Janssen Research & Development *

Clinical Protocol

A Phase 2b, Multicenter, Double-blind, Active-controlled, Randomized Study to Investigate the Efficacy and Safety of Different Combination Regimens Including JNJ-73763989 and/or JNJ-56136379 for the Treatment of Chronic Hepatitis B Virus Infection

The REEF-1 Study

Protocol 73763989HPB2001; Phase 2b
AMENDMENT 4

JNJ-73763989 and JNJ-56136379

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United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug regulations (21 CFR Part 312).

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 4	24-November-2021
Amendment 3	30-September-2021
Amendment 2	27-January-2020
Amendment 1	14-November-2019
Original Protocol	17-May-2019

Amendment 4 (24 November 2021)

Overall Rationale for the Amendment: The primary reason for this amendment is to update the criteria for post-treatment monitoring and for nucleos(t)ide analog (NA) re-treatment for participants who discontinued NA treatment at Week 48.

With Amendment 3, changes were introduced to the criteria for post-treatment monitoring and NA re-treatment for patients who discontinued NA treatment. These changes were triggered by a case of hepatitis B reactivation with subacute hepatic failure (initially reported as severe clinical ALT flare) following NA treatment cessation as per protocol in the REEF-2 (73763989PAHPB2002) study which led to listing of the patient for high urgency liver transplantation. The patient received a donor liver at Week 14 post-stopping NA and has since then showed an uneventful post-operative recovery.

To further protect the safety of study participants, the current amendment includes additional changes to the criteria for post-treatment monitoring and for NA re-treatment for participants who discontinued NA treatment.

These changes are based on additional follow-up information from participants in the REEF-2 study who stopped all treatment including NA per protocol and is incorporating recommendations from Health Authorities and the independent data monitoring committee.

Description of Change	Brief Rationale	Section Number and Name
Update of criteria for post-treatment monitoring and for NA re-treatment	In further off-treatment analysis of REEF-2 with all participants having reached at least 12 weeks of follow-up post stopping NA, some participants show a pattern of fast increase of HBV DNA followed by significant elevations of ALT that improved after re-starting of NA treatment. Based on these observations it was decided to implement more conservative rules for post-treatment monitoring and re-treatment criteria for all participants who met NA treatment completion criteria and stopped NA treatment.	1.1 Synopsis 1.3.2 Schedule of Activities – Follow-up Phase 2.3.3 Benefit-risk Assessment for Study Participation 4.2 Scientific Rationale for Study Design 6.7 NA Re-treatment Criteria 10.14 Appendix 14: NA Re-treatment and Monitoring After Stopping of NA
Corrections were made to footnote numbering	Minor errors were noted	1.3.2 Schedule of Activities – Follow-up Phase

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1.1. Synopsis

A Phase 2b, Multicenter, Double-blind, Active-controlled, Randomized Study to Investigate the Efficacy and Safety of Different Combination Regimens Including JNJ-73763989 and/or JNJ-56136379 for the Treatment of Chronic Hepatitis B Virus Infection

JNJ-73763989 (JNJ-3989) is a liver-targeted antiviral therapeutic for subcutaneous injection designed to treat chronic hepatitis B virus (HBV) infection via a ribonucleic acid interference (RNAi) mechanism. Engagement of the cellular RNAi machinery by JNJ-3989 results in specific cleavage of HBV ribonucleic acid (RNA) transcripts, thereby reducing the levels of HBV proteins and the pre-genomic ribonucleic acid (pgRNA), the precursor of viral relaxed circular deoxyribonucleic acid (DNA). The RNAi triggers in JNJ-3989 injection are designed to target all HBV RNA transcripts derived from covalently closed circular DNA (cccDNA), as well as transcripts derived from integrated viral DNA. The latter has been suggested to be a significant source of hepatitis B surface antigen (HBsAg) in hepatitis B e antigen (HBeAg)-negative patients or patients on long-term treatment with nucleos(t)ide analogs (NAs), the current standard of care.

JNJ-56136379 (JNJ-6379) is an orally administered capsid assembly modulator that is being developed for the treatment of chronic HBV infection. JNJ-6379 binds to hepatitis B core protein and interferes with the viral capsid assembly process, thereby preventing the polymerase-bound pgRNA encapsidation. This results in the formation of HBV capsids, devoid of HBV DNA or RNA (non-functional capsids), and ultimately in the inhibition of HBV replication. In addition, JNJ-6379 also acts at an early stage of the viral life cycle by inhibiting the de-novo formation of cccDNA potentially by interfering with the capsid disassembly process.

Study intervention refers to JNJ-3989 or placebo, JNJ-6379 or placebo, and NA.

OBJECTIVES AND ENDPOINTS

The primary and secondary objectives and endpoints of this study are listed below.

Objectives	Endpoints
Primary	
• To establish the dose-response relationship for antiviral activity of 3 doses of JNJ-3989+NA and to evaluate the efficacy of combination regimens of JNJ-3989+NA (with and without JNJ-6379) and of JNJ-6379+NA.	• Proportion of participants meeting the NA treatment completion criteria at Week 48 (see Individual Participant NA Treatment Completion Criteria).
Secondary	
• To evaluate the safety and tolerability of the study intervention throughout the study.	• Proportion of participants with (serious) adverse events ([S]AEs) and abnormalities in clinical laboratory tests (including hematology, blood biochemistry, blood coagulation, urinalysis, urine chemistry, and renal biomarkers), 12-lead electrocardiograms (ECGs), and vital signs.

Objectives	Endpoints
• To evaluate the efficacy of the study intervention during the follow-up phase*.	• Proportion of participants with HBsAg seroclearance 24 weeks after completion of all study intervention at Week 48. • Proportion of participants with HBsAg seroclearance 48 weeks after completion of all study intervention at Week 48. • Proportion of participants with HBV DNA <lower limit of quantification (LLOQ) 24 and 48 weeks, respectively, after completion of all study intervention at Week 48. • Proportion of participants meeting the NA treatment completion criteria during follow-up. • Proportion of participants with HBsAg seroclearance 24 and 48 weeks, respectively, after completion of NA treatment at any time during follow-up. • Frequency of flares. • Proportion of participants requiring NA re-treatment during follow-up (see NA Re-treatment Criteria and Monitoring After Stopping of NA).
• To evaluate efficacy as measured by blood markers (such as HBsAg, HBeAg,** HBV DNA, and alanine aminotransferase [ALT]) during study intervention and follow-up.	• Proportion of participants with (sustained) reduction, suppression, and/or seroclearance considering single and multiple markers (such as HBsAg, HBeAg,** HBV DNA and ALT). • Proportion of participants with HBsAg and HBeAg** seroconversion. • Change from baseline over time in HBsAg, HBeAg,** and HBV DNA. • Time to achieve HBsAg and HBeAg** seroclearance. • Proportion of participants with HBsAg levels and/or changes from baseline below/above different cut-offs (eg, HBsAg <100 IU/mL or >1 $\log_{10}$ IU/mL reduction in HBsAg from baseline). • Proportion of HBeAg-positive participants with HBeAg** levels and/or changes from baseline below/above different cut-offs. • Proportion of participants with HBV DNA levels and/or changes from baseline below/above different cut-offs (eg, <LLOQ of the assay). • Proportion of participants with ALT decrease and normalization.
• To evaluate the frequency of virologic breakthrough.	• Proportion of participants with virologic breakthrough.

Objectives	Endpoints
• To evaluate the efficacy of NA re-treatment in participants who meet the criteria for NA re-treatment.	• Proportion of participants who reach HBV DNA undetectability after re-start of NA treatment during follow-up.
• To evaluate the pharmacokinetics (PK) of JNJ-3989 (JNJ-3976 and JNJ-3924), JNJ-6379, and NA, as applicable.	• PK parameters of JNJ-3989 (JNJ-3976 and JNJ-3924), JNJ-6379, and NA, as applicable.

[*] The follow-up phase has a maximum duration of 96 weeks.
[**] in HBeAg-positive participants only

Hypothesis

Based on the primary efficacy endpoint, the proportion of participants meeting the NA treatment completion criteria at Week 48, the primary hypotheses are as follows:

- There is a positive dose-response signal across the 3 doses of JNJ-3989 (40, 100, and 200 mg) on the background of NA compared with NA treatment alone (control Arm 6).
- One or both combination regimens JNJ-3989+JNJ-6379+NA and JNJ-6379+NA are more efficacious than NA treatment alone (control Arm 6).
- The combination regimen of JNJ-3989 (100 mg)+JNJ-6379+NA is more efficacious than JNJ-3989 (100 mg)+NA and/or JNJ-6379+NA combination regimens.

OVERALL DESIGN

This is a Phase 2b, randomized, double-blind, double-dummy, active-controlled, dose-finding, parallel, multicenter, interventional study in HBeAg-positive and -negative chronic HBV-infected participants who (1) are currently not being treated for their HBV infection (including chronic hepatitis B [CHB] treatment-naïve participants) or (2) who are virologically suppressed by current NA treatment (either entecavir [ETV], tenofovir disoproxil fumarate [TDF], or tenofovir alafenamide [TAF]). The efficacy, safety, and PK of the study intervention will be evaluated.

A target of 450 adult male and female participants, 18 (or the legal age of consent in the jurisdiction in which the study is taking place) to 65 years of age (inclusive), will be randomized in a 2:2:2:2:1:1 ratio to one of the following intervention arms:

- Arm 1: JNJ-3989 (100 mg) + JNJ-6379 (250 mg qd) + NA[*] (N=90)
- Arm 2: JNJ-3989 (200 mg) + Placebo + NA[*] (N=90)
- Arm 3: JNJ-3989 (100 mg) + Placebo + NA[*] (N=90)
- Arm 4: JNJ-3989 (40 mg) + Placebo + NA[*] (N=90)
- Arm 5: Placebo + JNJ-6379 (250 mg qd) + NA[*] (N=45)
- Arm 6 (control): Placebo + Placebo + NA[*] (N=45)

[*]NA: ETV, TDF, or TAF

After a fixed duration of 48 weeks, participants will complete treatment with JNJ-3989 and/or JNJ-6379. If the NA treatment completion criteria (outlined below) are met based on clinical laboratory tests performed at Week 44, treatment with NA will also be completed at Week 48 (ie, the next scheduled visit after Week 44). Participants who meet the NA treatment completion criteria will be monitored closely during the follow-up phase. NA treatment may need to be re-started based on protocol-defined NA re-treatment criteria (see below).

Randomization will be stratified by HBeAg status at screening (positive versus negative) and by treatment history (not currently treated versus virologically suppressed).

The aim is to include 40% not currently treated participants of whom it is expected that 40% are HBeAg-positive. As such subgroup enrollment may be closed prior to completion of study enrollment. All efforts will be undertaken to include a sufficient number of HBeAg-positive virologically suppressed participants.

The study will be conducted in the following phases:

- **Screening phase**: 4 weeks. If necessary, eg, for operational reasons, the screening phase may be extended up to a maximum of 6 weeks on a case-by-case basis and in agreement with the sponsor.
- **Double-blind study intervention phase**: from Day 1 (ie, baseline) up to Week 48.
- **Follow-up phase**: for 48 weeks after the end of investigational intervention. For participants who complete NA treatment during follow-up, the follow-up phase will be extended to 48 weeks after the end of NA treatment. The follow-up phase has a maximum duration of 96 weeks.

The duration of individual study participation will be between 100 and 150 weeks.

At Week 48 or at time of early discontinuation, it will be communicated to the investigators whether the participants were allocated to either an investigational arm (Arms 1 to 5) or the control arm (Arm 6) to allow the correct follow-up visit schedule to be followed (see Schedule of Activities). Only at Week 72, randomization codes (for Arms 1 to 5) will be fully disclosed to the investigators. The sponsor will be fully unblinded for the primary analysis at Week 48 (see below).

Participants will be considered to have completed the study if they have completed the assessments of the end of study visit ([Extended] Follow-up Week 48). After completing this study, participants may be invited to enroll into a long-term follow-up study.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study. In addition, an Independent Flare Expert Panel (IFLEP) will be appointed.

Individual Participant NA Treatment Completion Criteria

After a fixed duration of 48 weeks, participants will complete treatment with JNJ-3989 and/or JNJ-6379. If all of the following criteria are met based on clinical laboratory tests performed at Week 44, treatment with NA will also be completed at Week 48 (ie, the next scheduled visit after Week 44):

- The participant has ALT <3x upper limit of normal (ULN), AND
- The participant has HBV DNA <LLOQ, AND
- The participant is HBeAg-negative, AND
- The participant has HBsAg <10 IU/mL.

Note: In case of ALT elevation ≥3x ULN at Week 44 the investigator must consider different potential causes of increased ALT to ensure appropriate work up and management as needed. If the ALT elevation is unrelated to HBV activity and/or <3x ULN by treatment Week 48, NA completion may be considered at the discretion of the investigator and in consultation with the sponsor.

Participants who do not meet the above criteria at Week 48 should continue NA treatment during the 48-week follow-up. If the above criteria are met during the follow-up phase based on clinical laboratory tests performed at or before Follow-up Week 42 (Follow-up Week 36 for Arm 6), NA treatment should be stopped at or before Follow-up Week 48 (ie, the next scheduled visit after the laboratory test was performed) and the follow-up schedule should be extended to 48 weeks after the end of NA treatment. If NA treatment completion criteria are not met based on clinical laboratory tests performed at or before

Follow-up Week 42 (Follow-up Week 36 for Arm 6), the follow-up phase will not be extended, but the participant will continue NA treatment and complete the study at Follow-up Week 48.

The investigator should consider to re-start NA treatment per local standard of care at the EOS visit ([Extended] Follow-up Week 48) for participants who met the NA treatment completion criteria at Week 48 or during the follow-up phase, who did not re-start NA treatment during the follow-up phase, and who did not achieve and maintain HBsAg seroclearance. NA will not be provided by the sponsor after the final study visit.

If a participant prematurely discontinues investigational intervention (before Week 48), follow-up assessments should be obtained as per the Schedule of Activities until 48 weeks after the end of investigational intervention unless the participant withdraws consent. In this case, NA treatment may be continued or, in consultation with the sponsor, discontinued, based on the above-mentioned NA treatment completion criteria.

NA Re-treatment Criteria and Monitoring After Stopping of NA

Participants who meet the NA treatment completion criteria outlined above will be monitored closely during the follow-up phase.

After stopping NA treatment, participants should be monitored as follows:

- Regular monitoring visits will be every 4 weeks during the follow-up phase in accordance with the Schedule of Activities.
- A post-treatment HBV DNA value of >20,000 IU/mL should trigger re-testing of ALT/AST, HBV DNA, and total and direct bilirubin within a maximum of 7 days from receipt of the data and further repeats as necessary (ie, weekly until HBV DNA returns to <20,000 IU/mL).
- A post-treatment HBV DNA value of >2,000 IU/mL (but <20,000 IU/mL) should trigger a re-test within 14 days from receipt of the data and further repeats as necessary (ie, every other week until HBV DNA returns to <2,000 IU/mL).
- A post-treatment ALT value of >5x ULN should trigger re-testing of ALT, AST, ALP, total and direct bilirubin, International Normalized Ratio (INR), albumin, and HBV DNA on a weekly basis until ALT and AST levels have returned to <5x ULN.

After stopping NA treatment, participants should re-start NA treatment:

- Immediately with signs of decreasing liver function based on laboratory findings (eg, INR, direct bilirubin) or clinical assessment (eg, ascites, hepatic encephalopathy).
- Immediately with an HBV DNA value of >100,000 IU/mL (irrespective of confirmation and/or ALT increase).
- With confirmed post-treatment HBeAg seroreversion (HBeAg positive after it was negative at NA completion).
- With confirmed* post-treatment increases in HBV DNA >2,000 IU/mL and ALT >5x ULN.
- With confirmed* post-treatment increases in HBV DNA >20,000 IU/mL.

** At least 4 weeks apart – frequency of visits as described above*

Note: Additional re-testing and/or earlier restarting of NA treatment is at the investigator's discretion, even if the above cut-offs are not yet met.

To avoid delays in decision making, sites are encouraged to run local re-testing in parallel with central re-testing in the situations described above that require more frequent re-testing. Local test results are to be recorded in the CRF and/or source documents, including information on the HBV DNA assay used. In

addition, to avoid delays in NA re-treatment, it should be considered to dispense NA to participants who potentially met the NA re-treatment criteria (eg, pending confirmation) and who will not be available to come to the study site immediately at the time the confirmatory test results will become available. This should ensure that the participant can immediately re-start NA treatment if indicated, upon direct confirmation by the investigator.

In case NA treatment is re-started, participants will be followed until the end of the study or until clinical stabilization, whichever comes later.

Management of intervention-emergent ALT/aspartate aminotransferase (AST) elevations is discussed below.

NUMBER OF PARTICIPANTS

A target of 450 male and female participants will be randomized.

Description of Interventions

Intervention name	JNJ-3989	Placebo for JNJ-3989	JNJ-6379	Placebo for JNJ-6379	Entecavir (ETV) monohydrate	Tenofovir disoproxil fumarate (TDF)	Tenofovir alafenamide (TAF)***
Dosage formulation	Solution for injection	Solution for injection	Tablets	Tablets	Film-coated tablets	Film-coated tablets	Film-coated tablets
Unit dose strength(s)	200 mg/vial	0.9% saline	25 and 100 mg		0.5 mg	300 mg**	25 mg
Dosage regimen	100 mg once every 4 weeks (Arms 1 and 3) 200 mg once every 4 weeks (Arm 2) 40 mg once every 4 weeks (Arm 4)	0.5 mL once every 4 weeks (Arms 5 and 6)	250 mg qd (Arms 1 and 5)	qd (Arms 2, 3, 4, and 6)	Nucleoside-naïve patients: 0.5 mg qd Lamivudine-refractory patients: 1 mg* qd (but should preferably be treated with TDF or TAF instead)	300 mg qd	25 mg qd
Route of administration	Subcutaneous injection (in the abdomen)	Subcutaneous injection (in the abdomen)	Oral	Oral	Oral	Oral	Oral
Dosing instructions	Regardless of food intake	Regardless of food intake	Regardless of food intake	Regardless of food intake	On an empty stomach	With food	With food

qd: once daily
* 2 tablets of 0.5 mg
** 300 mg TDF is equivalent to tenofovir disoproxil 245 mg.
*** In countries where TAF is available, it will be one of the NA treatment options.

EFFICACY EVALUATIONS

Qualitative and quantitative HBsAg and HBeAg, and quantitative hepatitis B core-related antigen (HBcrAg) as well as anti-HBs and anti-HBe antibodies will be determined using standard commercially available serologic assays in a central laboratory. Samples for the determination of HBsAg and HBeAg will be processed in real-time. Samples for the determination of HBcrAg can be analyzed in batch and at the sponsor's discretion.

HBV DNA and HBV RNA will be quantified at central laboratories using commercially available in vitro nucleic acid amplification tests for the quantification of HBV DNA and HBV RNA. Samples for the determination of HBV DNA will be processed in real-time. Samples for the determination of HBV RNA can be analyzed in batch and at the sponsor's discretion.

In participants enrolled at a site with an on-site Fibroscan device, Fibroscan assessments will be performed to determine changes in fibrosis.

Samples may be used by the sponsor for additional exploratory assessments analyzing the serologic and virologic characteristics of HBV infection and efficacy or safety of the study intervention.

Sequencing

Viral genome sequence analysis will be performed to identify pre-existing baseline polymorphisms and to evaluate emergence of mutations associated with JNJ-3989, JNJ-6379, and/or NA treatment.

Patient-reported Outcomes

The impact of study intervention on participants' health-related quality of life (HRQoL), self-stigma level, and impression of change will be assessed using patient-reported outcomes (PROs). The following PRO instruments will be used: the Hepatitis B Quality of Life (HBQOL) scale, an HBV-specific self-stigma PRO scale, and the Patient Global Impression of Change (PGIC) scale. Patient-reported outcome data collected may also be used by the sponsor for additional exploratory assessments analyzing the effect of study intervention on HRQoL, self-stigma, and impression of change, and for assessing the psychometric properties of the PRO instruments.

SAFETY EVALUATIONS

Safety and tolerability will be assessed throughout the study from the time that the informed consent form is signed until completion of the last study-related activity, which may include contact for follow-up of safety. The evaluations of safety and tolerability will include monitoring of (S)AEs, physical examinations (including body weight), vital signs measurements, triplicate 12-lead ECGs, and clinical laboratory tests (including hematology, blood biochemistry, blood coagulation, urinalysis, urine chemistry, and renal biomarkers). Any clinically relevant changes occurring during the study must be recorded in the AE section of the case report form.

Specific toxicity management plans in line with the known pharmacological profile of the study intervention (and the drug classes) evaluated in this study are implemented.

Management of Intervention-emergent ALT/AST Elevation

Elevated liver enzyme activity can be triggered by the underlying HBV disease as well as by the study intervention.

Any intervention-emergent elevation of ALT and/or aspartate aminotransferase (AST) ≥3x ULN and ≥3x nadir (ie, lowest value during study participation) should trigger an assessment of confounding factors (alcohol intake, change in concomitant medication, and comorbidities) and should trigger a confirmatory study visit to repeat laboratory testing of AFP, ALT, AST, alkaline phosphatase (ALP),

bilirubin (total and direct), INR, albumin, and HBV DNA. The confirmatory visit should be scheduled as soon as possible, preferably within 7 days of the receipt of the initial ALT/AST results. In case the repeat laboratory testing shows an isolated ALT/AST elevation (ie, with stable albumin, bilirubin [total and direct], and INR) the participant may continue study intervention. In case of confirmed ALT elevation >1,000 U/L, investigational intervention should be discontinued. In both cases, NA treatment should be continued. The participant will be monitored on a weekly basis until ALT and/or AST levels have returned to 50% of the maximal value.

If the ALT and/or AST level is ≥3x ULN and ≥3x nadir and is associated with any of the following laboratory results or clinical symptoms:

- INR ≥1.5, OR
- direct bilirubin >1.5x ULN, OR
- serum albumin <3.0 g/dL, OR
- ascites, hepatic encephalopathy, or liver-related symptoms (eg, severe fatigue, nausea, vomiting, right upper quadrant pain in the absence of an alternative medical explanation), OR
- other indication of reduced liver function

the participant should discontinue investigational intervention and should be monitored on a weekly basis or as per good clinical practice until ALT and/or AST levels have returned to 50% of the maximal value and, if present, liver-related symptoms have improved. NA treatment should be continued.

For the NA re-treatment criteria during follow-up, see above.

PHARMACOKINETIC EVALUATIONS

Plasma concentration-time data for JNJ-3989 (JNJ-3976 and JNJ-3924), JNJ-6379 and, optionally, NA will be analyzed via noncompartmental methods for all participants who underwent intensive PK sampling. The main PK parameter will be the area of the concentration-time curve over the dosing interval (tau) at steady-state (AUC_{tau}). Additional exposure parameters may be calculated if applicable.

Data from this study may be combined with other studies via population PK modelling to enable the calculation of the above PK parameters also in participants who only underwent sparse PK sampling.

PHARMACOKINETICS/PHARMACODYNAMICS

Relationships of individual PK parameters (intensive PK and population PK, as applicable) for JNJ-3989 (JNJ-3976 and JNJ-3924) and/or JNJ-6379 and/or NA, as applicable, with selected efficacy and/or with selected safety endpoints will be evaluated, if applicable.

IMMUNE EVALUATIONS

At selected sites, peripheral blood mononuclear cell (PBMC) samples for immune analyses will be collected during study intervention and follow-up and will be analyzed centrally for HBV-specific responses by enzyme-linked immunospot (ELISpot) and/or intracellular cytokine staining (ICS) after stimulation with HBV-specific antigens. ELISpot detects T-cells that secrete gamma interferon (IFN-γ) in response to a specific antigenic stimulation, whereas ICS determines the frequency of CD4+ and CD8+ T-cells secreting cytokines such as IFN-γ, interleukin (IL)-2 and tumor necrosis factor (TNF)-α in response to a specific antigenic stimulation.

Additional experiments may be performed to further phenotypically and functionally characterize PBMCs using proliferation or cytotoxic assays or other methods such as cytometry by time of flight to evaluate

innate and adaptive immune responses. Leftover PBMC samples may be used at the sponsor's discretion for additional exploratory research related to HBV infection or study intervention (safety/efficacy).

Additional PBMC samples may be taken in case of ALT flares, upon discussion with the sponsor, which may require an unscheduled visit.

HOST GENETICS

A pharmacogenomic blood sample will be collected from participants who consent separately to this component of the study to allow for pharmacogenomic research, as necessary (where local regulations permit).

In addition, other samples may be used for exploratory genetic research in participants consenting separately to this part of the study. No genetic research will be performed on any sample in participants who have not provided the additional separate consent for host genetic research. Samples can only be used to investigate the potential association of host genetic factors with efficacy, safety, or PK of study intervention, or HBV infection, or may be used to develop tests/assays related to study intervention or HBV infection.

HOST BIOMARKERS

The study includes collection of blood samples for exploratory analysis of host blood biomarkers at the host RNA, protein, and cell level.

Samples can only be used for research related to study intervention or HBV infection or may be used to develop tests/assays related to study intervention or HBV infection.

Blood samples will be taken that can be used to explore immunogenicity of JNJ-3989. The emergence of antibodies to JNJ-3989 (antidrug antibodies) might be analyzed using assays such as an enzyme-linked immunosorbent assay.

STATISTICAL METHODS

The primary analysis will be performed at the time when all participants have completed Week 48 or discontinued earlier. The final analysis will be performed when all participants have completed the last study visit or discontinued earlier.

Statistical Hypotheses

Based on the primary efficacy endpoint, the proportion of participants meeting the NA treatment completion criteria at Week 48, the primary hypotheses are as follows:

- There is a positive dose-response signal across the 3 doses of JNJ-3989 (40, 100, and 200 mg) on the background of NA compared with NA treatment alone (control Arm 6).
- One or both combination regimens JNJ-3989+JNJ-6379+NA and JNJ-6379+NA are more efficacious than NA treatment alone (control Arm 6).
- The combination regimen of JNJ-3989 (100 mg)+JNJ-6379+NA is more efficacious than JNJ-3989 (100 mg)+NA and/or JNJ-6379+NA combination regimens.

After a positive dose-response signal is established with statistical significance using the Multiple Comparison Procedure-Modeling (MCP-Mod) approach, then the testing procedure continues in a fixed sequence, with the comparison of Arm 1 (JNJ-3989+JNJ-6379+NA) with control Arm 6 (Placebo+Placebo+NA) at a one-sided alpha of 0.05. If Arm 1 is found statistically superior to control Arm 6, then the combination regimen JNJ-6379+NA (Arm 5) is compared to control Arm 6 at 0.05 one-sided alpha level.

For the comparisons among regimens (Arm 1, 3, and 5), the statistical testing will control for the one-sided Type I error of 0.05 separately and independently from the comparisons against the control arm described above. The testing among the regimens (Arm 1, 3, and 5) will be performed using the min test approach. The JNJ-3989+JNJ-6379+NA (Arm 1) combination regimen will be declared statistically superior to the dual regimens (Arm 3 and 5) if both tests of Arm 1 vs Arm 3 and Arm 1 vs Arm 5 demonstrate statistical significance at the one-sided 0.05 level.

Sample Size Determination

The total study sample size is 450 participants with a 2:2:2:2:1:1 randomization ratio, where 90 participants will be randomly allocated to each of the arms including a JNJ-3989 dose (Arms 1 to 4) and 45 participants will be randomly assigned to each of the arms with no JNJ-3989 component (Arms 5 and 6). Statistical power to test a dose-response signal was assessed using the generalized version of the MCP-Mod applied to the binary primary efficacy endpoint on the logit scale using data from Arms 2, 3, and 4 (JNJ-3989 at 200, 100, and 40 mg dose, respectively +NA), and Arm 6 (Placebo+Placebo+NA) as control.

The power to conclude a positive dose-response trend over the 3 JNJ-3989 doses on the background of NA is ≥85% under all 5 candidate dose-response models for an absolute response rate of the highest dose of JNJ-3989 of at least 25% (one-sided alpha level of 5%).

Assuming a response rate of 5% in control Arm 6, the sample size of 90 participants each in combination Arms 1, 2, 3, and 4 and a sample size of 45 participants in combination Arm 5 (JNJ-6379+NA) and control Arm 6, provides a statistical power ≥84% to detect a difference of ≥20% in the primary endpoint between Arm 1 (JNJ-3989+JNJ-6379+NA) and control Arm 6, and power ≥76% for a difference ≥20% between Arm 5 (JNJ-6379+NA) and control Arm 6, using a fixed sequence approach for controlling for multiplicity.

The chosen study sample size and randomization allocation will also provide acceptable power levels for the comparison of different combination regimens, ie, JNJ-3989+JNJ-6379+NA (Arm 1, 100-mg dose of JNJ-3989) versus JNJ-3989+NA (Arm 3, 100-mg dose of JNJ-3989), and versus JNJ-6379+NA (Arm 5), respectively. Based on the min test approach, Table 7 shows that the power levels vary depending on both the rate difference between Arm 1 and Arm 3 as well as on the assumed rate for Arm 5. For example, for the same delta of 25% between Arm 1 and Arm 3 and between Arm 1 and Arm 5, the power to observe a statistically significant superiority of Arm 1 over the other 2 regimens is 87%.

Efficacy Analyses

To evaluate the efficacy, the primary analysis set will be the Intent-to-treat (ITT) population. All participants who were randomly assigned to any of the 6 intervention arms and received at least 1 dose of study intervention will be included in the ITT set.

The baseline measurements are defined as the measurements taken closest to but before the first dose of study intervention on Day 1.

Primary Efficacy Endpoint (Proportion of Participants Meeting the NA Treatment Completion Criteria at Week 48)

A hybrid methodology that combines aspects of multiple testing with modeling techniques (MCP-Mod) will be used for evaluating a dose-response trend and estimating the dose-response relationship of 3 JNJ-3989 doses in combination with NA versus NA treatment alone (control Arm 6).

Each of the dose-response shapes in the candidate set will be tested using the corresponding contrast t-test statistic, employing a critical value derived for the maximum of the t-test statistics (based on the associated multivariate t-distribution) to ensure appropriate multiplicity correction that preserves the

one-sided Type I error rate at 0.05. A dose-response trend is established when the maximum of the t-test statistics exceeds the critical value.

After establishing a significant dose-response signal, the testing procedures continue with the comparison of the percentage of participants who completed the 48-week study intervention and qualified for stopping NA treatment in Arms 1 and 5 against control Arm 6, respectively. The min test approach will be applied to control for multiplicity of the comparisons among the combination regimens, as described above. The Mantel-Haenszel (MH) test will be used in the pairwise comparisons at a one-sided alpha level of 0.05 adjusting for the randomization stratification factors of screening HBeAg status and treatment history. The Wilson test will be used at a one-sided alpha level of 0.05 with no adjustment for stratification factors.

Key Secondary Efficacy Endpoint of Functional Cure at Week 72 (HBsAg Seroclearance 24 Weeks After Completion of All Study Intervention at Week 48)

The functional cure rate at Week 72 is defined as the proportion of participants with HBsAg seroclearance 24 weeks after completion of all study intervention at Week 48, including stopping NA treatment. It will be used to support the JNJ-3989 dose selection and the regimen selection. The same multi-step testing strategy as the one implemented for the primary efficacy endpoint (see above), using MCP-Mod and additional treatment arms pairwise comparisons with NA control in a fixed sequence, as well as the min test approach applied separately for between-regimen comparisons, will be used for this key secondary endpoint. However, the comparisons with NA control in the testing strategy applied to this efficacy endpoint will be made against the NA historical control benchmark of 5%, instead of the study NA control arm (Arm 6).

To provide evidence of superior efficacy of the JNJ-3989+JNJ-6379+NA regimen against the JNJ-3989+NA and JNJ-6379+NA combination regimens, respectively, those tests will be performed at a one-sided 0.025 alpha level for regulatory consideration. This analysis aims to support the selection of the combination drug therapy to be studied in confirmatory studies.

Other Secondary and Exploratory Efficacy Endpoints

Descriptive statistics will be used for all efficacy endpoints which will be summarized by intervention arm. Comparisons among intervention arms will be done with no adjustment for multiplicity. Specific key selected endpoints may be analyzed using suitable categorical data approaches (eg, Cochran-Mantel-Haenszel or logistic regression for proportions or other categorical type of endpoint), longitudinal repeated measures models (eg, for continuous types of variables), or survival analysis based on the Kaplan-Meier estimates (for time-to-event variables), as appropriate.

Graphic data displays will also be used to summarize the efficacy data by intervention arm and over time.

Resistance Analyses

The results of HBV viral sequencing will be evaluated by the sponsor virologist. Pretreatment amino acid and/or nucleic acid substitutions in the HBV in all participants and relevant changes in the HBV in participants not responding to study intervention will be tabulated and described.

Additional exploratory characterization of the HBV viral sequence and phenotype may be performed and reported separately.

Patient-reported Outcome Analyses

Patient-reported outcome scores will be analyzed descriptively as mean scores over time, and (if applicable) evaluated based on the proportion of participants experiencing a clinically important improvement or worsening in PRO scores from baseline during study intervention and follow-up. Analyses will also be performed on PRO score changes from baseline at specific time points (Week 48,

72, 96) and between Week 48 and later time points for different subgroups: participants who meet the NA treatment completion criteria at Week 48 versus those who do not, and participants with versus participants without HBsAg seroclearance 24 weeks and 48 weeks after completion of all study intervention at Week 48.

Safety Analyses

The safety analysis set will be used for all safety analyses and includes all participants who received at least one dose of study intervention.

The incidence of AEs will be summarized by body system and preferred term for each intervention arm and study phase (ie, study intervention phase and follow-up phase). Values and changes from baseline over time in clinical laboratory parameters, vital signs, and ECG parameters will be presented descriptively (n, mean, standard deviation [SD], minimum, median, and maximum) by intervention arm. The percentage of participants with abnormal clinical laboratory findings, vital signs, and ECG parameters will be tabulated by intervention arm and study phase.

Other Analyses

Pharmacokinetic Analyses

Descriptive statistics (n, mean, SD, coefficient of variation [CV], geometric mean, median, minimum, and maximum) will be calculated for the plasma concentrations of JNJ-3989 (JNJ-3976 and JNJ-3924), JNJ-6379 and/or NA, as applicable, and for the derived plasma PK parameters (noncompartmental analysis and population PK analysis).

For each participant with intensive PK sampling, plasma concentration-time data of JNJ-3989 (JNJ-3976 and JNJ-3924), JNJ-6379, and/or NA will be graphically presented. Similarly, graphs of the mean plasma concentration-time profiles and overlay graphs with combined individual plasma concentration-time profiles will be produced. Pharmacokinetic parameters will be subjected to an exploratory graphical analysis, including various transformations, to get a general overview.

Population PK analysis of plasma concentration-time data of JNJ-3989 (JNJ-3976 and JNJ-3924), JNJ-6379, and/or NA (as applicable) will be performed using nonlinear mixed-effects modeling. Data may be combined with those from selected studies to support a relevant structural model. Available baseline participant characteristics (demographics, laboratory variables, genotypes, race, etc.) will be included in the model as necessary. Individual estimates of PK parameters will be generated from the population PK analysis for potential use in exposure-response analysis. For operational reasons, a snapshot date for PK samples to be analyzed will be defined, if required. Samples collected before this date will be analyzed for JNJ-3989 (JNJ-3976 and JNJ-3924), JNJ-6379, and/or NA (as applicable) and will be included in the population PK analysis. Samples collected after the snapshot date will be analyzed at a later date and may be included in a population PK re-analysis when they become available after database lock.

Pharmacokinetic/Pharmacodynamic Analyses

Relationships of PK parameters for JNJ-3989 (JNJ-3976 and JNJ-3924), JNJ-6379, and/or NA (ETV, TAF and/or tenofovir), as applicable, with selected efficacy and with selected safety endpoints will be evaluated, applying graphical tools and, if feasible, statistical models.

Immune Analyses

Descriptive statistics (n, mean, SD, CV, geometric mean, median, minimum, and maximum) will be used to describe the magnitude of the IFN-γ T cell response or the CD4+ and CD8+ T-cell responses (expressing at least 1 cytokine such as IL-2, TNF-α or IFN-γ specific to any HBV antigen) as defined by ELISpot and/or ICS, respectively. Changes from baseline (if present) will also be tabulated for PBMCs during study intervention and follow-up. The proportion (%) of CHB patients with positive responses

based on the magnitude of the IFN-γ T cell response or the CD4+ or CD8+ T cells expressing at least 1 of the cytokines amongst IL-2, TNF-α or IFN-γ for 1 of the HBV antigens as defined by ELISpot and/or ICS, respectively, will be determined.

Pharmacogenomic Analyses

The statistical approach for analyzing the exploratory host DNA research may depend on the objective of the analyses (efficacy, safety, and PK) and possibly relevant genes at the time of analysis. Analyses will be conducted at the sponsor's discretion, will always be under the sponsor's supervision, and results will be presented either in the clinical study report or a separate report.

Host Biomarker Analyses

Statistical approaches to explore correlations between clinical outcome and blood biomarkers vary and depend on the different data types of the applied technology platforms, as well as on the extent of observed differences between participants. Analyses will be conducted at the sponsor's discretion, will always be under the sponsor's supervision, and results will be presented either in the clinical study report or a separate report.

Interim Analyses

Interim analyses (IAs) will be conducted to monitor safety and evaluate the time course of different disease markers to support the sponsor's internal decision-making, interactions with health authorities, as well as inform decisions about additional studies and/or investigation of other treatment combinations. The IAs are planned when:

- All participants have completed Week 60 (ie, 12 weeks after completion of investigational intervention at Week 48), or discontinued earlier.
- All participants have completed Week 72 (ie, 24 weeks after completion of investigational intervention at Week 48), or discontinued earlier.
- All participants have completed Week 96 (ie, 48 weeks after completion of investigational intervention at Week 48), or discontinued earlier.

One additional IA may be performed at the sponsor's discretion when all participants, who completed NA treatment at Week 48 of follow-up, have completed Week 120, ie, Week 24 of the extended follow-up, or discontinued earlier, to support interactions with health authorities.

All IAs will be performed by the sponsor because occurring after the primary analysis, which will be conducted at the time when all participants have completed Week 48 or discontinued earlier. Both primary and interim analyses will be based on all data available at the predefined cut-off time, including data at later time points for those participants who have reached subsequent visits.

Independent Data Monitoring Committee

An IDMC will be established for continuous monitoring of SAEs, AEs leading to discontinuation, and ALT flares. In addition, the IDMC will review the unblinded results of the efficacy parameters measured by different HBV disease blood markers (eg, HBV DNA, HBeAg, HBsAg, etc).

The IDMC will have access and use the totality of unblinded results to make recommendations, including all safety and efficacy assessments available at a given interim milestone. Possible recommendations include, but are not limited to, stopping the study or any of the study interventions for safety concerns. The Sponsor Committee will review the time course of the different HBV disease blood markers to make further decisions. Decision rules will be detailed and listed in the IDMC charter and will be non-binding.

Independent Flare Expert Panel

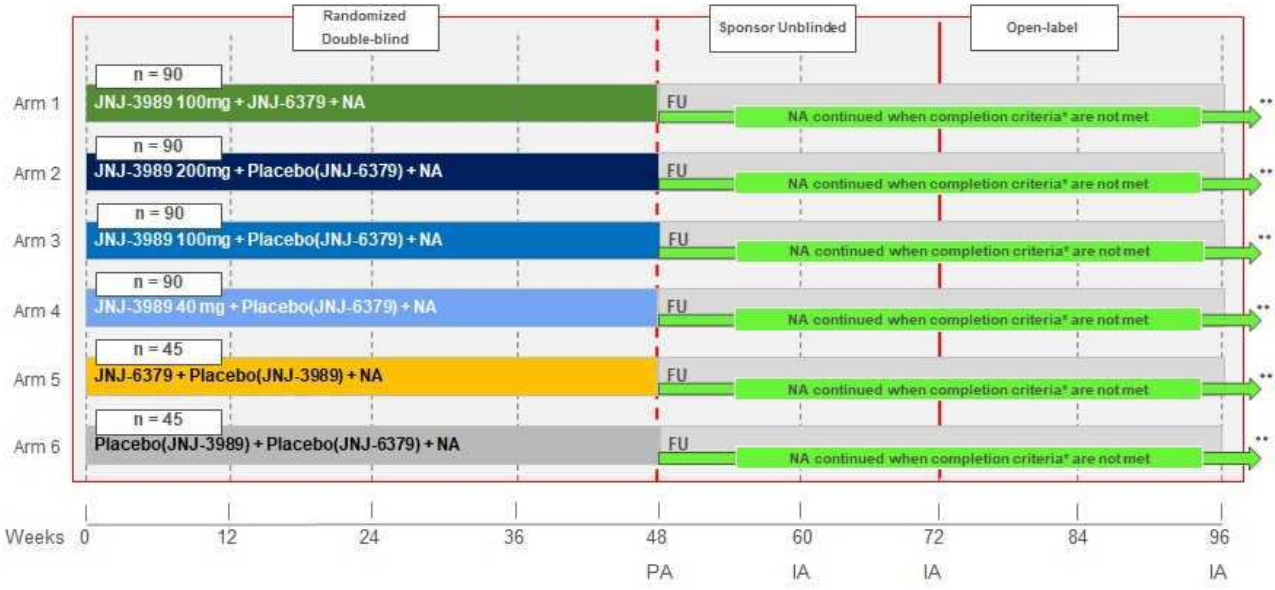
An IFLEP will also be appointed. The IFLEP is composed of 3 independent medical experts with experience and expertise in hepatitis B and its treatment. The IFLEP will monitor ALT flares and will make recommendations regarding flare management based on an analysis of aggregate data.

In order to allow for an unbiased assessment, members of the committee will not serve as study investigators or as members of the IDMC and will be blinded to the treatment assigned to each participant.

Further details on the IFLEP process will be included in the IFLEP charter.

1.2. Schema

Figure 1: Schematic Overview of the Study



FU=follow-up; NA=nucleos(t)ide analog; IA=interim analysis; PA=primary analysis

*Participants not meeting NA treatment completion criteria at Week 48 continue NA treatment during follow-up unless NA treatment completion criteria are met. HBsAg levels and NA treatment completion criteria will be re-assessed at every follow-up visit.

**If NA treatment is completed during follow-up (based on NA treatment completion criteria), the follow-up schedule will be extended to 48 weeks after the end of NA treatment.

Doses: JNJ-3989 40 mg, 100 mg, or 200 mg once every 4 weeks, JNJ-6379 250 mg qd, NA (ETV, TDF, or TAF) according to the prescribing information.

Notes:

- After completing this study, participants may be invited to enroll into a long-term follow-up study.
- One additional IA may be performed at the sponsor's discretion when all participants, who completed NA treatment at Week 48 of follow-up, have completed Week 120, ie, Week 24 of the extended follow-up, or discontinued earlier, to support interactions with health authorities.
- At Week 48 or at time of early discontinuation, it will be communicated to the investigators whether the participants were allocated to either an investigational arm (Arms 1 to 5) or the control arm (Arm 6) to allow the correct follow-up visit schedule to be followed (see Schedule of Activities). Only at Week 72, randomization codes (for Arms 1 to 5) will be fully disclosed to the investigators. The sponsor will be fully unblinded for the primary analysis at Week 48.

1.3. Schedule of Activities

1.3.1. Schedule of Activities – Screening and Study Intervention Phase

Study Phase	Screening[a]	Double-blind Study Intervention[b]															
Visit Day (D)/Week (W)	W 4 to 0[d]	D1[e]	W1	W2	W4	W6	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48/WD[c]
Study Day (Window)	28	1	8 +/ 2d	15 +/ 2d	29 +/ 2d	43 +/ 2d	57 +/ 2d	85 +/ 2d	113 +/ 3d	141 +/ 3d	169 +/ 3d	197 +/ 3d	225 +/ 3d	253 +/ 3d	281 +/ 3d	309 +/ 3d	337 +/ 3d
Screening/Administrative																	
ICF[f]	X																
Inclusion/exclusion criteria[g]	X																
Prestudy therapy (including prior anti HBV therapy)	X																
Medical/surgical history and demographics[h]	X																
Preplanned surgery/procedure(s)	X																
Fibroscan or liver biopsy[i]	X																
Abdominal ultrasound[j]	X																
HBV genotype[k]		X															
Serum IgM anti HBc antibody test	X																
Testing for hepatitis A, B, C, D, and E virus, HIV 1 and 2[w]	X																
FSH test (postmenopausal women only)[l]	X																
Serum pregnancy test (women of childbearing potential only)	X																
Study Intervention Administration																	
Randomization		X															
Communication of allocation to investigational versus control arm[m]																	X
Administer JNJ 3989 (or placebo)		X			X		X	X	X	X	X	X	X	X	X	X	
Intake of JNJ 6379 (or placebo) and NA[n]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense JNJ 6379 (or placebo) and NA		X			X		X	X	X	X	X	X	X	X	X	X	(X)[o]
Oral study intervention accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess NA treatment completion criteria																	X[p]
Safety Evaluations																	
Liver ultrasound[ll]											X						X
Complete physical examination[q]	X										X						X
Symptom directed physical examination[r]		X	X	X	X	X	X	X	X	X		X	X	X	X	X	
Vital signs[s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Triplicate 12 lead ECG[t]	X	X			X			X			X			X			X
Injection site reactions		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Phase	Screening[a]	Double-blind Study Intervention[b]															
Visit Day (D)/Week (W)	W 4 to 0[d]	D1[e]	W1	W2	W4	W6	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48/WD[c]
Study Day (Window)	28	1	8 +/ 2d	15 +/ 2d	29 +/ 2d	43 +/ 2d	57 +/ 2d	85 +/ 2d	113 +/ 3d	141 +/ 3d	169 +/ 3d	197 +/ 3d	225 +/ 3d	253 +/ 3d	281 +/ 3d	309 +/ 3d	337 +/ 3d
Clinical Laboratory Tests																	
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry (including liver function tests)[u,v,w]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood coagulation	X	X			X		X	X	X	X	X	X	X	X	X	X	X
Urinalysis and urine chemistry[x]	X	X			X		X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test (women of childbearing potential)		X			X		X	X	X	X	X	X	X	X	X	X	X
Renal biomarkers[y]		X						X			X			X			X
AFP[w]	X										X						X
Efficacy Evaluations																	
Fibroscan		(X)[z]															
HBV Virology																	
Blood sampling for HBV DNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sampling for HBV RNA[aa]	X	X	X	X	X		X	X	X	X	X		X		X		X
Sampling for viral genome sequencing[bb]	X	X			X		X	X		X	X		X		X		X
HBV Serology																	
Blood sampling for:																	
Anti HBs and anti HBe	X	X									X						X
HBsAg and HBeAg[cc] (qualitative)	X										X						X
HBsAg (quantitative)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBeAg[dd] (quantitative)	X	X		X	X		X	X	X	X	X		X		X	X	X
HBcrAg[aa]	X	X		X	X		X	X		X	X		X		X	X	X
Exploratory serology[ee]	X	X		X	X		X	X	X	X	X		X		X	X	X
Pharmacokinetics																	
Blood sampling for sparse PK of JNJ 3989, JNJ 6379, and/or NA[ff]		X[gg]			X[gg]			X[gg]			X[gg]						X[hh]
Blood sampling for intensive PK of JNJ 3989, JNJ 6379, and/or NA (PK subgroup)[ii]					X												
Exploratory Biomarkers																	
Whole blood RNA gene expression		X						X			X						X
Whole blood single cell profiling		X	X		X		X	X			X			X			X
Host serum proteins (eg, cytokines)		X	X	X	X		X	X			X		X		X		X
Antidrug antibodies (to JNJ 3989)		X					X		X		X		X		X		
Immune Monitoring																	
Immune cells (PBMCs) (selected sites only)[jj]		X									X						X

Study Phase	Screening[a]	Double-blind Study Intervention[b]															
Visit Day (D)/Week (W)	W 4 to 0[d]	D1[e]	W1	W2	W4	W6	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48/WD[c]
Study Day (Window)	28	1	8 +/ 2d	15 +/ 2d	29 +/ 2d	43 +/ 2d	57 +/ 2d	85 +/ 2d	113 +/ 3d	141 +/ 3d	169 +/ 3d	197 +/ 3d	225 +/ 3d	253 +/ 3d	281 +/ 3d	309 +/ 3d	337 +/ 3d
Pharmacogenomics (DNA)																	
Exploratory host genotyping (optional)[kk]		X															
PRO Evaluations[ll]																	
HBQOL		X						X			X			X			X
HBV specific self stigma	X	X						X			X			X			X
PGIC								X			X			X			X
Ongoing Participant Review																	
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

General Note: The PRO assessments and ECGs should be completed before any tests, procedures or other consultations for that visit.

AFP: alpha-fetoprotein; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CRF: case report form; CT: computed tomography; D/d: Day/days; DBP: diastolic blood pressure; DNA: deoxyribonucleic acid; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; FSH: follicle-stimulating hormone; HBc: hepatitis B core protein; HBe(Ag): hepatitis B e (antigen); HBcrAg: hepatitis B core-related antigen; HBQOL: Hepatitis B Quality of Life; HBs(Ag): hepatitis B surface (antigen); HBV: hepatitis B virus; HCC hepatocellular carcinoma; HIV-1 (-2): human immunodeficiency virus type 1 (type 2); ICF: informed consent form; IgM: immunoglobulin M; IWRS: interactive web response system; MRI: magnetic resonance imaging; NA: nucleos(t)ide analog; PBMC: peripheral blood mononuclear cells; PGIC: patient global impression of change; PK: pharmacokinetic; PRO: patient-reported outcome; RNA: ribonucleic acid; SBP: systolic blood pressure; ULN: upper limit of normal; W: Week; WD: withdrawal.

a. The aim is to include 40% not currently treated participants of whom it is expected that 40% are HBeAg-positive. As such, enrollment of subgroups may be closed prior to completion of study enrollment. All efforts will be undertaken to include a sufficient number of HBeAg-positive virologically suppressed participants.
b. All study visits are to be scheduled relative to the baseline (Day 1) visit date.
c. Participants who discontinue study intervention early will have an early WD visit and will enter follow-up unless they withdraw consent. Participants who withdraw consent will be offered an optional safety follow-up visit.
d. If necessary (eg, for operational reasons), the screening phase may be extended up to a maximum of 6 weeks in agreement with the sponsor.
e. Day 1 samples are to be collected before the first dose of study intervention.
f. The ICF must be signed before the first study-related activity.
g. Minimum criteria for the availability of documentation supporting the eligibility criteria are described in the Source Documents section of Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations. Check clinical status (including in- and exclusion criteria) again before first dose of study intervention. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study.
h. Medical history also includes mode of HBV transmission and stage of liver fibrosis. Historical HBV DNA, HBsAg, HBeAg, and ALT data, if available, will be recorded in the CRF.
i. Liver disease staging assessments will be performed based on Fibroscan or liver biopsy results, obtained within 6 months (in case of Fibroscan) or within 1 year (in case of liver biopsy) prior to screening or at the time of screening.

j. Participants must have absence of signs of HCC or clinically relevant renal abnormalities on an abdominal ultrasound performed within 6 months prior to screening or at the time of screening. In case of suspicious findings on conventional ultrasound the participant may still be eligible if HCC or clinically relevant renal abnormalities have been ruled out by a more specific imaging procedure (contrast enhanced ultrasound, CT or MRI).
k. HBV genotype will be determined at baseline using standard genotyping assay if HBV DNA levels are sufficiently high. For participants with low HBV DNA levels, available historical data on previous HBV genotype assessment will be collected in the CRF. Exploratory genotyping assays might be performed.
l. For postmenopausal women only: an FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to confirm a woman is not of childbearing potential.
m. At Week 48 or at time of early discontinuation, it will be communicated to the investigators whether the participants were allocated to either an investigational arm (Arms 1 to 5) or the control arm (Arm 6). Only at Week 72, randomization codes (for Arms 1 to 5) will be fully disclosed to the investigators. The sponsor will be fully unblinded for the primary analysis at Week 48.
n. In between study visits, participants will take oral study intervention at home and they will bring their study intervention with them to each study visit. At study visits, the study intervention should be taken on site.
o. NA will be dispensed at Week 48 in case the participant does not meet the NA treatment completion criteria.
p. If the NA treatment completion criteria are met based on clinical laboratory tests performed at Week 44, treatment with NA will be completed at Week 48.
q. Complete physical examination, including height (at screening only), body weight, skin examination, and other body systems.
r. Symptom-directed physical examination, including body weight.
s. Vital signs include supine SBP, DBP, pulse rate, and body temperature.
t. All ECGs will be read centrally. Only on Day 1, an ECG will be collected and assessed locally prior to dosing.
u. Biochemistry samples must be taken after fasting for at least 10 hours for measurement of phosphate, calcium, creatinine, and lipids.
v. Creatinine clearance (eGFR calculated by the CKD-EPI formula) will be assessed.
w. Intervention-emergent ALT/AST elevations (ie, ALT and/or AST ≥3x ULN and ≥3x nadir [ie, lowest value during study participation]), should trigger an assessment of confounding factors (alcohol intake, change in concomitant medication, and comorbidities) and a confirmatory visit, to be scheduled preferably within 7 days of the receipt of the initial ALT/AST results, to repeat laboratory testing of AFP, ALT, AST, ALP, bilirubin (total and direct), INR albumin, and HBV DNA. Additional tests should be considered based on clinical judgement. For more details and further management guidance refer to Section 8.3.6.1 Intervention-emergent ALT/AST Elevations and Section 10.6 Appendix 6: Intervention-emergent ALT/AST Elevations.
x. Urine chemistry sample (quantitative measurement): creatinine, sodium, phosphate, glucose, protein, and albumin.
Urinalysis by dipstick: specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic analysis if needed. In case of a positive dipstick result, a urine sample will be set aside for additional examination of the positive parameter at the central laboratory (eg, quantification as applicable).
y. Urine sample for selected renal biomarkers including retinol binding protein and beta-2-microglobulin.
z. Only applicable to participants who are enrolled at a site with an on-site Fibroscan device. A Fibroscan assessment will only be done at baseline if it was not done at screening.
aa. HBcrAg and HBV RNA samples may be batched and only selected samples may be tested at the sponsor's discretion. Samples can be used for assessment of other serologic/virologic markers of HBV.
bb. Sequencing at baseline (Day 1 predose) will be performed by default if HBV DNA levels are within the ranges required for the sequencing assay; other samples may be sequenced based on the sponsor virologist's request.
cc. Participants with undocumented (ie, no lab report) HBeAg status as part of their medical history must first complete HBeAg testing and have results reviewed by the investigator to confirm if they qualify for study participation. Documented HBeAg status within 12 months prior to screening is acceptable.
dd. Quantitative HBeAg assessment will only be performed in participants who are defined HBeAg-positive at screening based on a qualitative HBeAg assay.

ee. Exploratory serology samples may be analyzed at the sponsor's discretion. Samples may be used to assess virologic or serologic markers of HBV.
ff. All participants will have sparse PK sampling. For all samples, the time of the preceding 2 intakes of oral study intervention (JNJ-6379/placebo and NA) and the time of PK sampling should be recorded. Sparse PK sampling is not required if the participant is part of the intensive PK subgroup and has an intensive PK sampling at the same visit.
gg. One sample at any time between 2 and 8 hours after JNJ-3989/placebo dosing. Before leaving the study site, the participant's wellbeing should be confirmed.
hh. Only in case of early withdrawal.
ii. All participants who consent to participate in the intensive PK subgroup (optional) will undergo intensive PK sampling at Week 4. If necessary (eg, for operational reasons), this visit may be scheduled at Week 8, 12, or 16. The study intervention should be taken on site and time of dosing should be recorded. Pharmacokinetic samples will be taken predose and 15 minutes, 30 minutes, 1, 2, 3, 4, 6, 8,* 10,* and 24 hours postdose (*the 8 and 10 hours postdose samples are optional). All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within 20% of the nominal time from dosing (eg, within +/- 12 minutes of a 60-minute time point) will not be captured as a protocol deviation if the exact time of the sample collection is noted on the source document and CRF.
jj. PBMC samples will be collected at selected sites only. Additional PBMC samples may be taken in case of ALT flares, upon discussion with the sponsor, which may require an unscheduled visit.
kk. The pharmacogenomic (DNA) sample should preferably be collected at baseline. This sample is optional and will only be collected from participants who consent separately to this component of the study.
ll. PRO assessments will be performed by participants at sites where appropriate translations are available.
mm. A liver ultrasound is performed every 24 weeks from Day 1 for HCC screening in high-risk populations (ie, participants with a family history of HCC, Asian males >40 years, Asian females > 50 years; Africans and African Americans).[42]

1.3.2. Schedule of Activities – Follow-up Phase

After study intervention completion (or early discontinuation), all participants will enter the 48-week follow-up phase (unless they withdraw consent). In the control arm (Arm 6), the study visit frequency in this follow-up phase is lower than in Arms 1 to 5. Note that the participants in Arms 1 to 6 completing NA treatment at Week 48 will also follow a more frequent visit schedule with a study visit at least once every 4 weeks. In case NA re-treatment criteria are met, participants will switch to less frequent follow-up, provided that their HBV DNA and ALT values are stable.

The follow-up phase will be extended to 48 weeks after the end of NA treatment for participants who stop NA treatment during the follow-up phase based on meeting the NA treatment completion criteria. The visit frequency of participants from Arm 6 who enter the extended follow-up phase will be increased to match that of participants that enter the extended follow-up coming from Arms 1 to 5. In case NA re-treatment criteria are met, participants will switch to less frequent follow-up, provided that their HBV DNA and ALT values are stable.

The visit frequency during the follow-up phase and the extended follow-up phase is provided below for all intervention arms.

Study Phase	**Follow-up[a,b]**															
Follow up (FU) Week (W)	FU W2	FU W4	FU W6	FU W8	FU W12	FU W16	FU W20	FU W24	FU W28	FU W30	FU W32	FU W36	FU W40	FU W42	FU W44	FU W48 EOS
FU Study Day (Window)	15 +/ 4d	29 +/ 4d	43 +/ 4d	57 +/ 4d	85 +/ 4d	113 +/ 4d	141 +/ 4d	169 +/ 4d	197 +/ 4d	211 +/ 4d	225 +/ 4d	253 +/ 4d	281 +/ 4d	295 +/ 4d	309 +/ 4d	337 +/ 4d
Visits in Intervention Arms 1 to 6 (NA stopped)[c]	X	X	X	X	X	X	X	X	X		X	X	X		X	X
Visits in Intervention Arms 1 to 5 (NA continued)	X	X	X	X	X	X	X	X		X		X		X		X
Visits in Intervention Arm 6 (NA continued)					X			X				X				X
Extended Follow up (Ext FU) in participants who complete NA treatment during follow up[d]	Ext FU W2	Ext FU W4	Ext FU W6	Ext FU W8	Ext FU W12	Ext FU W16	Ext FU W20	Ext FU W24	Ext FU W28	Ext FU W30	Ext FU W32	Ext FU W36	Ext FU W40	Ext FU W42	Ext FU W44	Ext FU W48 EOS
Ext FU Study Day (Window)	15 +/ 4d	29 +/ 4d	43 +/ 4d	57 +/ 4d	85 +/ 4d	113 +/ 4d	141 +/ 4d	169 +/ 4d	197 +/ 4d	211 +/ 4d	225 +/ 4d	253 +/ 4d	281 +/ 4d	295 +/ 4d	309 +/ 4d	337 +/ 4d
Visits in Interventions Arms 1 to 6 (NA stopped)	X	X	X	X	X	X	X	X	X		X	X	X		X	X
Visits in Interventions Arms 1 to 6 (NA re-started)	X	X	X	X	X	X	X	X		X		X		X		X
Study Intervention Administration																
Administer/Dispense NA[e]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)[w]
Oral study intervention accountability[f]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Assess NA treatment completion or NA re treatment criteria, as applicable	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Phase	Follow-up[a,b]															
Follow up (FU) Week (W)	FU W2	FU W4	FU W6	FU W8	FU W12	FU W16	FU W20	FU W24	FU W28	FU W30	FU W32	FU W36	FU W40	FU W42	FU W44	FU W48 EOS
FU Study Day (Window)	15 +/ 4d	29 +/ 4d	43 +/ 4d	57 +/ 4d	85 +/ 4d	113 +/ 4d	141 +/ 4d	169 +/ 4d	197 +/ 4d	211 +/ 4d	225 +/ 4d	253 +/ 4d	281 +/ 4d	295 +/ 4d	309 +/ 4d	337 +/ 4d
Visits in Intervention Arms 1 to 6 (NA stopped)[c]	X	X	X	X	X	X	X	X	X		X	X	X		X	X
Visits in Intervention Arms 1 to 5 (NA continued)	X	X	X	X	X	X	X	X		X		X		X		X
Visits in Intervention Arm 6 (NA continued)					X			X				X				X
Extended Follow up (Ext FU) in participants who complete NA treatment during follow up[d]	Ext FU W2	Ext FU W4	Ext FU W6	Ext FU W8	Ext FU W12	Ext FU W16	Ext FU W20	Ext FU W24	Ext FU W28	Ext FU W30	Ext FU W32	Ext FU W36	Ext FU W40	Ext FU W42	Ext FU W44	Ext FU W48 EOS
Ext FU Study Day (Window)	15 +/ 4d	29 +/ 4d	43 +/ 4d	57 +/ 4d	85 +/ 4d	113 +/ 4d	141 +/ 4d	169 +/ 4d	197 +/ 4d	211 +/ 4d	225 +/ 4d	253 +/ 4d	281 +/ 4d	295 +/ 4d	309 +/ 4d	337 +/ 4d
Visits in Interventions Arms 1 to 6 (NA stopped)	X	X	X	X	X	X	X	X	X		X	X	X		X	X
Visits in Interventions Arms 1 to 6 (NA re-started)	X	X	X	X	X	X	X	X		X		X		X		X
Safety Evaluations																
Symptom directed physical examination[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Triplicate 12 lead ECG[i]		X														
Liver ultrasound[v]								X								X
Clinical Laboratory Tests																
Hematology	X	X		X		X		X				X				X
Blood chemistry (including liver function tests)[j,k,l]	X	X	X[m]	X[m]	X	X[m]	X[m]	X	X[m]	X[m]	X[m]	X	X[m]	X	X	X
Blood coagulation	X	X			X			X				X		X		X
Urinalysis and urine chemistry[n]		X														
Urine pregnancy test (women of childbearing potential only)		X		X	X	X	X	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X
AFP[t]								X								X
Efficacy Evaluations																
Fibroscan[p]								X								X
HBV Virology																
Blood sampling for HBV DNA and HBV RNA[q,x]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sampling for viral genome sequencing[r]		X			X		X					X				X
HBV Serology																
Blood sampling for:																
Anti HBs and anti HBe		X			X			X				X				X
HBsAg and HBeAg (qualitative)								X								X
HBsAg and HBeAg (quantitative)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBcrAg[q]		X			X			X				X				X
Exploratory serology[s]	X	X		X	X	X	X	X				X				X

Study Phase	Follow-up[a,b]															
Follow up (FU) Week (W)	FU W2	FU W4	FU W6	FU W8	FU W12	FU W16	FU W20	FU W24	FU W28	FU W30	FU W32	FU W36	FU W40	FU W42	FU W44	FU W48 EOS
FU Study Day (Window)	15 +/ 4d	29 +/ 4d	43 +/ 4d	57 +/ 4d	85 +/ 4d	113 +/ 4d	141 +/ 4d	169 +/ 4d	197 +/ 4d	211 +/ 4d	225 +/ 4d	253 +/ 4d	281 +/ 4d	295 +/ 4d	309 +/ 4d	337 +/ 4d
Visits in Intervention Arms 1 to 6 (NA stopped)[c]	X	X	X	X	X	X	X	X	X		X	X	X		X	X
Visits in Intervention Arms 1 to 5 (NA continued)	X	X	X	X	X	X	X	X		X		X		X		X
Visits in Intervention Arm 6 (NA continued)					X			X				X				X
Extended Follow up (Ext FU) in participants who complete NA treatment during follow up[d]	Ext FU W2	Ext FU W4	Ext FU W6	Ext FU W8	Ext FU W12	Ext FU W16	Ext FU W20	Ext FU W24	Ext FU W28	Ext FU W30	Ext FU W32	Ext FU W36	Ext FU W40	Ext FU W42	Ext FU W44	Ext FU W48 EOS
Ext FU Study Day (Window)	15 +/ 4d	29 +/ 4d	43 +/ 4d	57 +/ 4d	85 +/ 4d	113 +/ 4d	141 +/ 4d	169 +/ 4d	197 +/ 4d	211 +/ 4d	225 +/ 4d	253 +/ 4d	281 +/ 4d	295 +/ 4d	309 +/ 4d	337 +/ 4d
Visits in Interventions Arms 1 to 6 (NA stopped)	X	X	X	X	X	X	X	X	X		X	X	X		X	X
Visits in Interventions Arms 1 to 6 (NA re-started)	X	X	X	X	X	X	X	X		X		X		X		X
Exploratory Biomarkers																
Whole blood RNA gene expression		X						X								X
Whole blood single cell profiling		X		X	X	X		X				X				X
Host serum proteins (eg, cytokines)		X		X	X	X		X				X				X
Antidrug antibodies (to JNJ 3989)					X			X								X
Immune Monitoring																
Immune cells (PBMCs) (selected sites only)[t]					X			X								X
PRO Evaluations[u]																
HBQOL					X			X				X				X
HBV specific self stigma					X			X				X				X
PGIC					X			X				X				X
Ongoing Participant Review																
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

General Note: The PRO assessments and ECGs should be completed before any tests, procedures or other consultations for that visit.

AFP: alpha-fetoprotein; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; D/d: Day/days; DBP: diastolic blood pressure; DNA: deoxyribonucleic acid; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; EOS: end of study; Ext FU: extended follow-up; FU: follow-up; HBcrAg: hepatitis B core-related antigen; HBe(Ag): hepatitis B e (antigen); HBQOL: Hepatitis B Quality of Life; HBs(Ag): hepatitis B surface (antigen); HBV: hepatitis B virus; NA: nucleos(t)ide analog; PBMC: peripheral blood mononuclear cells; PGIC: patient global impression of change; PRO: patient-reported outcome; RNA: ribonucleic acid; SBP: systolic blood pressure; ULN: upper limit of normal; W: Week; WD: withdrawal.

a. All follow-up study visits are to be scheduled relative to the last dose of JNJ-3989/JNJ-6379/placebo. An unscheduled visit can be performed upon the investigator's discretion, in case of HBV DNA elevations, ALT elevations, other signs of worsening of liver disease, or for any other reason during follow-up.

b. Participants who withdraw consent during follow-up will be offered an optional safety follow-up visit to occur on the day of consent withdrawal. For the optional safety follow-up visit, assessments are at the investigator's discretion and could be similar to the early WD visit.
c. Participants in Arms 1 to 6 who discontinue NA treatment at Week 48 will be monitored more frequently, with a study visit at least once every 4 weeks. In case NA re-treatment criteria are met, participants will switch to less frequent follow-up, provided that their HBV DNA and ALT values are stable.
d. If NA treatment completion criteria are met based on clinical laboratory tests performed at or before FU W42 (FU W36 for Arm 6 [NA continued]), NA treatment should be stopped at or before Follow-up Week 48 (ie, the next scheduled visit after the laboratory test was performed) and the follow-up phase will be extended to 48 weeks after the end of NA treatment. If NA treatment completion criteria are not met based on clinical laboratory tests performed at or before FU W42 (FU W36 for Arm 6), the follow-up phase will not be extended, but the participant will continue NA treatment and complete the study at FU W48.
e. No JNJ-3989/JNJ-6379/placebo will be administered or dispensed during follow-up. Administration/Dispensation of NA is only applicable for participants who did not meet the NA treatment completion criteria yet, or for those who met the NA re-treatment criteria. In between study visits, participants will take NA at home and they will bring their NA treatment with them to each study visit. At study visits, the NA treatment should be taken on site.
f. For participants who take NA during follow-up.
g. Symptom-directed physical examination, including body weight.
h. Vital signs include supine SBP, DBP, pulse rate, and body temperature.
i. All ECGs will be read centrally.
j. Biochemistry samples must be taken after fasting for at least 10 hours for measurement of phosphate, calcium, creatinine, and lipids.
k. Creatinine clearance (eGFR calculated by the CKD-EPI formula) will be assessed.
l. ALT/AST elevations (ie, ALT and/or AST ≥3x ULN and ≥3x nadir [ie, lowest value during study participation]), should trigger an assessment of confounding factors (alcohol intake, change in concomitant medication, and comorbidities) and a confirmatory visit, to be scheduled preferably within 7 days of the receipt of the initial ALT/AST results, to repeat laboratory testing of AFP, ALT, AST, ALP, bilirubin (total and direct), INR albumin, and HBV DNA. Additional tests should be considered based on clinical judgement. For more details and further management guidance refer to Section 8.3.6.1 Intervention-emergent ALT/AST Elevations and Section 10.6 Appendix 6: Intervention-emergent ALT/AST Elevations.
m. Liver function tests only.
n. Urine chemistry sample (quantitative measurement): creatinine, sodium, phosphate, glucose, protein, and albumin.
Urinalysis by dipstick: specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic analysis if needed. In case of a positive dipstick result, a urine sample will be set aside for additional examination of the positive parameter at the central laboratory (eg, quantification as applicable).
o. Urine pregnancy tests for at-home use will be provided to the participants from (Extended) Follow-up Week 24 onwards as urine pregnancy test should be done at least every 4 weeks. Results will be reported at the next visit. If a urine pregnancy test is positive, the investigator needs to be informed immediately by the participant.
p. Only applicable to participants who are enrolled at a site with an on-site Fibroscan device.
q. HBcrAg and HBV RNA samples may be batched and only selected samples may be tested at the sponsor's discretion. Samples can be used for assessment of other serologic/virologic markers of HBV.
r. Samples may be sequenced based on the sponsor virologist's request.
s. Exploratory serology samples may be analyzed at the sponsor's discretion. Samples may be used to assess virologic or serologic markers of HBV.
t. PBMC samples may be collected at selected sites only. Additional PBMC samples may be taken in case of ALT flares, upon discussion with the sponsor, which may require an unscheduled visit.
u. PRO assessments will be performed by participants at sites where appropriate translations are available.

v. A liver ultrasound is performed every 24 weeks from start of FU for HCC screening in high-risk populations (ie, participants with a family history of HCC, Asian males >40 years, Asian females > 50 years; Africans and African Americans). Liver ultrasound evaluations for participants with increased risk of HCC should be continued also every 24 weeks relative to baseline for participants who participate in the extended follow-up period.[42]

w. The investigator should consider to re-start NA treatment per local standard of care at the EOS visit ([Extended] Follow-up Week 48) for participants who met the NA treatment completion criteria at Week 48 or during the follow-up phase, who did not re-start NA treatment during the follow-up phase, and who did not achieve and maintain HBsAg seroclearance. NA will not be provided by the sponsor after the final study visit.

x. NA treatment should be re-started in accordance with the NA re-treatment criteria (see Section 6.7, NA Re-treatment Criteria and Monitoring After Stopping of NA and Section 10.14 Appendix 14, for guidance after stopping NA treatment).

2. INTRODUCTION

Chronic Hepatitis B Infection

Hepatitis B virus (HBV) is a small deoxyribonucleic acid (DNA) virus that specifically infects the human liver. It consists of a nucleocapsid in which the viral DNA is packed with hepatitis B core protein (HBc) and a membraneous envelope containing hepatitis B surface antigen (HBsAg). The acute phase of the infection (less than 6 months) is either followed by an immune controlled state (spontaneous cure from the infection) or progresses to chronic hepatitis B (CHB) (more than 6 months). Chronic HBV infection may lead to serious illnesses such as liver cirrhosis and decompensation, and hepatocellular carcinoma (HCC), often with fatal outcome.[35]

The worldwide estimated prevalence of chronic HBV infection is 4.9% with about 292 million people affected.[29] Despite the availability of an efficacious prophylactic vaccine, yearly rates of new infections remain high. Approximately 680,000 people per year worldwide die from cirrhosis and HCC due to CHB.[33]

The natural course of HBV infection is the consequence of a complex interaction between the virus and the host which in the chronic setting might evolve over a duration of decades. This is associated with different disease phases or stages. The European Association for the Study of the Liver (EASL) guidelines differentiate between chronic infection and chronic hepatitis (Table 1).

Table 1: Various Stages of HBV Infection – Terminology and Characteristics (EASL 2017)[7]

	HBeAg-positive		HBeAg-negative	
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis
HBsAg	High	High/intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	$>10^7$ IU/mL	10^4-10^7 IU/mL	<2,000 IU/mL°°	>2,000 IU/mL
ALT	Normal	Elevated	Normal	Elevated*
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe
Old terminology	Immune tolerant	Immune reactive HBeAg-positive	Inactive carrier	HBeAg-negative chronic hepatitis

ALT: alanine aminotransferase; DNA: deoxyribonucleic acid; EASL: European Association for the Study of the Liver; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; IU/mL: International Units Per Millilitre
*Persistently or intermittently. °°HBV deoxyribonucleic acid (DNA) levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis.
Note that different definitions and naming of HBV disease phases may be used across different countries/regions.

According to the EASL treatment guidelines, the primary treatment goal for patients with CHB is to improve survival and quality of life by preventing progression of liver disease, particularly to cirrhosis, liver failure, and HCC. Risk factors associated with progression to advanced liver disease are persistently elevated levels of HBV DNA and liver enzymes such as alanine aminotransferase (ALT) in blood, male sex, older age, coinfection with hepatitis D virus (HDV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV), and coexistence of other liver diseases (particularly fatty liver disease).[6,7]

Irrespective of the hepatitis B e antigen (HBeAg) status, antiviral therapy is recommended for all patients with signs of active chronic hepatitis.[3,7,30,35] Approved therapies for CHB are pegylated

interferon (IFN) alpha and nucleos(t)ide analog inhibitors (ie, nucleos[t]ide analog [NA] treatment) of the HBV polymerase/reverse transcriptase, the enzyme synthesizing HBV DNA from pre-genomic ribonucleic acid (pgRNA).

Oral treatment with NAs is effective at suppressing viral DNA formation and lowering virus concentration in the blood to levels below the lower limit of quantification (LLOQ) of the HBV DNA assays commonly used. This is associated with normalization of liver enzymes and reduced or halted progression of liver disease to cirrhosis and/or decompensation and even with regression of cirrhotic transformation.[5,17,22,25,38] While the risk of HCC development is reduced as well, it is not eliminated.[17,22,25]

HBsAg seroclearance 24 weeks after end of treatment is currently considered to be associated with the most thorough suppression of HBV replication and has been termed “functional cure”.[21] Unfortunately, with currently available NA treatment strategies the rate of HBsAg seroclearance remains very low (around 3%) even under long-term treatment.

Pegylated IFN is associated with a slightly higher rate of HBsAg seroclearance compared to NAs and is recommended for a fixed treatment duration of 48 weeks, but is administered subcutaneously and is associated with higher toxicity than NAs.[27]

With the low rate of functional cure with current treatments, and persistently high global prevalence of HBV-associated mortality,[7,35] there is a medical need for more effective finite treatment options that lead to sustained HBsAg seroclearance ("functional cure"). In order to achieve an effective finite treatment, combination of therapies with different mechanisms of action, as is standard of care for other chronic viral infections like HCV and HIV, is deemed required.

JNJ-73763989 and JNJ-56136379

JNJ-73763989 (JNJ-3989) is a liver-targeted antiviral therapeutic for subcutaneous injection designed to treat chronic HBV infection via a ribonucleic acid interference (RNAi) mechanism. Engagement of the cellular RNAi machinery by JNJ-3989 results in specific cleavage of HBV ribonucleic acid (RNA) transcripts, thereby reducing the levels of HBV proteins and the pgRNA, the precursor of viral relaxed circular DNA. The RNAi triggers in JNJ-3989 injection are designed to target all HBV RNA transcripts derived from covalently closed circular DNA (cccDNA), as well as transcripts derived from integrated viral DNA. The latter has been suggested to be a significant source of HBsAg in HBeAg-negative patients or patients on long-term treatment with NAs, the current standard of care.[37]

JNJ-56136379 (JNJ-6379) is an orally administered capsid assembly modulator (CAM) that is being developed for the treatment of chronic HBV infection. JNJ-6379 binds to HBc and interferes with the viral capsid assembly process, thereby preventing the polymerase-bound pgRNA encapsidation. This results in the formation of HBV capsids, devoid of HBV DNA or RNA (non-functional capsids), and ultimately in the inhibition of HBV replication. In addition, JNJ-6379 also acts at an early stage of the viral life cycle by inhibiting the de-novo formation of cccDNA potentially by interfering with the capsid disassembly process.

For the most comprehensive nonclinical and clinical information regarding JNJ-3989 and JNJ-6379, refer to the latest version of the Investigator's Brochure (IB) and Addenda.[13,14,15]

The term “study intervention” throughout the protocol, refers to JNJ-3989 or placebo, JNJ-6379 or placebo, and NA.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

The term "participant" throughout the protocol refers to the common term "subject".

2.1. Study Rationale

There is a medical need for effective finite treatment with long-term clinical benefits (ie, reduced mortality and morbidity from cirrhosis and HCC) comparable to those achieved by patients with self-limited HBV infection.

The efficacy and safety of finite treatment duration will be assessed with a fixed 48-week treatment duration for JNJ-3989 and/or JNJ-6379 (in combination with NA treatment). The aim is to also complete NA treatment after 48 weeks, based on pre-specified response criteria outlined in Section 6.6.

The main goal of the study is to evaluate efficacy as measured by the proportion of participants who completed 48-week study intervention and qualified for stopping NA treatment at Week 48. In addition, off-treatment HBsAg seroclearance during follow-up (with focus on Follow-up Weeks 24 and 48) as well as other measures for off-treatment (ie, HBV DNA suppression in the presence of low HBsAg levels) and on-treatment response (eg, the kinetics of HBV DNA, HBsAg and of other viral markers) will be assessed.

2.2. Background

2.2.1. JNJ-3989 and JNJ-6379

Nonclinical Studies

Nonclinical assessments to support clinical development have been performed for the single agents JNJ-3989 and JNJ-6379, and pharmacokinetics (PK) and toxicology studies are (being) conducted for the combination.

JNJ-3989

Little potential for off-target inhibition of human gene expression in participants is expected, based on in silico human genome database screening.

The nonclinical safety profile of JNJ-3989 has been evaluated through a series of in vitro and in vivo studies. Repeat-dose subcutaneous toxicity studies of 2 weeks up to 24 or 37 weeks were conducted in rat and monkey, respectively. In the 2-week studies, JNJ-3989 was administered once weekly via subcutaneous injection at 30 up to 300 mg/kg. In the 24- or 37-week studies,

JNJ-3989 was administered once weekly for the first month, followed by once monthly thereafter at 30 up to 180 mg/kg. JNJ-3989 was well tolerated in these studies.

In the 2-week and the 24-week study in rat, JNJ-3989 related-target organs were the liver, the kidney, and the injection site. The mandibular and mesenteric lymph nodes were identified as target organ in the 24-week study only. In the liver, hepatocyte alteration and hepatocyte mitosis, accompanied by an increase in hepatocellular vacuoles, oval cell hyperplasia, Kupffer cell vacuolation and/or increased liver weights were observed. The hepatocyte findings correlated to increased alkaline phosphatase (ALP) activity levels seen in the 24-week study. Kidney findings were characterized by cytoplasmic alteration of the cortical tubule epithelium. At the injection site, mononuclear cell or vacuolated macrophage infiltrates, epidermal exudate, hemorrhages and/or interstitial granules were observed. Macrophage vacuolation was observed in the sinus spaces of the mandibular and mesenteric lymph nodes.

Liver findings persisted throughout the recovery period. Partial recovery was observed in the kidney. No findings were present anymore at the injection sites and the lymph nodes at the end of the recovery period.

All these changes likely represented the distribution, accumulation, and clearance of JNJ-3989 and were considered not to be adverse due to the nature of the findings and the low severity. These are commonly described findings for N-acetylgalactosamine-conjugated RNAi.[16] The no observed adverse effect level (NOAEL) was therefore considered to be the highest dose tested, ie, CCI mg/kg in the 24-week study.

In the 2-week study in monkey, apart from a minimally increased ALP activity which was considered not adverse, no JNJ-3989-related effects were observed. In the 37-week study, JNJ-3989-related target organs were the liver, mandibular and/or mesenteric lymph nodes, and the subcutaneous injection site. Findings included Kupffer cell basophilia/hypertrophy in the liver, vacuolated macrophages in the lymph nodes, and macrophage infiltrates in the injection site. Partial reversibility was observed for these findings. This likely represented the distribution, accumulation, and clearance of JNJ-3989 and was considered not to be adverse due to the low severity and/or nature of the findings. These are commonly described findings for N-acetylgalactosamine-conjugated RNAi.[16] A non-adverse minimally increased ALP activity was observed at 180 mg/kg without a microscopic correlate. The NOAEL in the monkey was considered to be the highest dose tested, ie, CCI mg/kg in the 37-week study.

In the embryofetal development (EFD) studies, JNJ-3989 was not teratogenic in rats and rabbits.

The fertility study showed no effects on parental and reproductive parameters in male and female rats given JNJ-3989 up to a dose of 180 mg/kg/week.

JNJ-3989 was shown to be non-genotoxic when tested in the bacterial reverse mutation assay, and in vitro and in vivo micronucleus test. Results of the non-Good Laboratory Practice (GLP) in vitro studies demonstrated there is no potential for induction of the innate immune system

(cytokine and complement activation), mitochondrial toxicity/cytotoxicity, or platelet aggregation associated with JNJ-3989 exposure at concentrations up to 250 µg/mL.

The animal-to-human exposure ratios were calculated using rat and monkey exposures at NOAEL from the 24-week and 37-week studies, respectively, and from EFD studies in pregnant rats and rabbits, and human exposures after a single subcutaneous injection of 400 mg JNJ-3989 in human volunteers (Study AROHBV1001) (Table 2).

Table 2: Animal/Human Exposure Ratios at NOAEL for JNJ-3989

	Sex	NOAEL (mg/kg)	C_{max} (ng/mL)	AUC[b] (ng.h/mL)	Ratio Total Concentration C_{max} A/H Ratio	Ratio Total Concentration AUC[b] A/H Ratio
JNJ-3976		CCI				
Human exposure [a]			4,282	64,529	-	-
24-week rat[c]	M		41,100	437,000	9.6	6.8
	F		43,100	270,000	10.1	4.2
37-week monkey[d]	M		73,200	1,230,000	17.1	19.1
	F		65,800	988,000	15.4	15.3
EFD rat	F		48,000	501,000	11.2	7.8
EFD rabbit	F		26,600	252,000	6.2	3.9
JNJ-3924						
Human exposure [a]			1,010	14,771		
24-week rat[c]	M		25,200	271,000	25.0	18.3
	F		26,200	163,000	25.9	11.0
37-week monkey[d]	M		21,600	383,000	21.4	25.9
	F		23,000	392,000	22.8	26.5
EFD rat	F		31,200	324,000	30.9	21.9
EFD rabbit	F		13,900	133,000	13.8	9.0

AUC: area under the plasma concentration time curve; $AUC_{0\text{-}24h}$: area under the plasma concentration time curve from administration to 24 h; $AUC_{0\text{-}last}$: area under the plasma concentration time curve from administration to last quantifiable sampling point; A/H: animal/human ratio; C_{max}: maximum plasma concentration; EFD: embryofetal development; F: female; M: male; NOAEL: no observed adverse effect level.

[a] single dose of 400 mg JNJ 3989 in healthy volunteers via subcutaneous injection (Study AROHBV1001).
[b] $AUC_{0\text{-}last}$ for human exposure; $AUC_{0\text{-}24h}$ for animal exposures
[c] once weekly dosing for 5 weeks, followed by once monthly dosing up to a total of 24 weeks
[d] once weekly dosing for 5 weeks followed by once monthly dosing, up to a total of 37 weeks
[e] daily dosing during organogenesis (GD6 17 in pregnant rats and GD6 19 in pregnant rabbits)

JNJ-6379

Following 6 months of treatment in rats, the kidney and female reproductive tract (irregular estrus cycle) were identified as target organs. However, after further assessment of the kidney findings and their clinical relevance, it is deemed unlikely that the retrograde nephropathy seen in 1 out of 20 male rats following 6 months of dosing with JNJ-6379 at 100 mg eq./kg/day are relevant for the clinical studies. The retrograde nephropathy was partially recovered after a 9-week recovery period. In the 6-month rat study, female rats (at 200 mg eq./kg/day) showed an irregular estrus cycle, from which they recovered at the end of the 9-week treatment-free period. These irregular estrus cycles were also apparent in the female fertility studies (main and mechanistic). These changes were related to lowered hormone levels (luteinizing hormone, progesterone, estradiol). JNJ-6379, however, did not affect female fertility. The fetal loss seen during the early stages of pregnancy was considered to result from low hormone levels. In the dog study, no changes were observed in the reproductive tract at higher exposures in dogs.

In the 9-month dog study, the target organs identified were the adrenal glands and bone marrow. The adrenal glands did not show degenerative changes or loss of function and were therefore considered as non-adverse target organs. One female dog out of 4 dosed at 25 mg eq./kg/day (the highest dose) was sacrificed on Day 61, after showing poor health condition. A JNJ-6379 plasma level of 42,000 ng/mL was observed for this animal on Day 61, at approximately 24 hours after last dosing. Pronounced clinical pathologic changes, including pancytopenia, were noted. Marked increase in plasma cell-like cells was seen in the bone marrow during histopathologic examination, resulting in a marked reduction of hematopoietic tissue and extramedullary hematopoiesis in liver and spleen. The cause of the deteriorating condition was likely related to changes in the bone marrow. A second dog in the same dose group with pancytopenia recovered after a drug holiday and was re-exposed uneventfully.

In the EFD studies, JNJ-6379 was not teratogenic in rats and rabbits.

JNJ-6379 was not genotoxic in the in vitro micronucleus and Ames tests, and in the in vivo micronucleus tests in rats.

Animal/human ratios at the NOAEL in rat and dog for human exposure at 250 mg JNJ-6379 once daily (qd) for 28 days are displayed in Table 3.

Table 3: Animal/Human Ratios at the NOAEL in Rat and Dog (Human Exposure at 250 mg JNJ-56136379 Once Daily for 28 Days [Study 56136379HPB1001])

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

AUC: area under the plasma concentration time curve; AUC_{0-24h}: area under the plasma concentration time curve from administration to 24 h; A/H: animal/human ratio; C_{max}: maximum plasma concentration; F: female; M: male; NOAEL: no observed adverse effect level; qd: once daily.

[a] 250 mg JNJ 6379 qd 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 CCI 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%).

JNJ-3989 and JNJ-6379

A combination PK study with JNJ-6379 and JNJ-3989 has been conducted in male rats (N 3/group), and a GLP, 1-month combination repeat-dose toxicity study (TOX13609) is completed in male and female rats.

In the combination PK study (FK13466), JNJ-6379 was administered orally at 100 mg eq./kg/day for 8 days in combination with JNJ-3989 administered subcutaneously on Days 0 and 7 at 30 or 180 mg/kg. In addition, two groups received JNJ-6379 alone (orally at 100 mg eq./kg/day for 8 days), or JNJ-3989 alone (at 180 mg/kg subcutaneously on Days 0 and 7).

Histopathological examinations were performed on the liver and kidney collected 25 hours postdose on Day 7. No adverse findings for JNJ-3989, JNJ-6379 or for the combination were noted. No additive or synergistic effects were noted when both compounds were coadministered.

When JNJ-6379 was administered in combination with JNJ-3989, mean maximum plasma concentration (C_{max}) values and mean area under the plasma concentration-time curve (AUC) values of JNJ-6379, JNJ-3976 and JNJ-3924 did not change significantly when compared to dosing both compounds alone.

Final data from the 28-day combination toxicity study in the rat are available (TOX13609). In the 1-month combination study, JNJ-3989 was administered weekly via SC injections at dose levels of 30 and 180 mg/kg when given in combination with JNJ-6379, and at 180 mg/kg for the monotherapy group. JNJ-6379 was administered daily via oral gavage at a dose level of 100 mg/kg. Control animals received both vehicles via the respective routes.

JNJ-3989-related findings at 180 mg/kg included increased vacuolation of hepatocytes and/or Kupffer cells, with correlating macroscopic pale discoloration and prominent lobular architecture, single cell necrosis, increased mitosis, karyomegaly of low incidence in females, and/or hypertrophy/hyperplasia of bile ducts of low incidence in males in the liver, vacuolation and basophilic granules in tubular epithelium of the kidney, macrophage vacuolation in lymph nodes and/or sinus histiocytosis (mesenteric, axillary and/or popliteal), and mixed cell infiltrate and infiltration of vacuolated macrophages with basophilic stippling in the administration site.

At 30 mg/kg increased vacuolation and increased mitosis in the liver, and mixed cell infiltrate in the administration site with infiltration of vacuolated macrophages and basophilic stippling were seen.

A minor increase in incidence and severity of decreased lymphoid cellularity in the thymus with lower thymus weights was seen in females in the 180/100 mg/kg group, compared to what was seen with the single agent JNJ-6379. The thymic change was considered non-adverse based on the minor severity. All remaining findings in the groups dosed with the combination of test articles were in line with the findings recorded for the groups dosed with the single compounds.

Exposure to JNJ-6379 in terms of C_{max} and $AUC_{0\ 24h}$ did not change significantly when dosed together with JNJ-3989 vs. when dosed as a single agent. Exposure to both analytes of JNJ-3989

in terms of C_{max} and $AUC_{0\ 24h}$ did not change significantly when dosed together with JNJ-6379 vs. when dosed as a single agent.

Based on these results, the NOAEL was considered to be CCI mg/kg after combination therapy (JNJ-3989/JNJ-6379). At the NOAEL the mean C_{max} and AUC values for analyte JNJ-3924 in males were 20,900 ng/mL and 178,000 ng·h/mL, and for females 21,300 ng/mL and 141,000 ng·h/mL, respectively. For analyte JNJ-3976, the mean C_{max} and AUC values in males were 35,200 ng/mL and 279,000 ng·h/mL, and for females 35,300 ng/mL and 218,000 ng·h/mL, respectively. C_{max} and AUC values for JNJ-6379 in males were 13,200 ng/mL and 181,000 ng·h/mL, and for females 15,500 ng/mL and 206,000 ng·h/mL, respectively, after 1 month of treatment.

In conclusion, weekly SC injection with JNJ-3989 at 30 or 180 mg/kg in combination with daily administration of JNJ-6379 at 100 mg/kg (oral) for one month was well tolerated with no clinical signs or treatment-related mortality. Changes in clinical pathology and histopathology were mostly similar to the findings for the monotherapy groups and were considered not adverse. There was no apparent interaction between JNJ-3989 and JNJ-6379.

Preliminary results of a 3-month combination toxicity study with JNJ-6379 and JNJ-3989 in the rat became available. In this study, the potential for toxicity of JNJ-6379 when given by daily oral gavage, and of JNJ-3989 when given by intermittent SC injection, and of both test items when given in combination, was assessed (TOX13608).

No test article-related mortalities were noted among animals dosed with JNJ-6379 alone, with JNJ-3989 alone or with JNJ-6379 + JNJ-3989 at 100/180 mg/kg.

One male rat dosed at 100/60 mg/kg JNJ-6379/JNJ-3989 was euthanized on Day 24 after showing severe clinical signs in the morning (decreased activity, erected fur, pallor and cold to touch). No clinical signs were noted for this animal until Day 23, and body weight and weight gain were unaffected during the first 3 weeks of the study; The cause of moribundity was considered to be a markedly decrease hematopoietic cellularity of the bone marrow with pancytopenia including markedly reduced platelet counts and consequent hemorrhages and blood loss. A relation to the treatment with JNJ-6379 and/or JNJ-3989 cannot be excluded. In addition, a mild decrease in platelet counts was observed in females in the combination group 100/60 mg/kg and 100/180 mg/kg JNJ-6379/JNJ-3989. For further information, refer to the IB Addenda.[40,41]

No relevant changes on urinary biomarkers were detected in male and female rats given JNJ-6379 at 100mg/kg/day (clusterin, albumin, ß2-microglobulin, Kidney Injury Molecule-1 (KIM-1), Neutrophil Gelatinase Associated Lipocalin (NGAL) and cystatin-C).

Clinical Studies

To date, no clinical information is available for the combination of JNJ-3989 with JNJ-6379. The following sections provide an overview of the current clinical background information for the two compounds separately.

JNJ-3989

Clinical data of JNJ-3989 are available from the ongoing Phase 1/2a AROHBV1001 study with a safety snapshot date of 26 March 2019. Twenty adult healthy participants have received single subcutaneous injections of JNJ-3989 (35, 100, 200, 300, and 400 mg) and 72 adult CHB participants have received multiple doses of JNJ-3989 (25, 50, 100, 200, 300, and 400 mg), administered as 3 subcutaneous injections separated by either 7-day, 14-day, or 28-day intervals. All participants either continued or started entecavir (ETV) or tenofovir disoproxil fumarate (TDF) on Day 1.

JNJ-3989 was generally safe and well tolerated with no deaths, serious adverse events (SAEs) considered at least possibly related to the study intervention, or adverse events (AEs) leading to study intervention discontinuation. All AEs were mild to moderate, with exception of 1 severe blood creatine phosphokinase increased in 1 CHB participant. All reported injection site reactions (ISRs) were mild. Adverse events and laboratory abnormalities were distributed across all dose levels and also occurred on placebo treatment, except for mild ISRs, which were only reported in participants on JNJ-3989 treatment. Most reported laboratory abnormalities were isolated incidences and resolved while on study treatment.

Efficacy was assessed using snapshot data through 02 May 2019. Antiviral activity data were available for 56 CHB participants who received 3 subcutaneous injections of 25 to 400 mg JNJ-3989 every 4 weeks. The antiviral activity data showed that administration of JNJ-3989 at doses of 25 to 400 mg resulted, on average, in pronounced HBsAg decline which was generally sustained at least until Day 168 (ie, 16 weeks after last dose) across all doses. No apparent dose response was observed at doses between 100 and 400 mg JNJ-3989; a reduced mean decline was observed at the lower dose of 25 mg. Data on the 50 mg dose were still emerging at the time of protocol writing. Treatment status (ie, virologically suppressed or not treated) did not seem to affect HBsAg changes. Other measurable serological and virological markers (HBV DNA, HBV RNA, HBeAg, hepatitis B core-related antigen [HBcrAg]) also showed responses to JNJ-3989, indicating that JNJ-3989 shows target activity on all detectable viral products.

JNJ-6379

At the time of protocol writing, 98 adult healthy and 41 CHB participants have been dosed with JNJ-6379 in 4 completed Phase 1 studies (56136379HPB1001, 56136379HPB1002, 56136379HPB1003, and 56136379HPB1004). Another Phase 1 study in healthy participants is also completed and clinical study report writing is currently ongoing (56136379HPB1005). In addition, data are available from 148 participants in the ongoing Phase 2a study, 56136379HPB2001, also referred to as Jade.

Human Pharmacokinetics and Product Metabolism

Single Dose Studies in Healthy Participants

In Study 56136379HPB1001, single ascending doses (25, 50, 150, 300 and 600 mg) of JNJ-6379 (or placebo) were administered under fasting conditions to healthy participants. No major differences were observed in the shape of the mean JNJ-6379 plasma concentration-time curves

for the different dose levels. Mean and individual PK profiles showed minimal lag-time. A single rather flat concentration peak was observed in the PK profiles of most participants. Plasma concentrations in the terminal phase declined generally in parallel for all dose levels. The C_{max} and AUC from administration to 24 hours ($AUC_{0\ 24h}$) increased proportionally with dose after single-dose administration of JNJ-6379 doses of 25 mg to 300 mg and less than dose proportionally at the dose of 600 mg. The AUC from administration to last quantifiable sampling point ($AUC_{0\ last}$) and the AUC to last sampling point from time zero extrapolated to infinity (AUC_{∞}) increased proportionally between JNJ-6379 25 mg and 600 mg. Mean values for terminal half-life ($t_{1/2term}$) were comparable for the 25-mg to 300-mg dose levels, and averaged between 93.3 hours and 110.5 hours. For the 600-mg dose group, the average $t_{1/2term}$ was 141.3 hours. Mean values for the total apparent oral clearance (CL/F) were comparable for the 25-mg, 50-mg and 150-mg dose level, and appeared to decrease at higher dose levels. Mean values of the apparent volume of distribution were generally comparable for the different dose groups.

In Study 56136379HPB1002, study drug exposure levels using a novel tablet formulation, containing hydroxypropylmethylcellulose E5 based spray-dried powder, were similar to exposure levels observed in study 56136379HPB1001 using the original formulation, both in fed conditions. The relative bioavailability of new 25-mg oral tablets of JNJ-6379 administered as a 150-mg dose under fasting and fed conditions, and of new 100-mg oral tablets of JNJ-6379 administered as a 300-mg dose under fasting conditions, was assessed in healthy adult participants. Assuming proportionality, based on the geometric mean ratios between the 3x 100-mg dose, fasting (test) and the 6x 25-mg dose, fasting (reference) of the dose-normalized PK parameters, C_{max} was 21.56% lower for the 100-mg tablet strength compared to the 25-mg tablet strength, and $AUC_{0\ last}$ and AUC_{∞} were similar. The median time to reach C_{max} (t_{max}) was around 1.75 hours when 150 mg JNJ-6379 was dosed as 6x 25-mg oral tablets, and around 3.00 hours when 300 mg JNJ-6379 was dosed as 3x 100-mg oral tablets.

In Study 56136379HPB1005, the oral bioavailability of a single 300-mg dose of JNJ-6379 administered as a 100-mg tablet containing hydroxypropylmethylcellulose-acetate succinate based spray-dried powder (test tablet) was assessed. All 14 healthy adult participants received a 300-mg dose of JNJ-6379 under fasted conditions. Preliminary PK analysis was performed and mean C_{max} was 3,105 ng/mL, mean $AUC_{0\ 72h}$ was 111,286 ng.h/mL and mean AUC_{∞} was 280,926 ng.h/mL. The median t_{max} was around 3.00 hours. These preliminary PK parameter values are comparable to the PK parameters obtained after administration of JNJ-6379 formulated as hydroxypropylmethylcellulose E5 based spray-dried powder tablet.

Multiple Dose Studies in Healthy Participants

In Session 7 of Study 56136379HPB1001, participants received 150 mg JNJ-6379 twice daily under fed conditions for the first 2 days of treatment, followed by 100 mg JNJ-6379 qd until Day 12. JNJ-6379 plasma concentrations accumulated during the study (accumulation ratio of approximately 6). The CL/F at steady-state and the $t_{1/2term}$ were similar to values observed after single-dose administration, suggesting time-linear PK.

In Study 56136379HPB1004, participants received 250 mg of JNJ-6379 twice daily on Days 6 and 7 (fed conditions), followed by 170 mg qd on Day 8 to 25 in fed conditions (with exception of Day 21). On Day 21, a single dose of JNJ-6379 170 mg and a single dose of drospirenone/ethinylestradiol 3 mg/0.02 mg and a single dose of midazolam 2 mg were administered under fasted conditions. Mean JNJ-6379 C_{max} and area under the plasma analyte concentration-time curve over a dose interval (AUC_{tau}) increased between Day 6 (first dose of JNJ-6379) and Day 20 as JNJ-6379 plasma concentrations accumulated due to the multiple-dose regimen administered in this study. Steady-state was reached before Day 20. Plasma concentration-time profiles of JNJ-6379 were similar to those observed in Study 56136379HPB1001.

Multiple Dose Studies in CHB Participants

In Sessions 8, 9, 10, 11, and A of Study 56136379HPB1001, treatment-naïve CHB-infected participants were administered multiple-dose regimens (25, 75, 150, and 250 mg) of JNJ-6379 for 28 days. Pharmacokinetics of JNJ-6379 were not markedly different between healthy participants and CHB participants. Mean JNJ-6379 exposures in CHB participants could be predicted from data in healthy participants. The PK data show that exposure of JNJ-6379 in CHB participants is dose proportional and CL/F is constant over time.

Food Interaction

Although Study 56136379HPB1001 suggested slightly higher exposure of JNJ-6379 in fed conditions, novel data from Study 56136379HBP1002 with higher number of participants showed that there is no food effect on JNJ-6379 exposure, and a preliminary PK analysis from Study 56136379HBP1005 suggests the same.

Drug-drug Interaction

Oral contraceptives: When administered simultaneously with 3 mg drospirenone/0.02 mg ethinylestradiol in Study 56136379HPB1004, JNJ-6379 increases the extent of exposure and decreases the CL/F of ethinylestradiol while the peak plasma concentration decreased. In contrast, JNJ-6379 has no clear effect on the extent of exposure and CL/F of drospirenone, a cytochrome P450 (CYP)3A4 sensitive progestin: peak plasma concentration decreased while no change in exposure and apparent clearance was observed. Consequently, oral contraceptives are still considered to be effective when administered simultaneously with JNJ-6379. However, as a precaution to avoid high exposure to ethinylestradiol, ethinylestradiol-containing contraceptives are only allowed if the ethinylestradiol content is ≤20 µg.

Midazolam: In Study 56136379HPB1004, coadministration of JNJ-6379 170 mg qd with oral midazolam as a CYP3A4 probe substrate showed a reduction of 41.7% in C_{max} and 53.9% in AUC of midazolam, implying that JNJ-6379 may induce the metabolism of CYP3A4 sensitive substrates.

Efficacy Studies

Antiviral activity data are available from Part II of Study 56136379HPB1001 (final analysis, 57 treatment-naïve participants treated with multiple-dose regimens of JNJ-6379 25 to 250 mg qd for 28 days, unblinded).

Available antiviral activity data for 4 weeks of treatment with JNJ-6379 in Study 56136379HPB1001 showed potent HBV DNA and RNA reductions but no changes in HBsAg, indicating that longer treatments are needed.

Interim efficacy data are available from the Phase 2a Jade study. Interim analysis (IA) 2 includes Week 12 data from 64 CHB participants not treated at screening of whom 26 received 75 mg qd JNJ-6379 monotherapy (open-label) and 38 received 75 mg qd JNJ-6379 or placebo in addition to an NA (blinded). Interim analysis 2 included unblinded Week 24 data from 44 virologically suppressed CHB participants of whom 33 received 75 mg qd JNJ-6379 and 11 received placebo in addition to an NA. Interim analysis 3 includes blinded Week 12 data from 40 virologically suppressed CHB participants who received 250 mg qd JNJ-6379 or placebo in addition to an NA.

The 12-week interim efficacy data in currently not treated participants on 75 mg JNJ-6379 monotherapy showed a mean reduction from baseline of HBV DNA of >3.5 $\log_{10}$ IU/mL at Week 12. This decline was similar to the mean decline in participants treated with JNJ-6379 or placebo in combination with an NA (data still blinded).

The 24-week interim efficacy data in virologically suppressed participants on 75 mg JNJ-6379 showed that most participants had HBV DNA levels below the limit of quantification at baseline. At 24 weeks of treatment, 5/21 (23.8%) of participants on JNJ-6379 experienced a mean reduction from baseline in HBV RNA of >2 $\log_{10}$ IU/mL versus 1/7 (14.3%) of participants on placebo. HBV RNA levels at Week 24 were undetectable for 21/21 (100.0%) of participants on JNJ-6379 and 4/7 (57.1%) of participants on placebo. No relevant mean changes from baseline in HBsAg and HBeAg were noted so far.

In the monotherapy arm with 75 mg JNJ-6379, 5 of 28 participants (status after IA cut-off date) experienced a viral breakthrough defined as confirmed on-treatment HBV DNA increase by >1 $\log_{10}$ from nadir level or confirmed on-treatment HBV DNA level >200 IU/mL in participants who had HBV DNA level below the LLOQ of the HBV DNA assay. All 5 participants with viral breakthrough had an emerging core amino acid mutation T33N, which is known to confer reduced JNJ-6379 activity in vitro. All 5 participants discontinued JNJ-6379 and started NA treatment. An urgent safety measure was implemented to discontinue JNJ-6379 treatment in all participants in this arm and offer NA treatment. No cases of viral breakthrough were observed in any of the arms combining JNJ-6379/placebo with NA treatment. A futility rule was implemented in the 250 mg JNJ-6379 monotherapy arm (if ≥1 participant in the 250 mg monotherapy arm experiences virological breakthrough during the first 24 weeks of treatment, NA treatment will be added to JNJ-6379 treatment as soon as possible for all remaining participants).

In the monotherapy arm with 250 mg JNJ-6379, 1 participant experienced viral breakthrough (status after IA cut-off date). The participant discontinued JNJ-6379 treatment and started NA treatment at the withdrawal visit, due to meeting non-response criteria. NA treatment will be added for all remaining participants in the JNJ-6379 250 mg monotherapy arm in accordance with the implemented futility rule.

Safety Studies

Data from 4 completed Phase 1 studies (56136379HPB1001, 56136379HPB1002, 56136379HPB1003 and 56136379HPB1004) in healthy and CHB participants (N 98 and 41, respectively), indicate that orally administered JNJ-6379 as single doses up to 600 mg or as multiple doses (250 mg twice daily for 2 days followed by 170 mg qd for 18 days or 150 mg twice daily for 2 days followed by 100 mg qd for 10 days) in healthy participants and as multiple doses up to 250 mg for 28 days in CHB participants was safe and well tolerated. No SAEs considered at least possibly related to the study intervention were reported. Most AEs were mild and not considered treatment-related, with no dose-related trends. Those observations were supported by the final safety data obtained for Phase 1 Study 56136379HPB1005, in which 14 healthy adult participants received single doses (300 mg) of JNJ-6379.

Safety data are also available from IAs 2 and 3 conducted for the Phase 2a Jade study, which were mentioned above. There were no deaths, SAEs considered at least possibly related to the study intervention, or AEs leading to discontinuation. Most AEs were grade 1 or 2 in severity. The majority of reported AEs were considered unrelated to JNJ-6379 by the investigator. Grade 2 to 4 AEs considered at least possibly related to JNJ-6379 by the investigator were grade 2 asthenia (3 participants), grade 4 ALT increased, grade 2 headache, grade 2 vertigo, grade 3 anemia (corrected to grade 2 by the investigator after the IA cut-off date), grade 2 hypertension, and grade 2 fatigue (all observed in 1 participant each).

Increased cholesterol is considered a laboratory abnormality of interest for JNJ-6379, based on safety review from nonclinical and clinical trials. Cholesterol increased was reported as an AE in 4 (4.1%) participants on JNJ-6379 for the pooled Phase 1 studies, in 1 (2.4%) participant on JNJ-6379 for the Phase 1 study 56136379HPB1005, and in none of the participants in the Phase 2a Jade study.

2.2.2. Combination of JNJ-3989 and JNJ-6379 with Entecavir or Tenofovir Prodrugs (Tenofovir Disoproxil Fumarate or Tenofovir Alafenamide)

Entecavir is an HBV NA reverse transcriptase inhibitor indicated for the treatment of chronic HBV infection in adults and children at least 2 years of age with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or aspartate aminotransferase [AST]) or histologically active disease. The most common adverse reactions (≥3% of participants) are headache, fatigue, dizziness, and nausea.

Tenofovir disoproxil fumarate is a first-generation oral prodrug of tenofovir that is indicated for the treatment of HBV infection in adult and pediatric patients at least 12 years of age. In addition, TDF in combination with other antiretrovirals is indicated for the treatment of HIV type

1 (HIV-1) infection in adult and pediatric patients at least 2 years of age. The most common adverse reactions (≥10% of participants) are abdominal pain, nausea, insomnia, pruritus, vomiting, dizziness, and pyrexia.

Tenofovir alafenamide (TAF) is an HBV NA reverse transcriptase inhibitor that is indicated for the treatment of chronic HBV infection in adults with compensated liver disease. It is an oral prodrug of tenofovir. The most common adverse reactions (≥5% of participants) are headache, abdominal pain, fatigue, cough, nausea, and back pain. Tenofovir alafenamide in combination with other antiretrovirals is also indicated for the treatment of HIV-1 infection in adult and pediatric patients.

For further information regarding ETV, TDF, and TAF, refer to the respective prescribing information.

There is no common target organ between JNJ-6379 or JNJ-3989 and ETV.[23]

The single common toxicity target organ between JNJ-6379, JNJ-3989, and TDF or TAF is the kidney.

In the chronic rat studies with JNJ-3989, slight alteration of the renal tubular epithelium was characterized by basophilic stippling and/or microvacuolation of the cytoplasm of renal tubules in the outer cortex in rats. These findings were not considered toxicologically meaningful since they were related to compound accumulation, there was no evidence of cellular damage (degeneration/necrosis) and there were no correlated clinical pathology indicators of changes in renal function.[10,16] These kidney findings have been observed in both the 2-week and 6-month studies and did not worsen over time. No kidney findings were observed in monkeys.

In the chronic rat study (6 months) with JNJ-6379, retrograde nephropathy, secondary to papillary or pelvic calculi/precipitates, was noted in male rats but not in dogs or female rats. This finding is mainly due to precipitation or calculi formation in distal parts of the kidney/lower urinary tract and is of limited relevance to man, due to differences in urinary composition and functional anatomy between (male) rats and humans. In general, compounds or metabolites of low solubility and high renal clearance may cause concretions in the kidneys/ urinary tract, especially at high doses, as the urine concentrates in the distal nephron and supersaturation of the compound can occur. Urinary pH, proteins and osmolality can also influence the formation of urinary concretions. Male rat urine normally has a high concentration of protein and high osmolality. In addition, rats may be predisposed to retrograde nephropathy because they are known to experience spontaneous urine reflux during micturition or urinary bladder contraction, and this reflux phenomenon can be increased or exacerbated by treatment induced obstructions. The retrograde nephropathy in male rats correlated with increased urea and creatinine in plasma and with urinary changes (red/brown discolored urine, increased volume, decreased pH, presence of blood and white and red blood cells in sediment).[4,34] No kidney findings were observed in dogs.

In clinic, dosing JNJ-6379 with NA for 12 weeks, did not show any clinically relevant changes in kidney parameters/glomerular function.

Although both compounds (JNJ-3989 and JNJ-6379) showed histological kidney findings in the rat, the primary anatomical location, mechanism and severity are different. For JNJ-3989 the renal findings are without anticipated clinical or clinicopathological consequences and located in the proximal part of the nephron (outer cortex) and intra-cellular (not in the tubular lumen). For JNJ-6379, the main findings are restricted to male rats and initiate in distal parts of the kidney (renal pelvis/ papilla) and/or in the lumen of the lower urinary tract with secondary more proximal changes due to reflux.

For TDF,[24] renal tubular epithelial karyomegaly was observed in rats, dogs, and monkeys. In dogs, the species most sensitive to TDF-related effects on the kidney, additional microscopic alterations following chronic administration of TDF (10 mg/kg/day for 42 weeks) included individual tubular cell necrosis, tubular dilatation, tubular degeneration/regeneration, pigment accumulation, and interstitial nephritis. This was associated with biochemical changes such as slight elevation in serum creatinine, glucosuria, proteinuria, and increased urine volume. The incidence and severity of nephrotoxicity was dose-related. Effects were reversible following cessation of treatment. In Rhesus monkeys, biochemical and/or histopathologic evidence of nephrotoxicity was observed at high doses. In rats, slight elevations in serum creatinine were observed without any histopathology correlation.

For TAF, minimal renal cortical tubular karyomegaly and/or basophilia was seen in rats and dogs. In addition, minimal renal cortical tubular degeneration/regeneration were reported in dogs. No renal findings were reported in monkeys.[8]

2.2.2.1. Overall Nonclinical Assessment of the Combination Therapy

Based on the points listed below, no clinically relevant drug-drug interactions (DDIs) and no specific concerns about additive or synergistic toxicities are expected in the kidneys when JNJ-6379 or JNJ-3989 are combined with ETV, or TDF, or TAF:

- available toxicology data described above (Sections 2.2.1 and 2.2.2)
- in vitro drug transporters
- metabolic interaction data
- absence of relevant DDIs in the combination toxicity studies with JNJ-6379 and JNJ-3989
- absence of synergistic or additive histology findings in the kidney observed in the 1-week combination PK study with JNJ-6379 and JNJ-3989
- available clinical data with JNJ-6379 (Jade study [56136379HPB2001]) up to 24 weeks treatment on the absence of systematic changes in kidney parameters/glomerular function.

In addition, pancytopenia in 1 rat and a mild platelet decrease were observed in the combination groups in the 3-month combination toxicity study (preliminary data, Section 2.2.1). No significant abnormalities of hematologic parameters have been observed in clinical studies to date. The sponsor is implementing additional monitoring of significant on-treatment hematologic

changes in clinical studies with dosing longer than 4 weeks (see Section 8.3.6.5). For further information, refer to the IB Addenda.[40,41]

2.3. Benefit-risk Assessment

More detailed information about the known and expected benefits and risks of JNJ-3989 and JNJ-6379 may be found in the respective IBs.[13,14]

For the benefit-risk evaluation of ETV, TDF, and TAF, refer to the respective prescribing information.

2.3.1. Benefits for Study Participation

2.3.1.1. Known Benefits

The clinical benefit of JNJ-3989 and JNJ-6379 remains to be established.

2.3.1.2. Potential Benefits

Results from clinical studies with JNJ-3989, JNJ-6379, and NAs may be useful for the development of a novel therapeutic approach for chronic HBV infection.

The combination of JNJ-6379 and JNJ-3989 on a background of NAs would target different stages of the viral life cycle. While NA treatment reduces HBV DNA to levels close to or below the LLOQ of the HBV DNA assay, HBV replication is not completely inhibited, resulting in replenishment of the cccDNA pool. The addition of JNJ-6379, which targets the HBV capsid assembly ("primary" mode of action [MoA]) and the de novo cccDNA formation ("secondary" MoA), is expected to more profoundly block HBV replication by inhibiting formation of HBV RNA and DNA containing particles, and to inhibit de novo cccDNA formation, ultimately leading to reduction in cccDNA levels/transcriptional activity and HBsAg seroclearance ("intensified viral suppression"). The addition of JNJ-3989 to an NA, or to JNJ-6379 in combination with an NA, is expected to intensify viral suppression (further) by downregulating levels of the HBV DNA precursor pgRNA. In addition, JNJ-3989 reduces levels of all viral proteins including HBsAg, which is known to interfere with the host immune response.[9,20,36] By acting on both viral replication and by reducing barriers to the host immune-response, higher functional cure rates may be achieved.

2.3.2. Risks for Study Participation

2.3.2.1. Known Risks

No known risks associated with JNJ-3989 or JNJ-6379 have been identified from clinical observations so far in the Phase 1 and 2 studies. Injection site reactions were identified as adverse drug reactions for JNJ-3989.

2.3.2.2. Potential Risks

All therapies have the potential to cause adverse experiences. In addition, the discontinuation of NA treatment bares a risk of hepatitis B flares.

Patients with positive HBV DNA and positive HBsAg can always experience increases in liver transaminases which may indicate immune activation and may result in the reduction of viral parameters such as HBV DNA and/or HBsAg. Whether this occurs at higher frequency during or after treatment with JNJ-6379 is not known.

2.3.2.2.1. Potential Risks for JNJ-3989

Reproductive Risks and Pregnancy

In the EFD studies, JNJ-3989 was not teratogenic in rats and rabbits. The fertility in male and female rats is not impacted with JNJ-3989 up to a dose of 180 mg/kg/week.

Based on the difference in metabolic pathways and in vitro data indicating absence of impact of JNJ-3989 on CYP enzymes and transporters, no clinically relevant interactions are anticipated between JNJ-3989 and oral contraceptives.

Potential Genotoxicity

JNJ-3989 is considered to be devoid of genotoxic activity. Nonclinical carcinogenicity studies have not been conducted.

Other Potential Toxicity/Events of Special Interest

JNJ-3989 is considered non-cytotoxic, did not activate human platelet aggregation, did not activate the innate immune system to a significant degree in vitro, and did not activate complement in vitro.

Viral Resistance

Treatment with JNJ-3989 may lead to viral resistance, but without impact to treatment with other small interfering RNAs (siRNAs). Using these agents in combination, especially in combination with ETV or TDF is expected to minimize the risk of emerging resistant viral variants.

2.3.2.2.2. Potential Risks for JNJ-6379

Reproductive Risks and Pregnancy

In the fertility study in females, early embryonic development was affected: an increase in pre- and post-implantation loss, reduction in implantation and live fetuses at 300 mg eq./kg/day. The fetal loss seen during the early stages of pregnancy was considered the result of low hormone levels (decreased luteinizing hormone, progesterone, estradiol) induced by treatment with JNJ-6379.

In the EFD studies, JNJ-6379 was not teratogenic in rats and rabbits.

In the EFD study in rats, fetal weights at 300 mg eq./kg/day were lowered, and there was retarded ossification from 100 mg eq./kg/day onwards. The NOAEL for EFD was considered to be CCI mg eq./kg/day. At this dose, the $AUC_{0\ 24h}$ was 84,000 ng.h/mL and the C_{max} was 5,190 ng/mL.

In the EFD study in rabbits, the NOAEL for EFD was considered to be the highest dose tested, ie, CCI mg eq./kg/day. At this dose, the $AUC_{0\ 24h}$ was 99,200 ng.h/mL and the C_{max} was 6,880 ng/mL.

Potential Genotoxicity

JNJ-56136379 was not genotoxic in the in vitro and in vivo tests.

JNJ-56136379 did not affect male or female fertility. Carcinogenicity studies are not yet conducted.

Other Potential Toxicity/Events of Special Interest

Based on nonclinical findings in rats and dogs and based on clinical findings, increased cholesterol was identified as a laboratory abnormality of interest.

Viral Resistance

Treatment with JNJ-6379 may lead to emergence of viral variants with reduced susceptibility or resistance to JNJ-6379. Based on nonclinical data, these variants remain susceptible to TDF and ETV but might affect treatment options with CAMs in the future.

Drug-drug Interactions

Based on results from DDI study 56136379HPB1004 investigating the potential effect of coadministration of JNJ-6379 with oral contraceptives, it is not anticipated that the efficacy of oral contraceptives will be impacted during coadministration with JNJ-6379 since the exposure of a progestin sensitive to CYP3A4 induction was not significantly affected by coadministration of JNJ-6379. In contrast, it is anticipated that coadministration with ethinylestradiol-containing contraceptives will result in an increased exposure to ethinylestradiol. Therefore, specific requirements on the use of ethinylestradiol-containing contraceptives are included in Section 6.5, Concomitant Therapy.

Please refer to Section 2.2, Background, for details on the safety results in the studies conducted to date.

2.3.3. Benefit-risk Assessment for Study Participation

Based on the available data and proposed safety measures, the overall risk/benefit assessment for JNJ-3989 and JNJ-6379 clinical studies is deemed acceptable for the following reasons:

- At the time of protocol writing, JNJ-3989 was generally safe and well tolerated during the ongoing Phase 1 Study AROHBV1001 (see Section 2.2.1, JNJ-3989 and JNJ-6379, Subsection "Clinical Studies"). All but one AE were mild or moderate in severity. All ISRs, identified as adverse drug reactions for JNJ-3989, were mild in intensity.
- No clinically significant safety concerns have previously been raised for JNJ-6379 based on the safety information from studies in healthy adult participants and participants with chronic HBV infection. Most observed AEs were mild in severity and considered not related

to JNJ-6379 by the investigator (see Section 2.2.1, JNJ-3989 and JNJ-6379, Subsection "Clinical Studies").

- Events of Special Interest are significant AEs that are judged to be of special interest because of clinical importance, known class effects or based on nonclinical signals. Events of Special Interest that will be carefully monitored during the study include ALT/AST elevations, ISRs, renal complications, hematologic abnormalities, and events related to cholesterol increase (Section 8.3.6, Specific Toxicities and Section 8.2.4, Clinical Safety Laboratory Assessments). In addition, the following toxicities will also be carefully monitored: rash and acute systemic allergic reactions (Section 8.3.6, Specific Toxicities).
- Continued careful assessment of the safety, efficacy, and PK during treatment is included in this study.
- To minimize potential risk and stress to participants:

  Utilization of selection criteria which exclude participants who may potentially be at higher risk of an AE (see Section 5, Study Population).

  Utilization of withdrawal criteria (see Section 7, Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal). If a participant drops out due to withdrawal of consent, he/she retains the option to participate in the safety follow-up procedures.

  At regular time points throughout the study (see Schedule of Activities), blood samples for biochemistry, blood coagulation, and hematology and urine samples for urinalysis, urine chemistry, and renal biomarkers will be collected. Vital signs (systolic and diastolic blood pressure [SBP and DBP], pulse rate, and temperature), height (at screening only), weight, and electrocardiograms (ECGs) will be recorded throughout the study. Physical examinations will be performed and AEs will be assessed (see Section 8.2, Safety Assessments). Events of Special Interest will be closely monitored (Section 8.3.6, Specific Toxicities).

  An Independent Data Monitoring Committee (IDMC) and an Independent Flare Expert Panel (IFLEP) will be established for continuous monitoring of SAEs, AEs leading to discontinuation, and ALT flares to ensure the continuing safety of the participants enrolled in the current study (see Section 9.5, Interim Analyses).

  Participants who meet the individual participant NA treatment completion criteria (Section 6.6) will be monitored for 48 weeks after completing NA treatment with frequent follow-up visits and pre-defined re-treatment criteria (Section 6.7).

  The post-treatment monitoring and NA re-treatment criteria were further updated based on findings from a case of post-treatment HBV reactivation with subacute hepatic failure and assessment of additional REEF-2 study data (Section 6.7).

  JNJ-3989 will be administered using a proper subcutaneous technique to decrease the risk of ISRs. ISRs will be managed as outlined in Section 8.3.6, Specific Toxicities.

  Any clinically significant abnormalities persisting at the end of the study/early discontinuation will be followed-up by the investigator until resolution (return to baseline) or until stabilization (to be agreed upon with the sponsor).

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To establish the dose-response relationship for antiviral activity of 3 doses of JNJ-3989+NA and to evaluate the efficacy of combination regimens of JNJ-3989+NA (with and without JNJ-6379) and of JNJ-6379+NA.	• Proportion of participants meeting the NA treatment completion criteria at Week 48 (see Section 6.6).
Secondary	
• To evaluate the safety and tolerability of the study intervention throughout the study.	• Proportion of participants with (S)AEs and abnormalities in clinical laboratory tests (including hematology, blood biochemistry, blood coagulation, urinalysis, urine chemistry, and renal biomarkers), 12-lead ECGs, and vital signs.
• To evaluate the efficacy of the study intervention during the follow-up phase.*	• Proportion of participants with HBsAg seroclearance 24 weeks after completion of all study intervention at Week 48. • Proportion of participants with HBsAg seroclearance 48 weeks after completion of all study intervention at Week 48. • Proportion of participants with HBV DNA <LLOQ 24 and 48 weeks, respectively, after completion of all study intervention at Week 48. • Proportion of participants meeting the NA treatment completion criteria during follow-up. • Proportion of participants with HBsAg seroclearance 24 and 48 weeks, respectively, after completion of NA treatment at any time during follow-up. • Frequency of flares. • Proportion of participants requiring NA re-treatment during follow-up (see Section 6.7).
• To evaluate efficacy as measured by blood markers (such as HBsAg, HBeAg,** HBV DNA, and ALT) during study intervention and follow-up.	• Proportion of participants with (sustained) reduction, suppression, and/or seroclearance considering single and multiple markers (such as HBsAg, HBeAg,** HBV DNA and ALT). • Proportion of participants with HBsAg and HBeAg** seroconversion. • Change from baseline over time in HBsAg, HBeAg,** and HBV DNA. • Time to achieve HBsAg and HBeAg**

Objectives	Endpoints
	seroclearance. • Proportion of participants with HBsAg levels and/or changes from baseline below/above different cut-offs (eg, HBsAg <100 IU/mL or >1 log_{10} IU/mL reduction in HBsAg from baseline). • Proportion of HBeAg-positive participants with HBeAg** levels and/or changes from baseline below/above different cut-offs. • Proportion of participants with HBV DNA levels and/or changes from baseline below/above different cut-offs (eg, <LLOQ of the assay). • Proportion of participants with ALT decrease and normalization.
• To evaluate the frequency of virologic breakthrough.	• Proportion of participants with virologic breakthrough.
• To evaluate the efficacy of NA re-treatment in participants who meet the criteria for NA re-treatment.	• Proportion of participants who reach HBV DNA undetectability after re-start of NA treatment during follow-up.
• To evaluate the PK of JNJ-3989 (JNJ-3976 and JNJ-3924), JNJ-6379, and NA, as applicable.	• PK parameters of JNJ-3989 (JNJ-3976 and JNJ-3924), JNJ-6379, and NA, as applicable.
Exploratory	
• To explore changes in the severity of liver disease at the end of follow-up versus screening/baseline.	• Changes in fibrosis (according to Fibroscan liver stiffness measurements).
• To explore the relationship between PK parameters (JNJ-3989 and/or JNJ-6379 and/or NA) and selected pharmacodynamic (PD) parameters of efficacy and/or safety, as applicable.	• Relationship between various PK parameters (JNJ-3989 and/or JNJ-6379 and/or NA) and selected efficacy and/or safety endpoints, as applicable.
• To explore efficacy as measured by HBV RNA and HBcrAg during study intervention and follow-up.	• Changes from baseline in HBV RNA and HBcrAg levels. • Time to reach undetectability of HBV RNA and HBcrAg.
• To explore the impact of the baseline HBeAg and treatment status factors on efficacy as measured by primary and secondary endpoints.	• Proportion of participants meeting the NA treatment completion criteria at Week 48. • Proportion of participants with HBsAg seroclearance 24 weeks after completion of all study intervention at Week 48. • Proportion of participants with HBsAg seroclearance 48 weeks after completion of all

Objectives	Endpoints
	study intervention at Week 48. • Proportion of participants with HBV DNA <LLOQ 24 and 48 weeks, respectively, after completion of all study intervention at Week 48. • Proportion of participants meeting the NA treatment completion criteria during follow-up. • Proportion of participants with HBsAg seroclearance 24 and 48 weeks, respectively, after completion of NA treatment at any time during follow-up. • Frequency of flares. • Proportion of participants requiring NA re-treatment during follow-up.
• To explore the association between viral and host baseline factors with efficacy and safety.	• Correlation of viral and host baseline characteristics (such as HBV genotype, baseline HBV DNA levels, age, gender, body mass index [BMI]) with selected efficacy and safety variables.
• To explore changes in the HBV genome sequence during study intervention and follow-up.	• Emergence of intervention-associated mutations.
• To explore the effect of any baseline variation in the HBV genome on efficacy.	• Correlation of HBV genome sequence with selected efficacy parameters.
• To explore HBV-specific T-cell responses during study intervention and follow-up.***	• Changes from baseline in HBV-specific peripheral blood T-cell responses.
• To explore the impact of study intervention on participants' health-related quality of life (HRQoL), self-stigma, and impression of change using patient-reported outcomes (PROs) during study intervention and follow-up.	• Changes over time in score on the Hepatitis B Quality of Life (HBQOL) scale and subscales. • Changes over time in score on the HBV-specific self-stigma PRO scale. • Participants' impression of change on the Patient Global Impression of Change (PGIC) scale.

* The follow-up phase has a maximum duration of 96 weeks.
** in HBeAg-positive participants only
*** Peripheral blood mononuclear cell (PBMC) samples for immune analyses will be collected at selected sites only.

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

For a definition of terms, refer to Section 10.1, Appendix 1, Abbreviations and Definitions of Terms.

HYPOTHESIS

Based on the primary efficacy endpoint, the proportion of participants meeting the NA treatment completion criteria at Week 48, the primary hypotheses are as follows:

- There is a positive dose-response signal across the 3 doses of JNJ-3989 (40, 100, and 200 mg) on the background of NA compared with NA treatment alone (control Arm 6).
- One or both combination regimens JNJ-3989+JNJ-6379+NA and JNJ-6379+NA are more efficacious than NA treatment alone (control Arm 6).
- The combination regimen of JNJ-3989 (100 mg)+JNJ-6379+NA is more efficacious than JNJ-3989 (100 mg)+NA and/or JNJ-6379+NA combination regimens.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2b, randomized, double-blind, double-dummy, active-controlled, dose-finding, parallel, multicenter, interventional study in HBeAg-positive and -negative chronic HBV-infected participants who (1) are currently not being treated for their HBV infection (including CHB treatment-naïve participants) or (2) who are virologically suppressed by current NA treatment (either ETV, TDF, TAF or approved tenofovir generics). The efficacy, safety, and PK of the study intervention will be evaluated.

A target of 450 adult male and female participants, 18 (or the legal age of consent in the jurisdiction in which the study is taking place) to 65 years of age (inclusive), will be randomized in a 2:2:2:2:1:1:1 ratio to one of the following intervention arms:

• Arm 1:	JNJ-3989 (100 mg) +	JNJ-6379 (250 mg qd) +	NA*	(N 90)
• Arm 2:	JNJ-3989 (200 mg) +	Placebo +	NA*	(N 90)
• Arm 3:	JNJ-3989 (100 mg) +	Placebo +	NA*	(N 90)
• Arm 4:	JNJ-3989 (40 mg) +	Placebo +	NA*	(N 90)
• Arm 5:	Placebo +	JNJ-6379 (250 mg qd) +	NA*	(N 45)
• Arm 6 (control):	Placebo +	Placebo +	NA*	(N 45)

* NA: ETV, TDF, or TAF

After a fixed duration of 48 weeks, participants will complete treatment with JNJ-3989 and/or JNJ-6379. If the NA treatment completion criteria (outlined in Section 6.6) are met based on clinical laboratory tests performed at Week 44, treatment with NA will also be completed at Week 48 (ie, the next scheduled visit after Week 44). Participants who meet the NA treatment completion criteria will be monitored closely during the follow-up phase. NA treatment may need to be re-started based on protocol-defined NA re-treatment criteria (see Section 6.7).

Randomization will be stratified by HBeAg status at screening (positive versus negative) and by treatment history (not currently treated versus virologically suppressed).

The aim is to include 40% not currently treated participants of whom it is expected that 40% are HBeAg-positive. As such, enrollment of subgroups may be closed prior to completion of study enrollment. All efforts will be undertaken to include a sufficient number of HBeAg-positive virologically suppressed participants.

The study will be conducted in the following phases:

- **Screening phase:** 4 weeks. If necessary, eg, for operational reasons, the screening phase may be extended up to a maximum of 6 weeks on a case-by-case basis and in agreement with the sponsor.
- **Double-blind study intervention phase:** from Day 1 (ie, baseline) up to Week 48.
- **Follow-up phase:** for 48 weeks after the end of investigational intervention. For participants who complete NA treatment during follow-up, the follow-up phase will be extended to 48 weeks after the end of NA treatment. The follow-up phase has a maximum duration of 96 weeks.

The duration of individual study participation will be between 100 and 150 weeks.

At Week 48 or at time of early discontinuation, it will be communicated to the investigators whether the participants were allocated to either an investigational arm (Arms 1 to 5) or the control arm (Arm 6) to allow the correct follow-up visit schedule to be followed (see Schedule of Activities). Only at Week 72, randomization codes (for Arms 1 to 5) will be fully disclosed to the investigators. The sponsor will be fully unblinded for the primary analysis at Week 48 (see Section 9).

Participants will be considered to have completed the study if they have completed the assessments of the end of study (EOS) visit ([Extended] Follow-up Week 48). After completing this study, participants may be invited to enroll into a long-term follow-up study.

Efficacy will be evaluated using different parameters including HBsAg and HBeAg (see Section 8.1).

Safety and tolerability, including (S)AEs, laboratory assessments, ECGs, vital signs, and physical examination, will be assessed throughout the study from the time of signing the informed consent form (ICF) until completion of the last study-related activity (see Section 8.2).

Three PRO instruments, including the HBQOL scale,[32] an HBV-specific self-stigma PRO scale, and the PGIC scale[11,18] will be used to exploratively assess the impact of study intervention on participants' HRQoL, self-stigma level, and impression of change (see Section 8.1.2).

Samples for HBV genome sequencing will be taken at the time points indicated in the Schedule of Activities (see Section 8.1.1).

A population PK analysis will be performed based on the available data for JNJ-3989, JNJ-6379 and, optionally, NA, potentially in combination with data from a selection of Phase 1 and 2

studies. PK parameters in participants undergoing intensive PK sampling will be calculated via noncompartmental methods (see Section 8.5).

Pharmacokinetic/pharmacodynamic relations will be explored (see Section 8.6).

Peripheral blood mononuclear cell (PBMC) samples for immune analyses will be collected at selected sites at the time points indicated in the Schedule of Activities (see Section 8.7)

A pharmacogenomic blood sample will be collected from participants who consent separately to this component of the study (see Section 8.8).

The study includes collection of blood samples for exploratory analysis of viral markers (see Section 8.1) and host blood biomarkers at the host RNA, protein, and cell level (see Section 8.9).

If a participant prematurely discontinues investigational intervention (before Week 48), the participant will enter the follow-up phase and complete the follow-up schedule as per the Schedule of Activities, unless the participant withdraws consent. In this case, NA treatment may be continued or, in consultation with the sponsor, discontinued based on investigator judgement or completed based on the NA treatment completion criteria (see Section 6.6).

If a participant withdraws consent before completing the study, the reason for withdrawal is to be documented in the case report form (CRF) and in the source documents. Participants who withdraw consent will be offered an optional safety follow-up visit.

An IDMC will be commissioned for this study. In addition, an IFLEP will be appointed (see Section 9.5).

A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

Study Population

Patients with CHB will be eligible if they have an indication for antiviral treatment according to current treatment guidelines.

Patients with liver cirrhosis are excluded, as the goal of the study is to assess the potential of a finite treatment to achieve functional cure, and discontinuation of treatment in patients with cirrhosis is not current practice due to concerns about poor tolerability of liver flares associated with increased viral replication. The safety of the combination regimens evaluated in this study will first be established in patients without liver cirrhosis prior to initiating studies in patients with more advanced liver disease.

Randomization and Stratification Factors

Randomization will be used to minimize bias in the assignment of participants to intervention arms, to increase the likelihood that known and unknown participant attributes (eg, demographic

and baseline characteristics) are evenly balanced across intervention arms, and to enhance the validity of statistical comparisons across intervention arms.

Randomization will be stratified by HBeAg status at screening (positive versus negative) and by treatment history (not currently treated versus virologically suppressed). Two stratification factors are considered maximally feasible. The two stratification factors selected, together with a minimum HBsAg level of 100 IU/mL required for inclusion, will provide a reasonably balanced representation of the 2 baseline factors across all intervention arms and will reduce the variability of HBsAg across the treatment arms.

Double-blind, Placebo-controlled Safety Comparison

The safety profile of NAs as background regimen is well established. The safety of the different investigational combinations will be characterized by comparing their tolerability to that of standard of care in a double-blind manner.

Efficacy Comparison Versus Control Arm

The analysis of the primary efficacy endpoint and other secondary endpoints will be based on comparisons of investigational combination arms with the control arm (see Section 9). Hence, it is considered important that participants in control Arm 6 remain in the study for the full duration of 96 weeks in order to support within-study efficacy measurements (including the primary endpoint and kinetics of viral parameters).

Criteria for Completion of NA Treatment

NA treatment completion criteria (described in Section 6.6) are included to explore the possibility of finite treatment. The treatment completion criteria which take ALT, HBV DNA, HBeAg and HBsAg levels into consideration, have been selected to ensure that only subjects with a chance of sustained off-treatment response are allowed to complete all study intervention. Across a range of studies, HBsAg levels below 100 IU/mL are consistently associated with favorable off-treatment response.[19,26] The stringent HBsAg cutoff of 10 IU/mL for NA treatment completion was chosen to account for the direct effect of JNJ-3989 on HBsAg levels.

Follow-up Procedures and Criteria for Re-initiation of NA Treatment

To ensure safety of patients during the follow-up phase, an ALT flare management plan is in place, including a high visit frequency for patients after completion of NA treatment (at Week 48 or later), and weekly visits for patients with ALT/AST ≥3x upper limit of normal (ULN) and ≥3x nadir until stabilization.

Increases in ALT and HBV DNA are frequently seen in patients after discontinuation of NA treatment. These ALT elevations can be reflecting an activation of the host cellular immune response and can as such lead to functional cure. Cases of fulminant HBV reactivation with fatal outcome were described after cessation of NA treatment, but the vast majority of such cases were described in patients with decompensated liver disease at the time of NA discontinuation. These patients are not eligible to participate in the study. Still, a vigilant follow-up of patients during this phase of the study is critical to ensure patient safety. Increases in ALT that are accompanied

by signs of decreased liver function, or an HBV DNA value of >100,000 IU/mL (irrespective of confirmation and/or ALT increase), will trigger immediate re-initiation of NA treatment based on protocol-defined NA re-treatment criteria (see Section 6.7).

Re-initiation of NA treatment is also required in case of confirmed HBeAg seroreversion (HBeAg positive after it was negative at NA completion), in case of confirmed* ALT increase (>5x ULN) in combination with increased HBV DNA replication (>2,000 IU/mL), and in case of confirmed* increased HBV DNA replication at higher levels (>20,000 IU/mL).
** At least 4 weeks apart*

A post-treatment HBV DNA value of >20,000 IU/mL should trigger re-testing of ALT/AST, HBV DNA, and total and direct bilirubin within a maximum of 7 days from receipt of the data and further repeats as necessary (ie, weekly until HBV DNA returns to <20,000 IU/mL). A post-treatment HBV DNA value of >2,000 IU/mL (but <20,000 IU/mL) should trigger a re-test within 14 days from receipt of the data and further repeats as necessary (ie, every other week until HBV DNA returns to <2,000 IU/mL). A post-treatment ALT value of >5x ULN should trigger re-testing of ALT, AST, ALP, total and direct bilirubin, INR, albumin, and HBV DNA on a weekly basis until ALT and AST levels have returned to <5x ULN. Additional re-testing and/or earlier restarting of NA treatment is at the investigator's discretion, even if the above cut-offs are not yet met.

To avoid delays in decision making, sites are encouraged to run local re-testing in parallel with central re-testing in the situations described above that require more frequent re-testing. Local test results are to be recorded in the CRF and/or source documents, including information on the HBV DNA assay used. In addition, to avoid delays in NA re-treatment, it should be considered to dispense NA to participants who potentially met the NA re-treatment criteria (eg, pending confirmation) and who will not be available to come to the study site immediately at the time the confirmatory test results will become available. This should ensure that the participant can immediately restart NA treatment if indicated, upon direct confirmation by the investigator.

The decision to re-start NA treatment should take into consideration the dynamics of HBV DNA and/or ALT values and should be discussed with the sponsor.

NA re-treatment criteria during follow-up are presented graphically in Section 10.14, Appendix 14.

Host DNA and Biomarker Collection

It is recognized that genetic variation can be an important contributory factor to interindividual differences in intervention distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to an intervention. The goal of the pharmacogenomic component is to collect DNA to allow the identification of genetic factors that may influence the efficacy, safety or PK of the study intervention, to identify genetic factors associated with HBV infection, or to develop assays for the study intervention or HBV infection.

Biomarker samples will be collected to evaluate the mechanism of action of JNJ-3989 and JNJ-6379 in combination with NA or help to explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to an intervention. The biomarker research can be used to address questions related to the safety, PK and efficacy of the study intervention and HBV infection or to develop assays for the study intervention or HBV infection.

Host DNA (pharmacogenomic) and biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

4.2.1. Study-specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

While all participants will receive the study intervention in combination with an approved therapy for HBV infection, some ethical consideration should be given to the fact that participants will not have access to potentially alternative or new effective therapies for the duration of the study (intervention and follow-up phase) since they may not begin any other approved or investigational therapies for treatment of HBV infection during this time. Participants with worsening HBV infection can discontinue the study intervention at any time, and the study intervention should be discontinued if a participant requires additional therapy for HBV infection.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the American Red Cross standard blood donation.[1]

4.3. Justification for Dose

The proposed dose and treatment duration are selected to maximize the chance for patients to achieve functional cure and are supported by scientific understanding of available data.

4.3.1. JNJ-3989

Clinical data of JNJ-3989 are available from the ongoing Phase 1/2a AROHBV1001 study with a safety snapshot date of 26 March 2019. Twenty adult healthy participants have received single subcutaneous injections of JNJ-3989 (35, 100, 200, 300, and 400 mg) and 72 adult CHB participants have received multiple doses of JNJ-3989 (25, 50, 100, 200, 300, and 400 mg), administered as 3 subcutaneous injections separated by either 7-day, 14-day, or 28-day intervals. All participants were started on ETV or TDF on Day 1. JNJ-3989 was generally safe and well tolerated at all doses.

Efficacy was assessed using snapshot data through 02 May 2019. Antiviral activity data were available for 56 CHB participants who received 3 subcutaneous injections of 25 to 400 mg JNJ-3989 every 4 weeks. The antiviral activity data showed that administration of JNJ-3989 at doses of 25 to 400 mg resulted, on average, in pronounced HBsAg decline which was generally sustained at least until Day 168 (ie, 16 weeks after last dose) across all doses. No apparent dose response was observed at doses between 100 and 400 mg JNJ-3989, suggesting that maximal HBsAg reduction in this short-term study is reached with those doses. A reduced mean decline was observed at the lower dose of 25 mg. Data on the 50 mg dose were still emerging at the time of protocol writing.

Thus, for the current study, 3 doses of JNJ-3989 (ie, 40, 100, and 200 mg, administered every 4 weeks) were selected to study the effect of the different doses and a potential dose response with longer treatment duration.

A dose of 100 mg JNJ-3989 is chosen for the combination treatment regimen of JNJ-3989+JNJ-6379+NA as this is the most likely JNJ-3989 dose to be selected. Based on the currently available HBsAg data, no discrimination between the 100 and 200 mg dose might be a plausible scenario translated to the functional cure rate endpoint (ie, a maximum effect (E_{max}) dose-response shape might be likely observed).

4.3.2. JNJ-6379

A dose of 250 mg JNJ-6379 qd is chosen for this study.

A dose of 250 mg of JNJ-6379 is being considered to ensure maximal viral inhibition via "primary" MoA (ie, interfering with the capsid assembly process). In addition, it ensures sufficient high exposures to engage the "secondary" MoA (ie, inhibition of de novo cccDNA formation). This dose selection is supported by translational PK/PD analyses and viral kinetic modeling. Analyses of the HBV DNA data from the 4-week 56136379HPB1001 study showed a profound but slightly less substantial reduction of plasma HBV DNA, as a measure of the "primary" MoA, in the 25 mg dose group compared to the 75 mg and higher dose groups, suggesting that for JNJ-6379 E_{max} in terms of HBV DNA inhibition via primary MoA is approached starting from a dose of 75 mg onwards. Since it is not possible to derive the engagement of the "secondary" MoA from the available short-term data, the in vitro primary human hepatocyte 90% effective concentration values in the presence of serum proteins obtained for both MoAs were used to translate from the "primary" to the "secondary" MoA.

Participants will be treated with JNJ-6379 for 48 weeks. Based on the MoA of JNJ-6379, it is expected that continued complete suppression of virus production and de novo cccDNA formation over many months is required to achieve reduction of the transcriptional active cccDNA pool, which is considered a prerequisite for HBsAg reduction and/or seroclearance.

Interim analysis data are available from the ongoing Phase 2a Jade study in which the 250-mg dose is being tested for 48 weeks. Blinded Week 12 data from 40 virologically suppressed CHB participants who received 250 mg qd JNJ-6379 or placebo in addition to an NA showed that

there were no deaths, Grade 4 AEs, or AEs leading to discontinuation. Most AEs were mild or moderate in severity.

4.4. End of Study Definition

End of Study Definition

The EOS is considered as the last visit ([Extended] Follow-up Week 48 or early discontinuation) for the last participant in the study.

Study Completion Definition

A participant will be considered to have completed the study if he or she has completed assessments at Week 48 of the (extended) follow-up phase.

5. STUDY POPULATION

Screening for eligible participants will be performed within 4 weeks before administration of the study intervention. If necessary, eg, for operational reasons, the screening phase may be extended up to a maximum of 6 weeks on a case-by-case basis and in agreement with the sponsor.

Retesting to assess eligibility will be allowed once, using an unscheduled visit during the screening phase.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. Adult male or female participants 18 (or the legal age of consent in the jurisdiction in which the study is taking place) to 65 years of age, inclusive.

2. Participants must be medically stable, with the exception of HBV disease, on the basis of physical examination, medical history, vital signs, and 12-lead ECG performed at screening. If there are abnormalities, they must be consistent with the underlying illness in the study population. This determination must be recorded in the participant's source documents and initialed by the investigator.

3. Participants must have chronic HBV infection documented by serum HBsAg positivity at screening. In addition, chronicity must be documented by serum HBsAg positivity at least 6 months prior to screening or alternative markers of chronicity (HBeAg positivity or HBV DNA positivity at least 6 months prior to screening, ALT elevation above ULN at least 6 months prior to screening without another cause than HBV infection, liver

biopsy, or documented transmission event at least 6 months prior to screening).

Note: if documentation of chronicity (as mentioned above) at least 6 months prior to screening is not available, participants may be included if HBsAg positive and negative for immunoglobulin M (IgM) antibodies to HBc antigen at screening.

4. Participants who are **not currently treated** (defined as not having been on HBV treatment, including NAs and IFN products within 6 months prior to screening), including **treatment-naïve** participants (defined as never having received HBV treatment, including NAs and IFN products) should have:

    a. Serum HBV DNA at screening ≥2,000 IU /mL for HBeAg-negative participants and ≥20,000 IU/mL for HBeAg-positive participants, AND

    b. ALT levels at screening <10x ULN AND >ULN on two measurements at least 3 months apart (one of which is at screening).

5. Virologically suppressed participants should:

    a. be on stable HBV treatment, defined as currently receiving NA treatment (ETV, TDF, or TAF) for at least 6 months prior to screening and having been on the same NA treatment regimen (at the same dose) as used in this study (see Section 6.1) for at least 3 months at the time of screening, AND

    b. have serum HBV DNA <60 IU/mL on two measurements at least 6 months apart (one of which is at screening), AND

    c. have ALT values ≤2x ULN on two measurements at least 6 months apart (one of which is at screening).

6. Participants must have HBsAg >100 IU/mL at screening.

7. Participants must have a BMI (weight in kg divided by the square of height in meters) between 18.0 and 35.0 kg/m^2, extremes included.

8. Participants must have:

    a. Fibroscan liver stiffness measurement ≤9.0 kPa within 6 months prior to screening or at the time of screening, OR

    b. If a fibroscan result is not available: a liver biopsy result classified as Metavir F0-F2 within 1 year prior to screening or at the time of screening.

Note: Other radiologic liver staging modalities (eg, acoustic radiation force impulse) might be used if standard practice at the site or if otherwise validated and agreed with the sponsor. Results should be equivalent to Metavir F0-F2.

Note: Conventional imaging procedures (eg, conventional liver ultrasound, computed tomography [CT] or magnetic resonance imaging [MRI]) and serum marker panels are not allowed to rule out severe fibrosis or cirrhosis.

9. Participants must sign an ICF indicating that they understand the purpose of, and procedures required for, the study and is willing to participate in the study.

10. Participants must sign a separate ICF if they agree to provide an optional DNA sample for research (where local regulations permit). Refusal to give consent for the optional DNA research sample does not exclude a participant from participation in the study.

11. Female participants of childbearing potential must have a negative highly sensitive serum pregnancy test (β-human chorionic gonadotropin) at screening and a negative urine pregnancy test on Day 1 before the first dose of study intervention.

12. Criterion modified per Amendment 1

    12.1 Female participants must be (as defined in Section 10.8, Appendix 8, Contraceptive and Barrier Guidance)

    a. Not of childbearing potential

    b. Of childbearing potential and practicing a highly effective, preferably user-independent method of contraception at least 30 days prior to screening (failure rate of <1% per year when used consistently and correctly) and agree to remain on a highly effective method while receiving study intervention and until 90 days after last dose.

       Examples of highly effective methods of contraception are located in Section 10.8, Appendix 8, Contraceptive and Barrier Guidance.

       Note: Female participants 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 at least 30 days prior to screening) should continue the same dose regimen until 90 days after the last dose of study intervention. Ethinylestradiol-containing contraceptives are only allowed if the ethinylestradiol content is ≤20 µg. Female participants stable on an ethinylestradiol-containing regimen with a dose >20 µg who switch to an ethinylestradiol-containing regimen with a dose ≤20 µg, should be on that new regimen for at least 1 week before the first dose of study intervention. For female participants of childbearing potential who will start a hormonal contraceptive treatment during the study, ethinylestradiol-containing contraceptives are not allowed.

13. Female participants must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction while receiving study intervention and until 90 days after the EOS.

14. Male participants must agree to wear a condom when engaging in any activity that allows for passage of ejaculate to another person while receiving study intervention and until 90 days after the last dose.

15. Male participants must agree not to donate sperm for the purpose of reproduction while receiving study intervention and until 90 days after the EOS.

16. In the investigator's opinion, the participant must be able to understand and comply with protocol requirements, instructions, and lifestyle restrictions (Section 5.3) and be likely to complete the procedures as planned for this study.

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. Criterion modified per Amendments 1 and 2

   1.1 Participants with evidence of hepatitis A virus infection (hepatitis A antibody IgM), HCV infection (HCV antibody), HDV infection (HDV antibody) or hepatitis E virus infection (hepatitis E antibody IgM), or HIV-1 or HIV-2 infection (confirmed by antibodies) at screening.

   Note:
   - Participants with a positive HCV antibody test can be enrolled if they have negative HCV RNA at screening and documented negative HCV RNA at least 6 months prior to screening.
   - Participants with a positive HDV antibody test may be enrolled after discussion with the Sponsor if an active HDV co-infection can be ruled out by documentation of negative HDV RNA.
   - Participants with a positive IgM antibody test for HEV infection may be enrolled after discussion with the Sponsor if an active HEV infection can be ruled out by documentation of negative anti-HEV IgG.

2. Criterion modified per Amendment 1

   2.1. Participants with any of the following laboratory abnormalities within 12 months prior to screening or at the time of screening:

   a. Total bilirubin >1.5x ULN,
   b. Direct bilirubin >1.2x ULN,
   c. Prothrombin time >1.3x ULN,
   d. Serum albumin <3.2 g/dL.

3. History or evidence of clinical signs/symptoms of hepatic decompensation including but not limited to: portal hypertension, ascites, hepatic encephalopathy, esophageal varices.

4. Participants with evidence of liver disease of non-HBV etiology. This includes but is not limited to hepatitis virus infections mentioned in exclusion criterion 1, drug- or alcohol-related liver disease, autoimmune hepatitis, hemochromatosis, Wilson's disease, α-1 antitrypsin deficiency, primary biliary cholangitis, primary sclerosing cholangitis, Gilbert's syndrome (mild cases are allowed, see exclusion criterion 2a), or any other

non-HBV liver disease considered clinically significant by the investigator.

5. Criterion modified per Amendment 1

5.1 Participants with signs of HCC or clinically relevant renal abnormalities on an abdominal ultrasound performed within 6 months prior to screening or at the time of screening. In case of suspicious findings on conventional ultrasound the participant may still be eligible if HCC or clinically relevant renal abnormalities has been ruled out by a more specific imaging procedure (contrast enhanced ultrasound, CT or MRI).

6. Criterion modified per Amendment 1

6.1 Participants with one or more of the following laboratory abnormalities at screening as defined by the Division of Acquired Immunodeficiency Syndrome (DAIDS) Toxicity Grading Scale (see Section 10.9, Appendix 9, DAIDS Table):

a. Estimated glomerular filtration rate (eGFR) ≥grade 3 (ie, <60 ml/min/1.73 m^2) at screening, calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula,
b. Pancreatic amylase ≥grade 3,
c. Lipase elevation ≥grade 3,
d. Hemoglobin ≤10.9 g/dL (males), ≤10.4 g/dL (females),
e. Platelet count ≤lower limit of normal (LLN),
f. Alpha-fetoprotein (AFP) >100 ng/mL,
g. Any other laboratory abnormality considered to be clinically significant by the investigator.

Note: Participants with AFP >ULN (but ≤100 ng/mL) may be eligible if HCC can be ruled out based on a sensitive imaging study (eg, CT with contrast or MRI) during screening.

7. Participants with hemoglobin A1c >8% at screening.

8. Participants with a history of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy, which is considered cured with minimal risk of recurrence).

9. Participants with abnormal sinus rhythm (heart rate <45 or >100 beats per minute [bpm]); QT interval corrected for heart rate according to Fridericia (QTcF) >450 ms for male participants and >470 ms for female participants; QRS ≥120 ms; PR interval >220 ms; abnormal conduction; or any other clinically significant abnormalities on a 12-lead ECG at screening.

10. Participants with a history of or current cardiac arrhythmias (eg, tachycardia at rest), history of risk factors for Torsade de Pointes syndrome (eg, hypokalemia, family history

of long QT Syndrome) or history or other clinical evidence of significant or unstable cardiac disease (eg, angina, congestive heart failure, myocardial infarction, diastolic dysfunction, significant arrhythmia, coronary heart disease), moderate to severe valvular disease, or uncontrolled hypertension at screening.

11. Participants with any current or previous illness for which, in the opinion of the investigator and/or sponsor, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments. This may include but is not limited to significant vascular, pulmonary (eg, chronic obstructive pulmonary disease), gastrointestinal (eg, significant diarrhea, gastric stasis, or constipation that in the investigator's opinion could influence drug absorption or bioavailability), endocrine (eg, thyroid disease), neurologic, hematologic, rheumatologic, psychiatric, neoplastic, or metabolic disturbances. Any condition possibly affecting drug absorption (eg, gastrectomy or other significant gastrointestinal tract surgery, such as gastroenterostomy, small bowel resection, or active enterostomy) will also lead to exclusion.

12. Participants with any history of or current clinically significant skin disease requiring regular or periodic treatment.

13. Participants with history of clinically relevant drug rash.

14. Criterion modified per Amendment 1

    14.1 Participants with known allergies, hypersensitivity, or intolerance to JNJ-3989 and JNJ-6379 or their excipients or excipients of the placebo content (refer to the IB).[13,14,15,39]

15. Participants with contraindications to the use of ETV, TDF, or TAF per local prescribing information.

16. Participants who have taken any disallowed therapies as noted in Section 6.5, Concomitant Therapy before screening.

17. Participants having received an investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 6 months before the planned first dose of study intervention or is currently enrolled in an investigational clinical study with an investigational intervention.

18. Female participants who are pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 90 days after the last dose of study intervention.

19. Male participants who plan to father a child while enrolled in this study or within 90 days after the last dose of study intervention.

20. Participants who had major surgery, (eg, requiring general anesthesia), excluding diagnostic surgery, within 12 weeks before screening, or will not have fully recovered from surgery, or have surgery planned during the time the participant is expected to participate in the study.

    Note: Participants with planned surgical procedures to be conducted under local anesthesia may participate.

21. Participants who have received an organ transplant (except for skin, hair, or cornea transplants).

22. Participants who are employees of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, or a family member of an employee or the investigator.

23. Criterion modified per Amendment 1

    23.1 Vulnerable participants (eg, incarcerated individuals, individuals under a legal protection measure).

Note: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. The required source documentation to support meeting the enrollment criteria are noted in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. Agree to follow all requirements outlined in Section 6.5, Concomitant Therapy regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria (eg, contraceptive requirements).

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened without agreement with the sponsor.

6. STUDY INTERVENTION

6.1. Study Intervention(s) Administered

Description of Interventions

Intervention name	JNJ-3989	Placebo for JNJ-3989	JNJ-6379	Placebo for JNJ-6379	Entecavir (ETV) monohydrate	Tenofovir disoproxil fumarate (TDF)	Tenofovir alafenamide (TAF)***
Dosage formulation	Solution for injection	Solution for injection	Tablets	Tablets	Film-coated tablets	Film-coated tablets	Film-coated tablets
Unit dose strength(s)	200 mg/vial	0.9% saline	25 and 100 mg		0.5 mg	300 mg**	25 mg
Dosage regimen	100 mg once every 4 weeks (Arms 1 and 3) 200 mg once every 4 weeks (Arm 2) 40 mg once every 4 weeks (Arm 4)	0.5 mL once every 4 weeks (Arms 5 and 6)	250 mg qd (Arms 1 and 5)	qd (Arms 2, 3, 4, and 6)	Nucleoside-naïve patients: 0.5 mg qd Lamivudine-refractory patients: 1 mg* qd (but should preferably be treated with TDF or TAF instead)	300 mg qd	25 mg qd
Route of administration	Subcutaneous injection (in the abdomen)	Subcutaneous injection (in the abdomen)	Oral	Oral	Oral	Oral	Oral
Dosing instructions	Regardless of food intake	Regardless of food intake	Regardless of food intake	Regardless of food intake	On an empty stomach	With food	With food

qd: once daily
* 2 tablets of 0.5 mg
** 300 mg TDF is equivalent to tenofovir disoproxil 245 mg.
*** In countries where TAF is available, it will be one of the NA treatment options.

Physical Description of Study Interventions

The JNJ-3989 supplied for this study will be provided as an aqueous clear, colorless to light yellow solution with 200 mg/mL of JNJ-3989 for subcutaneous injection[redacted]).

The JNJ-6379 supplied for this study is formulated as oral tablets containing [redacted] mg ([redacted]) and [redacted] mg ([redacted]) JNJ-56136379-AAA. The JNJ-6379 tablets should be swallowed as a whole.

JNJ-3989 and JNJ-6379 will be provided under the responsibility of the sponsor. Refer to the IBs for a list of excipients.[13,14,15]

The placebo for JNJ-3989 will be a solution for subcutaneous [redacted]. The matching placebo for JNJ-6379 consists of the oral tablets without active drug substance ([redacted] [placebo for [redacted] mg] and [redacted] [placebo for [redacted] mg]).

The NAs ETV, TDF, and TAF are formulated as oral film-coated tablets of 0.5-mg, 300-mg, and 25-mg strength, respectively.

Packaging and Labeling

All study interventions will be packaged with each unit labeled with a unique medication ID number. Packaging and labeling of JNJ-3989, the corresponding placebo, and the NAs will be done in an open-label way.

Commercial supplies of NAs and sodium chloride will be sourced and a clinical study label will be applied.

Study intervention labels will contain information to meet the applicable regulatory requirements.

JNJ-6379 and matching placebo will be dispensed in child-resistant packaging. NA treatment may also be repackaged into child-resistant packaging if this is not already the case.

No study interventions can be repacked or relabeled without prior approval from the sponsor.

Study Intervention Administration

Study intervention administration must be captured in the source documents.

JNJ-3989/placebo injections will be administered at the study site.

In between study visits, participants will take their oral study intervention (JNJ-6379/placebo/NA treatment) at home and they will bring their oral study intervention with them to each study visit. At study visits, the oral study intervention should be taken on site to allow biochemistry and renal biomarker samples to be taken in fasted conditions.

NA treatment will be provided by the sponsor through this study until the last study visit. Investigators should follow guidance detailed in the respective prescribing information, including special warnings and precaution for use.

Virologically suppressed participants who are already being treated with ETV, TDF, or TAF at screening, will continue their current NA treatment. In case participants experienced toxicity to ETV, TDF, or TAF prior to screening, they should be treated with one of the other two NAs during this study.

Participants who are not receiving any HBV treatment at screening will receive TDF during the study.

If clinically indicated, switching from one NA treatment (ETV, TDF, or TAF) to another NA treatment (ETV, TDF, or TAF) during the study is allowed for all participants after consultation with the sponsor.

For a definition of study intervention overdose, refer to Section 8.4, Treatment of Overdose.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

All study intervention must be stored as specified on the product-specific labeling.

Study-site personnel will instruct participants on how to store JNJ-6379/placebo/NA treatment for at-home use as indicated for this protocol.

Refer to the pharmacy manual/study site investigational product and procedures manual for additional guidance on study intervention preparation, handling, and storage.

Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The dispensing of JNJ-6379/placebo and NA to the participant, and the return of JNJ-6379/placebo and NA from the participant, must be documented on the intervention accountability form. Participants must be instructed to return all original containers, whether empty or containing study intervention. The JNJ-3989/placebo injections administered to the participant must be documented on the intervention accountability form. All study intervention will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study intervention containers.

Study intervention must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention, and study intervention returned by the participant, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study intervention, or used

returned study intervention for destruction, will be documented on the intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the intervention return form.

Study intervention should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to participants of this study. Returned study intervention must not be dispensed again, even to the same participant. An intermediate study intervention compliance check is not considered to be a re-dispensing. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 6 intervention arms with ratio 2:2:2:2:1:1 (Arms 1:2:3:4:5:6 as described in Section 4.1). Randomization will be based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by HBeAg status at screening (positive versus negative) and by treatment history (not currently treated versus virologically suppressed). The aim is to include 40% not currently treated participants of whom it is expected that 40% are HBeAg-positive. As such, enrollment of subgroups may be closed prior to completion of study enrollment. All efforts will be undertaken to include a sufficient number of HBeAg-positive virologically suppressed participants. The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant participant details to uniquely identify the participant.

Blinding

At Week 48 or at time of early discontinuation, it will be communicated to the investigators whether the participants were allocated to either an investigational arm (Arms 1 to 5) or the control arm (Arm 6) to allow the correct follow-up visit schedule to be followed (see Schedule of Activities). Only at Week 72, the randomization codes (for Arms 1 to 5) will be fully disclosed to the investigators.

The sponsor will be fully unblinded for the primary analysis at Week 48 (see Section 9).

Under normal circumstances, the blind should not be broken for a participant until this participant has completed Week 72 or discontinued earlier. The investigator may in an emergency determine the identity of the intervention by contacting the IWRS. While the responsibility to break the intervention code in emergency situations resides solely with the

investigator, it is recommended that the investigator contacts the sponsor or its designee to discuss the particular situation, before breaking the blind, only if this does not delay action with respect to treatment in an emergency situation. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented in the appropriate section of the CRF. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

In order to preserve the blinding during the study treatment phase, HBsAg, HBeAg, anti-HBs, and anti-HBe antibody tests cannot be done locally.

Sponsor personnel involved in the pharmacokinetic and pharmacodynamic modeling will have access to the pharmacokinetic and pharmacodynamic data before formal unblinding. Sponsor personnel involved in trial conduct, data management, and statistics will not have access to these data.

6.4. Study Intervention Compliance

JNJ-3989/placebo will be administered at the study site as a subcutaneous injection by qualified study-site personnel who are unblinded to treatment assignment and who are independent from any assessment activities with regard to the blinded study conduct. In order to protect the blind, the participant should be asked to not look at the injection, and investigator and blinded study personnel should not see the syringe and/or injection.

An optional medication diary to document oral study intervention intake can be made available for participants with an observed or known risk for study intervention non-compliance. The completed diaries are reviewed by the site staff and discussed with the participants for compliance monitoring and counseling. Completed diaries will be returned to the site staff to add to the source documents.

The participants will be requested to bring unused oral study interventions and empty packaging to the study site at each visit.

Every effort should be made to have the participant take the oral study interventions as indicated in the Schedule of Activities.

- In case a dose of JNJ-6379/placebo was missed, the dose should be given as soon as possible but within 12 hours after the scheduled time. Otherwise, the dose should be skipped and the next dose should be given at the next scheduled time point per the initial dosing schedule. If more than 3 consecutive doses are missed, the investigator should be contacted and the case should be discussed with the sponsor.

- If an injection of JNJ-3989 was missed, the injection should be given as soon as possible but within 3 weeks after the scheduled time. Otherwise, the injection should be skipped

and the next injection should be given at the next scheduled time point per the initial injection schedule.

- If a dose of NA is missed, the participant should follow the guidelines in the package insert.

If a participant's study intervention intake is not according to the protocol, the investigator will take the necessary measures to ensure future adherence to the protocol.

6.5. Concomitant Therapy

Prestudy therapies administered up to 30 days before the start of screening must be recorded at screening. If applicable, the participant's last anti-HBV treatment prior to screening must also be recorded.

Concomitant therapies must be recorded throughout the study, from signing of the ICF up to the last study visit. Concomitant therapies should also be recorded beyond the last study visit only in conjunction with new or worsening (S)AEs.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study intervention must be recorded in the CRF. Recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and its indication. Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a participant into the study.

An overview of disallowed medication is provided in Table 4.

Table 4: Disallowed Medication

Disallowed at any time prior to screening until end of follow-up:
• Any CAM and oligonucleotide-based treatment (eg, siRNA and antisense oligonucleotides), other than the study intervention taken in the context of this study.
Disallowed from 6 months prior to screening until end of follow-up:
• Any investigational agent, investigational vaccine, invasive investigational medical device, or investigational biological product (other than the study intervention taken in the context of this study).
Disallowed from 6 months prior to baseline until end of follow-up:
• For participants currently not being treated: Any anti-HBV drug (including vaccines) other than the study intervention taken in the context of this study. ***Note***: Prior hepatic treatment with herbal or nutritional products is allowed but should be stopped at screening. • Any systemically (eg, intravenously, intramuscularly, orally, subcutaneously) administered medication that directly or indirectly interferes with immune responses (eg, cyclosporine, interleukins, IFN, systemic corticosteroids exceeding 5 mg of prednisolone equivalent/day).

Disallowed from 1 month prior to screening until end of follow-up:

- Moderate and potent inhibitors of CYP3A4 (eg, azole anti-fungals, macrolide antibiotics, diltiazem, verapamil).
- Moderate and potent inducers of CYP3A4 (anti-epileptics: eg, carbamazepine, oxcarbazepine, [fos]phenytoin, and phenobarbital; anti-tuberculosis drugs: rifabutin, rifampin, and rifapentine; other: bosentan, modafinil).
- Inhibitors of P-glycoprotein transporter (eg, amiodarone, azithromycin clarithromycin, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, quinidine, ritonavir, verapamil).
- Inhibitors of breast cancer resistance protein (BCRP) transporter (eg, curcumin, cyclosporin A, eltrombopag).
- Any medication that reduces renal function or competes for active tubular secretion (eg cimetidine, probenecid, quinidine).
- Anticoagulants.
  Note: aspirin and other antiplatelet agents are allowed.

Disallowed from screening until end of follow-up:

- Products containing *Hypericum perforatum* (St. John's wort).
- Any anti-HBV drug (including vaccines) other than the study intervention taken in the context of this study.
- Biotin (>1 mg daily dose), either taken alone or as part of a multivitamin formulation.
  Note: The use of other vitamins is allowed.
- Topical steroids (>7 days) under occlusive dressing.

Disallowed from 1 week prior to baseline until 12 weeks after EOS intervention:

- Ethinylestradiol-containing contraceptives with an ethinylestradiol content >20 µg.
  Note: Starting treatment with ethinylestradiol-containing contraceptives during the study is not allowed.

An overview of concomitant medication that should be used with caution is described in Table 5.

Table 5: Concomitant Medication to be Used With Caution

The following concomitant medications are allowed but should be used with caution with monitoring of AEs and desired efficacy. Alternative medications or adjusted doses should be considered.

- Analgesics: ergoloid mesylates, ergotamine tartrate, dihydroergotamine and methylergonovine.
- Calcium channel blockers: eg, amlodipine, bepridil, nicardipine, nifedipine, and nisoldipine.
- Lipid-lowering drugs: eg, atorvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin.
- Phosphodiesterase 5 inhibitors: sildenafil, vardenafil, tadalafil.
- Sedatives/anxiolytics: midazolam, triazolam.
- Acid-reducing agents: antacids (eg, aluminium and magnesium hydroxide) (recommended to separate antacid and oral study intervention administration by 4 hours).
- Ethinylestradiol-containing contraceptives:
  - Only allowed if on a stable treatment regimen for ≥3 months prior to screening and the ethinylestradiol content is ≤20 µg.
  - Female participants stable on an ethinylestradiol-containing regimen with a dose >20 µg who switch to an ethinylestradiol-containing regimen with a dose ≤20 µg, should be on that new regimen for at least 1 week before the first dose of study intervention.
- Hormone replacement therapy in postmenopausal women: allowed if on a stable treatment regimen (ie, same dose and not starting or stopping for 2 weeks prior to baseline until 12 weeks after EOS intervention). Applicable procedures and treatment guidance based on package inserts should be respected.

Note: The lists of disallowed medication and concomitant medication to be used with caution are not exhaustive; for products falling in one of the categories and not mentioned by name, the sponsor should be contacted to determine whether the product can be allowed.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

The prescribing information for ETV, TDF, and TAF should be consulted for any additional prohibited medication.

6.6. Individual Participant NA Treatment Completion Criteria

After a fixed duration of 48 weeks, participants will complete treatment with JNJ-3989 and/or JNJ-6379. If all of the following criteria are met based on clinical laboratory tests performed at Week 44, treatment with NA will also be completed at Week 48 (ie, the next scheduled visit after Week 44):

- The participant has ALT <3x ULN, AND
- The participant has HBV DNA <LLOQ, AND
- The participant is HBeAg-negative, AND
- The participant has HBsAg <10 IU/mL.

Note: In case of ALT elevation ≥3x ULN at Week 44 the investigator must consider different potential causes of increased ALT to ensure appropriate work up and management as needed. If the ALT elevation is unrelated to HBV activity and/or <3x ULN by treatment Week 48, NA completion may be considered at the discretion of the investigator and in consultation with the sponsor.

Participants who do not meet the above criteria at Week 48 should continue NA treatment during the 48-week follow-up. If the above criteria are met during the follow-up phase based on clinical laboratory tests performed at or before Follow-up Week 42 (Follow-up Week 36 for Arm 6), NA treatment should be stopped at or before Follow-up Week 48 (ie, the next scheduled visit after the laboratory test was performed) and the follow-up schedule should be extended to 48 weeks after the end of NA treatment. If NA treatment completion criteria are not met based on clinical laboratory tests performed at or before Follow-up Week 42 (Follow-up Week 36 for Arm 6), the follow-up phase will not be extended, but the participant will continue NA treatment and complete the study at Follow-up Week 48.

The investigator should consider to re-start NA treatment per local standard of care at the EOS visit ([Extended] Follow-up Week 48) for participants who met the NA treatment completion criteria at Week 48 or during the follow-up phase, who did not re-start NA treatment during the follow-up phase, and who did not achieve and maintain HBsAg seroclearance. NA will not be provided by the sponsor after the final study visit.

If a participant prematurely discontinues investigational intervention (before Week 48), follow-up assessments should be obtained as per the Schedule of Activities until 48 weeks after the end of investigational intervention unless the participant withdraws consent. In this case, NA treatment may be continued or, in consultation with the sponsor, discontinued, based on the above-mentioned NA treatment completion criteria.

6.7. NA Re-treatment Criteria and Monitoring After Stopping of NA

Participants who meet the NA treatment completion criteria outlined in Section 6.6 will be monitored closely during the follow-up phase.

After stopping NA treatment, participants should be monitored as follows:

- Regular monitoring visits will be every 4 weeks during the follow-up phase in accordance with the Schedule of Activities.
- A post-treatment HBV DNA value of >20,000 IU/mL should trigger re-testing of ALT/AST, HBV DNA, and total and direct bilirubin within a maximum of 7 days from receipt of the data and further repeats as necessary (ie, weekly until HBV DNA returns to <20,000 IU/mL).
- A post-treatment HBV DNA value of >2,000 IU/mL (but <20,000 IU/mL) should trigger a re-test within 14 days from receipt of the data and further repeats as necessary (ie, every other week until HBV DNA returns to <2,000 IU/mL).
- A post-treatment ALT value of >5x ULN should trigger re-testing of ALT, AST, ALP, total and direct bilirubin, INR, albumin, and HBV DNA on a weekly basis until ALT and AST levels have returned to <5x ULN.

After stopping NA treatment, participants should re-start NA treatment:

- Immediately with signs of decreasing liver function based on laboratory findings (eg, INR, direct bilirubin) or clinical assessment (eg, ascites, hepatic encephalopathy).
- Immediately with an HBV DNA value of >100,000 IU/mL (irrespective of confirmation and/or ALT increase).
- With confirmed post-treatment HBeAg seroreversion (HBeAg positive after it was negative at NA completion).
- With confirmed* post-treatment increases in HBV DNA >2,000 IU/mL and ALT >5x ULN.
- With confirmed* post-treatment increases in HBV DNA >20,000 IU/mL.

** At least 4 weeks apart frequency of visits as described above*

Note: Additional re-testing and/or earlier restarting of NA treatment is at the investigator's discretion, even if the above cut-offs are not yet met.

To avoid delays in decision making, sites are encouraged to run local re-testing in parallel with central re-testing in the situations described above that require more frequent re-testing. Local test results are to be recorded in the CRF and/or source documents, including information on the HBV DNA assay used. In addition, to avoid delays in NA re-treatment, it should be considered to dispense NA to participants who potentially met the NA re-treatment criteria (eg, pending confirmation) and who will not be available to come to the study site immediately at the time the

confirmatory test results will become available. This should ensure that the participant can immediately re-start NA treatment if indicated, upon direct confirmation by the investigator.

In case NA treatment is re-started, participants will be followed until the end of the study or until clinical stabilization, whichever comes later.

NA re-treatment criteria and monitoring after stopping of NA are presented graphically in Section 10.14, Appendix 14.

Management of intervention-emergent ALT/AST elevations is discussed in Section 8.3.6.

6.8. Intervention After the End of the Study

Participants will be instructed that study intervention will not be made available to them after they have completed/discontinued study intervention and that they should return to their primary physician to determine standard of care.

The investigator should consider to re-start NA treatment per local standard of care at the EOS visit ([Extended] Follow-up Week 48) for participants who met the NA treatment completion criteria at Week 48 or during the follow-up phase, who did not re-start NA treatment during the follow-up phase, and who did not achieve and maintain HBsAg seroclearance. NA will not be provided by the sponsor after the final study visit.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's investigational intervention **must** be discontinued if any of the criteria listed below apply. In those cases, NA treatment may be continued or, in consultation with the sponsor, discontinued based on investigator judgement or completed based on the NA treatment completion criteria (see Section 6.6).

- The investigator believes that for safety or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue investigational intervention.
- The participant becomes pregnant.
- The participant has a ≥grade 3 rash (see Section 10.5, Appendix 5, Rash Management) or allergic reaction (see Section 8.3.6.3).
- The participant has signs of hepatic decompensation (ie, clinical evidence of ascites, bleeding varices, or hepatic encephalopathy).
- The participant has a confirmed ≥grade 3 estimated glomerular filtration rate (eGFR) abnormality and a drop from baseline of >10 mL/min/1.73 m^2, considered at least possibly related to JNJ-3989 or JNJ-6379. Change of NA treatment should be considered anytime, according to the prescribing information. (see Section 8.3.6.4).
- The participant has a confirmed QTcF prolongation (defined as a QTcF value of >500 ms, or an increase from baseline of >60 ms) at any given time point.

- The participant requires ≥7 days of treatment with any of the disallowed medications listed in Section 6.5 and does not intend to discontinue treatment with the disallowed medication.
- The participant has confirmed HBV virologic breakthrough (ie, confirmed on-treatment HBV DNA increase by >1 $\log_{10}$ IU/mL from nadir or confirmed on-treatment HBV DNA level >200 IU/mL in participants who had HBV DNA level <LLOQ of the HBV DNA assay). In case of virologic breakthrough, changing the NA should be considered in consultation with the sponsor.
- The participant has ALT/AST elevations, as described in Section 8.3.6.1, Intervention-emergent ALT/AST Elevations.

If a participant discontinues study intervention for any reason before Week 48, then the end-of-intervention assessments should be obtained. The participant will enter the follow-up phase and complete the follow-up schedule unless the participant withdraws consent. Participants who withdraw consent will be offered an optional safety follow-up visit. Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant will NOT be automatically withdrawn from the study if he or she has to discontinue study intervention before Week 48.

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up,
- Withdrawal of consent,
- Death.

If a participant withdraws before study completion, the reason for withdrawal is to be documented in the CRF and in the source documents. No additional participants will be enrolled in case a participant withdraws from the study.

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply as local regulations permit.

7.2.1. Withdrawal From the Use of Research Samples

A participant who withdraws from the study will have the following options regarding the optional research samples (ie, host DNA sample):

- The collected samples will be retained and used in accordance with the participant's original separate informed consent for optional research samples.
- The participant may withdraw consent for optional research samples, in which case the samples will be destroyed and no further testing will take place. To initiate the sample

destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

Withdrawal From the Optional Research Sample (ie, host DNA) While Remaining in the Main Study

The participant may withdraw consent for optional research samples while remaining in the study. In such a case, the optional research samples will be destroyed. The sample destruction process will proceed as described above.

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for future research (refer to Long-Term Retention of Samples for Additional Future Research in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF and in the separate ICF for optional research sample.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study-site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods). These contact attempts should be documented in the participant's medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities summarizes the frequency and timing of efficacy, PK, PD, immune, biomarker, pharmacogenomic, safety, and PRO measurements applicable to this study.

All PRO assessments and ECGs should be conducted/completed before any tests, procedures, or other consultations for that visit.

Actual dates and times of assessments will be recorded in the source documentation and CRF.

Blood collections for PK assessments should be kept as close to the specified time as possible. Samples obtained within 20% of the nominal time from dosing (eg, within +/- 12 minutes of a 60-minute time point) will not be captured as a protocol deviation if the exact time of the sample collection is noted on the source document and CRF.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

The total blood volume to be collected from each participant will be approximately 335 mL during the first 12 weeks of the intervention phase and including the screening visit. Between Week 16 and Week 48, the total blood volume will be approximately 350 mL. During the (extended) follow-up phase, up to approximately 430 mL of blood will be collected.

Note: The total blood volume to be collected from each participant may vary, depending on several factors (eg, unscheduled re-tests, re-sampling, individual variations, follow-up visits that are only applicable for participants who completed NA treatment during the follow-up period), but mainly driven by potential participation in the 48 weeks extended follow-up (see Section 6.6).

In addition, for PBMC samples, which will be collected at selected sites only, 180-240 mL blood will be collected. Optional intensive PK samples (approximately 66 mL) may be collected.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form.

Refer to the Schedule of Activities for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

Study-specific Materials

The investigator will be provided with the following supplies:

- Investigator's Brochure and any addenda for JNJ-3989 and JNJ-6379,

- Prescribing Information for ETV, TDF, and TAF,
- Pharmacy manual/study site investigational product and procedures manual,
- Laboratory manual,
- PRO instruments,
- IWRS Manual,
- CRF Completion Guidelines,
- Sample ICF.

8.1. Efficacy Assessments

Efficacy assessments will be performed at the time points indicated in the Schedule of Activities.

Qualitative and quantitative HBsAg and HBeAg, and quantitative HBcrAg as well as anti-hepatitis B surface (HBs) and anti-hepatitis B e (HBe) antibodies will be determined using standard commercially available serologic assays in a central laboratory. Samples for the determination of HBsAg and HBeAg will be processed in real-time. Samples for the determination of HBcrAg can be analyzed in batch and at the sponsor's discretion.

HBV DNA and HBV RNA will be quantified at central laboratories using commercially available in vitro nucleic acid amplification tests for the quantification of HBV DNA and HBV RNA. Samples for the determination of HBV DNA will be processed in real-time. Samples for the determination of HBV RNA can be analyzed in batch and at the sponsor's discretion.

HBsAg, HBeAg, anti-HBs, and anti-HBe antibody testing results from the Week 44 visit onwards will be provided for each participant to the investigator and the sponsor at the next visit (ie, from the Week 48 visit onwards). HBV DNA results will be provided to the investigator and the sponsor from screening until the end of follow-up. The blinded post-baseline results collected prior to the Week 44 visit will be provided to the investigator at the end of the study to complete the participant's medical records. In order to preserve the blinding during the study treatment phase, HBsAg, HBeAg, anti-HBs, and anti-HBe antibody tests cannot be done locally.

It is the responsibility of the investigator:

- To monitor HBV DNA results and ensure that investigational intervention is discontinued in participants with virologic breakthrough (see Section 7.1),
- To assess if NA treatment completion criteria are met (see Section 6.6),
- To assess whether re-start of NA treatment during follow-up is needed (see Section 6.7).

In participants enrolled at a site with an on-site Fibroscan device, Fibroscan assessments will be performed to determine changes in fibrosis.

Samples may be used by the sponsor for additional exploratory assessments analyzing the serologic and virologic characteristics of HBV infection and efficacy or safety of the study intervention.

8.1.1. Sequencing

Viral genome sequence analysis will be performed to identify pre-existing baseline polymorphisms and to evaluate emergence of mutations associated with JNJ-3989, JNJ-6379, and/or NA treatment.

Sequencing of the HBV genome will be performed to monitor HBV variants present at the time points indicated in the Schedule of Activities. Samples at baseline will be sequenced by default if HBV DNA levels are within the ranges required for the sequencing assay. The sequencing of samples after baseline may be triggered by the sponsor virologist based on changes in HBV DNA levels observed in each individual participant and the limits of the sequencing assay.

Samples may be used by the sponsor for additional assessments analyzing the serologic and virologic characteristics of HBV infection and efficacy and safety of the study intervention, including viral genotypic and phenotypic assessments.

8.1.2. Patient-reported Outcomes

The impact of study intervention on participants' HRQoL, self-stigma level, and impression of change will be assessed using PROs at predefined time points. The following PRO instruments will be used: the HBQOL scale, an HBV-specific self-stigma PRO scale, and the PGIC scale. Patient-reported outcome data collected may also be used by the sponsor for additional exploratory assessments analyzing the effect of study intervention on HRQoL, self-stigma, and impression of change, and for assessing the psychometric properties of the PRO instruments.

Patient-reported outcome assessments will be performed by all participants at sites where appropriate translations are available. Participants should complete these assessments in their native language or if there is no version available in their native language, a version in a language in which the participant is fluent and literate. It is preferable that participants are able to read and write to complete the assessments by themselves. If a participant is unable to read or has visual or other physical limitations that make it difficult to read or complete the assessments, trained study-site personnel may read the questions and responses aloud exactly as they appear on the assessment and record the participant's responses.

Study-site personnel will record in the CRF whether the PRO assessments were performed during the study visit.

The participant should be provided a quiet place to complete the PRO assessments. When deciding which answer to report, participants should not receive any help from anyone accompanying them (such as family members and friends) or study-site personnel; the responses should reflect the participant's interpretation and response.

Participants' responses to the PRO questionnaires will not be reported as AEs or SAEs.

Hepatitis B Quality of Life Instrument, Version 1.0

The HBQOL[32] version 1 is a 31-item disease-specific instrument designed to measure HRQoL for participants with CHB. The instrument includes 7 subscales/domains, including psychological well-being, anticipation anxiety, vitality, stigma, vulnerability, transmission, and viral response. Each of the 31 items is scored on a 5-level response scale. Each subscale score is simply calculated as the average score among the items included in that subscale. In addition to the 7 subscales, there is a single global score that reflects the results on all 31 items. The global score is the average score among all the items in the HBQOL. Responses are transformed along a 0 to 100-point scale, where lower scores denote less HRQoL impact, and higher scores denote more HRQoL impact (ie, 0 best score; 100 worst score).

It takes about 10 minutes to complete the HBQOL version 1.

See Section 10.10, Appendix 10, Hepatitis B Quality of Life Instrument for a representative example of the HBQOL version 1.

HBV-specific Self-stigma PRO Scale, Version 1.0

The HBV-specific self-stigma scale is an hepatitis B-specific PRO instrument designed to assess the experience and impact of self-stigma. The current version consists of 37 items. The items cover aspects of self-stigma such as a) devaluation, inferiority, and worthlessness, b) marginalization and alienation, c) secrecy and concealment, d) shame and guilt, and e) withdrawal and social isolation. Each of the 37 items is graded on a 5-point Likert scale (1 "Never", 2 "Rarely", 3 "Sometimes", 4 "Often", and 5 "Always"). It takes less than 15 minutes to complete the scale. The content validity of the scale is currently being evaluated and the data collected in this study will be used to assess the psychometric properties of the scale.

The HBV-specific self-stigma PRO scale version 1 is provided in Section 10.11, Appendix 11, HBV-specific Self-stigma PRO Scale.

Patient Global Impression of Change Scale, Version 1.0

The PGIC scale[11,18] is a single-item PRO scale aimed at assessing the participant's perceptions of change (improvement or worsening) in how they feel overall compared to the beginning of the study. Response options include: "Much better", "Better", "A little better", "No change", "A little worse", "Worse", "Much worse". It takes less than a minute to complete the scale. The PGIC responses will be used as anchors to perform responder analyses and to evaluate the ability to detect change for the HBQOL and the HBV-specific self-stigma PRO scale.

The PGIC scale version 1 is provided in Section 10.12, Appendix 12, Patient Global Impression of Change Scale.

8.2. Safety Assessments

Safety and tolerability will be assessed throughout the study from the time that the ICF is signed until completion of the last study-related activity, which may include contact for follow-up of safety. The evaluations of safety and tolerability will include monitoring of (S)AEs, physical examinations (including body weight), vital signs measurements, triplicate 12-lead ECGs, and clinical laboratory tests (including hematology, blood biochemistry, blood coagulation, urinalysis, urine chemistry, and renal biomarkers) at predefined time points as specified in the Schedule of Activities. Any clinically relevant changes occurring during the study must be recorded in the Adverse Event section of the CRF.

AEs will be reported and followed by the investigator as specified in Section 8.3, Adverse Events and Serious Adverse Events and Section 10.4, Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

Specific toxicity management plans in line with the known pharmacological profile of the study intervention (and the drug classes) evaluated in this study are implemented (Section 8.3.6).

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

Details regarding the IDMC and the IFLEP are provided in Section 9.5 and in the Committees Structure in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

8.2.1. Physical Examinations

A complete physical examination (including height [at screening only], body weight, skin examination, and other body systems) will be performed at screening, Week 24, and Week 48. A symptom-directed physical examination (including body weight) will be performed at the time points indicated in the Schedule of Activities.

A complete physical examination includes the following: general appearance, eyes, ears, nose, throat, cardiovascular system, respiratory system, gastro-intestinal system, and skin and mucous membranes. A neurological and musculoskeletal examination will be performed, as well as an examination of the lymph nodes. Body weight and temperature will be measured. Height will be measured at the screening visit only.

8.2.2. Vital Signs

Temperature, pulse rate, and supine SBP and DBP will be assessed at the time points indicated in the Schedule of Activities.

Blood pressure and pulse rate measurements will be assessed with a completely automated device. All values will preferably be registered on a built-in recorder so that measurements are observer independent. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

Clinically relevant abnormalities in vital signs are defined in Section 10.7, Appendix 7, Cardiovascular Safety Abnormalities.

8.2.3. Electrocardiograms

Twelve-lead triplicate ECGs will be collected at the time points indicated in the Schedule of Activities and when clinically indicated.

During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs.

At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 10 minutes.

Evaluation of the triplicate 12-lead ECGs will be based on the mean value of the triplicate parameters.

All ECGs will be read centrally. Preferably, all ECGs will be read and interpreted under supervision of one and the same qualified person. Day 1, pre-dose ECG assessment will also be done locally on-site to determine eligibility.

Clinically relevant abnormalities in ECG are defined in Section 10.7, Appendix 7, Cardiovascular Safety Abnormalities.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry, hematology, and coagulation, and a urine sample for urinalysis, urine chemistry, and renal biomarkers will be collected as noted in Section 10.2, Appendix 2, Clinical Laboratory Tests. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.

Participants need to have fasted for at least 10 hours before biochemistry samples are taken for measurement of phosphate, calcium, creatinine, and lipids. Participants are to bring their oral study intervention with them to each study visit and have that day's intake at the site.

If a grade 3 or grade 4 laboratory abnormality occurs, that is considered to be clinically significant by the investigator, a confirmatory test must be performed preferably within 48 hours but no later than 72 hours after the results have become available.

For this study, the laboratory abnormality of cholesterol increase is identified as laboratory abnormality of interest.

8.3. Adverse Events and Serious Adverse Events

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate) for the duration of the study.

For further details on AEs and SAEs (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to Section 10.4, Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety. Serious AEs, including those spontaneously reported to the investigator within 30 days after the last dose of study intervention, must be reported using the SAE Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the SAE Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax).

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

Solicited Adverse Events

Solicited AEs are predefined local (at the injection site) and systemic events for which the participant is specifically questioned.

Unsolicited Adverse Events

Unsolicited AEs are all AEs for which the participant is not specifically questioned.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

AEs, including pregnancy, will be followed by the investigator as specified in Section 10.4, Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

8.3.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the SAE Form. Any participant who becomes pregnant during the study must discontinue further investigational intervention.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.3.6. Specific Toxicities

For participants reporting ALT/AST elevations, rash, ISRs, acute systemic allergic reactions, and renal complications as specified in the DAIDS Toxicity Grading Scale (see Section 10.9, Appendix 9, DAIDS Table), the following should be done.

8.3.6.1. Intervention-emergent ALT/AST Elevations

Elevated liver enzyme activity can be triggered by the underlying HBV disease as well as by the study intervention.

Management of intervention-emergent ALT/AST elevations is presented graphically in Section 10.6, Appendix 6: Intervention-emergent ALT/AST Elevations, and is described below.

Any intervention-emergent elevation of ALT and/or AST ≥3x ULN and ≥3x nadir (ie, lowest value during study participation) should trigger an assessment of confounding factors (alcohol intake, change in concomitant medication, and comorbidities) and should trigger a confirmatory

study visit to repeat laboratory testing of AFP, ALT, AST, ALP, bilirubin (total and direct), INR, albumin, and HBV DNA. Additional tests should be considered based on clinical judgement (refer to Section 10.6, Appendix 6: Intervention-emergent ALT/AST Elevations). The confirmatory visit should be scheduled as soon as possible, preferably within 7 days of the receipt of the initial ALT/AST results. In case the repeat laboratory testing shows an isolated ALT/AST elevation (ie, with stable albumin, bilirubin [total and direct], and INR) the participant may continue study intervention. In case of confirmed ALT elevation >1,000 U/L and >3x the baseline value, investigational intervention should be discontinued. In both cases, NA treatment should be continued. The participant will be monitored (laboratory testing of ALT, AST, ALP, bilirubin [total and direct], INR, albumin, and HBV DNA) on a weekly basis until ALT and/or AST levels have returned to 50% of the maximal value.

If the ALT and/or AST level is ≥3x ULN and ≥3x nadir and is associated with any of the following laboratory results or clinical symptoms:

- INR ≥1.5, OR
- direct bilirubin >1.5x ULN, OR
- serum albumin <3.0 g/dL, OR
- ascites, hepatic encephalopathy, or liver-related symptoms (eg, severe fatigue, nausea, vomiting, right upper quadrant pain in the absence of an alternative medical explanation), OR
- other indication of reduced liver function

the participant should discontinue investigational intervention and should be monitored on a weekly basis or as per good clinical practice until ALT and/or AST levels have returned to 50% of the maximal value and, if present, liver-related symptoms have improved. NA treatment should be continued. Additional tests can be considered based on clinical judgement.

The NA re-treatment criteria during follow-up are presented in Section 6.7.

8.3.6.2. Rash

Participants should be informed that they should contact their doctor immediately when they notice any generalized skin reaction. This skin reaction should be evaluated in the clinic the same day (if possible) or the next day.

All rash events should be captured in the AE section of the CRF. A separate Rash page will be completed in case of a rash event.

Monitoring of the evolution of rash events will be performed as described in Table 9 in Section 10.5, Appendix 5, Rash Management.

When safety blood samples are drawn as per the rash management guidelines, these should be processed by the local laboratory. The following parameters will need to be tested: AST, ALT, sedimentation rate, complete blood cell count (including hemoglobin, hematocrit, red blood cell

[RBC] count, white blood cell [WBC] count, differential count [neutrophils, lymphocytes, monocytes, eosinophils, and basophils], and platelet count), and creatinine. The values of the local laboratory assessments need to be transcribed in the CRF by the study site personnel.

The participant may be treated symptomatically until the rash resolves. Oral antihistamines (eg, cetirizine, levocetirizine) and/or topical corticosteroids may provide symptomatic relief but effectiveness of these measures has not been established. If systemic corticosteroids exceeding 5 mg of prednisolone equivalent/day are required for treatment of rash, the study intervention needs to be permanently discontinued. If the rash is considered to be most likely due to concomitant illness or non-study drugs, standard management, including discontinuation of the likely causative agent, should be undertaken.

Injection Site Reactions

At the time points specified in the Schedule of Activities or at an unscheduled visit if needed, an evaluation of the injection site will be performed based on participant's description and/or physical examination. Evaluation will include at a minimum the time of occurrence, time of resolution and a description of the abnormality including its maximal diameter. For each ISR, information on pain, erythema, induration and pruritus should be obtained as specified in the DAIDS scale (see Section 10.9, Appendix 9, DAIDS Table).

All ISRs (including ISRs below grade 1) will need to be recorded in the special events section of the CRF.

Digital pictures will be taken when considered appropriate; all efforts should be made to collect images in case of grade 3 and 4 ISRs. Digital pictures will only be taken and collected from participants who consent separately to this component of the study. If digital pictures are required, they should be de-identified and provided to the sponsor.

8.3.6.3. Acute Systemic Allergic Reactions

Grade 1 (Localized Urticaria [Wheals] With no Medical Intervention Indicated)

Participants may continue the intake of study interventions.

Cetirizine, levocetirizine, topical corticosteroids or antipruritic agents may be prescribed.

Participants should be advised to contact the investigator immediately if there is any worsening of the acute systemic allergic reaction.

Grade 2 (Localized Urticaria With Intervention Indicated, or Mild Angioedema With no Intervention Indicated)

Participants may continue the intake of study interventions.

Cetirizine, levocetirizine, topical corticosteroids or antipruritic agents may be prescribed.

Participants should be advised to contact the investigator immediately if there is any worsening of the acute systemic allergic reaction, in which case the participant will permanently discontinue the intake of JNJ-3989 and JNJ-6379. Rechallenge is not allowed. The participant's NA treatment may be discontinued based on investigator judgement in consultation with the sponsor.

Grade 3 (Generalized Urticaria, Angioedema With Intervention Indicated, or Symptoms of Mild Bronchospasm) and Grade 4 (Acute Anaphylaxis, Life-Threatening Bronchospasm, or Laryngeal Edema)

Participants will permanently discontinue the intake of JNJ-3989 and JNJ-6379. Rechallenge is not allowed. The participant's NA treatment may be discontinued based on investigator judgement in consultation with the sponsor.

Participants will be treated as clinically appropriate. Participants should be followed until resolution of the AE and standard management should be undertaken.

8.3.6.4. Renal Complications

If renal complications develop, participants should be closely monitored for disturbances in creatinine clearance. Additional investigations can be performed at the investigator's discretion. Participants must be treated as clinically appropriate.

Participants who develop confirmed grade 3 or 4 eGFR abnormalities with reduction from baseline by at least 10 mL/min/1.73 m^2 will permanently discontinue the intake of JNJ-3989 and JNJ- 6379, if the abnormality is considered at least possibly related to JNJ-3989 or JNJ-6379, and should be followed appropriately until resolution of AE or toxicity. Rechallenge is not allowed. Change of NA treatment should be considered according to the prescribing information.

8.3.6.5. Hematologic Abnormalities

Mild thrombocytopenia was observed in recently conducted non-clinical toxicology studies with the combination of JNJ-3989 and JNJ-6379. In addition, in a 3-month combination study with 80 rats, 1 rat developed pancytopenia related to bone marrow depletion after 23 days of dosing. Previously, in a 9-month dog study in 24 dogs treated with JNJ-6379 alone, pancytopenia which correlated with a marked increase in plasma cell-like cells in the bone marrow was observed in 1 dog after 60 days of dosing. A second dog in the same dose group with pancytopenia recovered after a drug holiday and was re-exposed uneventfully.

No thrombocytopenia or pancytopenia has been observed in the ongoing Jade study (56136379HPB2001) investigating JNJ-6379/Placebo with or without NA treatment. All 232 participants have completed at least 24-week study treatment. In the Phase 1/2a AROHBV1001 study with JNJ-3989, mild transient thrombocytopenia (grade 1) was observed in 6 out of 84 participants receiving 3 SC injections of JNJ-3989 alone over a period of up to 12 weeks with background of NAs. The transient thrombocytopenia was not considered clinically significant. No thrombocytopenia or pancytopenia was observed in 12 patients when JNJ-3989 and JNJ-6379 were given in combination over a 12-week period.

Based on the non-clinical findings, any relevant abnormalities in hematologic parameters will be carefully monitored as described below:

- Platelet counts: <100,000 cells/mm^3 or <100 GI/L or reduction from baseline by at least 50%
- Hemoglobin: Decrease of at least 2 g/dL from baseline or at least Grade 2 (DAIDS)
- Reticulocytes: Reduction to <0.5% of the RBC count
- Neutrophil count: Treatment emergent reduction to at least Grade 2 (DAIDS)

In case any one of the above criteria are met, a confirmatory visit should be scheduled as soon as possible, preferably within 7 days of the receipt of the initial results. Confirmation of the results will trigger weekly or biweekly (every other week) unscheduled visits until improvement or stabilization of the respective parameter(s). Stabilization is defined as no further significant reduction over two consecutive visits.

In case of confirmed Grade 3 or Grade 4 hematologic abnormalities, discontinuation of investigational study treatment (JNJ-3989 and/or JNJ-6379/placebo) should be considered. In case of discontinuation, NA treatment should be continued.

8.4. Treatment of Overdose

For this study, any dose of JNJ-3989 and JNJ-6379 greater than the protocol-specified dose (refer to Section 6.1) will be considered an overdose. The sponsor does not recommend specific intervention for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities.
- Obtain a plasma sample for PK analysis as soon as possible from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Plasma samples will be used to evaluate the PK of JNJ-3989 (ie, JNJ-3976 and JNJ-3924) and/or JNJ-6379 and/or NA (ETV, TAF, or tenofovir), as applicable. Plasma collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period, or for analysis of plasma concentrations of co-medications.

8.5.1. Evaluations

Venous blood samples will be collected for measurement of plasma concentrations of JNJ-3989 (ie, JNJ-3976 and JNJ-3924) and/or JNJ-6379 and/or NA (ETV, TAF, or tenofovir), as applicable, at time points specified in the Schedule of Activities.

All participants will have sparse PK sampling. Participants who consent to participate in the intensive PK subgroup (optional) will also undergo intensive PK sampling.

8.5.2. Analytical Procedures

Pharmacokinetics

At the sponsor's discretion, a selection of plasma samples may be analyzed to determine concentrations of JNJ-3989 (ie, JNJ-3976 and JNJ-3924) and/or JNJ-6379 and/or NA as applicable, using a validated liquid chromatography-mass spectrometry method or liquid chromatography-fluorescence method, as applicable, by or under the supervision of the sponsor.

Plasma PK samples may be stored for future exploratory analysis of protein binding or the metabolite profile. Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

To allow selection of samples, the bioanalytical laboratory will receive randomization lists per IA and/or upon request of the bioanalytical scientist. Unblinding of the treatment code will be performed at the bioanalytical laboratory only and will be subjected to a procedure that will ensure that codes will not be revealed to anyone involved in the execution of the study.

8.5.3. Pharmacokinetic Parameters and Evaluations

Plasma concentration-time data for JNJ-3989 (ie, JNJ-3976 and JNJ-3924), JNJ-6379 and, optionally, NA will be analyzed via noncompartmental methods for all participants who underwent intensive PK sampling. The main PK parameter will be the area under the plasma concentration-time curve over the dosing interval (tau) at steady-state (AUC_{tau}). Additional exposure parameters may be calculated if applicable.

Data from this study may be combined with data from a selection of Phase 1 and 2 studies via population PK modelling to enable the calculation of the above PK parameters also in participants who only underwent sparse PK sampling. If performed, the population PK analysis will be described in a separate analysis plan and results will be reported separately.

8.6. Pharmacokinetics/Pharmacodynamics

Relationships of individual PK parameters (intensive PK and population PK, as applicable) for JNJ-3989 (ie, JNJ-3976 and JNJ-3924) and/or JNJ-6379 and/or NA, as applicable, with selected efficacy and/or with selected safety endpoints will be evaluated, if applicable.

8.7. Immune Assessments

At selected sites, PBMC samples for immune analyses will be collected during study intervention and follow-up and will be analyzed centrally for HBV-specific responses by enzyme-linked immunospot (ELISpot) and/or intracellular cytokine staining (ICS) after stimulation with HBV-specific antigens. ELISpot detects T-cells that secrete gamma interferon (IFN-γ) in response to a specific antigenic stimulation, whereas ICS determines the frequency of CD4+ and CD8+ T-cells secreting cytokines such as IFN-γ, interleukin (IL)-2 and tumor necrosis factor (TNF)-α in response to a specific antigenic stimulation.

Additional experiments may be performed to further phenotypically and functionally characterize PBMCs using proliferation or cytotoxic assays or other methods such as cytometry by time of flight to evaluate innate and adaptive immune responses. Leftover PBMC samples may be used at the sponsor's discretion for additional exploratory research related to HBV infection or study intervention (safety/efficacy).

Additional PBMC samples may be taken in case of ALT flares, upon discussion with the sponsor, which may require an unscheduled visit.

8.8. Host Genetics

A pharmacogenomic blood sample will be collected from participants who consent separately to this component of the study to allow for pharmacogenomic research, as necessary (where local regulations permit).

In addition, other samples may be used for exploratory genetic research in participants consenting separately to this part of the study. No genetic research will be performed on any sample in participants who have not provided the additional separate consent for host genetic research. Samples can only be used to investigate the potential association of host genetic factors with efficacy, safety, or PK of study intervention, or HBV infection, or may be used to develop tests/assays related to study intervention or HBV infection.

8.9. Host Biomarkers

The study includes collection of blood samples for exploratory analysis of host blood biomarkers at the host RNA, protein, and cell level. Sampling will be performed in all participants at the time points indicated in the Schedule of Activities.

Samples can only be used for research related to study intervention or HBV infection or may be used to develop tests/assays related to study intervention or HBV infection.

Blood samples will be taken at the time points indicated in the Schedule of Activities which can be used to explore immunogenicity of JNJ-3989. The emergence of antibodies to JNJ-3989 (antidrug antibodies) might be analyzed using assays such as an enzyme-linked immunosorbent assay.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

The primary analysis will be performed at the time when all participants have completed Week 48 or discontinued earlier. The final analysis will be performed when all participants have completed the last study visit or discontinued earlier. For the IAs, please refer to Section 9.5.

9.1. Statistical Hypotheses

Based on the primary efficacy endpoint, the proportion of participants meeting the NA treatment completion criteria at Week 48, the primary hypotheses are as follows:

- There is a positive dose-response signal across the 3 doses of JNJ-3989 (40, 100, and 200 mg) on the background of NA compared with NA treatment alone (control Arm 6).
- One or both combination regimens JNJ-3989+JNJ-6379+NA and JNJ-6379+NA are more efficacious than NA treatment alone (control Arm 6).
- The combination regimen of JNJ-3989 (100 mg)+JNJ-6379+NA is more efficacious than JNJ-3989 (100 mg)+NA and/or JNJ-6379+NA combination regimens.

A hybrid methodology that combines aspects of multiple testing with modeling techniques (Multiple Comparison Procedure-Modeling [MCP-Mod]) will be used for declaring a dose-response trend at 0.05 one-sided significance level and estimating the dose-response relationship of JNJ-3989 doses +NA versus control Arm 6 (Placebo+Placebo+NA). Because the primary efficacy endpoint is binary, the generalized MCP-Mod approach will be used on the logit scale.[28] A significant dose-response signal is declared if one or more prespecified models (see Figure 2) have been found to be significant (multiple contrast test approach). The statistically significant models form a model pool used to estimate the dose-response relationship and select a dose (modeling step).

After a positive dose-response signal is established with statistical significance, then the testing procedure continues in a fixed sequence, with the comparison of Arm 1 (JNJ-3989+JNJ-6379+NA) with control Arm 6 at a one-sided alpha of 0.05. If Arm 1 is found statistically superior to control Arm 6, then the combination regimen JNJ-6379+NA (Arm 5) is compared to control Arm 6 at 0.05 one-sided alpha level. The Mantel-Haenszel (MH) test for the difference of 2 proportions adjusted for the 2 randomization stratification factors will be applied.

For the comparisons among regimens (Arm 1, 3, and 5), the statistical testing will control for the one-sided Type I error of 0.05 separately and independently from the comparisons against the control arm described above. The testing among the regimens (Arm 1, 3, and 5) will be performed using the min test approach. The JNJ-3989+JNJ-6379+NA (Arm 1) combination regimen will be declared statistically superior to the dual regimens (Arm 3 and 5) if both tests of Arm 1 vs Arm 3 and Arm 1 vs Arm 5 demonstrate statistical significance at the one-sided 0.05

level. The MH test for the difference of 2 proportions adjusted for the 2 randomization stratification factors will be applied.

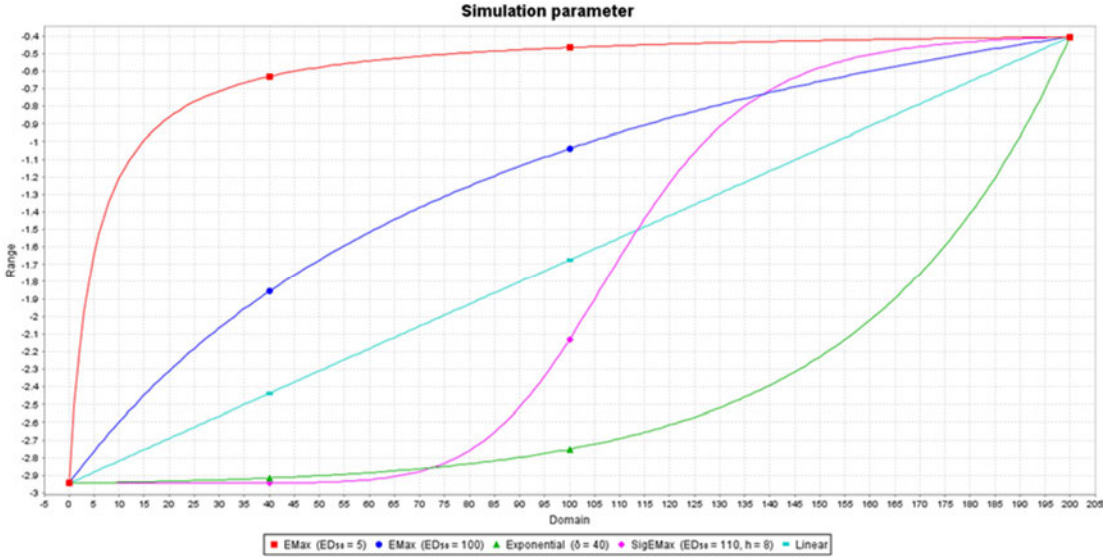
9.2. Sample Size Determination

The total study sample size is 450 participants with a 2:2:2:2:1:1 randomization ratio, where 90 participants will be randomly allocated to each of the arms including a JNJ-3989 dose (Arms 1 to 4) and 45 participants will be randomly assigned to each of the arms with no JNJ-3989 component (Arms 5 and 6).

Statistical power to test a dose-response signal was assessed using the generalized version of the MCP-Mod approach[28] applied to the binary primary efficacy endpoint on the logit scale for Arms 2, 3 and 4 (JNJ-3989 at 200, 100, and 40 mg dose, respectively +NA), and Arm 6 (Placebo+Placebo+NA) as control.

Five different assumptions were made for the dose-response relationship on the logit scale (see Figure 2) over the 3 doses of JNJ-3989 (40 mg, 100 mg and 200 mg) +NA.

Figure 2: Candidate Dose-response Models on the Logit Scale



Assuming a response rate for the highest dose of JNJ-3989 of at least 25%, and a one-sided alpha level of 5%, the power to conclude a positive dose-response trend over the 3 JNJ-3989 doses on the background of NA is ≥85% under all candidate models (see Table 6).

Table 6: Power to Conclude a Positive Dose-response Under the Assumed Candidate Dose-response Models

Response Rate for the Highest JNJ-3989 Dose	E_{max} (ED_{50}=5 mg)	E_{max} (ED_{50}=100 mg)	Linear	$SigE_{max}$ (ED_{50}=110 mg, h=8.0)	Exponential (δ = 40)
20%	0.582	0.794	0.877	0.930	0.949
25%	0.851	0.953	0.978	0.991	0.994
30%	0.956	0.992	0.999	0.999	1.000

ED_{50}: dose that produces half of E_{max}; E_{max}: maximum effect; $SigE_{max}$: sigmoid E_{max}

The operational characteristics of the sequential testing approach as described in Section 9.1 are summarized in Table 7 for a variety of scenarios. In all scenarios, the primary endpoint response rate of the JNJ-3989 100 mg +NA arm is set between 25% and 35% whereas the rate of JNJ-6379+NA and the combination regimen JNJ-3989 100-mg dose+JNJ-6379+NA vary. Under these scenarios, the probability to find a significant signal (max trend test for positive dose-response) is ≥87% for an absolute response rate in the 100 mg dose of JNJ-3989 (Arm 3) of at least 25 %.

Simulations were conducted using the normal approximation test for the difference in binomial proportions to determine the power level in the comparison of the primary efficacy endpoint among the combination regimens at one-sided alpha of 0.05.

Assuming a response rate of 5% in control Arm 6, the sample size of 90 participants each in combination Arms 1, 2, 3, and 4 and a sample size of 45 participants in combination Arm 5 (JNJ-6379+NA) and control Arm 6, provides a statistical power ≥84% to detect a difference of ≥20% in the primary endpoint between Arm 1 (JNJ-3989+JNJ-6379+NA) and control Arm 6, and power ≥76% for a difference ≥20% between Arm 5 (JNJ-6379+NA) and control Arm 6 (Table 7), using a fixed sequence approach for controlling for multiplicity.

Table 7: Simulated-based Assessment of the Power of the Sequential Testing Strategy Under a Variety of Scenarios (10,000 Runs/Scenario)

Response Rates				Comparisons vs. NA Control Arm 6 vs.			Comparisons Among Regimens Arm 1 vs.		
JNJ-3989+ JNJ-6379+ NA	JNJ-3989 +NA	JNJ-6379 +NA	Delta[a]	MCT	JNJ-3989+ JNJ-6379+ NA[b]	JNJ-6379+ NA[b]	JNJ-3989+NA	JNJ-6379+ NA	Min Test
Arm 1 (N=90)	Arm 3 (N=90)	Arm 5 (N=45)			Arm 1	Arm 5	Arm 3	Arm 5	Both Arm 3 and Arm 5 [c]
0.25	0.25	0.25	0	0.876	0.841	0.765	0.052	0.045	0.008
0.27	0.27	0.27	0	0.918	0.897	0.841	0.051	0.049	0.010
0.3	0.3	0.30	0	0.958	0.947	0.915	0.052	0.047	0.010
0.35	0.35	0.35	0	0.975	0.973	0.963	0.050	0.048	0.009
0.25	0.25	0.10	0	0.881	0.850	0.200	0.050	0.686	0.047
0.4	0.25	0.10	0.15	0.88	0.88	0.199	0.699	0.990	0.698
0.45	0.25	0.10	0.20	0.881	0.881	0.197	0.882	0.998	0.882
0.5	0.25	0.10	0.25	0.877	0.877	0.196	0.972	1.000	0.972
0.4	0.25	0.25	0.15	0.877	0.877	0.792	0.692	0.528	0.423
0.45	0.25	0.25	0.20	0.878	0.878	0.790	0.880	0.739	0.680
0.5	0.25	0.25	0.25	0.873	0.873	0.790	0.970	0.889	0.871
0.45	0.30	0.30	0.15	0.959	0.959	0.923	0.676	0.510	0.409
0.5	0.30	0.30	0.20	0.956	0.956	0.921	0.880	0.718	0.666

MCT: Multiple Contrast Test; NA: nucleos(t)ide analog
[a] Delta difference in primary endpoint response rate between JNJ 3989 (100 mg)+JNJ 6379+NA and JNJ 3989(100 mg) +NA
[b] Versus control Arm 6 with assumed response rate of 5%
[c] Min Test: probability that Arm 1 is statistically superior to both Arm 3 and Arm 5
Note: in this table "JNJ 3989" always refers to the JNJ 3989 100 mg dose

The chosen study sample size and randomization allocation will also provide acceptable power levels for the comparison of different combination regimens, ie, JNJ-3989+JNJ-6379+NA (Arm 1, 100-mg dose of JNJ-3989) versus JNJ-3989+NA (Arm 3, 100-mg dose of JNJ-3989), and versus JNJ-6379+NA (Arm 5), respectively (Table 7). Based on the min test approach, Table 7 shows that the power levels vary depending on both the rate difference between Arm 1 and Arm 3 and the assumed rate for Arm 5. For example, for the same delta of 25% between Arm 1 and Arm 3 and between Arm 1 and Arm 5, the power to conclude that Arm 1 is statistically superior to Arm 3 and Arm 5 is 87%, assuming a response rate of 25% in both Arm 3 and 5.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Randomized	All participants who were randomized in the study
Intent-to-treat (ITT)	All participants who were randomly assigned to any of the 6 intervention arms and received at least 1 dose of study intervention.
Safety	All participants who received at least 1 dose of study intervention.

9.4. Statistical Analyses

9.4.1. Efficacy Analyses

To evaluate the efficacy, the primary analysis set will be the ITT population. Participants will be analyzed according to the study intervention they were randomly assigned to.

All efficacy summaries will be presented with descriptive statistics by intervention arm. If the endpoint is continuous, the descriptive statistics will include the number of participants, mean, standard deviation (SD), median, and range. If the endpoint is binary or categorical, the frequency distribution with the number and percentage of participants in each category will be calculated. For time-to-event variables, a summary table including number of participants included in the analysis, number of participants censored, 25th and 75th percentiles and median time-to event will be shown by intervention arm. Graphic displays will also be used to summarize the data. Summaries will also be presented by randomization stratification factors, HBeAg status at screening and treatment history.

The baseline measurements are defined as the measurements taken closest to but before the first dose of study intervention on Day 1.

Inferential analyses will be specified for each of the endpoints in the following sections. In general, comparisons between intervention arms will be accompanied by appropriate confidence intervals (CIs).

9.4.1.1. Primary Efficacy Endpoint (Proportion of Participants Meeting the NA Treatment Completion Criteria at Week 48)

A hybrid methodology that combines aspects of multiple testing with modeling techniques (MCP-Mod) will be used for evaluating a dose-response trend and estimating the dose-response relationship of 3 JNJ-3989 doses in combination with NA versus NA treatment alone (control Arm 6). Because the primary efficacy endpoint is binary, the generalized MCP-Mod approach will be used on the logit scale. A significant dose-response signal is declared if one or more prespecified models have been found to be significant (multiple contrast test approach). The statistically significant models form a model pool used to estimate the dose-response relationship and select a dose (modeling step).

A set of 5 candidate models (see Figure 2) will be used to cover a suitable range of possible dose-response shapes in terms of the logit of the primary efficacy endpoint, the proportion of participants meeting the NA treatment completion criteria at Week 48.

Each of the dose-response shapes in the candidate set will be tested using the corresponding contrast t-test statistic, employing a critical value derived for the maximum of the t-test statistics (based on the associated multivariate t-distribution) to ensure appropriate multiplicity correction that preserves the one-sided Type I error rate at 0.05. A dose-response trend is established when the maximum of the t-test statistics exceeds the critical value.

After establishing a significant dose-response signal, the testing procedures continue with the comparison of the percentage of participants who completed the 48-week study intervention and

qualified for stopping NA treatment in Arms 1 and 5 against control Arm 6, respectively. The Mantel-Haenszel (MH) test will be used in the pairwise comparisons at a one-sided alpha level of 0.05 adjusting for the randomization stratification factors of screening HBeAg status and treatment history. The Wilson test will be used at a one-sided alpha level of 0.05 with no adjustment for stratification factors as a secondary analysis.

The testing among the regimens (Arm 1 vs. Arm 3, and Arm 1 vs. Arm 5) will be performed using the min test approach. The JNJ-3989+JNJ-6379+NA (Arm 1) combination regimen will be declared statistically superior to the dual regimens (Arm 3 and 5) if both tests of Arm 1 vs Arm 3 and Arm 1 vs Arm 5 demonstrate statistical significance at the one-sided 0.05 level. The MH test for the difference of 2 proportions adjusted for the 2 randomization stratification factors will be applied to all pairwise comparisons.

As a secondary analysis, the primary efficacy endpoint will be compared between intervention arms in a logistic regression model with factors for treatment arm, treatment status and HBeAg status at screening. The potential impact of each intervention-by-randomization factor interaction will be assessed by comparing the model with and without interaction terms. Appropriate 90% CIs will be also calculated without multiplicity adjustment. Exploratory subgroup summaries will be displayed graphically in forest plots.

9.4.1.2. Key Secondary Efficacy Endpoint of Functional Cure at Week 72 (HBsAg Seroclearance 24 Weeks After Completion of All Study Intervention at Week 48)

The functional cure rate at Week 72 is defined as the proportion of participants with HBsAg seroclearance 24 weeks after completion of all study intervention at Week 48, including stopping NA treatment. It will be used to support the JNJ-3989 dose selection and the regimen selection. The same multi-step testing strategy as the one implemented for the primary efficacy endpoint (see Section 9.4.1.1), using MCP-Mod and additional treatment arms pairwise comparisons with NA control in a fixed sequence, as well as the min test approach separately for between-regimen comparisons, will be used for this key secondary endpoint. However, the comparisons with NA control in the testing strategy applied to this efficacy endpoint will be made against the NA historical control benchmark of 5%, instead of the study NA control arm (Arm 6).

To provide evidence of superior efficacy of the JNJ-3989+JNJ-6379+NA regimen against the JNJ-3989+NA and JNJ-6379+NA combination regimens, respectively, those tests will be performed at a one-sided 0.025 alpha level for regulatory consideration. This analysis aims to support the selection of the combination drug therapy to be studied in confirmatory studies.

Additionally, the functional cure efficacy endpoint will be summarized for the control Arm 6 with the point estimate paired with its 90% CI using the Clopper-Pearson exact method to assess the consistency with the assumed historical control value.

As a secondary analysis, this key secondary endpoint will be compared between intervention arms in a logistic regression model with factors for treatment arm, treatment status and HBeAg status at screening. The potential impact of each randomization factor will be assessed by

comparing the model with and without treatment-by-randomization interaction terms. Appropriate 90% CIs will be also calculated without multiplicity adjustment. Exploratory subgroup summaries will be displayed graphically in forest plots.

The comparison of functional cure rate at Week 72 against a historical control value is to leverage the large amount of historical data available for more than 15 years of NA treatment, where consistently low HBsAg loss rates were reported across different patient subpopulations characterized by different baseline HBeAg status and treatment history status. The choice of 5% as the historical control percentage for the HBsAg seroclearance 24 weeks after completion of all study intervention at Week 48 is based on the results of a meta-analysis[31] of the HBsAg seroclearance rates after 48 weeks of treatment with NA (ETV, TDF or TAF) in 3 different subgroups based on treatment history and HBeAg status (see Table 8).

Table 8: Meta-analysis of % HBsAg Seroclearance After 48 Weeks of Treatment

				Meta analytic (Predictive) Distribution		Heterogeneity assessment	
	Cohorts	N	mean	95% CI	95% PI	Qp	I^2
Not currently treated and HBeAg positive	24	2,410	0.67	[0.29, 1.56]	[0.11, 4.17]	0.050	34.6
Not currently treated and HBeAg negative	20	2,864	0.19	[0.04, 0.84]	[0.01, 3.33]	0.108	29.3
NA suppressed any HBeAg status	13	679	0.15	[0.02, 1.06]	[0.02, 1.06]	0.987	0.0

CI confidence interval, PI prediction interval, Qp p value of Cochrane's Q statistic for heterogeneity
Note: Meta analysis results (data on file). Preliminary results presented at the 68th Annual Meeting of the American Association for the Study of Liver Diseases (2017).[31] Draft publication in progress.

Although there was some variability between subgroups as well as trial heterogeneity, the mean percentage of HBsAg seroclearance after 48 weeks of treatment with NA was consistently low (<1%). The upper limit of the 95% prediction interval (PI) based on the meta-analytical predictive probability distribution was the largest (4.17%) in the subgroup of treatment-naïve HBeAg-positive patients. As the current study will enroll patients in all subgroups of treatment history and HBeAg status, the value of 5% can be considered a conservative estimate for percentage of HBsAg seroclearance after 48 weeks of NA treatment.

Given that the percentage of HBsAg seroclearance at the end of 48 weeks of NA treatment is not expected to differ substantially from that percentage 24 weeks later, the 5% value derived from this meta-analysis provides an adequate and conservative historical control treatment estimate of this efficacy endpoint.

9.4.1.3. Other Secondary and Exploratory Efficacy Endpoints

Descriptive statistics will be used for all efficacy endpoints which will be summarized by intervention arm. Comparisons among intervention arms will be done with no adjustment for multiplicity. Specific key selected endpoints may be analyzed using suitable categorical data

approaches (eg, Cochran-Mantel-Haenszel [CMH] or logistic regression for proportions or other categorical type of endpoint), longitudinal repeated measures models (eg, for continuous types of variables), or survival analysis based on the Kaplan-Meier estimates (for time-to-event variables), as appropriate. Details will be described in the SAP.

The efficacy of the study intervention during the follow-up phase will be evaluated. The proportion of participants with HBsAg seroclearance 48 weeks after completion of all study intervention at Week 48, the proportion of participants with HBV DNA <LLOQ 24 and 48 weeks after completion of all study intervention at Week 48, the proportion of participants meeting the NA treatment completion criteria during follow-up, the proportion of participants with HBsAg seroclearance 24 and 48 weeks after completion of NA treatment at any time during follow-up, the frequency of flares, and the proportion of participants requiring NA re-treatment during follow-up will be tabulated by intervention arm. The comparison among the intervention arms will be done using CMH chi-square test stratified by HBeAg status at screening (positive versus negative) and treatment history (naïve or NA suppressed) and corresponding 90% CIs without adjustment for multiple intervals.

The proportion of participants who reach HBV DNA undetectability after re-start of NA treatment during follow-up will also be tabulated by intervention arm and the comparison among the intervention arms will be done using the CMH chi-square test as described above.

The blood markers (such as HBsAg, HBeAg, HBV DNA, and ALT) during study intervention and follow-up will also be summarized by treatment arm over time and plotted. The proportion of participants with (sustained) reduction, suppression, and/or seroclearance considering single and multiple markers (such as HBsAg, HBeAg, HBV DNA, and ALT) will be summarized during follow-up. The proportion of participants with HBsAg and HBeAg seroconversion will be tabulated by intervention arm. Descriptive statistics on values and changes from baseline over time in HBsAg, HBeAg, and HBV DNA will be summarized by intervention arm. Additional summaries will be provided by the randomization stratification factors (HBeAg status at screening and treatment history).

The time to achieve HBsAg and HBeAg seroclearance will be summarized based on Kaplan-Meier estimates in tables and graphs. The proportion of participants with HBsAg levels and/or changes from baseline below/above different cut-offs, the proportion of HBeAg-positive participants with HBeAg levels and/or changes from baseline below/above different cut-offs, and the proportion of participants with HBV DNA levels and/or changes from baseline below/above different cut-offs will be analyzed as appropriate by intervention arm and over time. The proportion of participants with ALT decrease and normalization will be tabulated by intervention arm. The proportion of participants with virologic breakthrough will be summarized by intervention arm.

Graphic data displays will also be used to summarize the efficacy data by intervention arm and over time.

In addition, the potential association between treatment outcome and baseline factors (including but not limited to HBeAg status at screening, treatment history, baseline HBsAg levels, and other HBV and host characteristics) will be explored by multivariate analyses and exploration of interaction terms.[2] Exploratory subgroup summaries will be displayed graphically in forest plots.

9.4.1.4. Resistance Analyses

The results of HBV viral sequencing will be evaluated by the sponsor virologist. Pretreatment amino acid and/or nucleic acid substitutions in the HBV in all participants and relevant changes in the HBV in participants not responding to study intervention will be tabulated and described.

Additional exploratory characterization of the HBV viral sequence and phenotype may be performed and reported separately.

9.4.1.5. Patient-reported Outcome Analyses

Patient-reported outcome scores will be analyzed descriptively as mean scores over time, and (if applicable) evaluated based on the proportion of participants experiencing a clinically important improvement or worsening in PRO scores from baseline during study intervention and follow-up. Analyses will also be performed on PRO score changes from baseline at specific time points (Week 48, 72, 96) and between Week 48 and later time points for different subgroups: participants who meet the NA treatment completion criteria at Week 48 versus those who do not, and participants with versus participants without HBsAg seroclearance 24 weeks and 48 weeks after completion of all study intervention at Week 48. Further details will be provided in the SAP.

9.4.2. Safety Analyses

The safety analysis set will be used for all safety analyses.

Safety will be evaluated by means of descriptive summaries of AEs, clinical laboratory tests, ECGs, vital signs, and physical examinations. The safety analysis will be done for each study phase separately (ie, study intervention phase and follow-up phase). Results will be presented in tabular format and/or graphically by intervention arm and over time, as appropriate.

Adverse Events

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities. Intervention-emergent AEs are AEs with onset during the intervention phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported intervention-emergent AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized. AEs of interest will be analyzed separately.

Frequency tabulations, listings, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue study intervention due to an AE, or who experience a severe or a serious AE.

Clinical Laboratory Tests

Laboratory data will be summarized by laboratory test. Descriptive statistics (n, mean, SD, minimum, median, and maximum) will be calculated for each laboratory analyte for observed values and changes from baseline at each scheduled time point by intervention arm and study phase. A graphical presentation of changes from baseline over time in selected laboratory tests will be also used by intervention arm.

The laboratory abnormalities will be determined according to the criteria specified in the DAIDS Toxicity Grading Scale (see Section 10.9, Appendix 9, DAIDS Table) or in accordance with the normal ranges of the clinical laboratory if no gradings are available. The number and percentage of the participants who experience (worst) laboratory abnormalities will be tabulated by intervention arm and study phase. Shifts in toxicity grades will be cross-tabulated by intervention arm and study phase.

Electrocardiogram

Electrocardiogram data will be summarized by ECG parameter. Descriptive statistics will be calculated for observed values and changes from baseline at each scheduled time point by intervention arm. Frequency tabulations of the abnormalities will be made.

The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, RR interval, QT interval, and QT interval corrected for heart rate according to Fridericia's (QTcF).[12]

The percentage of participants with QTc interval >450 ms, >480 ms, or >500 ms will be summarized, as will the percentage of participants with QTc interval increases from baseline >30 ms or >60 ms. Shifts in QTc interval categories will be cross-tabulated by intervention arm and study phase.

All clinically relevant abnormalities in ECG waveform that are changes from the baseline readings will be reported (eg, changes in T-wave morphology or the occurrence of U-waves).

Vital Signs

Descriptive statistics of temperature, pulse rate, and supine SBP and DBP will be calculated for observed values and changes from baseline at each scheduled time point. The percentage of participants with values beyond clinically important limits will be summarized by intervention arm.

9.4.3. Other Analyses

Pharmacokinetic Analyses

Descriptive statistics (n, mean, SD, coefficient of variation [CV], geometric mean, median, minimum, and maximum) will be calculated for the plasma concentrations of JNJ-3976, JNJ-3924, JNJ-6379 and/or NA, as applicable, and for the derived plasma PK parameters (noncompartmental analysis and population PK analysis).

For each participant with intensive PK sampling, plasma concentration-time data of JNJ-3976, JNJ-3924, JNJ-6379, and/or NA will be graphically presented. Similarly, graphs of the mean plasma concentration-time profiles and overlay graphs with combined individual plasma concentration-time profiles will be produced. Pharmacokinetic parameters will be subjected to an exploratory graphical analysis, including various transformations, to get a general overview.

Population PK analysis of plasma concentration-time data of JNJ-3976, JNJ-3924, JNJ-6379, and/or NA (as applicable) will be performed using nonlinear mixed-effects modeling. Data may be combined with those from selected studies to support a relevant structural model. Available baseline participant characteristics (demographics, laboratory variables, genotypes, race, etc.) will be included in the model as necessary. Individual estimates of PK parameters will be generated from the population PK analysis for potential use in exposure-response analysis. For operational reasons, a snapshot date for PK samples to be analyzed will be defined, if required. Samples collected before this date will be analyzed for JNJ-3989 (ie, JNJ-3976 and JNJ-3924), JNJ-6379, and/or NA (as applicable) and will be included in the population PK analysis. Samples collected after the snapshot date will be analyzed at a later date, and may be included in a population PK re-analysis when they become available after database lock. Details of the population PK analysis will be described in a separate analysis plan and results will be reported separately.

Pharmacokinetic/Pharmacodynamic Analyses

Relationships of PK parameters for JNJ-3976, JNJ-3924, JNJ-6379, and/or NA (ETV, TAF and/or tenofovir), as applicable, with selected efficacy and with selected safety endpoints will be evaluated, applying graphical tools and, if feasible, statistical models.

Immune Analyses

Descriptive statistics (n, mean, SD, CV, geometric mean, median, minimum, and maximum) will be used to describe the magnitude of the IFN-γ T cell response or the CD4+ and CD8+ T-cell responses (expressing at least 1 cytokine such as IL-2, TNF-α or IFN-γ specific to any HBV antigen) as defined by ELISpot and/or ICS, respectively. Changes from baseline (if present) will also be tabulated for PBMCs during study intervention and follow-up. The proportion (%) of CHB patients with positive responses based on the magnitude of the IFN-γ T cell response or the CD4+ or CD8+ T cells expressing at least 1 of the cytokines amongst IL-2, TNF-α or IFN-γ for 1 of the HBV antigens as defined by ELISpot and/or ICS, respectively, will be determined.

Analyses will be conducted at the sponsor's discretion.

Pharmacogenomic Analyses

The statistical approach for analyzing the exploratory host DNA research may depend on the objective of the analyses (efficacy, safety, and PK) and possibly relevant genes at the time of analysis. Analyses will be conducted at the sponsor's discretion, will always be under the sponsor's supervision, and results will be presented either in the clinical study report or a separate report.

Host Biomarkers Analyses

Statistical approaches to explore correlations between clinical outcome and blood biomarkers vary and depend on the different data types of the applied technology platforms, as well as on the extent of observed differences between participants. Analyses will be conducted at the sponsor's discretion, will always be under the sponsor's supervision, and results will be presented either in the clinical study report or a separate report.

9.5. Interim Analyses

Interim analyses will be conducted to monitor safety and evaluate the time course of different disease markers to support the sponsor's internal decision-making, interactions with health authorities, as well as inform decisions about additional studies and/or investigation of other treatment combinations. The IAs are planned when:

- All participants have completed Week 60 (ie, 12 weeks after completion of investigational intervention at Week 48), or discontinued earlier.
- All participants have completed Week 72 (ie, 24 weeks after completion of investigational intervention at Week 48), or discontinued earlier.
- All participants have completed Week 96 (ie, 48 weeks after completion of investigational intervention at Week 48), or discontinued earlier.

One additional IA may be performed at the sponsor's discretion when all participants, who completed NA treatment at Week 48 of follow-up, have completed Week 120, ie, Week 24 of the extended follow-up, or discontinued earlier, to support interactions with health authorities.

All IAs will be performed by the sponsor because occurring after the primary analysis, which will be conducted at the time when all participants have completed Week 48 or discontinued earlier. Both primary and interim analyses will be based on all data available at the predefined cut-off time, including data at later time points for those participants who have reached subsequent visits.

Detailed approaches to define the decision rules, and the methods for IA of the safety and efficacy endpoints of interest will be described in the IA SAP.

9.5.1. Independent Data Monitoring Committee

An IDMC will be established for continuous monitoring of SAEs, AEs leading to discontinuation, and ALT flares. In addition, the IDMC will review the unblinded results of efficacy parameters measured by different HBV disease blood markers (eg, HBV DNA, HBeAg, HBsAg, etc).

The IDMC will have access and use the totality of unblinded results to make recommendations, including all safety and efficacy assessments available at a given interim milestone. Possible recommendations include, but are not limited to, stopping the study or any of the study interventions for safety concerns. The Sponsor Committee will review the time course of the

different HBV disease blood markers to make further decisions. Decision rules will be detailed and listed in the IDMC charter and will be non-binding.

The IDMC members will be appointed before the start of the study to review unblinded interim data for both safety and efficacy and formulate recommendation(s) to the Sponsor Committee, who will make the final decision(s). The Sponsor Committee includes representatives from the sponsor's Clinical, Biostatistics, Global Medical Safety and Virology departments who are not involved in the study conduct.

Details on the roles and responsibilities of the IDMC and Sponsor Committee, as well as the flows of communication, will be documented in the IDMC charter.

9.5.2. Independent Flare Expert Panel

An IFLEP will also be appointed. The IFLEP is composed of 3 independent medical experts with experience and expertise in hepatitis B and its treatment. The IFLEP will monitor ALT flares and will make recommendations regarding flare management based on an analysis of aggregate data.

In order to allow for an unbiased assessment, members of the committee will not serve as study investigators or as members of the IDMC and will be blinded to the treatment assigned to each participant.

Further details on the IFLEP process will be included in the IFLEP charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Definitions of Terms

AE	adverse event
AFP	alpha-fetoprotein
A/H	animal/human ratio
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{0\text{-}xh}$	area under the plasma concentration-time curve from administration to x h
$AUC_{0\text{-}last}$	area under the plasma concentration-time curve from administration to last quantifiable sampling point
AUC_{tau}	area under the plasma concentration-time curve over the dosing interval (tau) at steady-state
AUC_{∞}	area under the plasma concentration-time curve to last sampling point from time zero extrapolated to infinity
BCRP	breast cancer resistance protein
BMI	body mass index
bpm	beats per minute
CAM	capsid assembly modulator
cccDNA	covalently closed circular deoxyribonucleic acid
CHB	chronic hepatitis B
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	total apparent oral clearance
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CT	computed tomography
CV	coefficient of variation
CYP	cytochrome P450
DAIDS	Division of Acquired Immunodeficiency Syndrome
DBP	diastolic blood pressure
DDI	drug-drug interaction
DNA	deoxyribonucleic acid
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
ED_{50}	dose that produces half of E_{max}
eDC	electronic data capture
EFD	embryofetal development
eGFR	estimated glomerular filtration rate
ELISpot	enzyme-linked immunospot
E_{max}	maximum effect
Ext FU Wx	Extended Follow-up Week x
EOS	end of study
ETV	entecavir
FSH	Follicle-stimulating hormone
FU Wx	Follow-up Week x
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBc	hepatitis B core protein
HBQOL	Hepatitis B Quality of Life
HBcrAg	hepatitis B core-related antigen
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBs	hepatitis B surface

HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
HIV-1(-2)	human immunodeficiency virus type 1 (type 2)
HRQoL	health-related quality of life
HRT	hormonal replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ICS	intracellular cytokine staining
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFLEP	Independent Flare Expert Panel
IFN	interferon
IFN-γ	gamma interferon
IgM	immunoglobulin M
IL	interleukin
INR	International Normalized Ratio
IRB	Institutional Review Board
ISR	injection site reaction
ITT	Intent-to-treat
IU/mL	International Units Per Milliliter
IWRS	interactive web response system
LLN	lower limit of normal
LLOQ	lower limit of quantification
MCP-Mod	Multiple Comparison Procedure-Modeling
MCT	Multiple Contrast Test
MH	Mantel-Haenszel
MoA	mode of action
MRI	magnetic resonance imaging
NA	nucleos(t)ide analog
NOAEL	no observed adverse effect level
PD	pharmacodynamic(s)
PGIC	Patient Global Impression of Change
PK	pharmacokinetic(s)
PBMC	peripheral blood mononuclear cell
pgRNA	pre-genomic ribonucleic acid
PI	prediction interval
PQC	Product Quality Complaint
PRO	patient-reported outcome
qd	once daily
QTcF	QT interval corrected for heart rate according to Fridericia
RBC	red blood cell
RNA	ribonucleic acid
RNAi	ribonucleic acid interference
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
$SigE_{max}$	sigmoid E_{max}
siRNA	small interfering RNA
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2term}$	terminal half-life

t_{max}	time to reach the maximum plasma concentration
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TNF	tumor necrosis factor
ULN	upper limit of normal
US	United States
WBC	white blood cell

Definitions of Terms

Study intervention	JNJ-73763989 or placebo, JNJ-56136379 or placebo, and NA (either ETV, TDF, or TAF)
Functional cure	HBsAg seroclearance 24 weeks after end of treatment
HBsAg or HBeAg seroclearance	HBsAg or HBeAg negativity, respectively, based on the assay used
HBsAg or HBeAg seroconversion	HBsAg or HBeAg negativity and anti-HBs or anti-HBe antibody positivity, respectively
Virologic breakthrough	Confirmed on-treatment HBV DNA increase by >1 $\log_{10}$ IU/mL from nadir or confirmed on-treatment HBV DNA level >200 IU/mL in participants who had HBV DNA level <LLOQ of the HBV DNA assay
ALT/AST nadir	Lowest ALT/AST value during study participation

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the central laboratory:

Protocol-required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="3">Parameters</th></tr>
<tr><td rowspan="2">Hematology</td><td>Platelet count
RBC count
Hemoglobin
Hematocrit
Reticulocyte count
Reticulocyte Index</td><td><u>RBC Indices:</u>
Mean corpuscular volume
Mean corpuscular hemoglobin
Mean corpuscular hemoglobin concentration</td><td><u>WBC count with Differential:</u>
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td colspan="3">Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. A RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.</td></tr>
<tr><td rowspan="2">Clinical Chemistry</td><td colspan="2">Sodium
Potassium
Chloride
Bicarbonate
Blood urea nitrogen
Creatinine
Glucose
AST/Serum glutamic-oxaloacetic
ALT/Serum glutamic-oxaloacetic
Gamma-glutamyltransferase (GGT)
Total, conjugated and unconjugated bilirubin
Alkaline phosphatase
Creatine phosphokinase</td><td>Lactic acid dehydrogenase
Uric acid
Calcium
Phosphate
Albumin
Total protein
Total cholesterol
High-density lipoprotein cholesterol
Low-density lipoprotein cholesterol
Triglycerides
Magnesium
Lipase
Amylase</td></tr>
<tr><td colspan="3">Note: Creatinine clearance (eGFR calculated by the CKD-EPI formula) will be assessed.

Note: Reflex testing of pancreatic amylase should be done in case of amylase or lipase increase from screening onwards.</td></tr>
<tr><td rowspan="2">Routine Urinalysis</td><td colspan="2"><u>Dipstick</u>
Specific gravity
pH
Glucose
Protein
Blood
Ketones
Bilirubin
Urobilinogen
Nitrite
Leukocyte esterase</td><td><u>Sediment (if dipstick result is abnormal)</u>
RBCs
WBCs
Epithelial cells
Crystals
Casts
Bacteria</td></tr>
<tr><td colspan="3">In case of a positive dipstick result, a urine sample will be set aside for additional examination of the positive parameter at the central laboratory (eg, quantification as</td></tr>
</table>

	applicable).	
Urine Chemistry (quantitative measurement)	Creatinine Sodium Phosphate	Glucose Protein Albumin
Renal Biomarkers	Retinol binding protein Beta-2-microglobulin	
	Note: These renal biomarkers are to assess proximal renal tubular function.	
Other Screening Tests	• Serum pregnancy testing for women of childbearing potential at screening. • Urine pregnancy testing for women of childbearing potential at the time points indicated in the Schedule of Activities. • Follicle-stimulating hormone (FSH) testing for postmenopausal women at screening. • Testing for hepatitis A, B, C, D, and E virus and HIV-1 and -2 at screening. • Testing for HBsAg, HBeAg, HBcrAg, and anti-HBs and anti-HBe antibodies at the time points indicated in the Schedule of Activities. • Determination of coagulation parameters will be performed at the time points indicated in the Schedule of Activities. INR will be calculated by the central laboratory. • Alpha-fetoprotein at screening.	
Other optional tests in response to ALT flare (refer to Section 10.6 Appendix 6: Intervention-emergent ALT/AST Elevations)	Testing for HIV-1 and -2, and hepatitis A, C, and E Testing for CMV, HSV, EBV infection Ig-Electrophoresis	

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments

- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study intervention
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants

- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

FINANCIAL DISCLOSURE

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may

entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of his or her disease. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

Participants will be asked for consent to provide optional host DNA samples for research (where local regulations permit). After informed consent for the study is appropriately obtained, the participant will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the participant.

If the participant is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the participant is obtained.

DATA PROTECTION

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review,

and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory DNA, PK/PD, and biomarker research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

LONG-TERM RETENTION OF SAMPLES FOR ADDITIONAL FUTURE RESEARCH

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand JNJ-3989 and JNJ-6379, and the NAs (ETV, TDF, and TAF), to understand chronic HBV infection, to understand differential intervention responders, and to develop tests/assays related to JNJ-3989 and JNJ-6379, the NAs (ETV, TDF, and TAF), and chronic HBV infection. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal From the Use of Research Samples).

COMMITTEES STRUCTURE

Independent Data Monitoring Committee

An IDMC will be established for continuous monitoring of SAEs, AEs leading to discontinuation, and ALT flares. In addition, at prespecified IA time points, the IDMC will review the unblinded results of the IAs of efficacy parameters measured by different HBV disease blood markers (eg, HBV DNA, HBeAg, HBsAg, etc).

The IDMC members will be appointed before the start of the study to review unblinded interim data for both safety and efficacy and formulate recommendation(s) to the Sponsor Committee, who will make the final decision(s). The Sponsor Committee includes representatives from the sponsor's Clinical, Biostatistics, Global Medical Safety and Virology departments who are not involved in the study conduct.

Details on the roles and responsibilities of the IDMC and Sponsor Committee, as well as the flows of communication, will be documented in the IDMC charter.

Independent Flare Expert Panel

An IFLEP will also be appointed. The IFLEP is composed of 3 independent medical experts with experience and expertise in hepatitis B and its treatment. The IFLEP will monitor ALT flares and will make recommendations regarding flare management based on an analysis of aggregate data.

In order to allow for an unbiased assessment, members of the committee will not serve as study investigators or as members of the IDMC and will be blinded to the treatment assigned to each participant.

Further details on the IFLEP process will be included in the IFLEP charter.

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

All information, including but not limited to information regarding JNJ-3989 and JNJ-6379 or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of JNJ-3989 and JNJ-6379, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of pharmacogenomic or exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the

sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the EOS in order to ensure the statistical analyses are relevant.

DATA QUALITY ASSURANCE

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review CRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

CASE REPORT FORM COMPLETION

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in CRF. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the participant's source documents. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

All participative measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the electronic data capture (eDC) tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

SOURCE DOCUMENTS

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the CRF and will be considered source data:

- Race
- Blood pressure and pulse/heart rate
- Height and weight
- Details of physical examination

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the CRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the CRF.

MONITORING

The sponsor will use a combination of monitoring techniques (central, remote, or on-site monitoring) to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will

be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

ON-SITE AUDITS

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

RECORD RETENTION

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

STUDY AND SITE START AND CLOSURE

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product (Definition per ICH).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last AE recording).

Serious Adverse Event

An SAE based on ICH and European Union Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (eg, death from anaphylaxis), the event

must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For JNJ-3989 and JNJ-6379, the expectedness of an AE will be determined by whether or not it is listed in the IB. For ETV, TDF, and TAF with a marketing authorization, the expectedness of an AE will be determined by whether or not it is listed in the package insert/summary of product characteristics.

Adverse Event Associated With the Use of the Intervention

An AE is considered associated with the use of the intervention if the attribution is possible, probable, or very likely by the definitions listed below (see Attribution Definitions).

ATTRIBUTION DEFINITIONS

Not Related

An AE that is not related to the use of the intervention.

Doubtful

An AE for which an alternative explanation is more likely, eg, concomitant treatment(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An AE that might be due to the use of the intervention. An alternative explanation, eg, concomitant treatment(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An AE that might be due to the use of the intervention. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant treatment(s), concomitant disease(s).

Very Likely

An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant treatment(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

SEVERITY CRITERIA

An assessment of severity grade will be made by the investigator using the general categorical descriptors outlined in the DAIDS Toxicity Grading Scale (see Section 10.9, Appendix 9, DAIDS Table).

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

SPECIAL REPORTING SITUATIONS

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Medication error involving a sponsor product (with or without participant/patient exposure to the sponsor study intervention, eg, name confusion)
- Exposure to a sponsor study intervention from breastfeeding

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the CRF.

PROCEDURES

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICFs, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

The cause of death of a participant in a study, whether or not the event is expected or associated with the study intervention, is considered an SAE.

CONTACTING SPONSOR REGARDING SAFETY

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure

appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

10.5. Appendix 5: Rash Management

Table 9: Management of Rash Events by Severity Grade

	Definition	Study Intervention Action	Activities by Day[a]	Referral to Dermatologist and Dermatology Activities
Grade 1 rash (with or without pruritus)[b]	Erythema	Study intervention intake may be continued at the investigator's discretion	Day 0: optional on site visit for initial rash evaluation may be performed at the investigator's discretion. Safety laboratory assessments may be performed at the investigator's discretion (recommended if visit occurs). Digital pictures* of skin lesions may be taken at the investigator's discretion. Determine if participant was adhering to the recommended sun-protective measures. If appropriate, provide sun protection counseling. Day 1 and thereafter: appropriate follow-up visits at the investigator's discretion until resolution of rash. Safety laboratory assessments and photography (digital pictures* of skin lesions) may be performed at the investigator's discretion. * Digital pictures to be taken at the clinical site upon consent of the participant.	Not required
Grade 2 rash (with or without pruritus)[b]	Diffuse, maculopapular rash, or dry desquamation	Study intervention intake may be continued at the investigator's discretion	Day 0: required on-site visit (if a visit is not possible, telephone contact with the participant should take place to collect information and give advice on the necessary measures to be taken).	Referral to dermatologist at the discretion of the investigator[c] Biopsy not required,

Table 9: Management of Rash Events by Severity Grade

	Definition	Study Intervention Action	Activities by Day[a]	Referral to Dermatologist and Dermatology Activities
			Safety laboratory assessments may be performed at the investigator's discretion (recommended). Digital pictures* of skin lesions may be taken at the investigator's discretion. Digital pictures* of skin lesions are recommended in case consultation of a dermatologist is required. Determine if participant was adhering to the recommended sun-protective measures. If appropriate, provide sun protection counseling. Day 1 and thereafter: appropriate follow-up visits at the investigator's discretion until resolution of rash or until clinical stability is reached. Safety laboratory assessments are required on Day 1 and are required thereafter only if the previous values were abnormal (but may be performed at the investigator's discretion). If the rash progresses to a higher grade, safety laboratory assessments of the higher grade should be followed. Digital pictures* of skin lesions may be taken at the investigator's discretion. * Digital pictures to be taken at the clinical site upon consent of the participant.	but may be performed at the dermatologist's discretion

Table 9: Management of Rash Events by Severity Grade

	Definition	Study Intervention Action	Activities by Day[a]	Referral to Dermatologist and Dermatology Activities
Grade 3 rash[b]	Vesiculation, moist desquamation, or ulceration OR Any cutaneous event with 1 of the following: - Elevations in AST/ALT >2×baseline value - Fever >38°C or 100°F - Eosinophils >1.00×10^3/μL - Serum sickness-like reaction	Must permanently discontinue JNJ-3989 and JNJ-6379; no rechallenge allowed NA treatment may be discontinued based on investigator judgement in consultation with the sponsor	Day 0: required on-site visit. Safety laboratory assessments required to be performed. Digital pictures* of skin lesions may be taken at the investigator's discretion (recommended). Determine if participant was adhering to the recommended sun-protective measures. If appropriate, provide sun protection counseling. Day 1: required on-site visit. Safety laboratory assessments required to be performed. Digital pictures* of skin lesions may be taken at the investigator's discretion (recommended). Further visit(s): appropriate follow-up required until resolution of rash or until clinical stability is reached. Safety laboratory assessments and photography (digital pictures* of skin lesions) are recommended to be performed until the rash severity resolves to grade 2 or grade 1. * Digital pictures to be taken at the clinical site upon consent of the participant.	Required[c] Biopsy not required, but may be performed at the dermatologist's discretion.

Table 9: Management of Rash Events by Severity Grade

	Definition	Study Intervention Action	Activities by Day[a]	Referral to Dermatologist and Dermatology Activities
Grade 4 rash	Exfoliative dermatitis OR Mucous membrane involvement in at least 2 distinct sites OR Erythema multiforme major OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis OR Necrosis requiring surgery	Must permanently discontinue JNJ-3989 and JNJ-6379; no rechallenge allowed NA treatment may be discontinued based on investigator judgement in consultation with the sponsor	Day 0: required on-site visit. Safety laboratory assessments required to be performed. Digital pictures* of skin lesions may be taken at the investigator's discretion (recommended). Determine if participant was adhering to the recommended sun-protective measures. If appropriate, provide sun protection counseling. Day 1: required on-site visit. Safety laboratory assessments required to be performed. Digital pictures* of skin lesions may be taken at the investigator's discretion (recommended). Further visit(s): appropriate follow-up required until resolution of rash or until clinical stability is reached. Safety laboratory assessments and photography (digital pictures* of skin lesions) are recommended to be performed until the rash severity resolves to grade 2 or grade 1. * Digital pictures to be taken at the clinical site upon consent of the participant.	Required[c] Biopsy required and to be performed as soon as possible after the onset of the rash.

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; NA: nucleos(t)ide analog.

[a] Day 0 of the rash is the first day of investigator assessment and not the first day of rash as reported by the participant. The initial visit should be conducted as soon as

Table 9: Management of Rash Events by Severity Grade				
	Definition	**Study Intervention Action**	**Activities by Day[a]**	**Referral to Dermatologist and Dermatology Activities**

possible after the participant contacts the investigator to report the AE (ie, preferably on Day 0). The initial visit and subsequent visits to manage the rash may require unscheduled visit(s).

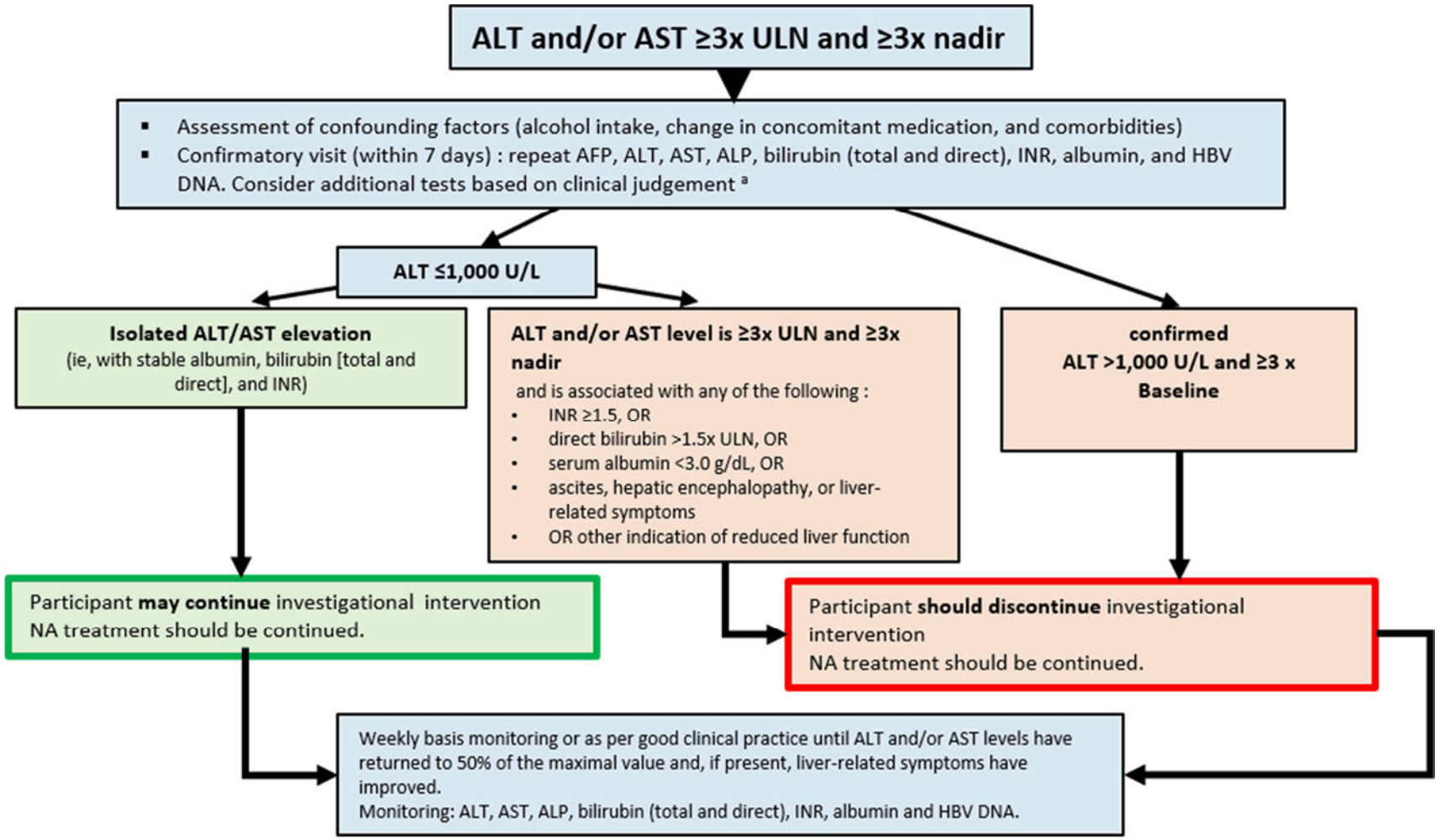
[b] The participant should be advised to contact the investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms appear, or if mucosal involvement develops. In case the rash evolves to a higher grade than that first observed, management of the rash should follow the guidelines indicated for the higher grade.

[c] If applicable, dermatologist visit should occur preferably within 24 hours after onset of rash.

Notes:

- Local laboratory assessments are to be used for rash management. The values of the local laboratory assessments need to be transcribed in the eCRF by the study site personnel.
- Digital pictures that are collected, dermatological consultation reports or biopsy reports that become available, should be de-identified and provided to the sponsor.

10.6. Appendix 6: Intervention-emergent ALT/AST Elevations



a: Additional tests may be considered based on clinical judgement in case of confirmed ALT flares
- Hepatitis A, Delta, C, E: IgM anti-HAV; delta IgM, IgG & PCR, HCV RNA, IgM & IgG anti-HEV, HEV RNA
- CMV, HSV, EBV infection: IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV, PCR
- HIV
- Ig –Electrophoresis

10.7. Appendix 7: Cardiovascular Safety – Abnormalities

ECG

All important abnormalities from the ECG readings will be listed.

Abnormality Code	ECG parameter			
	Heart Rate	PR	QRS	$QT_{corrected}$
Abnormalities on actual values				
Abnormally low	<45 bpm	NAP	-	-
Abnormally high	≥120 bpm	>220 ms	≥120 ms	-
Borderline prolonged QT	-	-	-	450 ms < QTc ≤480 ms
Prolonged QT	-	-	-	480 ms < QTc ≤500 ms
Pathologically prolonged QT	-	-	-	QTc >500 ms
Abnormalities on changes from baseline (ΔQTc)				
Normal QTc change	-	-	-	ΔQTc <30 ms
Borderline QTc change	-	-	-	30 ms ≤ ΔQTc ≤60 ms
Abnormally high QTc change	-	-	-	ΔQTc >60 ms

ECG: electrocardiogram; NAP = not applicable
For absolute QTc parameters the categories are defined based on the ICH E14 GuidanceF[a]

Vital Signs[b]

The following abnormalities will be defined for vital signs:

Abnormality Code	Vital Signs parameter		
	Pulse	DBP	SBP
Abnormalities on actual values			
Abnormally low	≤45 bpm	≤50 mmHg	≤90 mmHg
Grade 1 or mild	-	>90 mmHg - <100 mmHg	>140 mmHg - <160 mmHg
Grade 2 or moderate	-	≥100 mmHg - <110 mmHg	≥160 mmHg - <180 mmHg
Grade 3 or severe	-	≥110 mmHg	≥180 mmHg
Abnormally high	≥120 bpm	-	-

DBP: diastolic blood pressure; SBP: systolic blood pressure

[a] The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs CHMP/ICH/2/04, May 2005.
[b] The classification of AEs related to hypotension and hypertension will be done according to the DAIDS grading scale.

10.8. Appendix 8: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Section 10.4, Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

  If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device
• Intrauterine hormone-releasing system
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] oral intravaginal transdermal injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] oral injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
[b] Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention.
[c] Male condom and female condom should not be used together (due to risk of failure with friction).

10.9. Appendix 9: DAIDS Table

DIVISION OF AIDS (DAIDS) TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS, VERSION 2.1, PUBLISH DATE: JULY, 2017

The DAIDS grading table is a descriptive terminology to be utilized for AE reporting in this study. A grading (severity) scale is provided for each AE term.

General Instructions

Grading Adult and Pediatric Adverse Events

When a single parameter is not appropriate for grading an AE in both adult and pediatric populations, separate parameters with specified age ranges are provided. If there is no distinction between adult and pediatric populations, the listed parameter should be used for grading an AE in both populations.

Determining Severity Grade for Parameters Between Grades

If the severity of an AE could fall under either 1 of 2 grades (eg, the severity of an AE could be either grade 2 or grade 3), sites should select the higher of the 2 grades.

Laboratory normal ranges should be taken into consideration to assign gradings to a laboratory value.

Definitions

Basic self-care functions	Adults: activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding Young children: activities that are age and culturally appropriate (eg, feeding self with culturally appropriate eating implements)
Usual social & functional activities	Activities which adults and children perform on a routine basis and those which are part of regular activities of daily living, for example: Adults: adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, or pursuing a hobby Young Children: activities that are age and culturally appropriate (eg, social interactions, play activities, learning tasks)
Intervention	Medical, surgical, or other procedures recommended or provided by a healthcare professional for the treatment of an AE.

Estimating Severity Grade for Parameters not Identified in the Grading Table

The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical AE **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life threatening symptoms causing inability to perform basic self care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

NOTE: Laboratory abnormalities may have their grading defined in the DAIDS table below, however, all laboratory abnormalities do not necessarily represent an AE. If a laboratory abnormality is considered an AE, the AE need not have the same grade as the laboratory abnormality itself. The AE grade for a laboratory abnormality should be defined by the table above.

MAJOR CLINICAL CONDITIONS				
CARDIOVASCULAR				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non urgent intervention indicated	Non life threatening symptoms AND Non urgent intervention indicated	Life threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities[a] ***Hypertension*** *(with the lowest reading taken after repeat testing during a visit)* *aged ≥18 years*	140 to <160 mmHg systolic OR 90 to <100 mmHg diastolic	≥160 to <180 mmHg systolic OR ≥100 to <110 mmHg diastolic	≥180 mmHg systolic OR ≥110 mmHg diastolic	Life threatening consequences in a participant not previously diagnosed with hypertension (eg, malignant hypertension) OR Hospitalization indicated
aged <18 years	>120/80 mmHg	≥95th to <99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life threatening consequences in a participant not previously diagnosed with hypertension (eg, malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only 1*	NAP	NAP	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction

ECG: electrocardiogram; IV: intravenous; NAP: not applicable

[a] Blood pressure norms for children aged <18 years can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Pediatrics 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009 2107C.

MAJOR CLINICAL CONDITIONS				
CARDIOVASCULAR				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (eg, hypoxemia) OR Intervention indicated (eg, oxygen)	Life threatening consequences OR Urgent intervention indicated (eg, vasoactive medications, ventricular assist device, heart transplant)
Hemorrhage (with significant acute blood loss)	NAP	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤2 units packed RBCs indicated	Life threatening hypotension OR Transfusion of >2 units packed RBCs (for children, packed RBCs >10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only 1* *aged >16 years*	PR interval 0.21 to <0.25 seconds	PR interval ≥0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥3.0 seconds	Complete AV block
aged ≤16 years	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥3.0 seconds	Complete AV block
Prolonged QTc Interval as per Fridericia's formula[b]	0.45 to 0.47 seconds	>0.47 to 0.50 seconds	>0.50 seconds OR ≥0.06 seconds above baseline	Life threatening consequences (eg, TdP, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only 1*	NAP	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life threatening embolic event (eg, pulmonary embolism, thrombus)

AV: atrioventricular; NAP: not applicable; RBC: red blood cell; TdP: Torsades de Pointes
[b] Modified by the sponsor.

DERMATOLOGIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Alopecia (scalp only)	Detectable by participant, representative, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NAP	NAP
Bruising	Localized to 1 area	Localized to more than 1 area	Generalized	NAP
Cellulitis	NAP	Nonparenteral treatment indicated (eg, oral antibiotics, antifungals, antivirals)	IV treatment indicated (eg, IV antibiotics, antifungals, antivirals)	Life threatening consequences (eg, sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NAP	NAP
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NAP	NAP
Petechiae	Localized to 1 area	Localized to more than 1 area	Generalized	NAP
Pruritus[c] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NAP
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae OR superficial ulcerations of mucous membrane limited to 1 site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving 2 or more distinct mucosal sites OR Stevens Johnson syndrome OR Toxic epidermal necrolysis

IV: intravenous; NAP: not applicable

[c] For pruritus associated with injections or infusions, refer to the SITE REACTIONS TO INJECTIONS AND INFUSIONS section.

ENDOCRINE AND METABOLIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life threatening consequences (eg, ketoacidosis, hyperosmolar nonketotic coma, end organ failure)
Gynecomastia	Detectable by participant, representative, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NAP
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life threatening consequences (eg, thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life threatening consequences (eg, myxedema coma)
Lipoatrophy[d]	Detectable by participant, representative, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NAP
Lipohypertrophy[e]	Detectable by participant, representative, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NAP

NAP: not applicable

[d] A disorder characterized by fat loss in the face, extremities, and buttocks.

[e] A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

GASTROINTESTINAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life threatening consequences OR Aggressive intervention indicated (eg, tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (eg, diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life threatening consequences
Bloating or Distension *Report only 1*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NAP
Cholecystitis	NAP	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life threatening consequences (eg, sepsis, perforation)
Constipation	NAP	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life threatening consequences (eg, obstruction)
Diarrhea *aged ≥1 year*	Transient or intermittent episodes of unformed stools OR Increase of ≤3 stools over baseline per 24 hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24 hour period	Increase of ≥7 stools per 24 hour period OR IV fluid replacement indicated	Life threatening consequences (eg, hypotensive shock)
aged <1 year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life threatening consequences (eg, liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia *Report only 1 and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life threatening consequences (eg, hypotensive shock)

IV: intravenous; NAP: not applicable

GASTROINTESTINAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Mucositis or Stomatitis *Report only 1 and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life threatening consequences (eg, aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (<24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for >48 hours OR Rehydration indicated (eg, IV fluids)	Life threatening consequences (eg, hypotensive shock)
Pancreatitis	NAP	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life threatening consequences (eg, circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NAP	NAP	Intervention indicated	Life threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life threatening consequences (eg, perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NAP	NAP
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (eg, IV fluids)	Life threatening consequences (eg, hypotensive shock)

IV: intravenous; NAP: not applicable

MUSCULOSKELETAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self care functions
Osteonecrosis	NAP	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self care functions
Osteopenia[f] *aged ≥30 years*	BMD t score 2.5 to 1	NAP	NAP	NAP
aged <30 years	BMD z score 2 to 1	NAP	NAP	NAP
Osteoporosis[f] *aged ≥30 years*	NAP	BMD t score < 2.5	Pathologic fracture (eg, compression fracture causing loss of vertebral height)	Pathologic fracture causing life threatening consequences
aged <30 years	NAP	BMD z score < 2	Pathologic fracture (eg, compression fracture causing loss of vertebral height)	Pathologic fracture causing life threatening consequences

BMD: bone mineral density; NAP: not applicable

[f] Bone mineral density t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

NEUROLOGIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Acute CNS Ischemia	NAP	NAP	Transient ischemic attack	Cerebral vascular accident (eg, stroke with neurological deficit)
Altered Mental Status (for Dementia, refer to *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full time basis indicated	Disability causing inability to perform basic self care functions OR Institutionalization indicated
Developmental Delay *Specify type, if applicable* *aged <18 years*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function

CNS: central nervous system; NAP: not applicable

NEUROLOGIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self care functions
Seizures ***New Onset Seizure*** *aged ≥18 years*	NAP	NAP	1 to 3 seizures	Prolonged and repetitive seizures (eg, status epilepticus) OR Difficult to control (eg, refractory epilepsy)
aged <18 years (includes new or pre existing febrile seizures)	Seizure lasting <5 minutes with <24 hours postictal state	Seizure lasting 5 to <20 minutes with <24 hours postictal state	Seizure lasting ≥20 minutes OR >24 hours postictal state	Prolonged and repetitive seizures (eg, status epilepticus) OR Difficult to control (eg, refractory epilepsy)
Pre existing Seizure	NAP	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (eg, severity or focality)	Prolonged and repetitive seizures (eg, status epilepticus) OR Difficult to control (eg, refractory epilepsy)
Syncope	Near syncope without loss of consciousness (eg, pre syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NAP

NAP: not applicable

PREGNANCY, PUERPERIUM, AND PERINATAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Stillbirth (report using mother's participant ID) *Report only 1*	NAP	NAP	Fetal death occurring at ≥20 weeks gestation	NAP
Preterm Birth (report using mother's participant ID)	Live birth at 34 to <37 weeks gestational age	Live birth at 28 to <34 weeks gestational age	Live birth at 24 to <28 weeks gestational age	Live birth at <24 weeks gestational age
Spontaneous Abortion or Miscarriage[g] (report using mother's participant ID) *Report only 1*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NAP

ID: identity, NAP: not applicable
[g] A pregnancy loss occurring at <20 weeks gestational age.

PSYCHIATRIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NAP
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self care functions
Suicidal Ideation or Attempt *Report only 1*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

NAP: not applicable

RESPIRATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥70% to <80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50% to <70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25% to <50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow <25% OR Life threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only 1*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90% to <95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry <90%	Respiratory failure with ventilator support indicated (eg, CPAP, BPAP, intubation)

BPAP: biphasic positive airway pressure; CPAP: continuous positive airway pressure; NAP: not applicable

SENSORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hearing Loss *aged ≥12 years*	NAP	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (>80 dB at 2 kHz and above) OR Nonserviceable hearing (ie, >50 dB audiogram and <50% speech discrimination)
aged <12 years (based on a 1, 2, 3, 4, 6, and 8 kHz audiogram)	>20 dB hearing loss at ≤4 kHz	>20 dB hearing loss at >4 kHz	>20 dB hearing loss at ≥3 kHz in 1 ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NAP
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medical intervention indicated	Posterior or pan uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

dB: decibel; kHz: kilohertz; NAP: not applicable

SYSTEMIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NAP
Cytokine Release Syndrome[h]	Mild signs and symptoms AND Therapy (ie, antibody infusion) interruption not indicated	Therapy (ie, antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life threatening consequences (eg, requiring pressor or ventilator support)
Fatigue or Malaise *Report only 1*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self care functions
Fever (non axillary temperatures only)	38.0°C to <38.6°C or 100.4°F to <101.5°F	≥38.6°C to <39.3°C or ≥101.5°F to <102.7°F	≥39.3°C to <40.0°C or ≥102.7°F to <104.0°F	≥40.0°C or ≥104.0°F
Pain[i] (not associated with study intervention injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self care functions OR Hospitalization indicated
Serum Sickness[j]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (eg, antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (eg, steroids or IV fluids)	Life threatening consequences (eg, requiring pressor or ventilator support)

IV: intravenous; NAP: not applicable

[h] A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.

[i] For pain associated with injections or infusions, refer to the SITE REACTIONS TO INJECTIONS AND INFUSIONS section.

[j] A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.

SYSTEMIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Underweight[k] *aged >5 to 19 years*	WHO BMI z score < 1 to 2	WHO BMI z score < 2 to 3	WHO BMI z score < 3	WHO BMI z score < 3 with life threatening consequences
aged 2 to 5 years	WHO Weight for height z score < 1 to 2	WHO Weight for height z score < 2 to 3	WHO Weight for height z score < 3	WHO Weight for height z score < 3 with life threatening consequences
aged <2 years	WHO Weight for length z score < 1 to 2	WHO Weight for length z score < 2 to 3	WHO Weight for length z score < 3	WHO Weight for length z score < 3 with life threatening consequences
Unintentional Weight Loss (excludes postpartum weight loss)	NAP	5% to <9% loss in body weight from baseline	≥9% to <20% loss in body weight from baseline	≥20% loss in body weight from baseline OR Aggressive intervention indicated (eg, tube feeding, total parenteral nutrition)

BMI: body mass index; NAP: not applicable; WHO: World Health Organization

[k] WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007 bmi for age/en/ for participants aged >5 to 19 years and http://www.who.int/childgrowth/standards/chart catalogue/en/ for those aged ≤5 years.

URINARY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Urinary Tract Obstruction	NAP	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life threatening consequences

NAP: not applicable

SITE REACTIONS TO INJECTIONS AND INFUSIONS				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Injection Site Pain or Tenderness *Report only 1*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self care function OR Hospitalization indicated
Injection Site Erythema or Redness[1] *Report only 1* *aged >15 years*	2.5 to <5 cm in diameter OR 6.25 to <25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥5 to <10 cm in diameter OR ≥25 to <100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥10 cm in diameter OR ≥100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life threatening consequences (eg, abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
aged ≤15 years	≤2.5 cm in diameter	>2.5 cm in diameter with <50% surface area of the extremity segment involved (eg, upper arm or thigh)	≥50% surface area of the extremity segment involved (eg, upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life threatening consequences (eg, abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only 1* *aged >15 years*	Same as for **Injection Site Erythema or Redness**, *aged >15 years*	Same as for **Injection Site Erythema or Redness**, *aged >15 years*	Same as for **Injection Site Erythema or Redness**, *aged >15 years*	Same as for **Injection Site Erythema or Redness**, *aged >15 years*
aged ≤15 years	Same as for **Injection Site Erythema or Redness**, *aged ≤15 years*	Same as for **Injection Site Erythema or Redness**, *aged ≤15 years*	Same as for **Injection Site Erythema or Redness**, *aged ≤15 years*	Same as for **Injection Site Erythema or Redness**, *aged ≤15 years*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in <48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NAP

NAP: not applicable

[1] Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

LABORATORY VALUES[m]				
CHEMISTRIES				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Acidosis	NAP	pH ≥7.3 to <LLN	pH <7.3 without life threatening consequences	pH <7.3 with life threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to <LLN *30 to <LLN*	≥2.0 to <3.0 *≥20 to <30*	<2.0 *<20*	NAP
ALP, High	1.25 to <2.5×ULN	2.5 to <5.0×ULN	5.0 to <10.0×ULN	≥10.0×ULN
Alkalosis	NAP	pH >ULN to ≤7.5	pH >7.5 without life threatening consequences	pH >7.5 with life threatening consequences
ALT or SGPT, High *Report only 1*	1.25 to <2.5×ULN	2.5 to <5.0×ULN	5.0 to <10.0×ULN	≥10.0×ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only 1*	1.1 to <1.5×ULN	1.5 to <3.0×ULN	3.0 to <5.0×ULN	≥5.0×ULN
AST or SGOT, High *Report only 1*	1.25 to <2.5×ULN	2.5 to <5.0×ULN	5.0 to <10.0×ULN	≥10.0×ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to <LLN *16.0 to <LLN*	11.0 to <16.0 *11.0 to <16.0*	8.0 to <11.0 *8.0 to <11.0*	<8.0 *<8.0*
Bilirubin ***Direct Bilirubin,[n] High*** *aged >28 days*	NAP	NAP	>ULN with other signs and symptoms of hepatotoxicity	>ULN with life threatening consequences (eg, signs and symptoms of liver failure)
aged ≤28 days	ULN to ≤1 mg/dL	>1 to ≤1.5 mg/dL	>1.5 to ≤2 mg/dL	>2 mg/dL
Total Bilirubin, High *aged >28 days*	1.1 to <1.6×ULN	1.6 to <2.6×ULN	2.6 to <5.0×ULN	≥5.0×ULN
aged ≤28 days	Refer to Appendix A[o]	Refer to Appendix A[o]	Refer to Appendix A[o]	Refer to Appendix A[o]

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LLN: lower limit of normal; mEq: milliequivalent; NAP: not applicable; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamate pyruvate transaminase; ULN: upper limit of normal

[m] Reminder: An asymptomatic abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited time frame unless it meets protocol specific reporting requirements.

[n] Direct bilirubin >1.5 mg/dL in a participant aged <28 days should be graded as grade 2, if <10% of the total bilirubin.

[o] Appendix A "Total Bilirubin Table for Term and Preterm Neonates" is provided together with the DAIDS table corrected version 2.1 at the following URL: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf. Appendix A is not applicable for this study.

LABORATORY VALUES				
CHEMISTRIES				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Calcium, High (mg/dL; *mmol/L*) *aged ≥7 days*	10.6 to <11.5 *2.65 to <2.88*	11.5 to <12.5 *2.88 to <3.13*	12.5 to <13.5 *3.13 to <3.38*	≥13.5 *≥3.38*
aged <7 days	11.5 to <12.4 *2.88 to <3.10*	12.4 to <12.9 *3.10 to <3.23*	12.9 to <13.5 *3.23 to <3.38*	≥13.5 *≥3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	>ULN to <6.0 *>ULN to <1.5*	6.0 to <6.4 *1.5 to <1.6*	6.4 to <7.2 *1.6 to <1.8*	≥7.2 *≥1.8*
Calcium, Low (mg/dL; *mmol/L*) *aged ≥7 days*	7.8 to <8.4 *1.95 to <2.10*	7.0 to <7.8 *1.75 to <1.95*	6.1 to <7.0 *1.53 to <1.75*	<6.1 *<1.53*
aged <7 days	6.5 to <7.5 *1.63 to <1.88*	6.0 to <6.5 *1.50 to <1.63*	5.50 to <6.0 *1.38 to <1.50*	<5.50 *<1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	<LLN to 4.0 *<LLN to 1.0*	3.6 to <4.0 *0.9 to <1.0*	3.2 to <3.6 *0.8 to <0.9*	<3.2 *<0.8*
Cardiac Troponin I, High	NAP	NAP	NAP	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to <6×ULN	6 to <10×ULN	10 to <20×ULN	≥20×ULN
Creatinine, High *Report only 1*[p]	1.1 to 1.3×ULN	>1.3 to 1.8×ULN OR Increase to 1.3 to <1.5×participant's baseline	>1.8 to <3.5×ULN OR Increase to 1.5 to <2.0×participant's baseline	≥3.5×ULN OR Increase of ≥2.0×participant's baseline
Creatinine Clearance[q] **or eGFR, Low** *Report only 1*[p]	NAP	<90 to 60 ml/min or ml/min/1.73 m^2 OR 10% to <30% decrease from participant's baseline	<60 to 30 ml/min or ml/min/1.73 m^2 OR 30% to <50% decrease from participant's baseline	<30 ml/min or ml/min/1.73 m^2 OR ≥50% decrease from participant's baseline or dialysis needed
Glucose (mg/dL; *mmol/L*) ***Fasting, High***	110 to 125 *6.11 to <6.95*	>125 to 250 *6.95 to <13.89*	>250 to 500 *13.89 to <27.75*	>500 *≥27.75*
Nonfasting, High	116 to 160 *6.44 to <8.89*	>160 to 250 *8.89 to <13.89*	>250 to 500 *13.89 to <27.75*	>500 *≥27.75*
Glucose, Low (mg/dL; *mmol/L*) *aged ≥1 month*	55 to 64 *3.05 to <3.55*	40 to <55 *2.22 to <3.05*	30 to <40 *1.67 to <2.22*	<30 *<1.67*
aged <1 month	50 to 54 *2.78 to <3.00*	40 to <50 *2.22 to <2.78*	30 to <40 *1.67 to <2.22*	<30 *<1.67*
Lactate, High	ULN to <2.0×ULN without acidosis	≥2.0×ULN without acidosis	Increased lactate with pH <7.3 without life threatening consequences	Increased lactate with pH <7.3 with life threatening consequences

eGFR: estimated glomerular filtration rate; LLN: lower limit of normal; NAP: not applicable; ULN: upper limit of normal

[p] Reminder: Choose the method that selects for the higher grade.

[q] Use the applicable formula (ie, Cockcroft Gault in mL/min or Schwartz, modification of diet in renal disease study [MDRD], or Chronic Kidney Disease Epidemiology Collaboration [CKD EPI] in mL/min/1.73m^2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.

LABORATORY VALUES				
CHEMISTRIES				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Lipase, High	1.1 to <1.5×ULN	1.5 to <3.0×ULN	3.0 to <5.0×ULN	≥5.0×ULN
Lipid Disorders (mg/dL; *mmol/L*) ***Cholesterol, Fasting, High*** *aged ≥18 years*	200 to <240 *5.18 to <6.19*	240 to <300 *6.19 to <7.77*	≥300 *≥7.77*	NAP
aged <18 years	170 to <200 *4.40 to <5.15*	200 to <300 *5.15 to <7.77*	≥300 *≥7.77*	NAP
LDL, Fasting, High *aged ≥18 years*	130 to <160 *3.37 to <4.12*	160 to <190 *4.12 to <4.90*	≥190 *≥4.90*	NAP
aged >2 to <18 years	110 to <130 *2.85 to <3.34*	130 to <190 *3.34 to <4.90*	≥190 *≥4.90*	NAP
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to 1,000 *>5.7 to 11.4*	>1,000 *>11.4*
Magnesium[r], Low (mEq/L; *mmol/L*)	1.2 to <1.4 *0.60 to <0.70*	0.9 to <1.2 *0.45 to <0.60*	0.6 to <0.9 *0.30 to <0.45*	<0.6 *<0.30*
Phosphate, Low (mg/dL; *mmol/L*) *aged >14 years*	2.0 to <LLN *0.65 to <LLN*	1.4 to <2.0 *0.45 to <0.65*	1.0 to <1.4 *0.32 to <0.45*	<1.0 *<0.32*
aged 1 to 14 years	3.0 to <3.5 *0.97 to <1.13*	2.5 to <3.0 *0.81 to <0.97*	1.5 to <2.5 *0.48 to <0.81*	<1.5 *<0.48*
aged <1 year	3.5 to <4.5 *1.13 to <1.45*	2.5 to <3.5 *0.81 to <1.13*	1.5 to <2.5 *0.48 to <0.81*	<1.5 *<0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to <6.0 *5.6 to <6.0*	6.0 to <6.5 *6.0 to <6.5*	6.5 to <7.0 *6.5 to <7.0*	≥7.0 *≥7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to <3.4 *3.0 to <3.4*	2.5 to <3.0 *2.5 to <3.0*	2.0 to <2.5 *2.0 to <2.5*	<2.0 *<2.0*
Sodium, High (mEq/L; *mmol/L*)	146 to <150 *146 to <150*	150 to <154 *150 to <154*	154 to <160 *154 to <160*	≥160 *≥160*
Sodium, Low (mEq/L; *mmol/L*)	130 to <135 *130 to <135*	125 to <130 *125 to <130*	120 to <125 *120 to <125*	<120 *<120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to <10.0 *0.45 to <0.59*	10.0 to <12.0 *0.59 to <0.71*	12.0 to <15.0 *0.71 to <0.89*	≥15.0 *≥0.89*

LDL: low density lipoprotein; LLN: lower limit of normal; mEq: milliequivalent; NAP: not applicable; ULN: upper limit of normal

[r] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

LABORATORY VALUES				
HEMATOLOGY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Absolute CD4+ Count, Low (cells/mm³; *cells/L*) *aged >5 years (not HIV infected)*	300 to <400 *0.300×10⁹ to <0.400×10⁹*[s]	200 to <300 *0.200×10⁹ to <0.300×10⁹*[s]	100 to <200 *0.100×10⁹ to <0.200×10⁹*[s]	<100 *<0.100×10⁹*[s]
Absolute Lymphocyte Count, Low (cells/mm³; *cells/L*) *aged >5 years (not HIV infected)*	600 to <650 *0.600×10⁹ to <0.650×10⁹*	500 to <600 *0.500×10⁹ to <0.600×10⁹*	350 to <500 *0.350×10⁹ to <0.500×10⁹*	<350 *<0.350×10⁹*
Absolute Neutrophil Count, Low (cells/mm³; *cells/L*) *aged >7 days*	800 to 1,000 *0.800×10⁹ to 1.000×10⁹*	600 to 799 *0.600×10⁹ to 0.799×10⁹*	400 to 599 *0.400×10⁹ to 0.599×10⁹*	<400 *<0.400×10⁹*
aged 2 to 7 days	1,250 to 1,500 *1.250×10⁹ to 1.500×10⁹*	1,000 to 1,249 *1.000×10⁹ to 1.249×10⁹*	750 to 999 *0.750×10⁹ to 0.999×10⁹*	<750 *<0.750×10⁹*
aged ≤1 day	4,000 to 5,000 *4.000×10⁹ to 5.000×10⁹*	3,000 to 3,999 *3.000×10⁹ to 3.999×10⁹*	1,500 to 2,999 *1.500×10⁹ to 2.999×10⁹*	<1,500 *<1.500×10⁹*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to <200 *1.00 to <2.00* OR 0.75 to <1.00×LLN	75 to <100 *0.75 to <1.00* OR ≥0.50 to <0.75×LLN	50 to <75 *0.50 to <0.75* OR 0.25 to <0.50×LLN	<50 *<0.50* OR <0.25×LLN OR Associated with gross bleeding
Hemoglobin[t], Low (g/dL; *mmol/L*)[u] *aged ≥13 years (male only)*	10.0 to 10.9 *6.19 to 6.76*	9.0 to <10.0 *5.57 to <6.19*	7.0 to <9.0 *4.34 to <5.57*	<7.0 *<4.34*
aged ≥13 years (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to <9.5 *5.25 to <5.88*	6.5 to <8.5 *4.03 to <5.25*	<6.5 *<4.03*
aged 57 days to <13 years (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to <9.5 *5.25 to <5.88*	6.5 to <8.5 *4.03 to <5.25*	<6.5 *<4.03*
aged 36 to 56 days (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to <8.5 *4.32 to <5.26*	6.0 to <7.0 *3.72 to <4.32*	<6.0 *<3.72*
aged 22 to 35 days (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to <9.5 *4.94 to <5.88*	6.7 to <8.0 *4.15 to <4.94*	<6.7 *<4.15*
aged 8 to ≤21 days (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to <11.0 *5.57 to <6.81*	8.0 to <9.0 *4.96 to <5.57*	<8.0 *<4.96*
aged ≤7 days (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to <13.0 *6.19 to <8.05*	9.0 to <10.0 *5.59 to <6.19*	<9.0 *<5.59*

HIV: human immunodeficiency virus; LLN: lower limit of normal

[s] Revised by the sponsor.

[t] Male and female sex are defined as sex at birth. For transgender participants aged ≥13 years who have been on hormone therapy for more than 6 consecutive months, grade hemoglobin based on the gender with which they identify (ie, a transgender female should be graded using the female sex at birth hemoglobin laboratory values).

[u] The most commonly used conversion factor to convert g/dL to mmol/L is 0.6206. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for the particular laboratory.

LABORATORY VALUES				
HEMATOLOGY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
INR, High (not on anticoagulation therapy)	1.1 to <1.5×ULN	1.5 to <2.0×ULN	2.0 to <3.0×ULN	≥3.0×ULN
Methemoglobin (% hemoglobin)	5.0% to <10.0%	10.0% to <15.0%	15.0% to <20.0%	≥20.0%
PTT, High (not on anticoagulation therapy)	1.1 to <1.66×ULN	1.66 to <2.33×ULN	2.33 to <3.00×ULN	≥3.00×ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to <125,000 *100.000×10^9 to <125.000×10^9*	50,000 to <100,000 *50.000×10^9 to <100.000×10^9*	25,000 to <50,000 *25.000×10^9 to <50.000×10^9*	<25,000 *<25.000×10^9*
PT, High (not on anticoagulation therapy)	1.1 to <1.25×ULN	1.25 to <1.50×ULN	1.50 to <3.00×ULN	≥3.00×ULN
WBC, Decreased (cells/mm^3; *cells/L*)				
aged >7 days	2,000 to 2,499 *2.000×10^9 to 2.499×10^9*	1,500 to 1,999 *1.500×10^9 to 1.999×10^9*	1,000 to 1,499 *1.000×10^9 to 1.499×10^9*	<1,000 *<1.000×10^9*
aged ≤7 days	5,500 to 6,999 *5.500×10^9 to 6.999×10^9*	4,000 to 5,499 *4.000×10^9 to 5.499×10^9*	2,500 to 3,999 *2.500×10^9 to 3.999×10^9*	<2,500 *<2.500×10^9*

INR: International Normalized Ratio; NAP: not applicable; PT: prothrombin time; PTT: partial thromboplastin time; ULN: upper limit of normal; WBC: white blood cell

LABORATORY VALUES				
URINALYSIS				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤250 mg	2+ or >250 to ≤500 mg	>2+ or >500 mg	NAP
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to <10 RBCs per high power field	≥10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NAP

NAP: not applicable; RBC: red blood cell

10.10. Appendix 10: Hepatitis B Quality of Life Instrument

HBQOL v1.0 QUESTIONNAIRE

Some people with hepatitis B say that having hepatitis B affects the way they feel socially and mentally.

Below is a list of statements about how hepatitis B might make you feel socially or mentally. Please read each one carefully and circle the number that best describes how frequently, if ever, you feel that way. Circle only one number for each statement and do not skip any items.

		Never	Rarely	Sometimes	A Lot of the Time	All of the Time
F1	I feel ashamed because of hepatitis B	1	2	3	4	5
F2	I feel stigmatized because of hepatitis B	1	2	3	4	5
F3	I feel sad because of hepatitis B	1	2	3	4	5
F4	I feel frustrated because of hepatitis B	1	2	3	4	5
F5	I feel worn out and tired because of hepatitis B	1	2	3	4	5
F6	I feel anxious because of hepatitis B	1	2	3	4	5
F7	I feel angry because of hepatitis B	1	2	3	4	5
F8	I feel isolated from others because of hepatitis B	1	2	3	4	5
F9	I feel like something bad might happen because of hepatitis B	1	2	3	4	5
F10	I feel my life is less enjoyable because of hepatitis B	1	2	3	4	5
F11	I feel like sexual activity is difficult for me because of hepatitis B	1	2	3	4	5
F12	I feel like I am less productive because of hepatitis B	1	2	3	4	5
F13	I feel scared because of hepatitis B	1	2	3	4	5

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Some people have concerns about their hepatitis B.

Below there is a list of possible concerns that some people have expressed about hepatitis B. For each one, please think about whether you also have that concern and, if so, how much of a concern it is to you. Circle the number that best describes your level of concern for each statement. Circle only one number for each statement and do not skip any items.

	How concerned are you that…	Not at All Concerned	A Little Bit Concerned	Moderately Concerned	Quite a Bit Concerned	Extremely Concerned
C1	One day you could develop liver failure because of your hepatitis B	1	2	3	4	5
C2	You might develop liver cancer because of your hepatitis B	1	2	3	4	5
C3	Someone influential, like your boss, might find out about your hepatitis B	1	2	3	4	5
C4	You could transmit hepatitis B to a child	1	2	3	4	5
C5	Your hepatitis B may flare up at any time	1	2	3	4	5
C6	It is easier to get other illnesses because of having hepatitis B	1	2	3	4	5
C7	You could transmit hepatitis B to a partner through sex	1	2	3	4	5
C8	You have to watch what medicines you take because you have hepatitis B	1	2	3	4	5
C9	Hepatitis B might affect your life expectancy	1	2	3	4	5
C10	You are overly self-conscious because of hepatitis B	1	2	3	4	5

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	How concerned are you that…	Not at All Concerned	A Little Bit Concerned	Moderately Concerned	Quite a Bit Concerned	Extremely Concerned
C11	You could be socially isolated because of hepatitis B	1	2	3	4	5
C12	Something serious might be wrong because of your hepatitis B	1	2	3	4	5
C13	You have to watch what you eat because you have hepatitis B	1	2	3	4	5
C14	You might be embarrassed because of your hepatitis B	1	2	3	4	5
C15	Your health might unexpectedly get worse because of hepatitis B	1	2	3	4	5

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Some people with hepatitis B say that having hepatitis B affects the way they feel physically.

Below is a list of physical symptoms. Please read each one carefully and circle the number that best describes how frequently, if ever, you think that hepatitis B (as opposed to other conditions) causes that symptom.

	How frequently do you feel…	Never	Rarely	Sometimes	A Lot of the Time	All of the Time
P1	Tiredness	1	2	3	4	5
P2	Memory problems	1	2	3	4	5
P3	Muscle aches	1	2	3	4	5

**** END OF QUESTIONNAIRE ****

Thank you for your time and effort in answering these questions. Please check over your responses to make sure you did not skip any questions.

Scaling and Scoring Instructions

There are 31 scored items included in the HB-QOL, including 13 items regarding how HBV makes patients feel socially or mentally (F1-F13), 15 items regarding HBV-related concerns (C1-C15), and 3 items regarding HBV-related physical impacts.

Each item is scored on a 5-level response scale ranging from 1 through 5. Each response is transformed along a 0 to 100-point scale, where lower scores denote less HRQOL impact, and higher scores denote more HRQOL impact (i.e. 0=best score; 100=worst score), as follows:

Level 1 – 0 points
Level 2 – 25 points
Level 3 – 50 points
Level 4 – 75 points
Level 5 – 100 points

The items are combined to form 7 subscales, as follows:

Psychological Well-Being (8 Items)

Anxious (F6)
Frustrated (F4)
Sad (F3)
Angry (F7)
Less Enjoyable (F10)
Scared (F13)
Bad (F19)
Isolated (F8)

Anticipation Anxiety (6 Items)

Concern Failure (C1)
Concern Cancer (C2)
Concern Worsen (C15)
Concern Serious (C12)
Concern Survival (C9)
Concern Flare (C5)

Vitality (5 Items)

Tiredness (P1)
Worn Out (F5)
Muscle Aches (P3)
Memory Problems (P2)
Unproductive (F13)

Stigma (6 Items)

Concern Embarrassed (C14)
Ashamed (F1)
Concern Self-Conscious (C10)
Concern Socially Isolated (C11)
Concern Boss (C3)
Stigmatized (F2)

Vulnerability (3 Items)

Concern Eat (C13)
Concern Sick Easily (C6)
Concern Medicines (C8)

Transmission (3 Items)

Concern Transmit Sex (C7)
Concern Transmit Child (C4)
Sex Difficult (F11)

Viral Response (4 Items)

Concern Transmit Sex (C7)
Concern Transmit Child (C4)
Concern Eat (C13)
Concern Medicines (C8)

In addition, there is a single **global score** that reflects the results on all 31 items.

Each subscale score is simply calculated as the average score among the items included in that subscale. The global score is simply the average score among all the items in the HBQOL.

For example, consider these sample scores for items in the vulnerability scale:

Item Number	Item Name	Raw Score	Scaled Score
C13	Concern eat	2	25
C6	Concern sick easily	4	75
C8	Concern medicines	3	50
		Average	**50**

The score on this subscale is 50 out of a possible score of 100, where higher scores denote more severe negative impact of HBV on HRQOL.

10.11. Appendix 11: HBV-specific Self-stigma PRO Scale

The following questions ask about your experience of self-stigma because of your hepatitis B. Please select the most appropriate answer based on how often you felt that way over the past **four weeks**.

Over the past four weeks…	Never	Rarely	Sometimes	Often	Always
1. I felt inferior to others because I have hepatitis B	❑	❑	❑	❑	❑
2. I felt worthless because I have hepatitis B	❑	❑	❑	❑	❑
3. I had low self esteem because I have hepatitis B	❑	❑	❑	❑	❑
4. I expected people to think less of me because I have hepatitis B	❑	❑	❑	❑	❑
5. I felt I couldn't pursue an opportunity because I have hepatitis B	❑	❑	❑	❑	❑
6. I couldn't achieve what I wanted because I have hepatitis B	❑	❑	❑	❑	❑
7. I felt I was excluded because I have hepatitis B	❑	❑	❑	❑	❑
8. I felt isolated because I have hepatitis B	❑	❑	❑	❑	❑
9. I felt people were avoiding me because I have hepatitis B	❑	❑	❑	❑	❑
10. I expected rejection when others found out I have hepatitis B	❑	❑	❑	❑	❑
11. I was very careful who I told that I have hepatitis B	❑	❑	❑	❑	❑
12. I worried that people would find out I have hepatitis B	❑	❑	❑	❑	❑
13. I have told people close to me to keep my hepatitis B status a secret	❑	❑	❑	❑	❑
14. I felt I could not visit a local clinic/hospital because I worried about people knowing my hepatitis B status	❑	❑	❑	❑	❑
15. I felt guilty because I have hepatitis B	❑	❑	❑	❑	❑
16. I felt ashamed because I have hepatitis B	❑	❑	❑	❑	❑
17. I felt embarrassed because I have hepatitis B	❑	❑	❑	❑	❑
18. I have avoided social situations because I have hepatitis B	❑	❑	❑	❑	❑
19. I have isolated myself because I have hepatitis B	❑	❑	❑	❑	❑
20. I have avoided eating with other people because I have hepatitis B	❑	❑	❑	❑	❑
21. I have avoided intimacy because I have hepatitis B	❑	❑	❑	❑	❑
22. I have avoided becoming close to other people because I have hepatitis B	❑	❑	❑	❑	❑
23. I have avoided a romantic relationship because I have hepatitis B	❑	❑	❑	❑	❑
24. Hepatitis B has had a damaging effect on my work	❑	❑	❑	❑	❑
25. Hepatitis B has had a damaging effect on my education	❑	❑	❑	❑	❑
26. My family life has been disrupted because I have hepatitis B	❑	❑	❑	❑	❑

27. I have stopped socialising with some people because of their reactions to me having hepatitis B	❑	❑	❑	❑	❑
28. Some people have treated me differently because I have hepatitis B	❑	❑	❑	❑	❑
29. People discriminated against me because I have hepatitis B	❑	❑	❑	❑	❑
30. I felt like people were avoiding touching me because of my hepatitis B	❑	❑	❑	❑	❑
31. I worried that people would reject me when they found out I have hepatitis B	❑	❑	❑	❑	❑
32. I have been hurt by how people reacted because I have hepatitis B	❑	❑	❑	❑	❑
33. I felt frustrated by other people's lack of understanding of hepatitis B	❑	❑	❑	❑	❑
34. I was not afraid to tell people I had hepatitis B	❑	❑	❑	❑	❑
35. I was comfortable with others knowing I have hepatitis B	❑	❑	❑	❑	❑
36. I was ashamed to seek medical care because of my hepatitis B	❑	❑	❑	❑	❑
37. I was afraid to seek medical care because of my hepatitis B	❑	❑	❑	❑	❑

10.12. Appendix 12: Patient Global Impression of Change Scale

Please select how you feel about yourself now in comparison to how you felt about yourself at the beginning of this study. (Select one response)

- ❑ Much better
- ❑ Better
- ❑ A little better
- ❑ No change
- ❑ A little worse
- ❑ Worse
- ❑ Much worse

10.13. Appendix 13: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 3 (30 September 2021)

Overall Rationale for the Amendment:

The primary reason for this amendment is to add a new nucleos(t)ide analog (NA) re-treatment criterion for participants who discontinued NA treatment at Week 48 or during the follow-up phase, and to include more frequent monitoring for participants who discontinued NA treatment.

A severe clinical alanine aminotransferase (ALT) flare following discontinuation of NA treatment was reported in a virologically suppressed hepatitis B e antigen (HBeAg) negative participant on long-term tenofovir disoproxil fumarate (TDF) treatment, who was randomized to the control arm (placebo + placebo + NA) in the REEF-2 (73763989PAHPB2002) study. The participant presented with hepatitis B virus (HBV) DNA levels that increased rapidly, before any relevant changes in liver markers were noted. Discontinuation of NA treatment followed the protocol-defined criteria and was in line with recent European Association for the Study of the Liver (EASL) treatment guidelines.[7] Flares following NA discontinuation are not unexpected, but the rapid evolution and clinical deterioration seen in this participant who was anti-HBe antibody positive at screening and had no history or evidence of liver cirrhosis was unforeseeable. Therefore, to protect safety of participants, the protocol was amended as detailed below.

Other clarifications and corrections were also made as detailed below.

Description of Change	Brief Rationale	Section Number and Name
A new NA re-treatment criterion was added for participants who discontinued NA treatment at Week 48 or during the follow-up phase.	To ensure that participants with significant HBV DNA increases during treatment free follow-up are monitored at least weekly and/or immediately re-start NA treatment irrespective of ALT levels.	1.1 Synopsis, 1.3.2 Schedule of Activities – Follow-up Phase,2.3.2.2 Potential Risks, 4.2 Scientific Rationale for Study Design, 6.6 Individual Participant NA Treatment Completion Criteria, 6.7 NA Re-treatment Criteria , 6.8 Intervention After the End of the Study 10.14 Appendix 14: NA Re-treatment
Participants who discontinue NA treatment at Week 48 or during the follow-up phase will be monitored more frequently, with a study visit at least once every 4 weeks. The visit frequency for participants who continue NA treatment or have restarted NA treatment during the follow-up period and for whom the HBV DNA and ALT values are stable remains unchanged. For participants with increased follow-up, the total blood volume to be collected during the study will increase.	To further protect the safety of participants.	1.1 Synopsis, 1.3.2 Schedule of Activities – Follow-up Phase, 6.7 NA Re-treatment Criteria , 8 STUDY ASSESSMENTS AND PROCEDURES
Clarifications were made to the urine pregnancy testing during (extended) follow-up.	Clarification	1.3.2 Schedule of Activities – Follow-up Phase

Description of Change	Brief Rationale	Section Number and Name
Clarifications were made concerning the optional safety follow-up visit for participants who withdraw consent during follow-up.	Clarification	1.3.2 Schedule of Activities – Follow-up Phase
The formulations numbers for JNJ-6379 were corrected and formulation numbers for placebo were added.	Correction	6.1 Study Intervention(s) Administered
Minor grammatical, formatting, or spelling changes and template updates were made.	Minor errors were noted	Throughout the protocol

Amendment 2 (27 January 2020)

Overall Rationale for the Amendment: Based on a nonclinical finding from the preliminary results of the 3-month combination toxicity study with JNJ-6379 and JNJ-3989 in the rat, the protocol was amended to include hematologic abnormalities as an event of special interest, to trigger a mandatory higher visit frequency with unscheduled visits in case of significant on-treatment reduction in hematologic parameters, and to include treatment discontinuation criteria in relation to hematological abnormalities as precautionary measures. No significant abnormalities of hematologic parameters have been observed in clinical trials to date. Furthermore, clarifications, additions and corrections were made throughout the protocol.

Main Changes		
Section Number and Name	**Description of Change**	**Brief Rationale**
2.3.3 Benefit-risk Assessment for Study Participation 8.3.6.5 Hematologic Abnormalities	Addition of management of hematologic abnormalities	In response to a serious and unexpected adverse nonclinical finding, any relevant abnormalities in hematologic parameters will be carefully monitored to trigger a mandatory higher visit frequency in case of significant on-treatment reduction in hematologic parameters to ensure closer follow-up.
2.2.1 JNJ-3989 and JNJ-6379 2.2.2.1 Overall Nonclinical Assessment of the Combination Therapy	Preclinical update: Addition of preliminary results from 3-month combination toxicity study with JNJ-3989 and JNJ-6379	Preliminary results of the 3-month combination toxicity study with JNJ-6379 and JNJ-3989 in the rat include an update on the sacrifice of one male rat receiving JNJ-6379 orally at 100 mg/kg/day and JNJ-3989 subcutaneous at 60 mg/kg related to bone marrow depletion with pancytopenia including marked thrombocytopenia.
10.2. Appendix 2: Clinical Laboratory Tests	Addition of reticulocyte count and reticulocyte index to all study visits	To allow for early detection of changes in hematologic parameters.

Clarifications, Additions, and Corrections		
Section Number and Name	**Description of Change**	**Brief Rationale**
1.3.1 Schedule of Activities – Screening and Study Intervention Phase	ECG at baseline needs to be performed and assessed locally prior to dosing but is not part of eligibility	Clarification

Clarifications, Additions, and Corrections		
Section Number and Name	**Description of Change**	**Brief Rationale**
	criteria assessed after screening.	
1.3.1 Schedule of Activities – Screening and Study Intervention Phase 1.3.2 Schedule of Activities – Follow-up Phase 10.6 Appendix 6: Intervention-emergent ALT/AST Elevations	Add alpha-fetoprotein measurement every 24 weeks and at the time of ALT flares	Alpha-fetoprotein is of interest to link to liver ultrasound assessment for the screening of HCC every 6 months. In addition, alpha-fetoprotein has been reported to be associated with HBsAg decline. Thus, it is relevant to assess this marker.
8.3.6.1 Intervention-emergent ALT/AST Elevations 10.2 Appendix 2: Clinical Laboratory Tests	Added wording for ALT/AST elevations management, added baseline value as reference for stopping criteria, and ensure that all relevant liver tests are performed	For closer patient safety monitoring and management
10.6 Appendix 6: Intervention-emergent ALT/AST Elevations	Added Appendix 6. Consequently, all subsequent appendices are renumbered.	Clarification
1.3.1 Schedule of Activities – Screening and Study Intervention Phase 1.3.2 Schedule of Activities – Follow-up Phase 8 STUDY ASSESSMENTS AND PROCEDURES	The recommendation regarding the timing of the PRO assessments and the ECGs was changed.	The PRO assessments and ECGs should be prioritized, but the order of the other assessments is of less importance.
5.1 Inclusion Criteria 5.2 Exclusion Criteria	The note "Retesting to assess eligibility will be allowed once, using an unscheduled visit during the screening phase." was moved up as it applies to both inclusion as well as exclusion criteria.	Clarification
5.2 Exclusion Criteria	The note in exclusion criterion 1 was modified to allow participants with positive HCV, HDV or HEV antibody test to enroll if an active infection can be ruled out.	To only exclude patients with active infection. Some patients may carry antibodies after an acute infection, which never developed into a chronic infection.
6.3 Measures to Minimize Bias: Randomization and Blinding 8.1 Efficacy Assessments	Addition of "In order to preserve the blinding during the study treatment phase, HBsAg, HBeAg, anti-HBs, and anti-HBe antibody tests cannot be done locally."	Clarification to avoid local unblinding via assessment of these parameters
2.3.2.2.1 Potential Risks for JNJ-3989	Potential risk on viral resistance to JNJ-3989 was moved from Section 2.3.2.2.2 to Section 2.3.2.2.1 as appropriate.	Correction
8.3.5 Pregnancy	Discontinuation of "study intervention" during pregnancy has been updated to "investigational intervention"	Correction
2.2.1 JNJ-3989 and JNJ-6379	Limited updates were made to the nonclinical sections where relevant	Correction
2.3.2.2.1 Potential Risks for JNJ-3989	The sentence "The fertility in male and female rats is not impacted with JNJ-3989 up to a dose of	Correction

Clarifications, Additions, and Corrections		
Section Number and Name	**Description of Change**	**Brief Rationale**
	180 mg/kg/week." was moved from Potential Genotoxicity to Reproductive Risks and Pregnancy	
10.2 Appendix 2: Clinical Laboratory Tests	Timing of the reflex testing of pancreatic amylase in case of amylase or lipase increase has been changed from "post-screening" to "screening onwards"	Correction
8 STUDY ASSESSMENTS AND PROCEDURES	A time window was added for intensive PK sampling and "within 12 minutes" was changed to +/- 12 minutes for clarity"	For completeness and consistency
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS 8.5 Pharmacokinetics 8.5.1 Evaluations 8.5.2 Analytical Procedures 8.5.3 Pharmacokinetic Parameters and Evaluations 8.6 Pharmacokinetics/Pharmacodynamics 9.4.3 Other Analyses	Addition of "(JNJ-3976 and JNJ-3924)" and changed 'JNJ-3989' to 'JNJ-3976 and JNJ-3924' where applicable	For completeness
6.1 Study Intervention(s) Administered	Formulation numbers were added for JNJ-3989 and for the 25 mg and 100 mg JNJ-6379 tablets.	Clarification
1.3.1 Schedule of Activities – Screening and Study Intervention Phase	Minor grammatical, formatting, or spelling changes were made.	Minor errors corrected.

Amendment 1 (14 November 2019)

Overall Rationale for the Amendment: Pursuant to Health Authority (HA) and Independent Ethics Committee (IEC)/Institutional Review Board (IRB) feedback, the protocol was amended as specified below. Furthermore, clarifications, additions and corrections were made throughout the protocol.

HA and IEC/IRC Feedback		
Description of Change	**Brief Rationale**	**Section Number and Name**
A liver ultrasound was added in participants with increased risk for HCC, every 24 weeks during the study intervention phase and (extended) follow-up.	To monitor for development of HCC in participants with increased risk for HCC.[42]	1.3.1 Schedule of Activities – Screening and Study Intervention Phase, 1.3.2 Schedule of Activities – Follow-up Phase
A timeframe of at least 30 days prior to screening was added for the use of a highly effective method of contraception by female participants of childbearing potential.	The minimum time period for contraceptive use prior to screening ensures adequate protection of females of childbearing potential.	5.1 Inclusion Criteria

Exclusion criterion #14 was updated to also include known allergies, hypersensitivity, or intolerance to excipients of the placebo formulations.	For completeness, to safeguard all patients, including those on placebo, who may react to certain content of the formulations.	5.2 Exclusion Criteria
Individuals under a legal protection measure were added to criterion #26 as an additional example of vulnerable participants.	For completeness	5.2 Exclusion Criteria
Description of the unblinding procedure for the investigator was updated to ensure that discussion with the sponsor is not delaying action with respect to treatment in case of emergency.	For clarity	6.3 Measures to Minimize Bias: Randomization and Blinding
BCRP inhibitors (eg, curcumin, cyclosporin A, and eltrombopag) were added to the list of disallowed concomitant medications.	JNJ-6379 is a substrate of BCRP.	6.5 Concomitant Therapy
The description of the control of the Type I error rate for multiple testing in the analysis of the primary efficacy endpoint and the key secondary efficacy endpoint was clarified. In line with this clarification, the simulation results for the statistical power levels achieved with the planned sample size have been updated.	To clarify that the control of the Type I error rate at one-sided 0.05 level is conducted separately and independently for the comparisons against the control arm as opposed to the comparisons among the active combination regimens.	1.1 Synopsis, 3 OBJECTIVES AND ENDPOINTS 9.1 Statistical Hypotheses, 9.2 Sample Size Determination, 9.4 Statistical Analyses

Clarifications and Additions		
Description of Change	**Brief Rationale**	**Section Number and Name**
A time frame of maximal 12 months was added for documented HBeAg status as part of the medical history at prescreening.	Within 12 months prior to screening is acceptable to assess documented HBeAg status as part of the medical history at prescreening.	1.3.1 Schedule of Activities – Screening and Study Intervention Phase
A time window was added for intensive PK sampling.	For completeness	1.3.1 Schedule of Activities – Screening and Study Intervention Phase
Language was added for participants in the intensive PK subgroup, such that the sparse PK sample does not need to be collected at the time of an intensive PK visit.	To avoid unnecessary duplication of PK sampling for participants in the intensive PK subgroup.	1.3.1 Schedule of Activities – Screening and Study Intervention Phase
Quantitative HBeAg assessment will be performed for all participants during FU, instead of only those who are defined HBeAg-positive at screening.	For completeness	1.3.2 Schedule of Activities – Follow-up Phase
The recommendation regarding the order of assessments in case of multiple assessments at the same time point was removed.	For more flexibility in timing of the assessments. The PRO assessment should be prioritized, but the order of the other assessments is not deemed important.	1.3.1 Schedule of Activities – Screening and Study Intervention Phase, 1.3.2 Schedule of Activities – Follow-up Phase, 8.2.3 Electrocardiograms

Clarifications and Additions		
Description of Change	**Brief Rationale**	**Section Number and Name**
Updated language, explaining that the abdominal ultrasound 6 months prior to screening or at screening will also be used to rule out any clinically relevant renal abnormalities.	To evaluate for the presence of structural kidney disease.	1.3.1 Schedule of Activities – Screening and Study Intervention Phase, 5.2 Exclusion Criteria
Final data from the 28-day combination toxicity study in rats are added.	For completeness	2.2.1 JNJ-3989 and JNJ-6379, 2.3.2.2.1 Potential Risks for JNJ-3989
Approved tenofovir generics were added as an acceptable NA treatment option.	For completeness	4.1 Overall Design
The note in exclusion criterion #1 was modified to allow participants with positive anti-HCV antibody test to enroll, if they have negative HCV RNA at screening and documented negative HCV RNA at least 6 months prior to screening and/or documentation of prior HCV treatment.	To identify patients with resolved HCV infection (spontaneously or after treatment) who can participate in this study.	5.2 Exclusion Criteria
Exclusion criterion #2 was adapted to describe that the listed laboratory abnormalities are exclusionary within 12 months prior to screening but also at the time of screening.	For clarity	5.2 Exclusion Criteria
Added language to explain that rescreening is not allowed without the sponsor's approval.	For clarity	5.4 Screen Failures
Subcutaneous injection of JNJ-3989 is now unambiguously described to be administered in the abdomen, instead of by preference.	For clarity and consistency in approach.	1.1 Synopsis, 6.1 Study Intervention(s) Administered
The volume of the placebo for JNJ-3989 was added to the dosage regimen.	For completeness	1.1 Synopsis, 6.1 Study Intervention(s) Administered
"Once monthly" in the dosage regimen of JNJ-3989 was adjusted to "once every 4 weeks".	For clarity	1.1 Synopsis, 1.2 Schema, 6.1 Study Intervention(s) Administered
Specification on NA treatments available for the study was adapted.	To account for import restrictions with regards to tenofovir alafenamide (TAF) in some participating countries and clarify that TAF will only be one of the NA options in the countries where it is available.	1.1 Synopsis, 6.1 Study Intervention(s) Administered
Language was added instructing investigators to follow guidance during NA treatment as detailed in the respective prescribing information, in particular with reference to special warnings and precautions for use.	For completeness	6.1 Study Intervention(s) Administered
Instructions for handling of missed or delayed injections with JNJ-3989 were added.	For completeness, to ensure adequate treatment in case of missed or delayed injections with JNJ-3989.	6.4 Study Intervention Compliance

Clarifications and Additions		
Description of Change	**Brief Rationale**	**Section Number and Name**
Table 5 (Concomitant Medications to be Used With Caution) was adapted to provide more general recommendations regarding alternative medications or adjusted doses.	For clarity	6.5 Concomitant Therapy
Over-the-counter products, herbal medications and dietary supplements were removed from the disallowed concomitant medication list.	For clarity. Only products containing *Hypericum perforatum* are disallowed.	6.5 Concomitant Therapy
This section was updated to describe that only participants who have taken the disallowed concomitant medication for ≥7 days and have no intention to discontinue the concomitant medication will be discontinued from the study intervention.	To avoid accidental intake of disallowed concomitant medication triggering the discontinuation of study intervention.	7.1 Discontinuation of Study Intervention
The discontinuation criterion for a confirmed ≥grade 3 eGFR abnormality and a drop from baseline of >10 mL/min/1.73 m² was adjusted to include the relationship to the investigational intervention and to propose consideration of changing NA treatment.	Multiple conditions, including treatment with TDF can lead to eGFR abnormalities. Therefore, the relationship to the investigational intervention should be taken into consideration before treatment discontinuation and a switch from TDF to ETV or TAF should be considered as the first step.	7.1 Discontinuation of Study Intervention, 8.3.6.4 Renal Complications
The word 'optional' was removed for PBMC samples. A note was added with regards to total blood volume.	To clarify that PBMC samples are only taken at selected sites and at these sites, PBMC samples will be collected from all subjects. To clarify that the total blood volume to be collected from each participant may vary, depending on the timing of potential participation in the extended FU.	8 STUDY ASSESSMENTS AND PROCEDURES
Management of grade 3 and 4 laboratory abnormalities is adapted to request a repeat analysis (within 72 hours) only in case the abnormality is considered to be clinically significant.	To avoid unnecessary, unscheduled visits.	8.2.4 Clinical Safety Laboratory Assessments
It was specified that digital pictures can only be taken if the participant has specifically consented to this. Language on the collection of digital pictures was updated to describe that if digital pictures are required, they should be de-identified and will be provided to the sponsor. Wording was modified such that all ISRs will need to be reported in the CRF, but not by default as an AE.	To protect the participant's privacy. To clarify that the pictures are optional and explain the proper steps to follow. For clarity	8.3.6.2 Rash, 10.5 Appendix 5: Rash Management

Clarifications and Additions		
Description of Change	**Brief Rationale**	**Section Number and Name**
Added language specifying sponsor staff that will also have access to PK and pharmacodynamic unblinded data during study conduct (for PK and pharmacodynamic modeling) in addition to the IDMC. It was specified that the IDMC can monitor unblinded safety and efficacy data on a continuous basis.	Unblinded PK and pharmacodynamic data will be used for compound development decision making. For completeness	1.1 Synopsis, 6.3 Measures to Minimize Bias: Randomization and Blinding 9.5.1 Independent Data Monitoring Committee 10.3 Appendix 3: Regulatory, Ethical, and Study Oversight Considerations
A statistical test for the difference in proportions, adjusted for the randomization stratification factors, has been added.	To take into account the randomization stratification factors of screening HBeAg status and treatment history in the analysis of the primary and the secondary efficacy endpoints. For completeness of the inferential analysis.	1.1 Synopsis, 9.1 Statistical Hypotheses, 9.4.1 Efficacy Analyses 10.1 Appendix 1: Abbreviations and Definitions of Terms
'Bilateral tubal occlusion/ligation procedures' was removed from the definition of 'permanently sterile'.	In line with the updated guidance from the Clinical Trials Facilitation and Coordination Group (CTFG), the definition of 'permanently sterile' was updated.	10.8 Appendix 8: Contraceptive and Barrier Guidance

Corrections		
Description of Change	**Brief Rationale**	**Section Number and Name**
Urinalysis assessment was moved from FU Week 48 to FU Week 4.	Correction, as safety analysis of the treatment phase will be done up to 4 weeks after end of investigational treatment.	1.3.2 Schedule of Activities – Follow-up Phase
Approximations of total blood volumes were modified.	Correction	8 STUDY ASSESSMENTS AND PROCEDURES
The term relapse is replaced by flare across the document.	Relapse implies a lack of efficacy while some increases in ALT and/or HBV DNA might occur in patients with favorable response to treatment. Increases that do not lead to treatment action (discontinuation if during the treatment phase or re-start if during the follow up phase) will be referred to as flares instead of relapses. As such, a distinction will be made in the analysis to differentiate between frequency of patients with flares and frequency of patients that meet criteria to re-start treatment during follow up.	1.1 Synopsis, 2.3.3 Benefit-risk Assessment for Study Participation, 3 OBJECTIVES AND ENDPOINTS, 9.4.1.3 Other Secondary and Exploratory Efficacy Endpoints,

Corrections		
Description of Change	**Brief Rationale**	**Section Number and Name**
Minor grammatical, formatting, or spelling changes were made.	Minor errors corrected.	1.1 Synopsis, 3 OBJECTIVES AND ENDPOINTS, 5.1 Inclusion Criteria 5.2 Exclusion Criteria, 7.1 Discontinuation of Study Intervention, 9.4.1.2 Key Secondary Efficacy Endpoint of Functional Cure at Week 72 (HBsAg Seroclearance 24 Weeks After Completion of All Study Intervention at Week 48) 9.4.1.3 Other Secondary and Exploratory Efficacy Endpoints, 10.3 Appendix 3: Regulatory, Ethical, and Study Oversight Considerations, 10.9 Appendix 9: DAIDS Table

10.14. Appendix 14: NA Re-treatment and Monitoring After Stopping of NA

Participants who meet the NA treatment completion critera will be monitored for NA re-treatment during the follow-up phase

Frequency of monitoring:

- Regular monitoring visits will be every 4 weeks during the follow up phase in accordance with the schedule of activities (SoA)
- A post-treatment HBV DNA value of >20,000 IU/mL should trigger re-testing of ALT/AST, HBV DNA, and total and direct bilirubin within a maximum of 7 days from receipt of the data and further repeats as necessary (ie, weekly until HBV DNA returns to <20,000 IU/mL)
- A post-treatment HBV DNA value of >2,000 IU/mL (but <20,000 IU/mL) should trigger a re-test within 14 days from receipt of the data and further repeats as necessary (ie, every other week until HBV DNA returns to <2,000 IU/mL)
- A post-treatment ALT value of >5x ULN should trigger re-testing of ALT, AST, ALP, total and direct bilirubin, INR, albumin, and HBV DNA on a weekly basis until ALT and AST levels have returned to <5x ULN

Re-start of NA treatment:

- immediately with signs of decreasing liver function based on laboratory findings (eg, INR, direct bilirubin) or clinical assessment (eg, ascites, hepatic encephalopathy)
- immediately with an HBV DNA value of >100,000 IU/mL (irrespective of confirmation and/or ALT increase)
- with confirmed post-treatment HBeAg seroreversion (HBeAg positive after it was negative at NA completion)
- with confirmed* post-treatment increases in HBV DNA >2,000 IU/mL and ALT >5x ULN
- With confirmed* post-treatment increases in HBV DNA >20,000 IU/mL

* At least 4 weeks apart – frequency of visits as described above

Note: Additional re-testing and/or earlier restarting of NA-treatment is at the investigator's discretion also if the above cut-offs are not yet met.

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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	25-Nov-2021 08:31:01 (GMT)	Document Approval

Janssen Research & Development *

Clinical Protocol

COVID-19 Appendix

Protocol Title

A Phase 2b, Multicenter, Double-blind, Active-controlled, Randomized Study to Investigate the Efficacy and Safety of Different Combination Regimens Including JNJ-73763989 and/or JNJ-56136379 for the Treatment of Chronic Hepatitis B Virus Infection

The REEF-1 study

Protocol 73763989HPB2001; Phase 2b

JNJ-73763989 and JNJ-56136379

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

EudraCT NUMBER: 2019-000622-22

Status: Approved
Date: 15 May 2020
Prepared by: Janssen Research & Development, a division of Janssen Pharmaceutica NV
EDMS number: EDMS-RIM-48855, 1.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL 73763989HPB2001 (EDMS-ERI-180130107)

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

COVID-19 APPENDIX

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study-related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff and maintain oversight of delegated trial activities. If, at any time, a participant's safety is considered at risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the participant, investigator, or the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL

The following emergency provisions are meant to ensure participant safety on study while site capabilities are compromised by COVID-19 related restrictions. Remote medical consultation and alternatives to study intervention dispensing, administration, and clinical laboratory assessments may allow continued study participation for participants in this trial. Before implementing any of these emergency provisions, the sponsor should be consulted to perform a benefit-risk analysis and to ensure the measures are executed and documented correctly.

As restrictions are lifted and the acute phase of the COVID-19 pandemic resolves, sites should revert to original protocol conduct as soon as feasible and in accordance with any country-specific regulatory requirements.

Dispensing/administration of study intervention:

- For participants able to visit the study site, but who request to reduce visit frequency, or for whom limited access to the site is expected, an additional supply of oral study intervention can be provided.
- For participants unable to visit the study site, direct-to-patient (DTP) shipment or handover to a caregiver or delegate of oral study intervention may be implemented, where allowed per local regulations and if requested by the investigator. Where DTP shipments or handover to delegates are deemed necessary, the process must be coordinated between the site and sponsor staff following DTP procedures for arranging shipment and adhering to associated approvals and documentation requirements.
- JNJ-3989/placebo should always be administered by an unblinded nurse at the study site or, if site visits are not possible, at the participant's home. Per protocol amendment 1, if a scheduled injection of JNJ-3989/placebo was missed, the injection should be given as soon as possible but within 3 weeks after the scheduled time. Otherwise, the injection should be skipped and the next injection should be given at the next scheduled time point per the initial injection schedule.

Continuation of study intervention:

- Any issue with continuation and/or provision of study intervention should be discussed with the sponsor and should be well documented.
- Study intervention should be continued if, in the assessment of the investigator, it does not result in risk to the participant. If at any time the participant's safety is considered at risk due to study intervention, study intervention will be temporarily or permanently discontinued, while every effort should be made to maintain follow-up on study. The benefit of continuing study intervention should be assessed by the investigator for each individual participant, considering the potential impact of reduced direct clinical supervision on participant safety.
    - If a participant develops a SARS-CoV-2 infection, the investigator should contact the sponsor to discuss plans for study intervention and follow-up. A decision to continue study intervention should be made by the investigator depending on symptoms and concomitant medication used for the treatment of COVID-19.
    - When a participant, for whom study intervention has been interrupted, recovers from suspected or confirmed SARS-CoV-2 infection or related disease and all AEs related to

SARS-CoV-2 infection improve to Grade ≤1, the investigator should discuss with the sponsor about resuming study intervention.

Study visits and assessments:

- If possible, central laboratory testing as outlined in the Schedule of Activities is to be continued. If central laboratory tests cannot be performed, the use of a local laboratory is allowed for study evaluations. A copy of the local laboratory report should be reviewed by the investigator and filed with the source documents, along with reference ranges; to maintain treatment blinding, HBsAg, HBeAg, anti-HBs and anti-HBe antibody tests during the study intervention phase cannot be done locally (unless instructed otherwise by the sponsor).
- To safely maintain participants on study intervention while site capabilities are compromised by COVID-19-related restrictions, study visits may be performed by a nurse (who received study-specific training) at the patient's home (home health nurse) until such time that on-site visits can be resumed. The following activities may be completed as required per the Schedule of Activities and as feasible:
  - Sampling, processing and shipping of laboratory samples (as described above).
  - Checking study compliance: medication diary (if available), intake of oral study intervention, storage of oral study intervention
  - Performing ECGs
  - Collecting patient-reported outcomes (where appropriate translations and licensing are available)
  - If JNJ-3989/placebo is administered at the patient's home, it will need to be done by an unblinded nurse (who received study-specific training)
  - Delivering oral study interventions
- Any data related to adverse events, concomitant medication, vital signs, and ECGs will be reviewed and assessed by the investigator.
- In addition, participants may have tele-health visits conducted by blinded qualified site personnel via phone or video conversation as per local regulation. Assessments may include review of adverse events (including injection site reactions), concomitant medications, study intervention accountability. Participants will also be questioned regarding general health status to fulfill any physical examination requirement. Patient-reported outcomes may be collected (where appropriate translations and licensing are available) following the Site Assisted Administration Process Guidance.
- Procedures and timings should follow the Schedule of Activities as closely as possible. Standard Adverse Event/Serious Adverse Event reporting requirements apply.

Informed consent:

- Consenting and re-consenting of participants for the measures taken (including also remote consenting by phone or video consultation) will be performed as applicable and according to local guidance for informed consent applicable during the COVID-19 pandemic. The process is to be documented in the source documents.

Source data verification/monitoring:

- In case on-site monitoring visits are not possible, the site monitor may contact the investigator to arrange monitoring visits and activities remotely (in accordance with site and local requirements). Additional on-site monitoring visits may be needed in the future to catch up on source data verification.

Site audits:

- During the COVID-19 pandemic and at the impacted sites, study site GCP audits with direct impact/engagement from the investigator and study site personnel would not be conducted in order to comply with national, local, and/or organizational social distancing restrictions. Additional quality assurance activities such as remote audits or focused review of study related documents may take place with limited impact/engagement if possible.

INVESTIGATOR AGREEMENT

I have read this document and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: electronic signature appended at the end of the protocol Date: _____
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	18-May-2020 08:08:56 (GMT)	Document Approval