post-dose.
5. Urine pregnancy test for females of childbearing potential only. Pre-dose on dosing days.
6. AE/SAE data capture begins from time of informed consent.
7. Clinical Chemistry, Hematology, Coagulation and Urinalysis pre-dose.
8. Performed for females not of childbearing potential to confirm postmenopausal status.
9. Anti-drug antibodies collected pre-dose, Day 57 and on Day 113 or EOS.
10. 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. Cellular immunology studies to be conducted on Days 1 (pre-dose), 43 and 113 in New Zealand only.

15. **Section/page:** 3, List of Abbreviations, pp. 21-22

Added:

B-cell	**Lymphocyte not processed by the thymus and producing antibodies**
HBcAg	**HBV core antigen**
HBcrAg	**HBV core related antigen**
HBeAg	**HBV E (envelope) antigen**
HBsAg	**HBV S (surface) antigen**
NHV	**Normal Healthy Volunteer**
NK cell	**Natural Killer Cell**
T-cell	**Lymphocyte produced or processed by thymus gland**

16. **Section/page:** 5.3, Exploratory Objectives, pp. 29-30

Added:

- ***To evaluate the effect of multiple doses of ARO-HBV on HBV patient immune cell profile including T-cells, NK cells, B cells and monocytes in a limited number of HBV patients in New Zealand only (if scientifically feasible).***
- ***To evaluate the effect of multiple doses of ARO-HBV on HBV antigen specific T-cell response in a limited number of HBV patients in New Zealand only (if scientifically feasible).***

17. Section/page: 6.1, Study Design, pp. 31-33

From:

HBeAg negative or HBeAg positive CHB patients, aged 18-65 years with BMI between 19.0 and 38.0 kg/m² (Cohorts 2b, 3b, 4b, 5b, 6, 7, 8, and 9) will be enrolled. Cohort 8 will enroll HBeAg positive treatment naïve patients (no prior chronic exposure to NUCs or Interferon) and Cohort 9 will enroll HBeAg positive NUC experienced patients (on entecavir or tenofovir for at least 12 months). Cohorts 2b, 3b, 4b, 5b, 6 and 7 will enroll either HBeAg positive or negative patients regardless of previous

NUC or PEG IFN treatment experience. All patients will be started on entecavir or tenofovir on Day 1. Patients currently on PEG IFN will not be allowed.

Summary of Participant Profile by Cohort:

- Cohorts 1-5: NHVs, adult males and females, aged 18-55 years
- Cohorts 2b, 3b, 4b, 5b, 6, 7: Any CHB patient regardless of HBeAg or prior therapy status (as long as other Inclusion and Exclusion criteria are met.
- Cohort 8: HBeAg positive treatment naïve patients (no prior chronic exposure to NUCs or Interferon)
- Cohort 9: HBeAg positive NUC experienced patients (on entecavir or tenofovir for at least 12 months).

CHB patients regardless of HBeAg status or NUC/Interferon use history will enroll sequentially in cohorts 2b through 7) into a total of 6 open label cohorts (4 patients per cohort) at planned dose levels of 100 mg (Cohort 2b), 200 mg (Cohort 3b), 300 mg (Cohort 4B) and 400 mg (Cohort 5b) to receive three doses (Q28 days) of active treatment in an open label fashion. Cohort 6 will enroll 4 CHB subjects (after cohort 5b has completed enrollment) to receive three doses two weeks apart. Cohort 7 will enroll 4 CHB patients (after Cohort 6 has completed enrollment) to receive three doses a week apart. Cohort 8 will enroll 4 HBeAg positive treatment naïve CHB patients to receive three monthly doses of ARO-HBV. Cohort 9 will enroll 4 HBeAg positive entecavir or tenofovir experienced CHB patients to receive three monthly doses of ARO-HBV. The dose used for Cohorts 6, 7, 8 and 9 will be ≤ 400 mg with an expected dose level of 400 mg. An additional cohort using an intermediate dose level and dose frequency may be added with approval of the HDEC (or local equivalent) and DSC. CHB patient Screening for all CHB cohorts may start when Cohort 1 opens for enrollment. However, no CHB patients may be dosed until their respective cohort is approved for dosing by the DSC. CHB dosing may begin and NHV dose escalation may occur based on DSC approval which can occur by vote after cumulative data through Day 8 from the current NHV cohort is available. See **Figure 1** for dose escalation schedule).

To:

HBeAg negative or HBeAg positive CHB patients, aged 18-65 years with BMI between 19.0 and 38.0 kg/m² (Cohorts 2b, 3b, 4b, 5b, 6, 7, 8, 9, ***10 and 11***) will be enrolled. Cohort 8 will enroll HBeAg positive treatment naïve patients (no prior chronic exposure to NUCs or Interferon) and Cohort 9 will enroll HBeAg positive NUC experienced patients (on entecavir or tenofovir for at least 12 months).

Cohorts 2b, 3b, 4b, 5b, 6, 7, ***10 and 11*** will enroll either HBeAg positive or negative patients regardless of previous NUC or PEG IFN treatment experience. All patients will be started on entecavir or tenofovir on Day 1. Patients currently on PEG IFN will not be allowed.

Summary of Participant Profile by Cohort:

- Cohorts 1-5: NHVs, adult males and females, aged 18-55 years
- Cohorts 2b, 3b, 4b, 5b, 6, 7, ***10 and 11***: Any CHB patient regardless of HBeAg or prior therapy status (as long as other Inclusion and Exclusion criteria are met).
- Cohort 8: HBeAg positive treatment naïve patients (no prior chronic exposure to NUCs or Interferon)
- Cohort 9: HBeAg positive NUC experienced patients (on entecavir or tenofovir for at least 12 months).

CHB patients regardless of HBeAg status or NUC/Interferon use history will enroll sequentially in Cohorts 2b through 7 ***and Cohorts 10 and 11***) into a total of ***8*** open label cohorts (4 patients per cohort) at planned dose levels of 100 mg (Cohort 2b), 200 mg (Cohort 3b), 300 mg (Cohort 4b) and 400 mg (Cohort 5b) to receive three doses (Q28 days) of active treatment in an open label fashion. Cohort 6 will enroll 4 CHB subjects (after Cohort 5b has completed enrollment) to receive three doses two weeks apart. Cohorts 7, ***10 and 11*** will enroll 4 CHB patients ***sequentially*** (after Cohort 6 has completed enrollment) to receive three doses a week apart ***at increasing dose levels starting with a dose equal to Cohort 6. Cohorts 5b through 7 and Cohorts 10 and 11 will enroll sequentially (after being opened at the final planned DSC meeting) with enrollment and dosing in a later cohort not initiating until all subjects in the earlier cohort have received at least their first scheduled dose.*** Cohort 8 will enroll 4 HBeAg positive treatment naïve CHB patients to receive three monthly doses of ARO-HBV. Cohort 9 will enroll 4 HBeAg positive entecavir or tenofovir experienced CHB patients to receive three monthly doses of ARO-HBV. The dose used for Cohorts 6, 7, 8, ***9, 10 and 11*** will be ≤ 400 mg with an expected dose level of ***between 100 mg to*** 400 mg.

From:

Any patient volunteering for inclusion in cohort 8 or 9 that has signed an informed consent at the time that the fourth patient in that cohort is enrolled, may also be enrolled if enrolment can be accomplished within 14 days of the fourth patient being dosed.

To:

Any patient volunteering for inclusion in ***Cohort 5b***, 8 or 9 that has signed an informed consent at the time that the fourth patient in that cohort is enrolled, may also be enrolled if enrolment can be accomplished within 14 days of the fourth patient being dosed.

From:

In Cohorts 2b, 3b, 4b, 5b, 6, 7, 8 and 9, 4 eligible CHB patients who have signed an HDEC (or local equivalent) approved informed consent form will receive three doses of ARO-HBV at dose intervals ranging from once every week to once every 4 weeks in an open label fashion. Screening for the CHB cohorts can begin once Cohort 1 dosing has commenced. These cohorts will be opened for accrual once the corresponding NHV cohort receiving the same dose level has reached Day 8, based on agreement of the DSC that it is safe to proceed. Cohorts 6, 7, 8 and 9 can be opened for enrollment concurrently with or any time after Cohort 5 has reached Day 8 and there is sufficient viral antigen response data from CHB patients to determine a dose level for these cohorts. The planned dose level for Cohorts 6 through 9 is ≤ 400 mg. Cohorts 2b through Cohort 7 will be enrolled in sequence (as shown in Figure 1). Cohorts 8 and 9 may be enrolled in parallel with other CHB cohorts after the DSC has voted post Cohort 5 to open the remaining CHB patient cohorts and once a specified dose (≤ 400 mg) has been identified.

To:

In Cohorts 2b, 3b, 4b, 5b, 6, 7, 8, ***9, 10 and 11***, 4 eligible CHB patients who have signed an HDEC (or local equivalent) approved informed consent form will receive three doses of ARO-HBV at dose intervals ranging from once every week to once every 4 weeks in an open label fashion. Screening for the CHB cohorts can begin once Cohort 1 dosing has commenced. These cohorts will be opened for accrual once the corresponding NHV cohort receiving the same dose level has reached Day 8, based on agreement of the DSC that it is safe to proceed. Cohorts 6, 7, 8, ***9, 10 and 11*** can be opened for enrollment any time after Cohort 5 has reached Day 8 ***(and DSC has approved opening of such cohorts)*** and there is sufficient viral antigen response data from CHB patients to determine a dose level for these cohorts. The planned dose level for Cohorts 6 through ***11*** is between ***100 and*** 400 mg. Cohorts 2b through Cohort 7 ***and Cohorts 10 and 11*** will be enrolled in sequence (as shown in Figure 1). Cohorts 8 and 9 may be enrolled in parallel with other CHB cohorts after the DSC has voted post Cohort 5 to open the remaining CHB patient cohorts and once a specified dose (≤ 400 mg) has been identified.

Added:

For clarity, after Cohort 5 is through Day 8, the DSC will review all available safety data and vote to open Cohorts 5b, 6, 7, 8, 9, 10 and 11. Cohorts 5b, 8 and 9 may enroll and dose patients in parallel. Cohorts 5b through 7 and Cohorts 10 and 11 must enroll sequentially, meaning that Cohort 5b must be fully enrolled with each subject receiving at least a first dose before Cohort 6 can enroll. Cohort 6 must be fully enrolled with each subject receiving at least a first dose before Cohort 7 can enroll. Cohort 7 must be fully enrolled with each subject receiving at least a first dose before Cohort 10 can enroll and Cohort 10 must be fully enrolled with each subject receiving at least a first dose before Cohort 11 can enroll. It is the intent that Cohorts 7, 10 and 11 will be treated at increasing dose levels starting with a dose equal to Cohort 6.

18. **Section/page:** 7.1, Number of Subjects, p. 38

From:

A total of approximately 30 NHV and 32 CHB participants (not including potential replacements) may be enrolled in the study.

To:

A total of approximately 30 NHV and ***40*** CHB participants (not including potential replacements) may be enrolled in the study.

19. **Section/page:** 9.1, Overview of Procedures, p. 51

From:

For CHB patients in Cohorts 2b, 3b, 4b, 5b, 6, 7, 8 and 9, 4 eligible CHB patients who have signed an HDEC (or local equivalent) approved informed consent form will receive three doses of ARO-HBV at dose intervals ranging from once every week to once every 4 weeks in an open label fashion. Screening for the CHB cohorts can begin once Cohort 1 dosing has commenced. These cohorts will be opened for accrual once the corresponding NHV cohort receiving the same dose level has reached Day 8, based on agreement of the DSC that it is safe to proceed. Cohorts 6, 7, 8 and 9 can be opened for enrollment concurrently with or any time after Cohort 5 has reached Day 8 and there is sufficient viral antigen response data from CHB patients to determine a dose level for these cohorts. The planned dose level for Cohorts 6-9 is ≤ 400 mg. Cohorts 2b through Cohort 7 will be enrolled in sequence (as shown in **Figure 1**). Cohorts 8 and 9 may be enrolled in parallel with other CHB cohorts after the DSC has voted

post Cohort 5 to open the remaining CHB patient cohorts and once a specified dose (≤ 400 mg) has been identified.

To:

For CHB patients in Cohorts 2b, 3b, 4b, 5b, 6, 7, 8, ***9, 10 and 11***, 4 eligible CHB patients who have signed an HDEC (or local equivalent) approved informed consent form will receive three doses of ARO-HBV at dose intervals ranging from once every week to once every 4 weeks in an open label fashion. Screening for the CHB cohorts can begin once Cohort 1 dosing has commenced. These cohorts will be opened for accrual once the corresponding NHV cohort receiving the same dose level has reached Day 8, based on agreement of the DSC that it is safe to proceed. Cohorts 6, 7, 8, ***9, 10 and 11*** can be opened for enrollment any time after Cohort 5 has reached Day 8 ***(and DSC has approved opening of such cohorts)*** and there is sufficient ***safety and*** viral antigen response data from CHB patients to determine a dose level for these cohorts. ***It is the intent that Cohorts 7, 10 and 11 will be treated at increasing dose levels starting with a dose equal to Cohort 6.*** The planned dose level for Cohorts 6-11 is ≤ 400 mg ***(expected to be between 100 mg and 400 mg)***. Cohorts 2b through Cohort 7 ***and Cohorts 10 and 11*** will be enrolled in sequence (as shown in **Figure 1**). Cohorts 8 and 9 may be enrolled in parallel with other CHB cohorts after the DSC has voted post Cohort 5 to open the remaining CHB patient cohorts and once a specified dose (≤ 400 mg) has been identified.

20. **Section/page:** 9.3.6, Clinical Laboratory Tests and Pharmacodynamic Values, p. 54

Added:

Cellular Immunology Studies: For all CHB patient cohorts, blood samples to evaluate changes in anti-viral host immunologist profile will be collected on Day 1 (pre-dose), 43 and 113. This will include T cell subsets (activation and exhaustion state), NK cell subsets (activation and exhaustion state), B cell subset, monocyte subsets and HBV antigen specific T cell response (including HBcAg, HBsAg). Cellular immunology studies will be conducted if scientifically feasible.

21. **Section/page:** 9.5, Study Formulation Administration, p. 56

From:

Table 2: Injection number and volume per cohort

Cohort	Dose	Concentration	Total Injection Volume	# Injections per planned dose
1	35 mg	200 mg/mL	0.175 mL	Single
2	100 mg	200 mg/mL	0.5 mL	Single
3	200 mg	200 mg/mL	1.0 mL	Single
4	300 mg	200 mg/mL	1.5 mL	Single
5	400 mg	200 mg/mL	2.0 mL	Two (at separate sites)

To:

Table 2: Injection number and volume per cohort

Cohort*	Dose	Concentration	Total Injection Volume	# Injections per planned dose
1	35 mg	200 mg/mL	0.175 mL	Single
2, ***2b***	100 mg	200 mg/mL	0.5 mL	Single
3, ***3b***	200 mg	200 mg/mL	1.0 mL	Single
4, ***4b***	300 mg	200 mg/mL	1.5 mL	Single
5, ***5b***	400 mg	200 mg/mL	2.0 mL	Two (at separate sites)

****Dose for Cohorts 6, 7, 8, 9, 10 and 11 to be determined based on safety and viral antigen response seen in Cohorts 2b, 3b, 4b, and 5b. The planned dose level for Cohorts 6 through 11 is between 100 and ≤ 400 mg.***

22. **Section/page:** 11.5, Pharmacodynamic Data, pp. 67-68

From:

The whole blood collected for pharmacodynamic analysis following multiple doses of ARO-HBV at different dose levels will undergo analysis for changes in HBV-DNA, HBV-RNA (if scientifically feasible) and viral antigens based on reference laboratory (VIDRL) generated values.

To:

The whole blood collected for pharmacodynamic analysis following multiple doses of ARO-HBV at different dose levels will undergo analysis for changes in HBV-DNA, HBV-RNA (if scientifically feasible) and viral antigens based on reference laboratory (VIDRL) generated values. ***Cellular immunologic assessments will also be conducted (if scientifically feasible) at University of Auckland.***

Immunology assessments (CHB patients only)

- ***Changes in profile from pre-dose to post-dose time points for: 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.***
- ***Changes from pre-dose to post-dose time points for: HBV antigen specific T cell response (including HBcAg, HBsAg). To be conducted if scientifically feasible.***

PROTOCOL AMENDMENT SUMMARY OF CHANGES

PROTOCOL NUMBER:	**AROHBV1001**
STUDY TITLE:	**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**
VERSION/DATE:	**Version 3.0, 26 July 2018**

OVERVIEW/RATIONALE:

This amendment:

1. Based on previous experience with siRNA compounds targeting HBV (including ARC-520) subjects continued to experience anti-viral effects and in some cases HBsAg becoming undetectable even six months or more after the last dose received. For these reasons, infrequent follow up to measure further changes in viral antigens every 2 months for approximately 1 year after the last planned dose will allow optimal monitoring of patient benefit.

2. Language is clarified to allow a limited number of CHB patients who are eligible to be enrolled into cohorts 2b through 5b (previously filled) so as not to turn down eligible patients from the study. This is done by expanding the maximum number of patients to be enrolled into cohorts 2b through 5b from 4 up to 8 patients. Additionally, this increased cohort size in the dose escalation part of the study should help sponsor to better understand dose response allowing for selection of an optimal dose for later stage clinical trials.

3. Language is added to define the term “HBsAg loss” which is traditionally a reduction in HBsAg below the level of quantitation (< 0.05 IU/mL).

4. Language is added that if feasible, final HBsAg pharmacodynamic analysis will be done on batched samples run at the end of the study to limit inter-test variability.

5. Corrects any administrative, grammatical, formatting errors and inconsistencies; rewording for clarity

SUMMARY OF CHANGES:

1. **Section/page:** Title Page, page 1

   Added:

   This amendment provides for additional follow up to track safety and HBV antiviral effect after the last dose in CHB patients and expands the size of select cohorts.

2. **Section/page:** 1 Protocol Synopsis, Study Population/Patient Number, pp. 3-4

From:

CHB cohorts will each enroll 4 subjects in an open label fashion to receive escalating multiple doses of ARO-HBV. In addition, any patient volunteering for inclusion in Cohort 5b, 8 or 9 that has signed an informed consent at the time that the fourth patient in that cohort is enrolled, may also be enrolled if enrolment can be accomplished within 14 days of the fourth patient being dosed.

CHB patients regardless of HBeAg status or NUC/Interferon use history will enroll sequentially into a total of 8 open label cohorts (Cohorts 2b through 7 and Cohorts 10 and 11, 4 patients per cohort) at planned dose levels of 100 mg (Cohort 2b), 200 mg (Cohort 3b), 300 mg (Cohort 4b) and 400 mg (Cohort 5b) to receive three doses (Q28 days) of active treatment in an open label fashion. Cohort 6 will enroll 4 CHB subjects (after Cohort 5b has completed enrollment) to receive three doses two weeks apart. Cohorts 7, 10 and 11 will enroll 4 CHB patients sequentially (after Cohort 6 has completed enrollment) to receive three doses a week apart at increasing dose levels starting with a dose equal to Cohort 6. Cohorts 5b through 7 and Cohorts 10 and 11 will enroll sequentially (after being opened at the final planned DSC meeting) with enrollment and dosing in a later cohort not initiating until all subjects in the earlier cohort have received at least their first scheduled dose. Cohort 8 will enroll 4 HBeAg positive treatment naïve CHB patients to receive three monthly doses of ARO-HBV. Cohort 9 will enroll 4 HBeAg positive entecavir or tenofovir experienced CHB patients to receive three monthly doses of ARO-HBV.

To:

CHB cohorts 2b, 3b, 4b and 5b will each enroll a minimum of 4 and a maximum of 8 subjects in an open label fashion to receive escalating multiple doses of ARO-HBV. Cohorts 6, 7, 8, 9, 10 and 11 will each enroll a maximum of 4 subjects.

CHB patients regardless of HBeAg status or NUC/Interferon use history will enroll sequentially into a total of 8 open label cohorts (Cohorts 2b through 7 and Cohorts 10 and 11). ***Cohorts 2b through 5b will enroll at planned dose levels of 100 mg (Cohort 2b), 200 mg (Cohort 3b), 300 mg (Cohort 4b) and 400 mg (Cohort 5b) to receive three doses (Q28 days) of active treatment in an open label fashion.*** Cohort 6 will enroll CHB subjects (after Cohort 5b has completed enrollment) to receive three doses two weeks apart. Cohorts 7, 10 and 11 will enroll CHB patients sequentially (after Cohort 6 has completed enrollment) to receive three doses a week apart at increasing dose levels starting with a dose equal to Cohort 6. Cohorts 5b through 7 and Cohorts 10 and 11 will enroll sequentially (after

being opened at the final planned DSC meeting) with enrollment and dosing in a later cohort not initiating until all subjects in the earlier cohort have received at least their first scheduled dose. Cohort 8 will enroll HBeAg positive treatment naïve CHB patients to receive three monthly doses of ARO-HBV. Cohort 9 will enroll HBeAg positive entecavir or tenofovir experienced CHB patients to receive three monthly doses of ARO-HBV.

From:

A total of approximately 30 NHV and 40 CHB participants (not including potential replacements) may be enrolled in the study.

To:

A total of approximately 30 NHV and ***a minimum of 40 or a maximum of 56 CHB participants*** (not including potential replacements) may be enrolled in the study.

3. **Section/page:** 1 Protocol Synopsis, Study Duration , p. 4

From:

For each CHB patient in the multi-dose Cohorts 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10 and 11 the duration of the study clinic visits is approximately 25 weeks from screening to the Day 113 EOS examination.

To:

For each CHB patient in the multi-dose Cohorts 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10 and 11 the duration of the study clinic visits is approximately 25 weeks from screening to the Day 113 EOS examination. ***CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after the last dose. Subjects consenting to additional follow up will continue on NUCs. Subjects not consenting to additional follow up will be followed per protocol based on Schedule of Assessment Tables 1.2, 1.3 and 1.4.***

4. **Section/page:** 1 Protocol Synopsis, Study Design/Methods, p. 5

   From:

   CHB patients:

   In Cohorts 2b, 3b, 4b, 5b, 6, 7, 8 and 9, ***4*** eligible CHB patients per cohort who have signed an HDEC (or local equivalent) approved informed consent form will receive three doses of ARO-HBV at dose intervals ranging from once every week to once every 4 weeks in an open label fashion.

   To:

   CHB patients:

   In Cohorts 2b, 3b, 4b, 5b, 6, 7, 8, 9, ***10 and 11***, eligible CHB patients who have signed an HDEC (or local equivalent) approved informed consent form will receive three doses of ARO-HBV at dose intervals ranging from once every week to once every 4 weeks in an open label fashion.

   Added:

   CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after the last dose. Subjects consenting to additional follow up will continue on NUCs. Subjects not consenting to additional follow up will be followed per protocol based on Schedule of Assessment Tables 1.2, 1.3 and 1.4.

5. **Section/page:** 1 Protocol Synopsis, Data Analysis, p. 9

   Added:

   Two separate data analyses will be performed, one for all subjects through EOS (Day 29 for NHVs and Day 113 for CHB patients), and one additional and separate analysis for CHB patients who consent to the additional follow up.

6. **Section/page:** 1 Protocol Synopsis, Data Analysis, pp. 9-10

   From:

   Virology assessments (CHB patients only)

   Virologic parameters will be summarized by cohort for the following:

   - Percent of patients with loss of HBsAg at EOS and time to occurrence (Kaplan Meier)

To:

Virology assessments (CHB patients only)

Virologic parameters will be summarized by cohort for the following:

- Percent of patients with loss of HBsAg ***(defined as HBsAg < 0.05 IU/mL)*** at EOS and time to occurrence (Kaplan Meier)

7. **Section/page:** Schedule of Assessments, p. 16

Added:

Table 1.5: Additional Follow-Up Schedule of Assessments (All CHB Cohorts)

Assessment	**Day 169 (±5)**	**Day 225 (±5)**	**Day 281 (±5)**	**Day 337 (±5)**	**Day 393 (±5)**	**Early Termination**
Physical Exam[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
Vital Signs (BP, temp, RR, heart rate)	X	X	X	X	X	X
Clinical Labs (heme, coag, chem, UA)	X	X	X	X	X	X
Quantitative HBsAg, HBcrAg, HBeAg (e+ only) HBV DNA, HBV RNA	X	X	X	X	X	X
Quantitative anti-HBs, qualitative anti-HBe (e+ only)	X	X	X	X	X	X
HBV genotyping (if technically feasible)	X	X	X	X	X	X
HBV sequencing (if technically feasible)	X	X	X	X	X	X
Concomitant Meds/Therapies	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X

1. Symptom-directed PEs to be performed by visit as necessary.

8. **Section/page:** 6.1, Study Design, pp. 31-32

From:

Summary of Participant Profile by Cohort:

- Cohorts 1-5: NHVs, adult males and females, aged 18-55 years
- Cohorts 2b, 3b, 4b, 5b, 6, 7, 10 and 11: Any CHB patient regardless of HBeAg or prior therapy status (as long as other Inclusion and Exclusion criteria are met).
- Cohort 8: HBeAg positive treatment naïve patients (no prior chronic exposure to NUCs or Interferon)
- Cohort 9: HBeAg positive NUC experienced patients (on entecavir or tenofovir for at least 12 months).

CHB patients regardless of HBeAg status or NUC/Interferon use history will enroll sequentially in Cohorts 2b through 7 and Cohorts 10 and 11) into a total of 8 open label cohorts (4 patients per cohort) at planned dose levels of 100 mg (Cohort 2b), 200 mg (Cohort 3b), 300 mg (Cohort 4b) and 400 mg (Cohort 5b) to receive three doses (Q28 days) of active treatment in an open label fashion. Cohort 6 will enroll 4 CHB subjects (after Cohort 5b has completed enrollment) to receive three doses two weeks apart. Cohorts 7, 10 and 11 will enroll 4 CHB patients sequentially (after Cohort 6 has completed enrollment) to receive three doses a week apart at increasing dose levels starting with a dose equal to Cohort 6. Cohorts 5b through 7 and Cohorts 10 and 11 will enroll sequentially (after being opened at the final planned DSC meeting) with enrollment and dosing in a later cohort not initiating until all subjects in the earlier cohort have received at least their first scheduled dose. Cohort 8 will enroll 4 HBeAg positive treatment naïve CHB patients to receive three monthly doses of ARO-HBV. Cohort 9 will enroll 4 HBeAg positive entecavir or tenofovir experienced CHB patients to receive three monthly doses of ARO-HBV.

To:

Summary of Participant Profile by Cohort and Cohort Size:

- Cohorts 1-5: NHVs, adult males and females, aged 18-55 years
    - ***6 NHV subjects per cohort***
- Cohorts 2b, 3b, 4b, 5b, 6, 7, 10 and 11: Any CHB patient regardless of HBeAg or prior therapy status (as long as other Inclusion and Exclusion criteria are met).

- ***Cohorts 2b, 3b, 4b and 5b will enroll a minimum of 4 and a maximum of 8 patients per cohort.***
- ***Cohorts 6, 7, 10 and 11 will enroll a maximum of 4 patients per cohort.***

- Cohort 8: HBeAg positive treatment naïve patients (no prior chronic exposure to NUCs or Interferon)
  - ***Cohort 8: Maximum of 4 patients per cohort***
- Cohort 9: HBeAg positive NUC experienced patients (on entecavir or tenofovir for at least 12 months).
  - ***Cohort 9: Maximum of 4 patients per cohort***

CHB patients regardless of HBeAg status or NUC/Interferon use history will enroll sequentially in Cohorts 2b through 7 and Cohorts 10 and 11) into a total of 8 open label cohorts. Cohorts 2b through 5b will enroll at planned dose levels of 100 mg (Cohort 2b), 200 mg (Cohort 3b), 300 mg (Cohort 4b) and 400 mg (Cohort 5b) to receive three doses (Q28 days) of active treatment in an open label fashion. Cohort 6 will enroll CHB subjects (after Cohort 5b has completed enrollment) to receive three doses two weeks apart. Cohorts 7, 10 and 11 will enroll CHB patients sequentially (after Cohort 6 has completed enrollment) to receive three doses a week apart at increasing dose levels starting with a dose equal to Cohort 6. Cohorts 5b through 7 and Cohorts 10 and 11 will enroll sequentially (after being opened at the final planned DSC meeting) with enrollment and dosing in a later cohort not initiating until all subjects in the earlier cohort have received at least their first scheduled dose. Cohort 8 will enroll HBeAg positive treatment naïve CHB patients to receive three monthly doses of ARO-HBV. Cohort 9 will enroll HBeAg positive entecavir or tenofovir experienced CHB patients to receive three monthly doses of ARO-HBV.

Deleted:

Any patient volunteering for inclusion in Cohort 5b, 8 or 9 that has signed an informed consent at the time that the fourth patient in that cohort is enrolled, may also be enrolled if enrolment can be accomplished within 14 days of the fourth patient being dosed.

Added (p. 33):

CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after the last dose. Subjects consenting to additional follow up will continue on NUCs. Subjects not consenting

to additional follow up will be followed per protocol based on Schedule of Assessment Tables 1.2, 1.3 and 1.4.

9. **Section/page:** 6.4, Duration of the Study, pp. 37-38

   From:

   For each CHB patient in the multi-dose cohorts the duration of the study clinic visits is approximately 25 weeks from screening to the Day 113 EOS examination.

   To:

   For each CHB patient in the multi-dose cohorts the duration of the study clinic visits is approximately 25 weeks from screening to the Day 113 EOS examination. ***CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after the last dose. Subjects consenting to additional follow up will continue on NUCs. Subjects not consenting to additional follow up will be followed per protocol based on Schedule of Assessment Tables 1.2, 1.3 and 1.4.***

10. **Section/page:** 7.1, Number of Subjects, p. 38

    From:

    A total of approximately 30 NHV and 40 CHB participants (not including potential replacements) may be enrolled in the study.

    To:

    A total of approximately 30 NHV and **a minimum of 40 or a maximum of 56** CHB participants (not including potential replacements) may be enrolled in the study.

11. **Section/page:** 9.1, Overview of Procedures, pp. 51-52

    Added:

    CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after the last dose. Subjects consenting to additional follow up will continue on NUCs. Subjects not consenting to additional follow up will be followed per protocol based on Schedule of Assessment Tables 1.2, 1.3 and 1.4.

12. **Section/page:** 9.3.9, Follow-Up Procedures, p. 55

From:

Follow-Up Procedures: Day 90 (± 5 days) Telephone Call

Documented telephone contact with each participant to verify compliance with contraceptive measures and absence of any known pregnancy.

To:

Follow-Up Procedures

Day 90 (± 5 days) Telephone Call

Documented telephone contact with each participant to verify compliance with contraceptive measures and absence of any known pregnancy ***at 90 days post EOS (Day 29 for NHVs and Day 113 for CHB patients).***

Additional CHB Follow-up

CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after the last dose. Subjects consenting to additional follow up will continue on NUCs. Subjects not consenting to additional follow up will be followed per protocol based on Schedule of Assessment Tables 1.2, 1.3 and 1.4.

13. **Section/page:** 11, , Data Analysis and Statistical Considerations, p. 66

Added:

11.1 Data analysis through EOS and Additional follow-up

Two separate data analyses will be performed, one for all subjects through EOS (Day 29 for NHVs and Day 113 for CHB patients), and one additional and separate analysis for CHB patients who consent to the additional follow up.

14. **Section/page:** 11.6, Pharmacodynamic Data, pp. 68-69

From:

Virology assessments (CHB patients only)

- Virologic parameters will be summarized by cohort for the following:

- Quantitative HBsAg (qHBsAg): Log change from baseline to nadir and duration of response from nadir back to approximately 20% of baseline or EOS (HBsAg will not be followed beyond EOS)
- Percent of patients with loss of HBsAg at EOS and time to occurrence (Kaplan Meier)
- Percent of patients with anti-HBS seroconversion at EOS and time to occurrence (Kaplan Meier).
- Change in Anti-HBs (quantitative) over time
- Quantitative HBV DNA (when quantifiable at baseline): Log change from baseline to EOS
- Quantitative HBV RNA: Log change from baseline to nadir and duration of response from baseline to EOS (if scientifically feasible)
- Quantitative HBcrAg: Log change from baseline to nadir and duration of response from baseline to EOS
- Quantitative HBeAg (HBeAg positive only): Log change from baseline to nadir and duration of response from baseline to EOS
- Emergence of HBV mutations (sequencing of ARO-HBV target site, Core/pre-core, HBsAg epitope, any other mutations by deep sequencing)

Descriptive statistics of virologic parameters will include mean, median, count, SD, minimum, and maximum. Additional details will be provided in the statistical analysis plan. Separate analysis will 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.

To:

Virology assessments (CHB patients only)

- Virologic parameters will be summarized by cohort for the following:
- Quantitative HBsAg (qHBsAg): Log change from baseline to nadir and duration of response from nadir back to approximately 20% of baseline or EOS. ***In CHB patients who consent to additional follow up, HBsAg will be followed until the end of the additional follow-up period or early termination and summarized separately.***
- Percent of patients with loss of HBsAg (defined as quantitative HBsAg < 0.05 IU/mL) at EOS and time to occurrence (Kaplan Meier). ***In CHB patients who consent to additional***

follow up, HBsAg loss will be monitored until the end of the additional follow-up period or early termination and summarized separately.

- Percent of patients with anti-HBS seroconversion at EOS and time to occurrence (Kaplan Meier). ***In CHB patients who consent to additional follow up, anti-HBS seroconversion will be monitored until the end of the additional follow-up period or early termination and summarized separately.***
- Change in Anti-HBs (quantitative) to EOS. ***In CHB patients who consent to additional follow up, change in Anti-HBs (quantitative) will be monitored until the end of the additional follow-up period or early termination and summarized separately.***
- Quantitative HBV DNA (when quantifiable at baseline): Log change from baseline to EOS. ***In CHB patients who consent to additional follow up, HBV DNA will be monitored until the end of the additional follow-up period or early termination and summarized separately.***
- Quantitative HBV RNA: Log change from baseline to nadir and duration of response from baseline to EOS (if scientifically feasible). ***In CHB patients who consent to additional follow up, HBV RNA will be monitored until the end of the additional follow-up period or early termination and summarized separately.***
- Quantitative HBcrAg: Log change from baseline to nadir and duration of response from baseline to EOS. ***In CHB patients who consent to additional follow up, HBcrAg will be monitored until the end of the additional follow-up period or early termination and summarized separately.***
- Quantitative HBeAg (HBeAg positive only): Log change from baseline to nadir and duration of response from baseline to EOS. ***In CHB patients who consent to additional follow up, HBeAg will be monitored until the end of the additional follow-up period or early termination and summarized separately.***
- Emergence of HBV mutations (sequencing of ARO-HBV target site, Core/pre-core, HBsAg epitope, any other mutations by deep sequencing) to EOS. ***In CHB patients who consent to additional follow up, HBV mutations will be monitored until the end of the additional follow-up period or early termination and summarized separately.***

Descriptive statistics of virologic parameters will include mean, median, count, SD, minimum, and maximum. Additional details will be provided in the statistical analysis plan. ***If feasible, Clinical***

Study Report analysis of, quantitative HBsAg through EOS will be based on a final batched analysis of samples.

Separate analysis will 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.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

PROTOCOL NUMBER:	**AROHBV1001**
STUDY TITLE:	**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**
VERSION/DATE:	**Version 4.0, 01 October 2018**

OVERVIEW/RATIONALE:

This amendment:

1. Adds two CHB open-label Cohorts 1b and 1c with 8 subjects each receiving ARO-HBV at 25 and 50 mg respectively every 28 days. Total number of CHB participants increases to minimum of 48 or a maximum of 72 subjects (not including potential subject replacements). These cohorts are being added to better understand HBV viral antigen dose response after already completing 100 mg through 400 mg dose levels.

2. Adds a whole blood sample collection for SNP analysis for IFN response genes for all CHB subjects if actively participating in the study, after consent for genetic testing is obtained.

3. Clarifies dose levels for Cohorts 6-11 (which are all already fully enrolled) decided from previous Data Safety Committee Meetings.

4. Defines study completion for CHB subjects at Day 113 EOS regardless of whether subject re-consents to continue Additional Follow-Up visits until Day 393.

5. Corrects protocol language stating Additional Follow Up visits for CHB subjects will be conducted every 56 days (± 5 days) for 5 additional visits after Day 113 to agree with Table 1.5 Schedule of Assessments.

6. Corrects any administrative, grammatical, formatting errors and inconsistencies; rewording for clarity

SUMMARY OF CHANGES:

1. **Section/page:** Title Page, page 1

   From:
   This amendment provides for additional follow up to track safety and HBV antiviral effect after the last dose in CHB patients and expands the size of select cohorts.

   To:
   This amendment ***adds two CHB open-label Cohorts 1b and 1c with 8 subjects each receiving ARO-HBV at 25 and 50 mg respectively every 28 days, whole blood sample collection for SNP analysis for IFN response genes for all CHB subjects, and clarifies dose levels for Cohorts 6-11***.

2. **Section/page:** 1 Protocol Synopsis, Study Objectives, p. 3

   Added:

   Exploratory Objectives
   - ***To evaluate the effect of interferon response gene single nucleotide polymorphisms (SNPs) including IL28B on response to ARO-HBV***

3. **Section/page:** 1 Protocol Synopsis, Study Population/Patient Number, pp. 3-4

   From:
   This study will be conducted in NHVs, adult males and females, aged 18-55 years with BMI between 19.0 and 35.0 kg/m² (Cohorts 1 – 5) and in HBeAg negative or HBeAg positive CHB patients, aged 18-65 years with BMI between 19.0 and 38.0 kg/m² (Cohorts 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10 and 11). Cohort 8 will enroll HBeAg positive treatment naïve patients (no prior chronic exposure to NUCs or Interferon) and Cohort 9 will enroll HBeAg positive NUC experienced patients (on entecavir or tenofovir for at least 12 months). Cohorts 2b, 3b, 4b, 5b, 6, 7, 10 and 11 will enroll either HBeAg positive or negative patients regardless of previous NUC or PEG IFN treatment experience. All patients will be started on entecavir or tenofovir on Day 1. Patients currently on PEG IFN will not be allowed.

   To:
   This study will be conducted in NHVs, adult males and females, aged 18-55 years with BMI between 19.0 and 35.0 kg/m² (Cohorts 1 – 5) and in HBeAg negative or HBeAg positive CHB patients, aged 18-65 years with BMI between 19.0 and 38.0 kg/m² (Cohorts ***1b, 1c,*** 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10 and 11). Cohort 8 will enroll HBeAg positive treatment naïve patients (no prior chronic exposure to NUCs or Interferon) and Cohort 9 will enroll HBeAg positive NUC experienced patients (on entecavir or tenofovir for at least 12 months). Cohorts ***1b, 1c,*** 2b, 3b, 4b, 5b, 6, 7, 10 and 11 will enroll either HBeAg positive or negative patients regardless of previous NUC or PEG IFN treatment experience. All patients will be started on entecavir or tenofovir on Day 1. Patients currently on PEG IFN will not be allowed.

   From:
   Summary of Participant Profile by Cohort:
   - Cohorts 2b, 3b, 4b, 5b, 6, 7, 10 and 11: Any CHB patient regardless of HBeAg or prior therapy status (as long as other Inclusion and Exclusion criteria are met).

   To:
   Summary of Participant Profile by Cohort:
   - Cohorts ***1b, 1c,*** 2b, 3b, 4b, 5b, 6, 7, 10 and 11: Any CHB patient regardless of HBeAg or prior therapy status (as long as other Inclusion and Exclusion criteria are met).

   Deleted:
   Additional intermediate dose cohorts may be added if approved by Sponsor, HDEC (or local equivalent) and the Data Safety Committee (DSC).

   From:
   CHB cohorts 2b, 3b, 4b and 5b will each enroll a minimum of 4 and a maximum of 8 subjects in an open label fashion to receive escalating multiple doses of ARO-HBV. Cohorts 6, 7, 8, 9, 10 and 11 will each enroll a maximum of 4 subjects.

To:
CHB cohorts ***1b, 1c,*** 2b, 3b, 4b and 5b will each enroll a minimum of 4 and a maximum of 8 subjects in an open label fashion to receive escalating multiple doses of ARO-HBV. Cohorts 6, 7, 8, 9, 10 and 11 will each enroll a maximum of 4 subjects.

From:

CHB patients regardless of HBeAg status or NUC/Interferon use history will enroll sequentially into a total of 8 open label cohorts (Cohorts 2b through 7 and Cohorts 10 and 11). Cohorts 2b through 5b will enroll at planned dose levels of 100 mg (Cohort 2b), 200 mg (Cohort 3b), 300 mg (Cohort 4b) and 400 mg (Cohort 5b) to receive three doses (Q28 days) of active treatment in an open label fashion. Cohort 6 will enroll CHB subjects (after Cohort 5b has completed enrollment) to receive three doses two weeks apart. Cohorts 7, 10 and 11 will enroll CHB patients sequentially (after Cohort 6 has completed enrollment) to receive three doses a week apart at increasing dose levels starting with a dose equal to Cohort 6. Cohorts 5b through 7 and Cohorts 10 and 11 will enroll sequentially (after being opened at the final planned DSC meeting) with enrollment and dosing in a later cohort not initiating until all subjects in the earlier cohort have received at least their first scheduled dose. Cohort 8 will enroll HBeAg positive treatment naïve CHB patients to receive three monthly doses of ARO-HBV. Cohort 9 will enroll HBeAg positive entecavir or tenofovir experienced CHB patients to receive three monthly doses of ARO-HBV. Cohorts 8 and 9 may enroll in parallel with Cohort 5b once opened by the DSC. The dose used for Cohorts 6, 7, 8, 9, 10 and 11 will be ≤ 400 mg with an expected dose level of between 100 mg to 400 mg. An additional cohort using an intermediate dose level and dose frequency may be added with approval of the HDEC (or local equivalent) and DSC. CHB patient Screening for all CHB cohorts may start when Cohort 1 opens for enrollment. However, no CHB patients may be dosed until their respective cohort is approved for dosing by the DSC. CHB dosing may begin and NHV dose escalation may occur based on DSC approval which can occur by vote after cumulative data through Day 8 from the current NHV cohort is available. See Figure 1 for dose escalation schedule). CHB patients on current 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. Either tenofovir disoproxil fumarate (including generic) or tenofovir alafenamide are acceptable.

To:

CHB patients regardless of HBeAg status or NUC/Interferon use history will enroll sequentially into a total of ***10*** open label cohorts (Cohorts 2b through 7***,*** and Cohorts 10 and 11***, and Cohort 1b and 1c***). Cohorts ***1***b***, and 1c*** through 5b will enroll at planned dose levels of ***25 mg (Cohort 1b), 50 mg (Cohort 1c),*** 100 mg (Cohort 2b), 200 mg (Cohort 3b), 300 mg (Cohort 4b) and 400 mg (Cohort 5b) to receive three doses (Q28 days) of active treatment in an open label fashion. Cohort 6 will enroll CHB subjects (after Cohort 5b has completed enrollment) to receive three doses two weeks apart. Cohorts 7, 10 and 11 will enroll CHB patients sequentially (after Cohort 6 has completed enrollment) to receive three doses a week apart at increasing dose levels starting with a dose equal to Cohort 6. Cohorts 5b through 7 and Cohorts 10 and 11 will enroll sequentially (after being opened at the final planned DSC meeting) with enrollment and dosing in a later cohort not initiating until all subjects in the earlier cohort have received at least their first scheduled dose. Cohort 8 will enroll HBeAg positive treatment naïve CHB patients to receive three monthly doses of ARO-HBV. Cohort 9 will enroll HBeAg positive entecavir or tenofovir experienced CHB patients to receive three monthly doses of ARO-HBV. Cohorts 8 and 9 may enroll in parallel with Cohort 5b once opened by the DSC. ***Cohorts 6 through 11 will enroll at planned dose levels of 100 mg (Cohorts 6 and 7), 200 mg (Cohort 10), and 300 mg (Cohorts 8, 9, and 11).*** CHB patient ***s***creening for all CHB cohorts may

start when Cohort 1 opens for enrollment. However, no CHB patients may be dosed until their respective cohort is approved for dosing by the DSC ***(not including Cohorts 1b and 1c)***. CHB dosing may begin and NHV dose escalation may occur based on DSC approval which can occur by vote after cumulative data through Day 8 from the current NHV cohort is available. See Figure 1 for dose escalation schedule). CHB patients on current 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. Either tenofovir disoproxil fumarate (including generic) or tenofovir alafenamide are acceptable.

From:

A total of approximately 30 NHV and a minimum of 40 or a maximum of 56 CHB participants (not including potential replacements) may be enrolled in the study.

To:

A total of approximately 30 NHV and a minimum of ***48*** or a maximum of ***72*** CHB participants (not including potential replacements) may be enrolled in the study.

4. **Section/page:** 1 Protocol Synopsis, Study Duration, p. 4

From:
For each CHB patient in the multi-dose Cohorts 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10 and 11 the duration of the study clinic visits is approximately 25 weeks from screening to the Day 113 EOS examination. CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after the last dose.

To:
For each CHB patient in the multi-dose Cohorts ***1b, 1c,*** 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10 and 11 the duration of the study clinic visits is approximately 25 weeks from screening to the Day 113 EOS examination. CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after ***Day 113***.

5. **Section/page:** 1 Protocol Synopsis, Study Design/Methods, pp. 5-6

From:
CHB patients:
In Cohorts 2b, 3b, 4b, 5b, 6, 7, 8 and 9, eligible CHB patients per cohort who have signed an HDEC (or local equivalent) approved informed consent form will receive three doses of ARO-HBV at dose intervals ranging from once every week to once every 4 weeks in an open label fashion.

To:
CHB patients:
In Cohorts ***1b, 1c,*** 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10 and 11, eligible CHB patients who have signed an HDEC (or local equivalent) approved informed consent form will receive three doses of ARO-HBV at dose intervals ranging from once every week to once every 4 weeks in an open label fashion.

From:
These cohorts will be opened for accrual once the corresponding NHV cohort receiving the same single dose level has reached Day 8, based on agreement of the DSC that it is safe to proceed.

To:
These cohorts ***(not including Cohorts 1b and 1c)*** will be opened for accrual once the corresponding NHV cohort receiving the same single dose level has reached Day 8, based on agreement of the DSC that it is safe to proceed.

From:
The planned dose level for Cohorts 6-11 is between 100 and 400 mg.

To:
Dose levels for Cohorts 6-11 is between 100 and ***300*** mg.

From:
Cohorts 8 and 9 may be enrolled in parallel with other CHB cohorts after the DSC has voted post Cohort 5 to open the remaining CHB patient cohorts and once a specified dose (≤ 400 mg) has been identified.

To:
Cohorts 8 and 9 may be enrolled in parallel with other CHB cohorts after the DSC has voted post Cohort 5 to open the remaining CHB patient cohorts and ***the*** specified dose (≤ ***300*** mg) has been identified. ***Cohorts 1b and 1c are open for enrollment with the addition of this protocol amendment and may enroll in parallel.***

From:
CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after the last dose.

To:
CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after ***Day 113***.

From:

Figure 1: 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		N/A	N/A
Cohort 2	100 mg		Cohort 2b (all eligible CHB patients regardless of NUC or HBeAg status)	100 mg dosed on Day 1, 29, 57
Cohort 3	200 mg		Cohort 3b (all eligible CHB patients regardless of NUC or HBeAg status)	200 mg dosed on Day 1, 29, 57

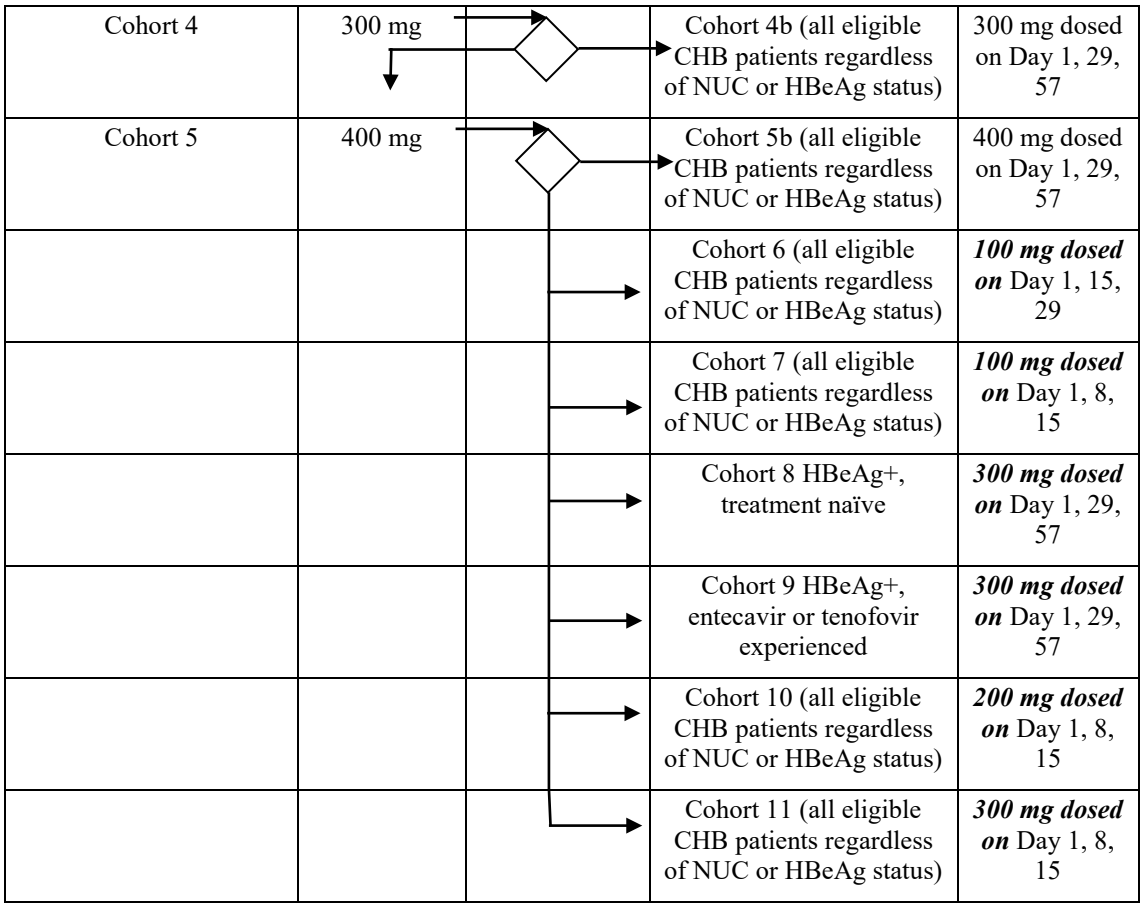
Cohort 4	300 mg		Cohort 4b (all eligible CHB patients regardless of NUC or HBeAg status)	300 mg dosed on Day 1, 29, 57
Cohort 5	400 mg		Cohort 5b (all eligible CHB patients regardless of NUC or HBeAg status)	400 mg dosed on Day 1, 29, 57
			Cohort 6 (all eligible CHB patients regardless of NUC or HBeAg status)	Dose TBD** Day 1, 15, 29
			Cohort 7 (all eligible CHB patients regardless of NUC or HBeAg status)	Dose TBD** Day 1, 8, 15
			Cohort 8 HBeAg+, treatment naïve	Dose TBD** Day 1, 29, 57
			Cohort 9 HBeAg+, entecavir or tenofovir experienced	Dose TBD** Day 1, 29, 57
			Cohort 10 (all eligible CHB patients regardless of NUC or HBeAg status)	Dose TBD** Day 1, 8, 15
			Cohort 11 (all eligible CHB patients regardless of NUC or HBeAg status)	Dose TBD** Day 1, 8, 15

* All Cohorts use 2 sentinel subjects

To:

Figure 1: 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)***	***25 mg dosed on Day 1, 29, 57***
			Cohort 1c (all eligible CHB patients regardless of NUC or HBeAg status)	***50 mg dosed on Day 1, 29, 57***
Cohort 2	100 mg		Cohort 2b (all eligible CHB patients regardless of NUC or HBeAg status)	100 mg dosed on Day 1, 29, 57
Cohort 3	200 mg		Cohort 3b (all eligible CHB patients regardless of NUC or HBeAg status)	200 mg dosed on Day 1, 29, 57



* All Cohorts use 2 sentinel subjects

Deleted:
** Dose for Cohort 6, 7, 8, 9, 10 and 11 to be determined based on safety and viral antigen response seen in Cohorts 2b, 3b, 4b, and 5b. The planned dose level for Cohorts 6-11 is ≤ 400 mg. Cohorts 6-11 may be opened for enrollment any time after Cohort 5 Day 8 safety evaluation with a vote from the DSC. Cohorts 2b through Cohort 7 and Cohorts 10 and 11 will be enrolled in sequence (as shown in Figure 1). Cohorts 8 and 9 may be enrolled in parallel with other CHB cohorts after the DSC has voted post Cohort 5 to open the remaining CHB patient cohorts and once a specified dose (≤ 400 mg) has been identified.

Deleted:
Additional intermediate dose cohorts may be added if approved by Sponsor, HDEC (or local equivalent) and the Data Safety Committee (DSC).

6. **Section/page:** 1 Protocol Synopsis, Study Assessments, p. 8

From:
Immunogenicity:
For Cohorts 2b, 3b, 4b, 5b, and 6-11 blood samples for the anti-drug antibodies test will be collected at screening, Day 57 and Day 113 or at the end of study visit.

To:
Immunogenicity:
For Cohorts ***1b, 1c,*** 2b, 3b, 4b, 5b, and 6-11 blood samples for the anti-drug antibodies test will be collected at screening, Day 57 and Day 113 or at the end of study visit.

Added:
Genetic Testing (CHBs only):
If subject consents to genetic testing while actively participating in the study, one whole blood sample will be collected on Day 1 or any time thereafter for SNP analysis for IFN response genes.

7. **Section/page:** 1 Protocol Synopsis, Data Analysis, p. 10

Deleted:
(HBsAg will not be followed beyond EOS)

Added:
Genetic Testing (CHBs only):
Evaluate mean and maximum nadir HBsAg decline in relationship to patient variants in interferon response genes (e.g. IL28B).

8. **Section/page:** 1 Protocol Synopsis, Table 1.2, p. 12-13

From:
Table 1.2: Cohorts 2b, 3b, 4b, 5b, 8 and 9 (CHB patients, three Q28 day doses)

To:
Table 1.2: Cohorts ***1b, 1c,*** 2b, 3b, 4b, 5b, 8 and 9 (CHB patients, three Q28 day doses)

Added:

Assessment	Screen (Days -60 to -1)		Day 1	Day 2	Day 8	Day 15 (± 2)	Day 29, 57 (± 2)	Day 43, 71 (± 2)	Day 85 (± 2)	Day 113 (± 2) EOS	Early Termination
SNP Analysis			***X[11]***								

11. If genetic testing consent is obtained, one-time whole blood sample collection will be on Day 1 or any time thereafter for SNP analysis for IFN response genes.

9. **Section/page:** 1 Protocol Synopsis, Table 1.3, p. 14

Added:

Assessment	Screen (Days -60 to -1)		Day 1	Day 2	Day 8	Day 15 (± 2)	Day 29, 57 (± 2)	Day 43, 71 (± 2)	Day 85 (± 2)	Day 113 (± 2) EOS	Early Termination

SNP Analysis			***X[12]***								

12. If genetic testing consent is obtained, one-time whole blood sample collection will be on Day 1 or any time thereafter for SNP analysis for IFN response genes.

10. **Section/page:** 1 Protocol Synopsis, Table 1.4, p. 16

Added:

Assessment	Screen (Days -60 to -1)		Day 1	Day 2	Day 8	Day 15 (± 2)	Day 29, 57 (± 2)	Day 43, 71 (± 2)	Day 85 (± 2)	Day 113 (± 2) EOS	Early Termination
SNP Analysis			***X[11]***								

11. If genetic testing consent is obtained, one-time whole blood sample collection will be on Day 1 or any time thereafter for SNP analysis for IFN response genes.

11. **Section/page:** 3 List of Abbreviations and Terms, pp. 21-22

Added:

IFN	**Interferon**
SNP	**Single Nucleotide Polymorphism**

12. **Section/page:** 4.5 Rationale for the Study, p. 26

Added:
The 25 and 50 mg dose levels (Cohorts 1b and 1c) are being added after enrollment and dosing of Cohorts 2b through 5b (dose levels of 100 mg through 400 mg) have been completed to better understand dose response at lower doses.

13. **Section/page:** 4.7 Justification for Starting Dose in Humans, p. 29

Added:
After dose escalation through 400 mg, to better understand dose response at low doses, protocol amendment 4.0 added a 25 and 50 mg X3 Q28 days cohort (Cohorts 1b and 1c).

14. **Section/page:** 5.3 Exploratory Objectives, p. 30

Added:

Exploratory Objectives
- ***To evaluate the effect of interferon response gene single nucleotide polymorphisms (SNPs) including IL28B on response to ARO-HBV***

15. **Section/page:** 6.1 Study Design, pp. 31-35

From:
CHB patients:
HBeAg negative or HBeAg positive CHB patients, aged 18-65 years with BMI between 19.0 and 38.0 kg/m² (Cohorts 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10 and 11) will be enrolled. Cohort 8 will enroll HBeAg positive treatment naïve patients (no prior chronic exposure to NUCs or Interferon) and Cohort 9 will enroll HBeAg positive NUC experienced patients (on entecavir or tenofovir for at least 12 months).

Cohorts 2b, 3b, 4b, 5b, 6, 7, 10 and 11 will enroll either HBeAg positive or negative patients regardless of previous NUC or PEG IFN treatment experience.

To:
CHB patients:
HBeAg negative or HBeAg positive CHB patients, aged 18-65 years with BMI between 19.0 and 38.0 kg/m² (Cohorts ***1b, 1c,*** 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10 and 11) will be enrolled. Cohort 8 will enroll HBeAg positive treatment naïve patients (no prior chronic exposure to NUCs or Interferon) and Cohort 9 will enroll HBeAg positive NUC experienced patients (on entecavir or tenofovir for at least 12 months). Cohorts ***1b, 1c,*** 2b, 3b, 4b, 5b, 6, 7, 10 and 11 will enroll either HBeAg positive or negative patients regardless of previous NUC or PEG IFN treatment experience.

From:
Summary of Participant Profile by Cohort and Cohort Size:

- Cohorts 2b, 3b, 4b, 5b, 6, 7, 10 and 11: Any CHB patient regardless of HBeAg or prior therapy status (as long as other Inclusion and Exclusion criteria are met).
    - Cohorts 2b, 3b, 4b and 5b will enroll a minimum of 4 and a maximum of 8 patients per cohort.

To:
Summary of Participant Profile by Cohort and Cohort Size:

- Cohorts ***1b, 1c,*** 2b, 3b, 4b, 5b, 6, 7, 10 and 11: Any CHB patient regardless of HBeAg or prior therapy status (as long as other Inclusion and Exclusion criteria are met).
    - Cohorts ***1b, 1c,*** 2b, 3b, 4b and 5b will enroll a minimum of 4 and a maximum of 8 patients per cohort.

From:
CHB patients regardless of HBeAg status or NUC/Interferon use history will enroll sequentially in Cohorts 2b through 7 and Cohorts 10 and 11) into a total of 8 open label cohorts. Cohorts 2b through 5b will enroll at planned dose levels of 100 mg (Cohort 2b), 200 mg (Cohort 3b), 300 mg (Cohort 4b) and 400 mg (Cohort 5b) to receive three doses (Q28 days) of active treatment in an open label fashion. Cohort 6 will enroll CHB subjects (after Cohort 5b has completed enrollment) to receive three doses two weeks apart. Cohorts 7, 10 and 11 will enroll CHB patients sequentially (after Cohort 6 has completed enrollment) to receive three doses a week apart at increasing dose levels starting with a dose equal to Cohort 6. Cohorts 5b through 7 and Cohorts 10 and 11 will enroll sequentially (after being opened at the final planned DSC meeting) with enrollment and dosing in a later cohort not initiating until all subjects in the earlier cohort have received at least their first scheduled dose. Cohort 8 will enroll HBeAg positive treatment naïve CHB patients to receive three monthly doses of ARO-HBV. Cohort 9 will enroll HBeAg positive entecavir or tenofovir experienced CHB patients to receive three monthly doses of ARO-HBV. The dose used for Cohorts 6, 7, 8, 9, 10 and 11 will be ≤ 400 mg with an expected dose level of between 100 mg to 400 mg. An additional cohort using an intermediate dose level and dose frequency may be added with approval of the HDEC (or local equivalent) and DSC. CHB patient Screening for all CHB cohorts may start when Cohort 1 opens for enrollment. However, no CHB patients may be dosed until their respective cohort is approved for dosing by the DSC. CHB dosing may begin and NHV dose escalation may occur based on DSC approval which can occur by vote after cumulative data through Day 8 from the current NHV cohort is available. (See Figure 1 for dose escalation schedule).

To:

CHB patients regardless of HBeAg status or NUC/Interferon use history will enroll sequentially in Cohorts 2b through 7**,** Cohorts 10 and 11***, and Cohorts 1b and 1c*** into a total of ***10*** open label cohorts. Cohorts ***1***b***, and 1c*** through 5b will enroll at planned dose levels of ***25 mg (Cohort 1b), 50 mg (Cohort 1c),*** 100 mg (Cohort 2b), 200 mg (Cohort 3b), 300 mg (Cohort 4b) and 400 mg (Cohort 5b) to receive three doses (Q28 days) of active treatment in an open label fashion***. Cohorts 6 through 11 will enroll at planned dose levels of 100 mg (Cohorts 6 and 7), 200 mg (Cohort 10), and 300 mg (Cohorts 8, 9, and 11).*** Cohort 6 will enroll CHB subjects (after Cohort 5b has completed enrollment) to receive three doses two weeks apart. Cohorts 7, 10 and 11 will enroll CHB patients sequentially (after Cohort 6 has completed enrollment) to receive three doses a week apart at increasing dose levels starting with a dose equal to Cohort 6. Cohorts 5b through 7 and Cohorts 10 and 11 will enroll sequentially (after being opened at the final planned DSC meeting) with enrollment and dosing in a later cohort not initiating until all subjects in the earlier cohort have received at least their first scheduled dose. Cohort 8 will enroll HBeAg positive treatment naïve CHB patients to receive three monthly doses of ARO-HBV. Cohort 9 will enroll HBeAg positive entecavir or tenofovir experienced CHB patients to receive three monthly doses of ARO-HBV. CHB patient ***s***creening for all CHB cohorts may start when Cohort 1 opens for enrollment. However, no CHB patients may be dosed until their respective cohort is approved for dosing by the DSC ***(not including Cohorts 1b and 1c)***. CHB dosing may begin and NHV dose escalation may occur based on DSC approval which can occur by vote after cumulative data through Day 8 from the current NHV cohort is available. (See Figure 1 for dose escalation schedule).

From:
In Cohorts 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10 and 11, eligible CHB patients who have signed an HDEC (or local equivalent) approved informed consent form will receive three doses of ARO-HBV at dose intervals ranging from once every week to once every 4 weeks in an open label fashion. Screening for the CHB cohorts can begin once Cohort 1 dosing has commenced. These cohorts will be opened for accrual once the corresponding NHV cohort receiving the same dose level has reached Day 8, based on agreement of the DSC that it is safe to proceed. Cohorts 6, 7, 8, 9, 10 and 11 can be opened for enrollment any time after Cohort 5 has reached Day 8 (and DSC has approved opening of such cohorts) and there is sufficient viral antigen response data from CHB patients to determine a dose level for these cohorts. The planned dose level for Cohorts 6 through 11 is between 100 and 400 mg. Cohorts 2b through Cohort 7 and Cohorts 10 and 11 will be enrolled in sequence (as shown in Figure 1). Cohorts 8 and 9 may be enrolled in parallel with other CHB cohorts after the DSC has voted post Cohort 5 to open the remaining CHB patient cohorts and once a specified dose (≤ 400 mg) has been identified.

To:
In Cohorts ***1b, 1c,*** 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10 and 11, eligible CHB patients who have signed an HDEC (or local equivalent) approved informed consent form will receive three doses of ARO-HBV at dose intervals ranging from once every week to once every 4 weeks in an open label fashion. Screening for the CHB cohorts can begin once Cohort 1 dosing has commenced. These cohorts ***(not including Cohort 1b and 1c)*** will be opened for accrual once the corresponding NHV cohort receiving the same dose level has reached Day 8, based on agreement of the DSC that it is safe to proceed. Cohorts 6, 7, 8, 9, 10 and 11 can be opened for enrollment any time after Cohort 5 has reached Day 8 (and DSC has approved opening of such cohorts) and there is sufficient viral antigen response data from CHB patients to determine a dose level for these cohorts. ***Dose levels*** for Cohorts 6 through 11 is between 100 and ***300*** mg. Cohorts 2b through Cohort 7 and Cohorts 10 and 11 will be enrolled in sequence (as shown in Figure 1). Cohorts 8 and 9 may be enrolled in parallel with other CHB cohorts after the DSC has voted post Cohort 5 to open the remaining CHB patient cohorts and once a specified dose (≤ 400 mg) has been identified. ***Cohorts 1b and 1c are open for enrollment with the addition of this protocol amendment and may enroll in parallel.***

From:
CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after the last dose.

To:
CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after ***Day 113***.

From:

Figure 1: 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		N/A	N/A
Cohort 2	100 mg		Cohort 2b (all eligible CHB patients regardless of NUC or HBeAg status)	100 mg dosed on Day 1, 29, 57
Cohort 3	200 mg		Cohort 3b (all eligible CHB patients regardless of NUC or HBeAg status)	200 mg dosed on Day 1, 29, 57
Cohort 4	300 mg		Cohort 4b (all eligible CHB patients regardless of NUC or HBeAg status)	300 mg dosed on Day 1, 29, 57
Cohort 5	400 mg		Cohort 5b (all eligible CHB patients regardless of NUC or HBeAg status)	400 mg dosed on Day 1, 29, 57
			Cohort 6 (all eligible CHB patients regardless of NUC or HBeAg status)	Dose TBD** Day 1, 15, 29
			Cohort 7 (all eligible CHB patients regardless of NUC or HBeAg status)	Dose TBD** Day 1, 8, 15
			Cohort 8 HBeAg+, treatment naïve	Dose TBD** Day 1, 29, 57
			Cohort 9 HBeAg+, entecavir or tenofovir experienced	Dose TBD** Day 1, 29, 57
			Cohort 10 (all eligible CHB patients regardless of NUC or HBeAg status)	Dose TBD** Day 1, 8, 15
			Cohort 11 (all eligible CHB patients regardless of NUC or HBeAg status)	Dose TBD** Day 1, 8, 15

* All Cohorts use 2 sentinel subjects

To:

Figure 1: 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)***	***25 mg dosed on Day 1, 29, 57***
			Cohort 1c (all eligible CHB patients regardless of NUC or HBeAg status)	***50 mg dosed on Day 1, 29, 57***
Cohort 2	100 mg		Cohort 2b (all eligible CHB patients regardless of NUC or HBeAg status)	100 mg dosed on Day 1, 29, 57
Cohort 3	200 mg		Cohort 3b (all eligible CHB patients regardless of NUC or HBeAg status)	200 mg dosed on Day 1, 29, 57
Cohort 4	300 mg		Cohort 4b (all eligible CHB patients regardless of NUC or HBeAg status)	300 mg dosed on Day 1, 29, 57
Cohort 5	400 mg		Cohort 5b (all eligible CHB patients regardless of NUC or HBeAg status)	400 mg dosed on Day 1, 29, 57
			Cohort 6 (all eligible CHB patients regardless of NUC or HBeAg status)	***100 mg dosed on*** Day 1, 15, 29
			Cohort 7 (all eligible CHB patients regardless of NUC or HBeAg status)	***100 mg dosed on*** Day 1, 8, 15
			Cohort 8 HBeAg+, treatment naïve	***300 mg dosed on*** Day 1, 29, 57
			Cohort 9 HBeAg+, entecavir or tenofovir experienced	***300 mg dosed on*** Day 1, 29, 57
			Cohort 10 (all eligible CHB patients regardless of NUC or HBeAg status)	***200 mg dosed on*** Day 1, 8, 15
			Cohort 11 (all eligible CHB patients regardless of NUC or HBeAg status)	***300 mg dosed on*** Day 1, 8, 15

* All Cohorts use 2 sentinel subjects

Deleted:

** Dose for Cohort 6, 7, 8, 9, 10 and 11 to be determined based on safety and viral antigen response seen in Cohorts 2b, 3b, 4b, and 5b. The planned dose level for Cohorts 6-11 is ≤ 400 mg. Cohorts 6-11 may be opened for enrollment any time after Cohort 5 Day 8 safety evaluation with a vote from the DSC. Cohorts 2b through Cohort 7 and Cohorts 10 and 11 will be enrolled in sequence (as shown in Figure 1). Cohorts 8 and 9 may be enrolled in parallel with other CHB cohorts after the DSC has voted post Cohort 5 to open the remaining CHB patient cohorts and once a specified dose (≤ 400 mg) has been identified.

Deleted:
Additional intermediate dose cohorts may be added if approved by Sponsor, HDEC (or local equivalent) and the Data Safety Committee (DSC).

16. **Section/page:** 6.4 Duration of the Study, p. 38

From:
CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after the last dose.

To:
CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after ***Day 113***.

Added:
All CHB subjects who complete the study until Day 113 EOS examination are considered to complete the study and may continue to attend the Additional Follow-Up visits per the Schedule of Assessments (Table 1.5) if re-consent is obtained. If a subject withdraws from the Additional Follow-Up visits before the Day 393 visit, he or she will still be considered as a completed subject and reason for not continuing with the Additional Follow-Up visits per protocol will be recorded.

17. **Section/page:** 7.1 Number of Subjects, p. 38

From:
A total of approximately 30 NHV and a minimum of 40 or a maximum of 56 CHB participants (not including potential replacements) may be enrolled in the study.

To:
A total of approximately 30 NHV and a minimum of ***48*** or a maximum of ***72*** CHB participants (not including potential replacements) may be enrolled in the study.

18. **Section/page:** 9.1 Overview of Procedures, pp. 51-52

From:
Based on observations for all NHV subjects in a cohort through Day 8, dosing will begin for the next NHV cohort and as applicable the next CHB cohort at the discretion of the DSC.

To:
Based on observations for all NHV subjects in a cohort through Day 8, dosing will begin for the next NHV cohort and as applicable the next CHB cohort at the discretion of the DSC ***(not including Cohorts 1b and 1c)***.

From:

For CHB patients in Cohorts 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10 and 11, eligible CHB patients who have signed an HDEC (or local equivalent) approved informed consent form will receive three doses of ARO-HBV at dose intervals ranging from once every week to once every 4 weeks in an open label fashion. Screening for the CHB cohorts can begin once Cohort 1 dosing has commenced. These cohorts will be opened for accrual once the corresponding NHV cohort receiving the same dose level has reached Day 8, based on agreement of the DSC that it is safe to proceed. Cohorts 6, 7, 8, 9, 10 and 11 can be opened for enrollment any time after Cohort 5 has reached Day 8 (and DSC has approved opening of such cohorts) and there is sufficient safety and viral antigen response data from CHB patients to determine a dose level for these cohorts. It is the intent that Cohorts 7, 10 and 11 will be treated at increasing dose levels starting with a dose equal to Cohort 6. The planned dose level for Cohorts 6-11 is ≤ 400 mg (expected to be between 100 mg and 400 mg). Cohorts 2b through Cohort 7 and Cohorts 10 and 11 will be enrolled in sequence (as shown in Figure 1). Cohorts 8 and 9 may be enrolled in parallel with other CHB cohorts after the DSC has voted post Cohort 5 to open the remaining CHB patient cohorts and once a specified dose (≤ 400 mg) has been identified.

To:
For CHB patients in Cohorts ***1b, 1c,*** 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10 and 11, eligible CHB patients who have signed an HDEC (or local equivalent) approved informed consent form will receive three doses of ARO-HBV at dose intervals ranging from once every week to once every 4 weeks in an open label fashion. Screening for the CHB cohorts can begin once Cohort 1 dosing has commenced. These cohorts ***(not including Cohorts 1b and 1c)*** will be opened for accrual once the corresponding NHV cohort receiving the same dose level has reached Day 8, based on agreement of the DSC that it is safe to proceed. Cohorts 6, 7, 8, 9, 10 and 11 can be opened for enrollment any time after Cohort 5 has reached Day 8 (and DSC has approved opening of such cohorts) and there is sufficient safety and viral antigen response data from CHB patients to determine a dose level for these cohorts. It is the intent that Cohorts 7, 10 and 11 will be treated at increasing dose levels starting with a dose equal to Cohort 6. ***Dose levels*** for Cohorts 6-11 is ≤ ***3***00 mg. Cohorts 2b through Cohort 7 and Cohorts 10 and 11 will be enrolled in sequence (as shown in Figure 1). Cohorts 8 and 9 may be enrolled in parallel with other CHB cohorts after the DSC has voted post Cohort 5 to open the remaining CHB patient cohorts and once a specified dose (≤ 400 mg) has been identified. ***Cohorts 1b and 1c are open for enrollment with the addition of this protocol amendment and may enroll in parallel.***

From:
CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after the last dose.

To:
CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after ***Day 113***.

19. **Section/page:** 9.3.6 Clinical Laboratory Tests & Pharmacodynamic Values, p. 55

Added:
Interferon Response Gene SNP testing: Patient's interferon response gene SNPs will be evaluated (if patient consents to limited genetic testing). A blood sample for pharmacogenomics (DNA) research is optional and will only be collected from subjects who consent separately to this component of the study. Subjects who are enrolled in the study at the time of this amendment will be contacted to ask for their consent for this component of the study. Sample can be collected any time after the consent has been signed. This sample can be used to assess impact of IL28B polymorphism on efficacy of ARO-HBV treatment. In addition, samples can be used to investigate the potential association of genetic factors with efficacy, safety, or pharmacokinetics of ARO-HBV,

CHB infection, or HBV-related disease or may be used to develop tests/assays related to ARO-HBV or HBV. These analyses will be performed at the sponsor's discretion, will always be under the sponsor's supervision, and may be reported separately.

20. **Section/page:** 9.3.9 Follow-Up Procedures, p. 56

From:
Additional CHB Follow-Up
CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after the last dose.

To:
Additional CHB Follow-Up
CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after ***Day 113***.

21. **Section/page:** 9.5 Study Formulation Administration, p. 57

From:
Table 2: Injection number and volume per cohort

Cohort*	**Dose**	**Concentration**	**Total Injection Volume**	**# Injections per planned dose**
1	35 mg	200 mg/mL	0.175 mL	Single
2, 2b	100 mg	200 mg/mL	0.5 mL	Single
3, 3b	200 mg	200 mg/mL	1.0 mL	Single
4, 4b	300 mg	200 mg/mL	1.5 mL	Single
5, 5b	400 mg	200 mg/mL	2.0 mL	Two (at separate sites)

To:

Table 2: Injection number and volume per cohort

Cohort	Dose	Concentration	Total Injection Volume	# Injections per planned dose
1	35 mg	200 mg/mL	0.175 mL	Single
1b	***25 mg***	***200 mg/mL***	***0.125 mL***	***Single***
1c	***50 mg***	***200 mg/mL***	***0.25 mL***	***Single***
2, 2b***, 6, 7***	100 mg	200 mg/mL	0.5 mL	Single
3, 3b***, 10***	200 mg	200 mg/mL	1.0 mL	Single
4, 4b***, 8, 9, 11***	300 mg	200 mg/mL	1.5 mL	Single
5, 5b	400 mg	200 mg/mL	2.0 mL	Two (at separate sites)

Deleted:
*Dose for Cohorts 6, 7, 8, 9, 10 and 11 to be determined based on safety and viral antigen response seen in Cohorts 2b, 3b, 4b, and 5b. The planned dose level for Cohorts 6 through 11 is between 100 and ≤ 400 mg.

22. **Section/page:** 11.6 Pharmacodynamic Data, Virology Assessments (CHB patients only) p. 70

Added:
- ***Virologic response parameters may be summarized based on presence of interferon response gene SNPs (e.g. IL28B).***

PROTOCOL AMENDMENT SUMMARY OF CHANGES

PROTOCOL NUMBER:	**AROHBV1001**
STUDY TITLE:	**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**
VERSION/DATE:	**Version 5.0, 04 January 2019**

OVERVIEW/RATIONALE:

This amendment which is specific to **Hong Kong only**:

1. Adds a single open-label CHB cohort (Cohort 12) with 12 subjects each receiving ARO-HBV at 200 mg every 28 days starting on Day 1, and the investigational capsid assembly modulator (CAM), JNJ-56136379 at 250 mg QD starting on Day 1 through Day 84. All subjects will continue on, or be started on entecavir or tenofovir (NUC) for the duration of the study.

2. Corrects any administrative, grammatical, formatting errors and inconsistencies; rewording for clarity

SUMMARY OF CHANGES:

1. Section/page: Title Page, page 1

From:
This amendment adds two CHB open-label Cohorts 1b and 1c with 8 subjects each receiving ARO-HBV at 25 and 50 mg respectively every 28 days, whole blood sample collection for SNP analysis for IFN response genes for all CHB subjects, and clarifies the dose levels for Cohorts 6-11.

To:
This amendment***, specific to Hong Kong only, adds a single open-label CHB cohort (Cohort 12) with 12 subjects each receiving ARO-HBV at 200 mg every 28 days starting on Day 1, and the investigational capsid assembly modulator (CAM), JNJ-56136379 at 250 mg QD starting on Day 1 through Day 84. All subjects will continue on, or be started on entecavir or tenofovir (NUC) for the duration of the study.***

2. Section/page: 1 Protocol Synopsis, Study Treatments, p. 2

From:
There will be two study treatments; one active (Test Formulation) and one placebo (Reference Formulation).

To:
There will be up to three study treatments (depending on the cohort); two active (Test Formulation) ARO-HBV and JNJ-56136379 (JNJ-6379) and one placebo (Reference Formulation).

3. Section/page: 1 Protocol Synopsis, Study Treatments, Test Formulations, p2

Added:
Cohort 12 only will add JNJ-56136379 (JNJ-6379) as a study treatment to be evaluated in CHB patients in combination with ARO-HBV. JNJ-6379 is a capsid assembly modulator (CAM) being developed for the treatment of hepatitis B infection. JNJ-6379 binds to the HBV core protein and interferes with the viral capsid assembly process and resulting in the formation of empty viral capsids devoid of HBV-DNA. JNJ-6379 also acts at an early stage of the viral life cycle by inhibiting the de novo formation of cccDNA.

4. Section/page: 1 Protocol Synopsis, Exploratory Objectives, pp. 2-3

From:
- To determine the reduction from Day 1 pre-dose baseline to post-dose nadir of HBcrAg, HBV RNA (if scientifically feasible) and HBeAg (e+ patients only), in response to ARO-HBV in CHB patients as a measure of activity.
- 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 NHVs.
- To evaluate the effect of single escalating doses of ARO-HBV on complement factors Bb, CH50, C5a, C4a, and C3a in NHVs.
- To collect plasma samples in NHVs for subsequent metabolite identification (reported in a separate report outside of this study)
- To collect urine samples in NHVs 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 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 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 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

To:
- To determine the reduction from Day 1 pre-dose baseline to post-dose nadir of HBcrAg, ***HBsAg,*** HBV RNA (if scientifically feasible) and HBeAg (e+ patients only), in response to ARO-HBV ***(alone or in combination with JNJ-6379)*** in CHB patients as a measure of activity.
- 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 NHVs.
- To evaluate the effect of single escdalating doses of ARO-HBV on complement factors Bb, CH50, C5a, C4a, and C3a in NHVs.

- To collect plasma samples in NHVs for subsequent metabolite identification (reported in a separate report outside of this study)
- To collect urine samples in NHVs 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).***

5. Section/page: 1 Protocol Synopsis, Study Population/Patient Number, pp. 3-4

From:
This study will be conducted in NHVs, adult males and females, aged 18-55 years with BMI between 19.0 and 35.0 kg/m² (Cohorts 1 – 5) and in HBeAg negative or HBeAg positive CHB patients, aged 18-65 years with BMI between 19.0 and 38.0 kg/m² (Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10 and 11). Cohort 8 will enroll HBeAg positive treatment naïve patients (no prior chronic exposure to NUCs or Interferon) and Cohort 9 will enroll HBeAg positive NUC experienced patients (on entecavir or tenofovir for at least 12 months). Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 10 and 11 will enroll either HBeAg positive or negative patients regardless of previous NUC or PEG IFN treatment experience. All patients will be started on entecavir or tenofovir on Day 1. Patients currently on PEG IFN will not be allowed.

To:
This study will be conducted in NHVs, adult males and females, aged 18-55 years with BMI between 19.0 and 35.0 kg/m² (Cohorts 1 – 5) and in HBeAg negative or HBeAg positive CHB patients, aged 18-65 years with BMI between 19.0 and 38.0 kg/m² (Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10, ***11 and 12***). Cohort 8 will enroll HBeAg positive treatment naïve patients (no prior chronic exposure to NUCs or Interferon) and Cohort 9 will enroll HBeAg positive NUC experienced patients (on entecavir or tenofovir for at least 12 months). Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, ***10, 11 and 12*** will enroll either HBeAg positive or negative patients regardless of previous NUC or PEG IFN treatment experience. ***Only Cohort 12 patients will start JNJ-6379 on Day 1 and continue until Day 84.*** All patients will be started on entecavir or tenofovir on Day 1. Patients currently on PEG IFN will not be allowed.

From:
Summary of Participant Profile by Cohort:
- Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 10 and 11: Any CHB patient regardless of HBeAg or prior therapy status (as long as other Inclusion and Exclusion criteria are met)

To:
Summary of Participant Profile by Cohort:
- Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, ***10, 11 and 12***: Any CHB patient regardless of HBeAg or prior therapy status (as long as other Inclusion and Exclusion criteria are met).

From:
CHB cohorts 1b, 1c, 2b, 3b, 4b and 5b will each enroll a minimum of 4 and a maximum of 8 subjects in an open label fashion to receive escalating multiple doses of ARO-HBV. Cohorts 6, 7, 8, 9, 10 and 11 will each enroll a maximum of 4 subjects.

To:
CHB cohorts 1b, 1c, 2b, 3b, 4b and 5b will each enroll a minimum of 4 and a maximum of 8 subjects in an open label fashion to receive escalating multiple doses of ARO-HBV. Cohorts 6, 7, 8, 9, 10 and 11 will each enroll a maximum of 4 subjects. ***Cohort 12 will enroll 12 CHB patients to each receive 250 mg daily oral JNJ-6379+NUCs+200mg ARO-HBV Q28 days X3 doses.***

From:

CHB patients regardless of HBeAg status or NUC/Interferon use history will enroll sequentially into a total of 8 open label cohorts (Cohorts 2b through 7 and Cohorts 10 and 11). Cohorts 2b through 5b will enroll at planned dose levels of 100 mg (Cohort 2b), 200 mg (Cohort 3b), 300 mg (Cohort 4b) and 400 mg (Cohort 5b) to receive three doses (Q28 days) of active treatment in an open label fashion. Cohort 6 will enroll CHB subjects (after Cohort 5b has completed enrollment) to receive three doses two weeks apart. Cohorts 7, 10 and 11 will enroll CHB patients sequentially (after Cohort 6 has completed enrollment) to receive three doses a week apart at increasing dose levels starting with a dose equal to Cohort 6. Cohorts 5b through 7 and Cohorts 10 and 11 will enroll sequentially (after being opened at the final planned DSC meeting) with enrollment and dosing in a later cohort not initiating until all subjects in the earlier cohort have received at least their first scheduled dose. Cohort 8 will enroll HBeAg positive treatment naïve CHB patients to receive three monthly doses of ARO-HBV. Cohort 9 will enroll HBeAg positive entecavir or tenofovir experienced CHB patients to receive three monthly doses of ARO-HBV. Cohorts 8 and 9 may enroll in parallel with Cohort 5b once opened by the DSC. The dose used for Cohorts 6, 7, 8, 9, 10 and 11 will be ≤ 400 mg with an expected dose level of between 100 mg to 400 mg. An additional cohort using an intermediate dose level and dose frequency may be added with approval of the HDEC (or local equivalent) and DSC. CHB patient Screening for all CHB cohorts may start when Cohort 1 opens for enrollment. However, no CHB patients may be dosed until their respective cohort is approved for dosing by the DSC. CHB dosing may begin and NHV dose escalation may occur based on DSC approval which can occur by vote after cumulative data through Day 8 from the current NHV cohort is available. See Figure 1 for dose escalation schedule). CHB patients on current 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. Either tenofovir disoproxil fumarate (including generic) or tenofovir alafenamide are acceptable.

To:

CHB patients regardless of HBeAg status or NUC/Interferon use history will enroll sequentially into a total of ***10*** open label cohorts (Cohorts 2b through 7***,*** and Cohorts 10 and 11***, and Cohort 1b and 1c***). Cohorts ***1***b***, and 1c*** through 5b will enroll at planned dose levels of ***25 mg (Cohort 1b), 50 mg (Cohort 1c),*** 100 mg (Cohort 2b), 200 mg (Cohort 3b), 300 mg (Cohort 4b) and 400 mg (Cohort 5b) to receive three doses (Q28 days) of active treatment in an open label fashion. Cohort 6 will enroll CHB subjects (after Cohort 5b has completed enrollment) to receive three doses two weeks apart. Cohorts 7, 10 and 11 will enroll CHB patients sequentially (after Cohort 6 has completed enrollment) to receive three doses a week apart at increasing dose levels starting with a dose equal to Cohort 6. Cohorts 5b through 7 and Cohorts 10 and 11 will enroll sequentially (after being opened at the final planned DSC meeting) with enrollment and dosing in a later cohort not initiating until all subjects in the earlier cohort have received at least their first scheduled dose. Cohort 8 will enroll HBeAg positive treatment naïve CHB patients to receive three monthly doses of ARO-HBV. Cohort 9 will enroll HBeAg positive entecavir or tenofovir experienced CHB patients to receive three monthly doses of ARO-HBV. Cohorts 8 and 9 may enroll in parallel with Cohort 5b once opened by the DSC. ***Cohorts 6 through 11 will enroll at planned dose levels of 100 mg (Cohorts 6 and 7), 200 mg (Cohort 10), and 300 mg (Cohorts 8, 9, and 11).*** CHB patient ***s***creening for all CHB cohorts may start when Cohort 1 opens for enrollment. However, no CHB patients may be dosed until their respective cohort is approved for dosing by the DSC ***(not including Cohorts 1b and 1c)***. CHB dosing may begin and NHV dose escalation may occur based on DSC approval

which can occur by vote after cumulative data through Day 8 from the current NHV cohort is available. See Figure 1 for dose escalation schedule). CHB patients on current 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. Either tenofovir disoproxil fumarate (including generic) or tenofovir alafenamide are acceptable.

Added:
Cohort 12 will enroll 12 CHB patients to receive ARO-HBV 200 mg on Days 1, 29 and 57. Like all other CHB cohorts, patients enrolling in Cohort 12 will either enter the study on NUCs or start NUCs on Day 1. Cohort 12 patients will also initiate daily JNJ-6379 250 mg on Day 1 and continue through Day 84.

From:
A total of approximately 30 NHV and a minimum of 48 or a maximum of 72 CHB participants (not including potential replacements) may be enrolled in the study

To:

A total of approximately 30 NHV and a minimum of ***60*** or a maximum of ***84*** CHB participants (not including potential replacements) may be enrolled in the study.

6. Section/page: 1 Protocol Synopsis, Number of Doses per Treatment, p. 4

From:
Single dose (Healthy Volunteer Cohorts 1 through 5) or three doses ranging in frequency from once weekly to once every 4 weeks (CHB patients).

To:
Single dose (Healthy Volunteer Cohorts 1 through 5) or three doses ***of ARO-HBV*** ranging in frequency from once weekly to once every 4 weeks (CHB patients).

Daily dose of JNJ-6379 250 mg from Day 1 through Day 84 (Cohort 12 CHB patients only).

7. Section/page: 1 Protocol Synopsis, Study Duration, p. 4

From:
For each CHB patient in the multi-dose Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10 and 11 the duration of the study clinic visits is approximately 25 weeks from screening to the Day 113 EOS examination. CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after Day 113.

To:
For each CHB patient in the multi-dose Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 8, 9, ***10, 11 and 12*** the duration of the study clinic visits is approximately 25 weeks from screening to the Day 113 EOS examination. CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after Day 113.

8. Section/page: 1 Protocol Synopsis, Study Design/Methods, pp. 5-7

From:
CHB patients:
In Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10 and 11, eligible CHB patients who have signed an HDEC (or local equivalent) approved informed consent form will receive three doses of ARO-HBV at dose intervals ranging from once every week to once every 4 weeks in an open label fashion. Screening for the CHB cohorts can begin once Cohort 1 dosing has commenced. These cohorts (not including Cohorts 1b and 1c) will be opened for accrual once the corresponding NHV cohort receiving the same single dose level has reached Day 8, based on agreement of the DSC that it is safe to proceed.

To:
CHB patients:
In Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 8, 9, ***10, 11 and 12***, eligible CHB patients who have signed an HDEC (or local equivalent) approved informed consent form will receive three doses of ARO-HBV at dose intervals ranging from once every week to once every 4 weeks in an open label fashion. ***In addition, Cohort 12 patients will also initiate daily JNJ-6379 250 mg on Day 1 and continue through Day 84.*** Screening for the CHB cohorts can begin once Cohort 1 dosing has commenced. These cohorts (not including Cohorts ***1b, 1c and 12***) will be opened for accrual once the corresponding NHV cohort receiving the same single dose level has reached Day 8, based on agreement of the DSC that it is safe to proceed.

From:
Cohorts 6, 7, 8, 9, 10 and 11 can be opened for enrollment any time after Cohort 5 has reached Day 8 (and DSC has approved opening of such cohorts) and there is sufficient viral antigen response data from CHB patients to determine a dose level for these cohorts (at the discretion of the DSC). Dose levels for Cohorts 6-11 is between 100 and 300 mg. Cohorts 2b through Cohort 7 and Cohorts 10 and 11, will be enrolled in sequence (as shown in Figure 1). Cohorts 8 and 9 may be enrolled in parallel with other CHB cohorts after the DSC has voted post Cohort 5 to open the remaining CHB patient cohorts and the specified dose (≤ 300 mg) has been identified. Cohorts 1b and 1c are open for enrollment with the addition of this protocol amendment and may enroll in parallel.

To:
Cohorts 6, 7, 8, 9, 10 and 11 can be opened for enrollment any time after Cohort 5 has reached Day 8 (and DSC has approved opening of such cohorts) and there is sufficient viral antigen response data from CHB patients to determine a dose level for these cohorts (at the discretion of the DSC). Dose levels for Cohorts ***6-12*** is between 100 and 300 mg. Cohorts 2b through Cohort 7 and Cohorts 10 and 11, will be enrolled in sequence (as shown in Figure 1). Cohorts 8 and 9 may be enrolled in parallel with other CHB cohorts after the DSC has voted post Cohort 5 to open the remaining CHB patient cohorts and the specified dose (≤ 300 mg) has been identified. ***Cohort 12 is open for enrollment in Hong Kong only.*** Cohorts 1b and 1c are open for enrollment with the addition of ***a*** protocol amendment and may enroll in parallel.

Added:
Enrollment in Cohort 12 can begin once enrollment is full in Cohorts 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10, 11. The ARO-HBV dose level for Cohort 12 is 200 mg Q28 days (Days 1, 29, 57). Cohort 12 patients will also initiate daily JNJ-6379 250 mg on Day 1 and continue through Day 84.

From:

Figure 1: 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)***	***25 mg dosed on Day 1, 29, 57***
			Cohort 1c (all eligible CHB patients regardless of NUC or HBeAg status)	***50 mg dosed on Day 1, 29, 57***
Cohort 2	100 mg		Cohort 2b (all eligible CHB patients regardless of NUC or HBeAg status)	100 mg dosed on Day 1, 29, 57
Cohort 3	200 mg		Cohort 3b (all eligible CHB patients regardless of NUC or HBeAg status)	200 mg dosed on Day 1, 29, 57
Cohort 4	300 mg		Cohort 4b (all eligible CHB patients regardless of NUC or HBeAg status)	300 mg dosed on Day 1, 29, 57
Cohort 5	400 mg		Cohort 5b (all eligible CHB patients regardless of NUC or HBeAg status)	400 mg dosed on Day 1, 29, 57
			Cohort 6 (all eligible CHB patients regardless of NUC or HBeAg status)	***100 mg dosed on*** Day 1, 15, 29
			Cohort 7 (all eligible CHB patients regardless of NUC or HBeAg status)	***100 mg dosed on*** Day 1, 8, 15
			Cohort 8 HBeAg+, treatment naïve	***300 mg dosed on*** Day 1, 29, 57
			Cohort 9 HBeAg+, entecavir or tenofovir experienced	***300 mg dosed on*** Day 1, 29, 57
			Cohort 10 (all eligible CHB patients regardless of NUC or HBeAg status)	***200 mg dosed on*** Day 1, 8, 15
			Cohort 11 (all eligible CHB patients regardless of NUC or HBeAg status)	***300 mg dosed on*** Day 1, 8, 15

* All Cohorts use 2 sentinel subjects

To:

Figure 1: 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

9. Section/page: 1 Protocol Synopsis, Treatment Stopping Rules, p. 8

From:
Escalation to the next cohort will proceed according to the study design through the 400 mg dose level and until all subsequent cohorts are completed unless the trial is stopped early by the DSC or Sponsor. A decision to stop the trial early or discontinue drug in an individual subject or group of subjects **may** be indicated based on any of the following:

1. A single Serious Adverse Event (SAE, defined in Section 9.1) considered at least possibly related to ARO-HBV
2. One of the following abnormal results at least possibly related to ARO-HBV:
   - In NHVs, treatment emergent ALT or AST > 3X ULN, which must be confirmed by repeat blood draw within 48 hours of initial results.
   - In CHB patients, treatment emergent ALT or AST > 3X Day 1 pre-dose baseline, confirmed by repeat blood draw within 48 hours of initial results **AND** ALT > 10X ULN **AND** any one of the following:
     - Total Bilirubin newly elevated to 2X ULN **AND** 2X Day 1 pre-dose baseline (confirmed on repeat lab draw within 48 hours) or
     - Decrease in serum albumin of 0.5 g/dL or greater confirmed on repeat lab draw within 48 hours

   - Treatment emergent platelet count < 70,000 per microliter in NHVs or < 50,000 in CHB patients, confirmed on repeat measure within 48 hours of initial results
   - Treatment emergent serum creatinine > 180 µmol/L confirmed by repeat blood draw within 48 hours of initial results

To:
Escalation to the next cohort will proceed according to the study design through the 400 mg dose level and until all subsequent cohorts are completed unless the trial is stopped early by the DSC or Sponsor. A decision to stop the trial early or discontinue drug in an individual subject or group of subjects **may** ***(following a case-by-case decision based on consultation between the sponsor, DSC and the PI)*** be indicated based on any of the following:

1. A single Serious Adverse Event (SAE, defined in Section 9.1) considered at least possibly related to ARO-HBV ***or JNJ-6379***
2. One of the following abnormal results at least possibly related to ARO-HBV ***or JNJ-6379***:
   - In NHVs, treatment emergent ALT or AST > 3X ULN, which must be confirmed by repeat blood draw within 48 hours of initial results.
   - In CHB patients, treatment emergent ALT or AST > 3X Day 1 pre-dose baseline, confirmed by repeat blood draw within 48 hours of initial results **AND** ALT > 10X ULN **AND** any one of the following:
     - Total Bilirubin newly elevated to 2X ULN **AND** 2X Day 1 pre-dose baseline (confirmed on repeat lab draw within 48 hours) or
     - Decrease in serum albumin of 0.5 g/dL or greater confirmed on repeat lab draw within 48 hours

   - Treatment emergent platelet count < 70,000 per microliter in NHVs or < 50,000 in CHB patients, confirmed on repeat measure within 48 hours of initial results
   - Treatment emergent serum creatinine > 180 µmol/L confirmed by repeat blood draw within 48 hours of initial results

10. Section/page: 1 Protocol Synopsis, Study Assessments, p. 9

From:
Immunogenicity:
For Cohorts 1b, 1c, 2b, 3b, 4b, 5b, and 6-11 blood samples for the anti-drug antibodies test will be collected at screening, Day 57 and Day 113 or at the end of study visit.

To:
Immunogenicity:
For Cohorts 1b, 1c, 2b, 3b, 4b, 5b, and ***6-12*** blood samples for the anti-drug antibodies test will be collected at screening, Day 57 and Day 113 or at the end of study visit.

From:
Pharmacokinetics (NHVs only):
Blood samples will be collected from each subject for pharmacokinetic analysis after dose 1 (Cohorts 1-5) per the Schedule of Assessments

To:
Pharmacokinetics (NHVs only ***and limited PK in Cohort 12***):
Blood samples will be collected from each subject for pharmacokinetic analysis after dose 1 (Cohorts 1-5) per the Schedule of Assessments ***and for Cohort 12 patients per the Schedule of Assessments***.

11. Section/page: 1 Protocol Synopsis, Data Analysis, pp. 10-11

From:
Two separate data analyses will be performed, one for all subjects through EOS (Day 29 for NHVs and Day 113 for CHB patients), and one additional and separate analysis for CHB patients who consent to the additional follow up.

To:
Two separate data analyses will be performed, one for all subjects through EOS (Day 29 for NHVs and Day 113 for CHB patients), and one additional and separate analysis for CHB patients who consent to the additional follow up ***through Day 393. Separate analyses including and excluding Cohort 12 may also be completed.***

From:
Safety population: All participants (NHV and CHB patients) that received at least one dose of study treatment.

To:
Safety population: All participants (NHV and CHB patients) that received at least one dose of ***ARO-HBV or JNJ-6379.***

From:
Pharmacokinetics (NHV subjects only):
Plasma concentrations of ARO-HBV product constituents will be used to calculate the following PK parameters: maximum observed plasma concentration (C_{max}), area under the plasma concentration time curve (AUC) from time 0 to 24 hours (AUC_{0-24}), AUC from time 0 extrapolated to infinity (AUC_{inf}), and terminal elimination half-life ($t_{½}$). Pharmacokinetic parameters will be determined using non-compartmental methods. Descriptive statistics of PK parameters will include mean, standard deviation (SD), coefficient of variation, median, minimum, and maximum. PK results will be analyzed for dose proportionality, and sex differences.

PK population: All NHV subjects that received at least one dose of active study treatment (ARO-HBV).

To:
Pharmacokinetics (NHV subjects ***and limited PK in Cohort 12***):

Plasma concentrations of ARO-HBV product constituents will be used to calculate the following PK parameters: maximum observed plasma concentration (C_{max}), area under the plasma concentration time curve (AUC) from time 0 to 24 hours (AUC_{0-24}), AUC from time 0 extrapolated to infinity (AUC_{inf}), and terminal elimination half-life ($t_{½}$). Pharmacokinetic parameters will be determined using non-compartmental methods. Descriptive statistics of PK parameters will include mean, standard deviation (SD), coefficient of variation, median, minimum, and maximum. PK results will be analyzed for dose proportionality, and sex differences.

Plasma concentrations of ARO-HBV, NUC and JNJ-6379 will be measured at a single post-dose time point in Cohort 12 only.

PK population: All NHV subjects ***and Cohort 12 patients*** that received at least one dose of active study treatment (ARO-HBV).

12. Section/page: 1 Protocol Synopsis, Table 1.6, p. 18-19

Added:

Table 1.6: Cohort 12 (CHB patients, ARO-HBV three Q28 day doses + JNJ-6379 daily)

Assessment	Screen (Days -60 to -1)		Day 1	Day 2	Day 8	Day 15 (± 2)	Day 29, 57 (± 2)	Day 43, 71 (± 2)	Day 85 (± 2)	Day 113 (± 2) EOS	Early Termination
Informed Consent	X	CONFIRM ELIGIBILITY									
Eligibility Criteria	X		X[9]								
Body Mass Index	X										
Demographics	X										
Medical History	X		X*								
Drug Screen	X										
Hepatitis/HIV Serology Screen	X										
Physical Exam[1]	X		X*	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X	X[1]
FSH	X[8]										
Pregnancy test	X[5]		X[5]				X[5]			X	X
ECG	X		X[2]				X[2]			X	X
Drug plasma concentrations (ARO-HBV, JNJ-6379, NUC)			X[13]				X[13]				
Vital Signs (BP, temp, RR, heart rate)	X		X[4]	X	X	X	X[4]	X	X	X	X
Hepatic Fibrosis Measure (FibroScan®)	X										
Clinical Labs (heme, coag, chem, UA, amylase, lipase)	X		X[7]	X	X	X	X[7]	X	X	X	X
HBeAg qualitative	X										
Quantitative HBsAg, HBcrAg, HBeAg (e+ only) HBV DNA, HBV RNA	X		X		X	X	X	X	X	X	X

Quantitative anti-HBs, qualitative anti-HBe (e+ only)			X		X	X	X	X	X	X	X
HBV genotyping	X										
HBV sequencing	X									X	X
Cytokines (Panel B) TNF alpha, IFN gamma, CXCL-9, and CXCL-10[3]			X		X	X	X	X	X	X	X
Concomitant Meds/Therapies	X		X	X	X	X	X	X	X	X	X
Adverse Events[6]			X	X	X	X	X	X	X	X	X
ARO-HBV Study Treatment			X				X				
Anti-drug antibodies[9]	X						X[9]			X	X
Start NUCs (naïve patients only)			X								
SNP Analysis			X[10]								
JNJ-6379 Study Treatment Begin			X								
JNJ-6379 Study Treatment End									X		
JNJ-6379 Treatment Dispensation[11]			X	X	X	X	X	X			
JNJ-6379 Treatment Reconciliation[12]				X	X	X	X	X	X		X

* Repeat if > 2 weeks from Screening
1. Symptom-directed PEs to be performed by visit as necessary.
2. ECGs: Measured pre-dose and at 1 and 2 hours post-dose; more frequently per hour if necessary. Performed prior to other invasive procedures.
3. Cytokines Panel B: (whole blood). Venous blood samples collected pre-dose on dosing days then as indicated. Collected samples will only be analyzed at discretion of and with notification by Sponsor.
4. Vitals: Measured pre-dose and at 5 min, 0.5, 1, and 2 hours post-dose.
5. Urine pregnancy test for females of childbearing potential only. Complete pre-dose on dosing days.
6. AE/SAE data capture begins from time of informed consent.
7. Clinical Chemistry, Hematology, Coagulation and Urinalysis pre-dose only on dosing days.
8. Performed for females not of childbearing potential to confirm postmenopausal status.
9. Anti-drug antibodies collected pre-dose, Day 57 and on Day 113 or EOS.
10. If genetic testing consent is obtained, one-time whole blood sample collection will be on Day 1 or any time thereafter for SNP analysis for IFN response genes.
11. JNJ-6379 bottles (both 25 and 100 mg) should be supplied to the patient for continuous daily dosing until the next scheduled visit. On Day 1 prior to JNJ-6379 initial treatment, subject should receive dosing administration training according to the Pharmacy Manual and will be provided a patient diary for daily dose recording.
12. Patients are instructed to bring all JNJ-6379 bottles at each visit to be reconciled against the patient diary.
13. Collect plasma two-hours post-ARO-HBV dose to measure plasma concentration of ARO-HBV, JNJ-6379 and NUC (ETV or TDF).

13. Section/page: 3 List of Abbreviations and Terms, pp. 24-25

Added:

CAM	**Capsid Assembly Modulator**
cccDNA	**Covalently Closed Circular DNA**
JNJ-6379	**JNJ-56136379, a capsid assembly modulator (CAM)**

14. Section/page: 4.1 Background Information, p. 27

Added:

JNJ-6379 is a capsid assembly modulator (CAM) being developed for the treatment of hepatitis B infection. JNJ-6379 binds to the HBV core protein and interferes with the viral capsid assembly process and resulting in the formation of empty viral capsids devoid of HBV-DNA. JNJ-6379 also acts at an early stage of the viral life cycle by inhibiting the de novo formation of cccDNA. It is thought that by using an siRNA approach to silence production of viral antigen in combination with NUCs to inhibit viral replication and JNJ-6379 which inhibits capsid assembly and cccDNA formation the response to treatment and potentially the rate of functional cure could be enhanced.

15. Section/page: 4.2 AROHBV and JNJ-6379 Pre-Clinical Pharmacology and Toxicology Studies, pp. 27-28

From:

4.2 ARO-HBV Pre-clinical Pharmacology and Toxicology Studies

ARO-HBV has been studied in rats and in monkeys in single and multi-dose toxicity studies up to doses of 300 mg/kg. Further details regarding the nonclinical safety results are provided in the Investigator's Brochure.

To:

4.2 ARO-HBV and JNJ-6379 Pre-clinical Pharmacology and Toxicology Studies

ARO-HBV has been studied in rats and in monkeys in single and multi-dose toxicity studies up to doses of 300 mg/kg. Further details regarding the nonclinical safety results are provided in the Investigator's Brochure. ***The human JNJ-6379 exposure at 28 days of 250 mg oral dose and the observed NOAEL in 6 month rat and 9 month dog exposure studies are described in Table 1. Details regarding nonclinical safety results using JNJ-6379 are provided in the JNJ-56136379 Investigator's Brochure.***

Added:

Table 1.

	Sex	NOAEL (mg eq./kg/day)	C_{max} (ng/mL)	AUC_{0-24h} (ng.h/mL)	Ratio Total Concentration		Ratio Concentration Corrected for Plasma Protein Binding[b]	
					C_{max} A/H Ratio	AUC_{0-24h} A/H Ratio	C_{max} A/H Ratio	AUC_{0-24h} A/H Ratio
Human exposure[a]			13,798	265,384	-	-		
	M	30	7,540	93,100	0.6	0.4	0.9	0.6
6M rat	M	100[c]	13,600[d]	180,000[d]	1.0	0.7	1.7	1.1
	F	100	19,900	233,000	1.4	0.9	2.4	1.5
9M dog	M	25	30,000	606,000	2.2	2.3	3.3	3.5
	F	12.5	22,500	383,000	1.6	1.4	2.5	2.2

250 mg JNJ-56136379 once daily for 28 days (Study 56136379HPB1001).

[b] Ratio of the total C_{max} or AUC corrected for species difference in plasma unbound fraction. Calculation: [animal C_{max} or AUC_{0-24h} x animal free fraction] / [human C_{max} or AUC_{0-24h} x human free fraction].

[c] A dose of 100 mg eq./kg/day in male rats is considered to be above the NOAEL due to kidney findings in male rats, which are likely not relevant for human.

[d] The plasma C_{max} of 13,600 ng/mL and AUC_{0-24h} of 180,000 ng.h/mL in male rats at 100 mg eq./kg/day corresponds to an unbound C_{max} of 1,754 ng/mL and AUC_{0-24h} of 23,220 ng.h/mL (fraction unbound rat plasma=12.9%). This unbound plasma exposure will be achieved in humans at a total plasma C_{max} of 22,784 ng/ml and AUC_{0-24h} of 301,558 ng h/mL (fraction unbound in human plasma=7.7%).

16. Section/page: 4.3 ARO-HBV Clinical Studies, pp. 29-30

Deleted: ***There have been no previous studies in humans with ARO-HBV.***

From:

The potent reductions in viral antigens seen using ARC-520/521 and as described in the Investigator Brochure provides strong proof of concept for testing of next generation siRNA compounds like ARO-HBV in HBV patients. Additionally, the human safety profile seen with ARC-520/521 across several multi-dose clinical studies in HBV patients and two SAD healthy volunteer studies is encouraging. Further details on ARC-521 and ARC-520 clinical experience are presented in the Investigator's Brochure.

To:

The potent reductions in viral antigens seen using ARC-520/521 and as described in the Investigator Brochure provides strong proof of concept for testing of next generation siRNA compounds like ARO-HBV in HBV patients. Additionally, the human safety profile seen with ARC-520/521 across several multi-dose clinical studies in HBV patients and two SAD healthy volunteer studies is encouraging. ***Updated interim clinical safety and pharmacologic activity data for ARO-HBV from the ongoing AROHBV1001 study are presented in the Investigator's Brochure 2nd Edition. These data indicate that ARO-HBV has been well tolerated and has demonstrated promising pharmacologic activity against the HBV virus based on reductions of viral antigens and HBV DNA. Pharmacodynamic data to date justify the further clinical development of ARO-HBV with the goal of developing finite regimens aimed at HBsAg clearance in patients with chronic HBV.***

17. Section/page: 4.4 JNJ-6379 Clinical Studies, p. 30-32

Added:

4.4 JNJ-6379 Clinical Studies

Antiviral Activity

Interim data of the ongoing clinical study 56136379HPB1001 (Sessions 8 to 11), in CHB-infected subjects show that JNJ-6379 administration at doses of 25- to 250-mg leads to reduction in HBV DNA. A mean (±SD) reduction in plasma HBV DNA levels of 2.16 (0.49) log10 IU/mL (25 mg), 2.89 (0.48) log10 IU/mL (75 mg), 2.70 (0.53) log10 IU/mL (150 mg), and 2.70 (0.33) log10 IU/mL (250 mg) from baseline was observed at Day 29. In the 250-mg dosing group, 5 out of 12 subjects achieved HBV DNA levels below the LLOQ of the HBV DNA assay, while 3 out of 12 subjects in both the 75-mg and 150-mg dosing groups and none (out of 12) of the subjects in the 25-mg dosing group achieved this. A more pronounced and consistent decline in HBV DNA levels was observed across subjects in the 75-mg, 150-mg, and 250-mg group compared with the 25-mg group.

In line with HBV DNA levels, reductions in HBV RNA levels were observed with JNJ-56136379 treatment. Baseline levels of HBV RNA were generally low and sometimes undetectable, especially in the higher dose groups, limiting the HBV RNA decline observable in this study. No notable changes in HBsAg or HBeAg were observed.

Safety

Healthy Subjects

In a pooled analysis of 123 adult healthy subjects, 98 subjects received at least one dose of JNJ-6379. Eleven subjects did not complete their treatment: due to withdrawal by subject (such as withdrawal of consent or withdrawal due to personal reasons) (4 [3.3%] subjects), lost to follow-up (1 [0.8%] subject), other reasons (2 [1.6%] subjects) or due to adverse events (AEs) (4 [3.3%] subjects, see below).

There were no deaths and 2 subjects experienced a serious adverse event (SAE), both considered not related to JNJ-6379: one during the screening phase (spontaneous abortion; moderate) in study 5636379HPB1004, and the other (wrist fracture right; severe) in study 563679HPB1002, 24 days after the last single dose of JNJ-56136379. Apart from the severe wrist fracture, no severe AEs were reported. In most cases AEs were mild and not considered related to JNJ-56136379.

Two subjects in study 56136379HPB1001 Part 1, single dose escalation phase, discontinued from further dosing with JNJ-56136379 in subsequent sessions due to an AE. One subject in study 56136379HPB1001 Part 2, multiple dose phase, discontinued JNJ-6379 treatment after administration of JNJ-6379 150 mg bid for 2 days, followed by JNJ-6379 100 mg for 9 days due to the AEs abdominal pain lower and dizziness postural. These AEs were considered by the investigator of mild severity and possibly related to JNJ-6379 and resolved after discontinuation.

Overall, the most common treatment-emergent AEs, experienced by >10% of all subjects treated with JNJ-6379 was headache (27 [27.6%] subjects on JNJ-56136379 versus 3 [12.0%] subjects on placebo).

Most graded laboratory abnormalities were grade 1 or 2, except for a grade 3 amylase and grade 4 lipase elevation in 1 subject in study 56136379HPB1002 (both observed during follow-up), a grade 3 lipase elevation in another subject in study 56136379HPB1002 (observed when subject on treatment), and 2 grade 3 LDL cholesterol elevations in one subject each from study 56136379HPB1002 and study 56136379HPB1003 (both observed when subjects on treatment). Based on these cases, lipase and amylase have been identified as laboratory abnormalities of interest. The pooled data show that 5 (5.1%) and 6 (6.1%) subjects on JNJ-6379 had lipase and amylase elevations, respectively versus none on placebo.

CHB Infected Subjects

In the unblinded 25-250 mg sessions of Part 2 of study 56136379HPB1001 in CHB-infected subjects, no deaths were reported. No other SAEs, AEs leading to discontinuation or grade 4 AEs were observed in the 25, 75 and 250 mg treatment groups.

One subject in the JNJ-6379 150 mg treatment group experienced several grade 3 SAEs (idiopathic intracranial hypertension, headache, epilepsy, gliosis, brain edema, brain neoplasm, brain compression) 2 days after completing treatment with JNJ-6379. The subject was withdrawn from the study. All SAEs were considered not related to study drug with outcome unknown. Despite several attempts to reach the patient, the patient was lost to follow-up.

One subject experienced the grade 3 AE AST increased and grade 4 AE ALT increased during JNJ-6379 150 mg treatment. Both AEs were considered probably related to study drug, which was withdrawn, due to the protocol defined stopping criteria. The AEs were considered resolved after end of treatment. The subject also had the AEs liver tenderness (grade 1, possibly related, resolved before end of treatment) and abdominal distension (grade 1, not related, resolved after end of treatment) for which study drug was withdrawn.

Other grade 3 AEs were reported for 1 subject during JNJ-56136379 25 mg treatment (amylase increased, possibly related, resolved before end of treatment), for 1 subject during JNJ-6379 75 mg treatment (ALT increased, possibly related, resolved after end of treatment) and 1 subject after JNJ-6379 150 mg treatment (AST increased, probably related, resolved).

The most frequently reported treatment-emergent AEs across all doses (>1 subject) on JNJ-6379 were headache (4 [11.8%] subjects on JNJ-6379 versus 6 [42.9%] subjects on placebo), nausea (2 [5.9%] subjects versus 0 subjects, respectively), dyspepsia (2 [5.9%] subjects versus 0 subjects, respectively), ALT increased (2 [5.9%] subjects versus 1 [7.1%] subject, respectively), amylase increased (2 [5.9%] subjects versus 0 subjects, respectively), and hypophosphatemia (2 [5.9%] subjects versus 0 subjects, respectively). All other AEs were reported in 1 subject at most. No dose-related trend in AEs was observed. The majority of AEs were grade 1.

The majority of laboratory abnormalities were grade 1 or 2. No grade 3 or 4 laboratory abnormalities were observed in the 250 mg treatment group. Grade 4 ALT elevations were observed in 1 subject each in the 75 and 150 mg treatment groups and were related to the AEs discussed above (for the subject in the 75 mg treatment group, this was observed during follow-up). Grade 3 pancreatic amylase (discussed above as AE) and grade 3 triglycerides (observed during follow-up) were observed in 1 subject each in the 25 mg treatment group. Grade 3 AST elevation was observed in 1 subject in the 75 mg treatment group (observed during follow-up) and in 2 subjects in the 150 mg group (for 1 subject observed during follow-up) (discussed as AE above). Grade 3 hyperkalemia was observed in 1 subject in the 150 mg treatment group.

No ECG-related or vital sign-related AEs were reported. No clinically relevant changes from baseline in ECG or vital signs values were observed.

Further details regarding clinical safety results using JNJ-6379 are provided in the JNJ-56136379 Investigator's Brochure.

18. Section/page: 4.5 ARO-HBV and JNJ-6379 Pre-Clinical Pharmacokinetic and Product Metabolism Studies, pp. 32-33

From:

4.4 ARO-HBV Pre-Clinical Pharmacokinetic and Product Metabolism Studies

PK parameters for ARO-HBV have been evaluated in both rats and monkeys. Results of these studies can be found in the Investigator's Brochure. In general, ARO-HBV will be unmeasurable in the circulation within 1-2 days following a single dose.

To:

4.5 ARO-HBV and JNJ-6379 Pre-Clinical Pharmacokinetic and Product Metabolism Studies

PK parameters for ARO-HBV have been evaluated in both rats and monkeys. Results of these studies can be found in the Investigator's Brochure. In general, ARO-HBV will be unmeasurable in the circulation within 1-2 days following a single dose. ***In healthy subjects, JNJ-6379 is rapidly absorbed from the oral tablets, with a median t_{max} ranging between 1.26 and 3 hours in fasting conditions, and around 4 hours in fed conditions. Mean terminal half-life ($t_{1/2term}$) was comparable between studies 56136379HPB1001 and 56136379HPB1003, ranging between 93.3 and 116 hours across the dose levels in both studies, suggesting no significant difference in clearance between Asian and non-Asian subjects. In study 56136379HPB1003, approximately 18% of the administered dose was excreted via the kidney, resulting in a mean renal clearance of 0.161 L/h. No significant difference was observed in healthy volunteers when compared to patients with CHB. Details regarding pharmacokinetics and metabolism of JNJ-6379 are provided in the latest ARO-HBV and JNJ-56136379 Investigator's Brochure.***

19. **Section/page:** 4.6 Rationale for the Study, p. 34

Added:
Cohort 12 uses a combination of NUCs + ARO-HBV + JNJ-6379. Throughout the study all patients have been treated with the combination of NUCs + ARO-HBV in all other cohorts (Cohorts 1b through 11). It is thought that by using an siRNA approach to silence production of viral antigens in combination with NUCs to inhibit viral replication and JNJ-6379 which inhibits capsid assembly and cccDNA formation the response to treatment and potentially the rate of functional cure could be enhanced. ARO-HBV + NUCs has been well tolerated throughout the AROHBV1001 study. JNJ-6379 in combination with NUCs has also been well tolerated in CHB clinical studies. In vitro, JNJ-6379 does not inhibit phosphorylation of tenofovir or entecavir. Based on results from GLP toxicology studies and in vitro assessments of drug metabolism and transport for both JNJ-6379 and ARO-HBV, as well as safety and tolerability results from prior human studies in healthy volunteers and CHB, there is no indication that JNJ-6379 and ARO-HBV will have overlapping or additive toxicity. As such, the benefit of this combination "triple" therapy is expected to outweigh risk of toxicity.

20. **Section/page:** 4.7 Risk Assessment for Participants, pp. 34-36

From:

4.6 Risk Assessment for Participants

- *Embryo-fetal toxicity:* Limited GLP toxicology as well as preliminary non-GLP embryo-fetal studies have been conducted. Accordingly, eligible participants enrolled in this study, both male and female (including partners), must agree to use two effective methods of contraception (double barrier contraception or hormonal contraception along with a barrier contraceptive) during the study and for 3 months post-dose, or agree to abstinence (acceptable only if this method is in alignment with the normal life style of the patient).

- *Injection Site Reaction Risk:* Other subcutaneously administered modified siRNA drug candidates evaluated in clinical studies have been associated with mild to moderate injection site reactions (e.g. pain, erythema). This study includes a protocol for evaluation and grading of injection site reactions based on pre-defined criteria for mild, moderate and severe reactions. Injection site reactions will be photographed for tracking resolution and/or progression. Additionally, steps will be taken to minimize injection site reactions such as rotating injection sites and allowing the ARO-HBV solution to come to room temperature prior to injecting.

- *Hepatic Toxicity (theoretical risk):* ARO-HBV targets the liver. Arrowhead has not seen meaningful drug induced transaminase changes with a previously studied liver targeted RNAi-based therapeutic (ARC-520/521) targeting HBV. However, another company (Alnylam Therapeutics) developing an siRNA for AATD has seen evidence of mild to moderate elevations in transaminases using hepatocyte targeted siRNA conjugates similar to those used by Arrowhead. Alnylam has described that these ALT changes were due to off- target effects of the siRNA seed region on microRNAs in the hepatocyte (Vaishnaw et al, 2017; Schlegel et al, 2017). The siRNA sequence of the ARO-HBV

sense and antisense molecules have been screened for potential mRNA and microRNA off-target effects. No such off-target effects are anticipated. Multi-dose (3 weekly doses) GLP toxicity studies with ARO-HBV in rats and monkeys demonstrate no evidence of hepatic toxicity up to doses of 300 mg/kg. To mitigate this risk, the proposed study has built in stopping rules for ALT and AST elevation. Labs to evaluate liver injury and liver function will be drawn frequently. The Drug Safety Committee will include a hepatologist member with extensive clinical trial experience and significant experience in evaluation of liver targeted therapeutics, including siRNAs. Additionally, the planned starting dose of 35 mg is approximately 1/50th (assuming weight based conversion and a 60-kg subject) of the lowest dose of 30 mg/kg used in both the multi-dose rat and monkey GLP toxicity studies. This starting dose provides a safety margin of over 500-fold from the monkey NOAEL.

- *Host or viral induced ALT flares (theoretical risk):* Fluctuations in ALT are part of the natural history of CHB infection. In fact, many experts believe that ALT increase represents innate immune responses against infected hepatocytes and is required for HBsAg seroclearance. ALT elevation can also be seen in the setting of rebounding (such as with NUC discontinuation) HBV DNA levels or fluctuations of HBV DNA such as with NUC non-compliance. It is likely that host induced ALT flares will be seen in ARO-HBV studies as part of the normal sequelae associated with HBV. This risk will be mitigated by starting all patients NUCs (entecavir or tenofovir) upon entering the study, or kept on NUCs if NUC experienced. Measures of liver injury (ALT, AST) and of liver function (bilirubin, albumin and coagulation factors) will be measured frequently. Stopping rules for adverse changes in liver function are included. Additionally, "ALT Flare Guidelines" are specified in Appendix 1 to help investigators evaluate ALT elevations during the study

To:

4.7 Risk Assessment for Participants

4.7.1 ARO-HBV:

- *Embryo-fetal toxicity:* Limited GLP toxicology as well as preliminary non-GLP embryo-fetal studies have been conducted. Accordingly, eligible participants enrolled in this study, both male and female (including partners), must agree to use two effective methods of contraception (double barrier contraception or hormonal contraception along with a barrier contraceptive) during the study and for 3 months post-dose, or agree to abstinence (acceptable only if this method is in alignment with the normal life style of the patient).

- *Injection Site Reaction Risk:* Other subcutaneously administered modified siRNA drug candidates evaluated in clinical studies have been associated with mild to moderate injection site reactions (e.g.

pain, erythema). This study includes a protocol for evaluation and grading of injection site reactions based on pre-defined criteria for mild, moderate and severe reactions. Injection site reactions will be photographed for tracking resolution and/or progression. Additionally, steps will be taken to minimize injection site reactions such as rotating injection sites and allowing the ARO-HBV solution to come to room temperature prior to injecting.

- *Hepatic Toxicity (theoretical risk):* ARO-HBV targets the liver. Arrowhead has not seen meaningful drug induced transaminase changes with a previously studied liver targeted RNAi-based therapeutic (ARC-520/521) targeting HBV. However, another company (Alnylam Therapeutics) developing an siRNA for AATD has seen evidence of mild to moderate elevations in transaminases using hepatocyte targeted siRNA conjugates similar to those used by Arrowhead. Alnylam has described that these ALT changes were due to off- target effects of the siRNA seed region on microRNAs in the hepatocyte (Vaishnaw et al, 2017; Schlegel et al, 2017). The siRNA sequence of the ARO-HBV sense and antisense molecules have been screened for potential mRNA and microRNA off-target effects. No such off-target effects are anticipated. Multi-dose (3 weekly doses) GLP toxicity studies with ARO-HBV in rats and monkeys demonstrate no evidence of hepatic toxicity up to doses of 300 mg/kg. To mitigate this risk, the proposed study has built in stopping rules for ALT and AST elevation. Labs to evaluate liver injury and liver function will be drawn frequently. The Drug Safety Committee will include a hepatologist member with extensive clinical trial experience and significant experience in evaluation of liver targeted therapeutics, including siRNAs. Additionally, the planned starting dose of 35 mg is approximately 1/50th (assuming weight based conversion and a 60-kg subject) of the lowest dose of 30 mg/kg used in both the multi-dose rat and monkey GLP toxicity studies. This starting dose provides a safety margin of over 500-fold from the monkey NOAEL.

- *Host or viral induced ALT flares (theoretical risk):* Fluctuations in ALT are part of the natural history of CHB infection. In fact, many experts believe that ALT increase represents innate immune responses against infected hepatocytes and is required for HBsAg seroclearance. ALT elevation can also be seen in the setting of rebounding (such as with NUC discontinuation) HBV DNA levels or fluctuations of HBV DNA such as with NUC non-compliance. It is likely that host induced ALT flares will be seen in ARO-HBV studies as part of the normal sequelae associated with HBV. This risk will be mitigated by starting all patients NUCs (entecavir or tenofovir) upon entering the study, or kept on NUCs if NUC experienced. Measures of liver injury (ALT, AST) and of liver function (bilirubin, albumin and coagulation factors) will be measured frequently. Stopping rules for adverse changes in liver function are included. Additionally, “ALT Flare Guidelines” are specified in Appendix 1 to help investigators evaluate ALT elevations during the study.

4.7.2. JNJ-6379:

- ***Changes in amylase, lipase, cholesterol: Based on data from Study 56136379HPB1002, lipase and amylase elevations were identified as laboratory abnormalities of interest. In addition, based on preclinical findings in rats and dogs, increased cholesterol was identified as laboratory abnormality of interest. Serum lipase, amylase and cholesterol will be monitored in patients.***

- ***Emergence of Resistance: Treatment with JNJ-56136379 may lead to emergence of viral variants with reduced susceptibility or resistance to JNJ-56136379. Based on pre-clinical data, these variants remain susceptible to TDF and ETV but might affect treatment options with CAMs in the future.***

4.7.3. ARO-HBV and JNJ-6379 combined

- ***Overlapping drug toxicity (theoretical risk): Cohort 12 proposes the addition of JNJ-6379 to the treatment regimen of ARO-HBV+NUC which has been used throughout the study. Based on available clinical and pre-clinical experience with each compound as well as combination clinical studies of ARO-HBV with NUCs and JNJ-6379 with NUCs, clinically significant overlapping toxicity is not expected in Cohort 12.***

21. Section/page: 4.8 Justification for Dose of ARO-HBV and JNJ-6379, p. 36-37

From:

4.6 Justification for Starting Dose in Humans

To:

4.8 Justification for <u>Dose of ARO-HBV and JNJ-6379</u>

Added:

For cohort 12, the dose of ARO-HBV administered will be 200mg on Days 1, 29, and 57. ARO-HBV has been shown to be well tolerated and and effective at reducing viral antigens at doses up to 400mg dosed on Days 1, 29 and 57 (see Investigator's Brochure 2nd Edition). Since there was no obvious dose response observed between 100mg and 400mg ARO-HBV dosed on Days 1, 29, and 57, the second lowest dose level of 200 mg was chosen for cohort 12. The JNJ-6379 dose to be administered will be 250 mg given once daily. This dose is currently tested for up to 48 weeks in the ongoing Phase 2a study 56136379HPB2001 and has been selected based on all safety, PK, and antiviral activity data available following completion of the highest JNJ-6379 dose group (who received 250 mg once daily) in the Phase 1 study 56136379HPB1001 in treatment-naïve CHB-infected subjects treated for 28 days. No SAEs or AEs leading to treatment discontinuation were reported for CHB-infected subjects who received 250 mg JNJ-6379 once daily for 28 days, and all AEs were grade 1. In addition, no treatment-emergent laboratory abnormalities of >grade 2, ECG or vital signs abnormalities of ≥grade 2 were reported for these subjects, and no abnormalities were reported as AEs. The dose of 250 mg once daily has been selected to efficiently inhibit HBV DNA replication across a broad spectrum of patients

and viral variants. In addition, 250 mg is expected to increase the potential to trigger the secondary mode of action (MoA) (i.e., inhibition of de novo cccDNA formation) which requires about 10-fold higher concentrations of JNJ-6379 than the primary MoA of inhibition, ie, interfering with capsid assembly (EC90 primary MoA=376 nM and EC90 secondary MoA=4019 nM).

22. Section/page: 5.3 Exploratory Objectives, pp. 38-39

From:

- To determine the reduction of HBcrAg, HBV RNA (if scientifically feasible) and HBeAg (e+ only), in response to ARO-HBV in CHB patients as a measure of activity
- 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 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 on HBV patient immune cell profile including T-cells, NK cells, B cells and monocytes in a limited number of HBV patients in New Zealand only (if scientifically feasible).
- To evaluate the effect of multiple doses of ARO-HBV on HBV antigen specific T-cell response in a limited number of HBV patients in New Zealand only (if scientifically feasible).
- To evaluate the effect of interferon response gene single nucleotide polymorphisms (SNPs) including IL28B on response to ARO-HBV

To:

- To determine the reduction of HBcrAg, , HBsAg, 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
- 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 in a limited number of HBV patients in New Zealand only (if scientifically feasible).
- To evaluate the effect of multiple doses of ARO-HBV on HBV antigen specific T-cell response in a limited number of HBV patients in New Zealand only (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).***

23. Section/page: 6.1 Study Design, pp. 40-44

From:
CHB patients:

HBeAg negative or HBeAg positive CHB patients, aged 18-65 years with BMI between 19.0 and 38.0 kg/m² (Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10 and 11) will be enrolled. Cohort 8 will enroll HBeAg positive treatment naïve patients (no prior chronic exposure to NUCs or Interferon) and Cohort 9 will enroll HBeAg positive NUC experienced patients (on entecavir or tenofovir for at least 12 months). Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 10 and 11 will enroll either HBeAg positive or negative patients regardless of previous NUC or PEG IFN treatment experience. All patients will be started on entecavir or tenofovir on Day 1. Patients currently on PEG IFN will not be allowed.

To:
CHB patients:

HBeAg negative or HBeAg positive CHB patients, aged 18-65 years with BMI between 19.0 and 38.0 kg/m² (Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 8, 9, ***10, 11 and 12***) will be enrolled. Cohort 8 will enroll HBeAg positive treatment naïve patients (no prior chronic exposure to NUCs or Interferon) and Cohort 9 will enroll HBeAg positive NUC experienced patients (on entecavir or tenofovir for at least 12 months). Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, ***10, 11 and 12*** will enroll either HBeAg positive or negative patients regardless of previous NUC or PEG IFN treatment experience. All patients will be started on entecavir or tenofovir on Day 1. ***Cohort 12 will start on JNJ-6379 on Day 1 and continue oral 250 mg QD through Day 84.*** Patients currently on PEG IFN will not be allowed.

From:

- Cohorts 1-5: NHVs, adult males and females, aged 18-55 years
    - 6 NHV subjects per cohort
- Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 10 and 11: Any CHB patient regardless of HBeAg or prior therapy status (as long as other Inclusion and Exclusion criteria are met).
    - Cohorts 1b, 1c, 2b, 3b, 4b and 5b will enroll a minimum of 4 and a maximum of 8 patients per cohort.
    - Cohorts 6, 7, 10 and 11 will enroll a maximum of 4 patients per cohort.
- Cohort 8: HBeAg positive treatment naïve patients (no prior chronic exposure to NUCs or Interferon)
    - Cohort 8: Maximum of 4 patients per cohort
- Cohort 9: HBeAg positive NUC experienced patients (on entecavir or tenofovir for at least 12 months).
    - Cohort 9: Maximum of 4 patients per cohort

To:

Summary of Participant Profile by Cohort and Cohort Size:

- Cohorts 1-5: NHVs, adult males and females, aged 18-55 years
    - 6 NHV subjects per cohort
- Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, ***10, 11 and 12***: Any CHB patient regardless of HBeAg or prior therapy status (as long as other Inclusion and Exclusion criteria are met).
    - Cohorts 1b, 1c, 2b, 3b, 4b and 5b will enroll a minimum of 4 and a maximum of 8 patients per cohort.
    - Cohorts 6, 7, 10 and 11 will enroll a maximum of 4 patients per cohort.
    - ***Cohort 12 will enroll 12 patients.***

- Cohort 8: HBeAg positive treatment naïve patients (no prior chronic exposure to NUCs or Interferon)
    - Cohort 8: Maximum of 4 patients per cohort
- Cohort 9: HBeAg positive NUC experienced patients (on entecavir or tenofovir for at least 12 months).
    - Cohort 9: Maximum of 4 patients per cohort

From:

CHB patients regardless of HBeAg status or NUC/Interferon use history will enroll sequentially in Cohorts 2b through 7, Cohorts 10 and 11, and Cohorts 1b and 1c into a total of 10 open label cohorts. Cohorts 1b, and 1c through 5b will enroll at planned dose levels of 25 mg (Cohort 1b), 50 mg (Cohort 1c), 100 mg (Cohort 2b), 200 mg (Cohort 3b), 300 mg (Cohort 4b) and 400 mg (Cohort 5b) to receive three doses (Q28 days) of active treatment in an open label fashion. Cohorts 6 through 11 will enroll at planned dose levels of 100 mg (Cohorts 6 and 7), 200 mg (Cohort 10), and 300 mg (Cohorts 8, 9, and 11). Cohort 6 will enroll CHB subjects (after Cohort 5b has completed enrollment) to receive three doses two weeks apart. Cohorts 7, 10 and 11 will enroll CHB patients sequentially (after Cohort 6 has completed enrollment) to receive three doses a week apart at increasing dose levels starting with a dose equal to Cohort 6. Cohorts 5b through 7 and Cohorts 10 and 11 will enroll sequentially (after being opened at the final planned DSC meeting) with enrollment and dosing in a later cohort not initiating until all subjects in the earlier cohort have received at least their first scheduled dose. Cohort 8 will enroll HBeAg positive treatment naïve CHB patients to receive three monthly doses of ARO-HBV. Cohort 9 will enroll HBeAg positive entecavir or tenofovir experienced CHB patients to receive three monthly doses of ARO-HBV. CHB patient screening for all CHB cohorts may start when Cohort 1 opens for enrollment. However, no CHB patients may be dosed until their respective cohort is approved for dosing by the DSC (not including Cohorts 1b and 1c). CHB dosing may begin and NHV dose escalation may occur based on DSC approval which can occur by vote after cumulative data through Day 8 from the current NHV cohort is available. (See **Figure 1** for dose escalation schedule).

CHB patients on current 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. Either tenofovir disoproxil fumarate (including generic) or tenofovir alafenamide are acceptable.

To:

CHB patients regardless of HBeAg status or NUC/Interferon use history will enroll sequentially in Cohorts 2b through 7, Cohorts 10 and 11, and Cohorts 1b and 1c into a total of 10 open label cohorts. Cohorts 1b, and 1c through 5b will enroll at planned dose levels of 25 mg (Cohort 1b), 50 mg (Cohort 1c), 100 mg (Cohort 2b), 200 mg (Cohort 3b), 300 mg (Cohort 4b) and 400 mg (Cohort 5b) to receive three doses (Q28 days) of active treatment in an open label fashion. Cohorts 6 through *12* will enroll at planned dose levels of 100 mg (Cohorts 6 and 7), 200 mg (Cohort 10***, 12***), and 300 mg (Cohorts 8, 9, and 11). Cohort 6 will enroll CHB subjects (after Cohort 5b

has completed enrollment) to receive three doses two weeks apart. Cohorts 7, 10 and 11 will enroll CHB patients sequentially (after Cohort 6 has completed enrollment) to receive three doses a week apart at increasing dose levels starting with a dose equal to Cohort 6. Cohorts 5b through 7 and Cohorts 10 and 11 will enroll sequentially (after being opened at the final planned DSC meeting) with enrollment and dosing in a later cohort not initiating until all subjects in the earlier cohort have received at least their first scheduled dose. Cohort 8 will enroll HBeAg positive treatment naïve CHB patients to receive three monthly doses of ARO-HBV. Cohort 9 will enroll HBeAg positive entecavir or tenofovir experienced CHB patients to receive three monthly doses of ARO-HBV. CHB patient screening for all CHB cohorts may start when Cohort 1 opens for enrollment. However, no CHB patients may be dosed until their respective cohort is approved for dosing by the DSC (not including Cohorts 1b***,1c and 12***). CHB dosing may begin and NHV dose escalation may occur based on DSC approval which can occur by vote after cumulative data through Day 8 from the current NHV cohort is available. (See **Figure 1** for dose escalation schedule).

CHB patients on current 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. Either tenofovir disoproxil fumarate (including generic) or tenofovir alafenamide are acceptable. ***During the extended follow up period after Day 113, NUCs may be discontinued at investigator discretion if subject becomes HBsAg undetectable (< 0.05 IU/mL).***

Added:

Cohort 12 will enroll 12 CHB patients in an open label fashion to receive 200 mg ARO-HBV on Days 1, 29 and 57 as well as JNJ-6379 250 mg oral once daily starting on Day 1 and continuing through Day 84. Like all other cohorts, patients enrolling in Cohort 12 will either enter the study on NUCs or start NUCs on Day 1. Enrollment in Cohort 12 can begin once enrollment is full in Cohorts 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10, 11. The ARO-HBV dose level for Cohort 12 is 200 mg Q28 days (Days 1, 29, 57). Cohort 12 is open for enrollment in Hong Kong only.

From:

In Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10 and 11, eligible CHB patients who have signed an HDEC (or local equivalent) approved informed consent form will receive three doses of ARO-HBV at dose intervals ranging from once every week to once every 4 weeks in an open label fashion. Screening for the CHB cohorts can begin once Cohort 1 dosing has commenced. These cohorts (not including Cohorts 1b and 1c) will be opened for accrual once the corresponding NHV cohort receiving the same dose level has reached Day 8, based on agreement of the DSC that it is safe to proceed. Cohorts 6, 7, 8, 9, 10 and 11 can be opened for enrollment any time after Cohort 5 has reached Day 8 (and DSC has approved opening of such cohorts) and there is sufficient viral antigen response data from CHB patients to determine a dose level for these cohorts. Dose levels for Cohorts 6 through 11 is between 100 and 300 mg. Cohorts 2b through Cohort 7 and Cohorts 10 and 11 will be enrolled in sequence (as shown in Figure 1). Cohorts 8 and 9 may be enrolled in parallel with other CHB

cohorts after the DSC has voted post Cohort 5 to open the remaining CHB patient cohorts and once a specified dose (≤ 400 mg) has been identified. Cohorts 1b and 1c are open for enrollment with the addition of this protocol amendment and may enroll in parallel.

To:

In Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 8, 9, ***10, 11 and 12***, eligible CHB patients who have signed an HDEC (or local equivalent) approved informed consent form will receive three doses of ARO-HBV at dose intervals ranging from once every week to once every 4 weeks in an open label fashion. Screening for the CHB cohorts can begin once Cohort 1 dosing has commenced. These cohorts (not including Cohorts 1b and 1c) will be opened for accrual once the corresponding NHV cohort receiving the same dose level has reached Day 8, based on agreement of the DSC that it is safe to proceed. Cohorts 6, 7, 8, 9, 10 and 11 can be opened for enrollment any time after Cohort 5 has reached Day 8 (and DSC has approved opening of such cohorts) and there is sufficient viral antigen response data from CHB patients to determine a dose level for these cohorts. Dose levels for Cohorts 6 through 11 is between 100 and 300 mg. Cohorts 2b through Cohort 7 and Cohorts 10 and 11 will be enrolled in sequence (as shown in Figure 1). Cohorts 8 and 9 may be enrolled in parallel with other CHB cohorts after the DSC has voted post Cohort 5 to open the remaining CHB patient cohorts and once a specified dose (≤ 400 mg) has been identified. Cohorts 1b,1c and Cohort 12 are open for enrollment with the addition of ***applicable*** protocol amendments and may enroll in parallel.

From:

CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after Day 113. Subjects consenting to additional follow up will continue on NUCs. Subjects not consenting to additional follow up will be followed per protocol based on Schedule of Assessment Tables 1.2, 1.3 and 1.4.

To:

CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after Day 113. Subjects consenting to additional follow up will continue on NUCs ***and may have NUCs discontinued at the investigator's discretion if patients become HBsAg undetectable (< 0.05 IU/mL)***. Subjects not consenting to additional follow up will be followed per protocol based on Schedule of Assessment Tables 1.2, 1.3 and 1.4.

From:

Figure 1. 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)	25 mg dosed on Day 1, 29, 57
			Cohort 1c (all eligible CHB patients regardless of NUC or HBeAg status)	50 mg dosed on Day 1, 29, 57
Cohort 2	100 mg		Cohort 2b (all eligible CHB patients regardless of NUC or HBeAg status)	100 mg dosed on Day 1, 29, 57
Cohort 3	200 mg		Cohort 3b (all eligible CHB patients regardless of NUC or HBeAg status)	200 mg dosed on Day 1, 29, 57
Cohort 4	300 mg		Cohort 4b (all eligible CHB patients regardless of NUC or HBeAg status)	300 mg dosed on Day 1, 29, 57
Cohort 5	400 mg		Cohort 5b (all eligible CHB patients regardless of NUC or HBeAg status)	400 mg dosed on Day 1, 29, 57
			Cohort 6 (all eligible CHB patients regardless of NUC or HBeAg status)	100 mg dosed on Day 1, 15, 29
			Cohort 7 (all eligible CHB patients regardless of NUC or HBeAg status)	100 mg dosed on Day 1, 8, 15
			Cohort 8 HBeAg+, treatment naïve	300 mg dosed on Day 1, 29, 57
			Cohort 9 HBeAg+, entecavir or tenofovir experienced	300 mg dosed on Day 1, 29, 57
			Cohort 10 (all eligible CHB patients regardless of NUC or HBeAg status)	200 mg dosed on Day 1, 8, 15
			Cohort 11 (all eligible CHB patients regardless of NUC or HBeAg status)	300 mg dosed on Day 1, 8, 15

*All cohorts will start with two sentinel subjects

To:

Figure 1. 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 250mg QD + ARO-HBV 200 mg dosed on Day 1, 29, 57***

*All ***NHV*** cohorts will start with two sentinel subjects

24. Section/page: 6.2 Rationale for Study Design, p. 45

Added:

Cohort 12 uses a combination of NUCs + ARO-HBV + JNJ-6379. Throughout the study all patients have been treated with the combination of NUCs + ARO-HBV. It is thought that by using an siRNA approach to silence production of viral antigen in combination with NUCs to inhibit viral replication and JNJ-6379 which inhibits capsid assembly and cccDNA formation the response to treatment and potentially the rate of functional cure could be enhanced. ARO-HBV + NUCs has been well tolerated throughout the AROHBV1001 study. JNJ-6379 in combination with NUCs has also been well tolerated in CHB clinical studies. In vitro, JNJ-6379 does not inhibit phosphorylation of tenofovir or entecavir. It is not expected that JNJ-6379 and ARO-HBV will have overlapping or additive toxicity. As such, the benefit of this combination "triple" therapy is expected to outweigh risk of toxicity.

25. Section/page: 6.3 Criteria for Dose-escalation and Stopping Rules, p. 46

From:

A decision to stop the trial early or discontinue drug in an individual subject or group of subjects **may** be indicated based on any of the following:

1. A single Serious Adverse Event(SAE) (defined in Section 9.1) considered at least possibly related to ARO-HBV
2. One of the following abnormal results at least possibly related to ARO-HBV:
    - In NHVs, treatment emergent ALT or AST > 3X ULN which must be confirmed by repeat blood draw within 48 hours of initial results.
    - In CHB patients, treatment emergent ALT or AST > 3X Day 1 pre-dose baseline confirmed by repeat blood draw within 48 hours of initial results **AND** ALT > 10X ULN **AND** any one of the following:
        - Total Bilirubin newly elevated to 2X ULN AND 2X Day-1 pre-dose baseline (confirmed on repeat lab draw within 48 hours) or
        - Decrease in serum albumin of 0.5 g/dL or greater (confirmed on repeat lab draw within 48 hours)
    - Treatment emergent platelet count < 70,000 per microliter in NHVs or < 50,000 in CHB patients, confirmed on repeat measure within 48 hours of initial results
    - Treatment emergent serum creatinine > 180 µmol/L confirmed by repeat blood draw within 48 hours of initial results

To:
A decision to stop the trial early or discontinue drug in an individual subject or group of subjects **<u>may</u>** ***(following a case-by-case decision based on consultation between the sponsor, DSC and the PI)*** be indicated based on any of the following:

1. A single Serious Adverse Event(SAE) (defined in Section 9.1) considered at least possibly related to ARO-HBV ***and/or JNJ-6379***
2. One of the following abnormal results at least possibly related to ARO-HBV ***and/or JNJ-6379***:
    - In NHVs, treatment emergent ALT or AST > 3X ULN which must be confirmed by repeat blood draw within 48 hours of initial results.
    - In CHB patients, treatment emergent ALT or AST > 3X Day 1 pre-dose baseline confirmed by repeat blood draw within 48 hours of initial results **<u>AND</u>** ALT > 10X ULN **<u>AND</u>** any one of the following:
        - Total Bilirubin newly elevated to 2X ULN AND 2X Day-1 pre-dose baseline (confirmed on repeat lab draw within 48 hours) or
        - Decrease in serum albumin of 0.5 g/dL or greater (confirmed on repeat lab draw within 48 hours)
    - Treatment emergent platelet count < 70,000 per microliter in NHVs or < 50,000 in CHB patients, confirmed on repeat measure within 48 hours of initial results
    - Treatment emergent serum creatinine > 180 μmol/L confirmed by repeat blood draw within 48 hours of initial results

26. Section/page: 7.1 Number of Subjects, p. 48

From:
A total of approximately 30 NHV and a minimum of 48 or a maximum of 72 CHB participants (not including potential replacements) may be enrolled in the study.

To:
A total of approximately 30 NHV and a minimum of ***50*** or a maximum of ***84*** CHB participants (not including potential replacements) may be enrolled in the study.

27. Section/page: 7.2 Inclusion Criteria for CHB Patient Cohorts, pp. 49-50

From:

5. Participants using two effective methods of contraception (double barrier contraception or hormonal contraception along with a barrier contraceptive, both male and female partners) during the study and for 3 months following the dose of ARO-HBV. Males must not donate sperm for at least 3 months after the last study treatment. Male partners of female subjects and female partners of male subjects must also use

contraception, if they are of childbearing potential. Females of childbearing potential must have a negative urine pregnancy test at Screening and on Day 1, pre-dose. Females not of childbearing potential must be post-menopausal (defined as cessation of regular menstrual periods for at least 12 months), confirmed by follicle-stimulating hormone (FSH) level in the post-menopausal range.

a. Using twice the normal protection of birth control by using a condom AND one other form of the following (abstinence is acceptable at PI's discretion):

- Birth control pills (The Pill)
- Depot or injectable birth control
- IUD (Intrauterine Device)
- Birth Control Patch (e.g., Ortho Evra)
- NuvaRing®
- Surgical sterilization, i.e., tubal ligation or hysterectomy for women or vasectomy for men or other forms of surgical sterilization

To:

5. Participants using two effective methods of contraception (double barrier contraception or hormonal contraception along with a barrier contraceptive, both male and female partners) during the study and for 3 months following the dose of ARO-HBV. Males must not donate sperm for at least 3 months after the last study treatment. Male partners of female patients and female partners of male patients must also use contraception, if they are of childbearing potential. Females of childbearing potential must have a negative urine pregnancy test at Screening and on Day 1, predose. Females not of childbearing potential must be post-menopausal (defined as cessation of regular menstrual periods for at least 12 months), confirmed by follicle-stimulating hormone (FSH) level in the post-menopausal range.

- Using twice the normal protection of birth control by using a condom AND one other form of the following (abstinence is acceptable at PI's discretion):
  - Birth control pills (The Pill)
    - ***Cohort 12 Only: Female subjects of childbearing potential who are on a stable treatment regimen with hormonal contraceptives (i.e., same dose and not starting or stopping hormonal contraceptive use) for ≥3 months prior to screening should continue the same dose regimen until 12 weeks after EOT. Ethinylestradiol-containing contraceptives are only allowed if the ethinylestradiol content is ≤20 µg. For female subjects of childbearing potential who will start a hormonal contraceptive treatment during the study, ethinylestradiol-containing contraceptives are not allowed.***
  - Depot or injectable birth control
  - IUD (Intrauterine Device)
  - Birth Control Patch (e.g., Ortho Evra)
  - NuvaRing®
  - Surgical sterilization. i.e, tubal ligation or hysterectomy for women or vasectomy for ment or other forms of surgical sterilization

From:

12. Patients with liver Elastography (i.e. FibroScan®) score ≤ 10.5 at or within 3 months of Screening

To:

12. Patients with liver Elastography (i.e. FibroScan®) score ≤ 10.5 at or within 3 months of Screening ***(for Cohort 12 patients must have FibroScan < 9.0 kPa)***

Added:

13. No prior use of capsid assembly modulators

28. Section/page: 7.5 Restrictions and Concomitant Medications, Concomitant Medications CHB Patients, pp. 55-56

Added:

Based on results from drug-drug interaction study 56136379HPB1004 investigating the potential effect of co-administration of JNJ-6379 with oral contraceptives, it is not anticipated that the efficacy of oral contraceptives will be impacted during co-administration with JNJ-6379 since the exposure of a progestin sensitive to CYP3A4 induction was not significantly affected by co-administration of JNJ-56136379. In contrast, it is anticipated that co-administration with ethinyl-estradiol-containing contraceptives will result in an increased exposure to ethinyl-estradiol. In the current study, female subjects of childbearing potential who are on a stable treatment regimen with hormonal contraceptives (ie, same dose and not starting or stopping hormonal contraceptive use) for ≥3 months prior to screening, should continue the same dose regimen until 12 weeks after EOT. Ethinyl-estradiol-containing contraceptives are only allowed if the ethinyl-estradiol content is ≤20 µg. For female subjects of childbearing potential who will start a hormonal contraceptive treatment during the study, ethinyl-estradiol-containing contraceptives are not allowed, given the observed increase in ethinyl-estradiol in study 56136379HPB1004. Co-administration of JNJ-6379 170 mg qd with oral midazolam as a CYP3A4 probe showed a reduction of 41.7% in Cmax and 53.9% in AUC (study 56136379HPB1004), implying that JNJ-6379 may induce the metabolism of CYP3A4 sensitive substrates. Questions regarding use of ARO-HBV or JNJ-6379 concomitantly with other medications should be discussed with Sponsor medical monitor.

29. Section/page: 8 Investigational Product, p. 56

Added:

Arrowhead Pharmaceuticals, Inc. is responsible for the supply to the clinical site of active drug supplies together with detailed instructions (in a pharmacy manual) describing preparation and administration of ARO-HBV and of JNJ-6379. The PBO (normal saline 0.9%) will be supplied by the clinical site.

30. Section/page: 8.1 ARO-HBV Description, Identification and Dosage, p. 56

From:

Arrowhead Pharmaceuticals, Inc. is responsible for the supply of active drug supplies together with detailed instructions (in a pharmacy manual) describing preparation and administration of ARO-HBV. The PBO (normal saline 0.9%) will be supplied by the clinical site.

Accordingly, ARO-HBV will be supplied as single sterile 2-mL vials containing ARO-HBV, with the correct dose of ARO-HBV prepared by the Pharmacy prior to dosing participants.

The placebo (PBO) will be 0.9% normal saline administered subcutaneously.

To:

ARO-HBV will be supplied as single sterile 2-mL vials containing ARO-HBV, with the correct dose of ARO-HBV prepared by the Pharmacy prior to dosing participants.

The placebo (PBO) will be 0.9% normal saline administered subcutaneously.

31. **Section/page:** 8.3 JNJ-6379 Physical Description of Study Drug(s), p. 57

Added:

8.3 JNJ-6379 Physical Description of Study Drug(s)

JNJ-56136379 supplied for this study is formulated as oral tablets containing 25 mg and 100 mg JNJ-56136379-AAA. Refer to the IB for a list of excipients.

32. **Section/page:** 8.4 Packaging and Storage, p. 57-58

Added:

8.4 Packaging and Storage

JNJ-56136379 will be packaged in bottles. All study drugs will be dispensed in child-resistant packaging. No study drugs can be repacked without prior approval from the sponsor.

JNJ-56136379 must be stored on site in the original package at controlled temperatures ranging from 15°C to 30°C. The NUCs ETV (Baraclude®) and TDF (Viread®) must be stored on site in the original package at controlled temperatures ranging from 15°C to 25°C. Refer to the pharmacy manual/study site investigational product and procedures manual for additional guidance on study drug preparation, handling, and storage.

33. **Section/page:** 8.5 Study Drug Handling, p. 58

From:

ARO-HBV will be supplied by Arrowhead Pharmaceuticals, Inc. and labeled with the drug name, batch number, expiration date (as applicable) and storage conditions. Individual doses will be dispensed by clinical trial site staff members at the time of dosing and recorded in the drug accountability records. A Pharmacy Manual will be prepared to define the procedures for dispensing.

To:

ARO-HBV ***and JNJ-6379*** will be supplied by Arrowhead Pharmaceuticals, Inc. and labeled with the drug name, batch number, expiration date (as applicable) and storage conditions. Individual doses will be dispensed by clinical trial site staff members at the time of dosing and recorded in the drug accountability records. A Pharmacy Manual will be prepared to define the procedures for dispensing.

34. **Section/page:** 8.6 Accountability of Study Supplies, pp. 59-60

From:

Used vials of ARO-HBV will be retained sequestered per participant and cohort and made available to the non-blinded CRA during study drug and placebo reconciliation, where allowable by local policy.

To:

Used vials of ARO-HBV will be retained sequestered per participant and cohort and made available to the non-blinded CRA during study drug and placebo reconciliation, where allowable by local policy. ***Used bottles of JNJ-6379 will be retained sequestered per participant and made available to the CRA for study drug reconciliation.***

From:

A Drug Dispensing Log must be kept current and will contain the following information:

- the identification of the participant to whom the drug was dispensed; and
- the date(s) and quantity of the drug dispensed to the participant.

The date and time of dose preparation and release will be maintained to support administration of study drug/PBO. The authorized pharmacist or qualified staff will be un-blinded to the doses. The pharmacy will dispense the study medication and the study center will administer the study medication only to participants included in this study following the procedures set out in the study protocol. Each participant will be given only the study medication carrying his/her study number. Study drug administration will be documented on the CRFs and/or other study drug record. The inventory must be available for inspection by the non-blinded monitor during the study. Drug supplies, excluding partially used or empty containers, will either be collected at the end of the study by the study monitor or returned by the PI or designee to Arrowhead Pharmaceuticals Inc. or its designee. When requested in writing by the Sponsor, following drug accountability and reconciliation, unused drug supplies may be destroyed by the PI or designee provided such disposition does not expose humans to risks from the drug and is permitted per the site's Standard Operating Procedures. Records shall be maintained by the PI of any such alternate disposition of the test drug. These records must show the identification and quantity of each unit disposed of, the method of destruction (considering the requirements of local law), and the person who disposed of the test substance. Such records must be submitted to the Sponsor.

To:

A Drug Dispensing Log must be kept current and will contain the following information:

- the identification of the participant to whom the drug was dispensed; and
- the date(s) and quantity of the drug dispensed to the participant.

The date and time of ***ARO-HBV/placebo*** dose preparation and release will be maintained to support administration of study drug/PBO. The authorized pharmacist or qualified staff will be un-blinded to the doses. The pharmacy will dispense ***ARO-HBV/placebo*** and the study center will administer ***ARO-HBV*** only to participants included in this study following the procedures set out in the study protocol. ***The pharmacy will dispense JNJ-6379 to the site staff who will provide it to the patients who will take their daily dose of 250 mg (oral) at home. Patients will record taking their daily dose of JNJ-6379 on a diary provided to the clinical site. Patients will bring their used bottles of JNJ-6379 and diaries with them to each subsequent visit so that the study staff may count the remaining tablets, compare the count to the patient's recorded diary and ascertain the level of patient compliance with study treatment. Patients will be provided with additional JNJ-6379 at each visit to cover the period of time until their next clinic visit. The pharmacy/clinical site will dispense JNJ-6379 only to participants included in this study following the procedures set out in the study protocol.***

Each participant will be given only the study medication carrying his/her study number. Study drug administration will be documented on the CRFs and/or other study drug record.

The ***study drug*** inventory must be available for inspection by the non-blinded monitor during the study. Drug supplies, excluding partially used or empty containers, will either be collected at the end of the study by the study monitor or returned by the PI or designee to Arrowhead Pharmaceuticals Inc. or its designee. When requested in writing by the Sponsor, following drug accountability and reconciliation, unused drug supplies may be destroyed by the PI or designee provided such disposition does not expose humans to risks from the drug and is permitted per the site's Standard Operating Procedures. Records shall be maintained by the PI of any such alternate disposition of the test drug. These records must show the identification and quantity of each unit disposed of, the method of destruction (considering the requirements of local law), and the person who disposed of the test substance. Such records must be submitted to the Sponsor.

35. Section/page: 8.7 Retention of Investigational Product Vials, p. 60

From:
For this study, used and partially used drug vials will be retained for an adequate period to allow accountability by the non-blinded CRA. No additional study drug samples will be retained.

To:
For this study, used and partially used drug vials **and bottles** will be retained for an adequate period to allow accountability by the non-blinded CRA. No additional study drug samples will be retained.

36. Section/page: 8.8 Allocation to Treatment, p. 60

Added:
Only patients enrolled into Cohort 12 will received JNJ-6379.

37. Section/page: 8.9 Blinding and Code Break, p. 60

From:
Blinding of study drug/PBO assignment is critical to the integrity of this clinical trial.

To:
Blinding of study drug ***(ARO-HBV)***/PBO assignment is critical to the integrity of this clinical trial.

38. Section/page: 9.1 Overview of Procedures, pp. 62-63

From:
For CHB patients in Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10 and 11, eligible CHB patients who have signed an HDEC (or local equivalent) approved informed consent form will receive three doses of ARO-HBV at dose intervals ranging from once every week to once every 4 weeks in an open label fashion.

To:
For CHB patients in Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 8, 9, ***10, 11 and 12***, eligible CHB patients who have signed an HDEC (or local equivalent) approved informed consent form will receive three doses of ARO-HBV at dose intervals ranging from once every week to once every 4 weeks in an open label fashion.

Added:

Cohort 12 will enroll 12 CHB patients in an open label fashion to receive 200 mg ARO-HBV on Days 1, 29 and 57 as well as JNJ-6379 250 mg oral once daily starting on Day 1 and continuing through Day 84. Like all other cohorts, patients enrolling in Cohort 12 will either enter the study on NUCs or start NUCs on Day 1. Enrollment in Cohort 12 can begin once enrollment is full in Cohorts 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10, 11.

39. Section/page: 9.3.6 Clinical Laboratory Tests & Pharmacodynamic Values, p. 65

From:
***Biochemistry*:** 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, C-reactive protein and Troponin l.

To:
Biochemistry*:** 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 and Troponin l.

40. Section/page: 9.3.7 Pharmacokinetics, pp. 66-67

From:
Samples for analysis of circulating AD04872 and AD05070 will be obtained at time points following the end of infusion outlined in the Schedule of Assessments.

To:
Samples for analysis of circulating AD04872 and AD05070 will be obtained at time points following the end of ***injection*** outlined in the Schedule of Assessments.

Plasma concentrations of ARO-HBV, NUC and JNJ-6379 will be measured at a single post-dose time point in Cohort 12 only.

41. Section/page: 9-4 Allocation of Formulations, p. 67

From:
Four NHV participants will receive active treatment and 2 participants will receive PBO in each dose level. Treatments will be administered per the randomized sequence kept by the pharmacy or in a secure place at the clinical site, under control of the un-blinded staff member. All CHB patients will receive active treatment.

To:
Four NHV participants will receive active treatment and 2 participants will receive PBO in each dose level. Treatments will be administered per the randomized sequence kept by the pharmacy or in a secure place at the clinical site, under control of the un-blinded staff member. All CHB patients will receive active treatment.
CHB patients in Cohort 12 will receive daily oral JNJ-6379 + ARO-HBV.

42. Section/page: 9.5 Study Formulation Administration, p. 68

From:
Appropriately trained employees of the clinical site will administer the study treatment.

To:
Appropriately trained employees of the clinical site will administer ***ARO-HBV/PBO***.

From:
Table 2. Injection number and volume per cohort

Cohort	Dose	Concentration	Total Injection Volume	# Injections per planned dose
1	35 mg	200 mg/mL	0.175 mL	Single
1b	25 mg	200 mg/mL	0.125 mL	Single
1c	50 mg	200 mg/mL	0.25 mL	Single
2, 2b, 6, 7	100 mg	200 mg/mL	0.5 mL	Single
3, 3b, 10	200 mg	200 mg/mL	1.0 mL	Single
4, 4b, 8, 9, 11	300 mg	200 mg/mL	1.5 mL	Single
5, 5b	400 mg	200 mg/mL	2.0 mL	Two (at separate sites)

To:

Table 2: Injection number and volume per cohort

Cohort	Dose	Concentration	Total Injection Volume	# Injections per planned dose
1	35 mg	200 mg/mL	0.175 mL	Single
1b	25 mg	200 mg/mL	0.125 mL	Single
1c	50 mg	200 mg/mL	0.25 mL	Single
2, 2b, 6, 7	100 mg	200 mg/mL	0.5 mL	Single
3, 3b, 10, ***12***	200 mg	200 mg/mL	1.0 mL	Single
4, 4b, 8, 9, 11	300 mg	200 mg/mL	1.5 mL	Single
5, 5b	400 mg	200 mg/mL	2.0 mL	Two (at separate sites)

Added:

JNJ-6379 will be dispensed to patients in Cohort 12 only who will take their daily dose (250 mg oral) at home. Patients will bring all remaining tablets to their subsequent visits for compliance assessment, and receive additional tablets to cover their daily doses until the next subsequent visit.

43. Section/page: 9.7 Safety Endpoints, p. 69

From:

The safety of ARO-HBV will be evaluated by collection of the following measurements performed at specified time points:

To:

The safety of ARO-HBV ***(alone or in combination with JNJ-6379)*** will be evaluated by collection of the following measurements performed at specified time points:

44. Section/page: 11.4 Safety/Tolerability Data, p. 79

From:
The whole blood collected for analysis following a single dose of ARO-HBV at different dose levels will undergo analysis for cytokines and complement changes. Results, percent change, and duration of response from baseline to 24 hours (or 48 hours, as necessary) will be analyzed where indicated by initial testing at pre-dose and at 2-hours post-administration. If cytokine or complement levels are elevated from pre-dose to 2-hours post-dose then all other specified timepoints (See Schedule of Assessments) will also be analyzed. Results for cytokines and complement will be summarized by dose cohort and treatment group.

To:
The whole blood collected for analysis following a single dose of ARO-HBV at different dose levels will undergo analysis for cytokines ***(Panel A)*** and complement changes. Results, percent change, and duration of response from baseline to 24 hours (or 48 hours, as necessary) will be analyzed where indicated by initial testing at pre-dose and at 2-hours post-administration. If cytokine or complement levels are elevated from pre-dose to 2-hours post-dose then all other specified timepoints (See Schedule of Assessments) will also be analyzed. ***Whole blood collected following multiple doses of ARO-HBV for cytokine Panel B samples will only be analyzed at discretion of and with notification by Sponsor. Results, percent change, and duration of response from baseline will be analyzed where indicated.*** Results for cytokines and complement will be summarized by dose cohort and treatment group.

45. Section/page: 11.5 Pharmacokinetic Data, p. 79

Added:
Plasma concentrations of ARO-HBV, NUC and JNJ-6379 will be measured at a single 2 hour post-dose time point in Cohort 12 only.

From:
Pharmacokinetic parameters will be tabulated and summarized by dose level. The concentration-time profiles for each participant and the mean concentration-time profiles by dose level will be plotted with concentration presented on both linear and logarithmic scales.

To:
Pharmacokinetic parameters will be tabulated and summarized by dose level ***where applicable***. The concentration-time profiles for each participant and the mean concentration-time profiles by dose level will be plotted with concentration presented on both linear and logarithmic scales. ***Cohort 12 CHB patient limited PK data will be evaluated separately from NHV PK data.***

46. Section/page: 14.1 Ownership, pp. 88-89

[redacted]

47.Section/page: 14.3 Publication, p. 89

[redacted]

PROTOCOL AMENDMENT SUMMARY OF CHANGES

PROTOCOL NUMBER:	**AROHBV1001**
STUDY TITLE:	**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**
VERSION/DATE:	**Version 6.0, 28 February 2020**

OVERVIEW/RATIONALE:

This amendment which is specific to **Hong Kong only**:

1. Reduces the protocol required follow-up period to Day 337 (±5 days) for the open-label CHB Cohort 12 patients only. All previously enrolled CHB cohorts will continue with follow-up visits until Day 393 (±5 days).

2. Corrects any administrative, grammatical, formatting errors and inconsistencies; rewording for clarity

SUMMARY OF CHANGES:

1. Section/page: Title Page, page 1

From:
225 South Lake Ave., Suite 1050,
Pasadena, CA 91101

To:
177 E. Colorado Blvd., Suite 700
Pasadena, CA ***91105***

2. Section/page: Title Page, page 1

From:
This amendment, specific to Hong Kong only, adds a single open-label CHB cohort (Cohort 12) with 12 subjects each receiving ARO-HBV at 200 mg every 28 days starting on Day 1, and the investigational capsid assembly modulator (CAM), JNJ-56136379 at 250 mg QD starting on Day 1 through Day 84. All subjects will continue on, or be started on entecavir or tenofovir (NUC) for the duration of the study.

To:
This amendment, specific to Hong Kong only, ***reduces the protocol required follow-up period to Day 337 (±5 days) for the open-label CHB Cohort 12 patients only. All previously enrolled CHB cohorts will continue with follow-up visits until Day 393 (±5 days).***

3. Section/page: 1 Protocol Synopsis, Study Duration, p. 4
6.4 Duration of the Study, p. 47

From:
For each CHB patient in the multi-dose Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10, 11 and 12 the duration of the study clinic visits is approximately 25 weeks from screening to the Day 113 EOS examination. CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after Day 113. Subjects consenting to additional follow up will continue on NUCs. Subjects not consenting to additional follow up will be followed per protocol based on Schedule of Assessment Tables 1.2, 1.3 and 1.4.

To:
For each CHB patient in the multi-dose Cohorts 1b, 1c, 2b, 3b, 4b, 5b, 6, 7, 8, 9, 10, 11 and 12 the duration of the study clinic visits is approximately 25 weeks from screening to the Day 113 EOS examination. ***With the exception of Cohort 12 patients, all other*** CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after Day 113. ***Only Cohort 12 patients will require follow-up until the Day 337 (±5 days) visit.*** Subjects consenting to additional follow up will continue on NUCs. Subjects not consenting to additional follow up will be followed per protocol based on Schedule of Assessment Tables 1.2, 1.3 and 1.4.

4. Section/page: 1 Protocol Synopsis, Study Design/Methods CHB patients, p. 6
6.1 Study Design, CHB Patients, p. 43
9.1 Study Methods and Schedules, Overview of Procedures, p. 63
9.3.9 Follow-up Procedures, Additional CHB Follow-up, p. 67

From:
CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after Day 113. Subjects consenting to additional follow up will continue on NUCs. Subjects not consenting to additional follow up will be followed per protocol based on Schedule of Assessment Tables 1.2, 1.3 and 1.4.

To:
With the exception of Cohort 12 patients, all other CHB patients consenting to additional follow up will be followed as per Additional Follow-Up Schedule of Assessments (Table 1.5), every 56 days (± 5 days) for 5 additional visits after Day 113. ***Only Cohort 12 patients will require follow-up until the Day 337 (±5 days) visit.*** Subjects consenting to additional follow up will continue on NUCs. Subjects not consenting to additional follow up will be followed per protocol based on Schedule of Assessment Tables 1.2, 1.3 and 1.4.

5. Section/page: 1 Protocol Synopsis, Data Analysis, p. 10

From:
Two separate data analyses will be performed, one for all subjects through EOS (Day 29 for NHVs and Day 113 for CHB patients), and one additional and separate analysis for CHB patients who consent to the additional follow up through Day 393. Separate analyses including and excluding Cohort 12 may also be completed.

To:

Two separate data analyses will be performed, one for all subjects throgh EOS (Day 29 for NHVs and Day 113 for CHB patients), and one additional and separate analysis for CHB patients who consent to the additional follow up through ***Day 337 (Cohort 12 only) or*** Day 393. Separate analyses including and excluding Cohort 12 may also be completed.

6. **Section/page:** 1 Protocol Synopsis, Table 1.5 Additional Follow-Up Schedule of Assessments (All CHB Cohorts), p. 17

   Add:
   Footnote 2 to the Day 337 (±5 days) visit column:
   2. Only Cohort 12 patients will require follow-up until the Day 337 (±5 days) visit.

7. **Section/page:** 1 Protocol Synopsis, Data Analysis, p. 10

   From:
   Two separate data analyses will be performed, one for all subjects through EOS (Day 29 for NHVs and Day 113 for CHB patients), and one additional and separate analysis for CHB patients who consent to the additional follow up through Day 393. Separate analyses including and excluding Cohort 12 may also be completed.

   To:
   Two separate data analyses will be performed, one for all subjects throgh EOS (Day 29 for NHVs and Day 113 for CHB patients), and one additional and separate analysis for CHB patients who consent to the additional follow up through ***Day 337 (Cohort 12 only) or*** Day 393. Separate analyses including and excluding Cohort 12 may also be completed.

8. **Section/page:** 6.4 Duration of the Study, p. 48

   From:
   All CHB subjects who complete the study until Day 113 EOS examination are considered to complete the study and may continue to attend the Additional Follow-Up visits per the Schedule of Assessments (Table 1.5) if re-consent is obtained. If a subject withdraws from the Additional Follow-Up visits before the Day 393 visit, he or she will still be considered as a completed subject and reason for not continuing with the Additional Follow-Up visits per protocol will be recorded.

   To:
   All CHB subjects who complete the study until Day 113 EOS examination are considered to complete the study and may continue to attend the Additional Follow-Up visits per the Schedule of Assessments (Table 1.5) if re-consent is obtained. If a subject withdraws from the Additional Follow-Up visits before the ***Day 337 (Cohort 12 only) or*** 393 visit, he or she will still be considered as a completed subject and reason for not continuing with the Additional Follow-Up visits per protocol will be recorded.