Janssen Research & Development *

Clinical Protocol

Intervention-specific Appendix 2 to Master Protocol PLATFORMPAHPB2001 AMENDMENT 3

A Randomized, Double-blind, Placebo-controlled Phase 2b Study to Evaluate Efficacy, Pharmacokinetics, and Safety of 48-week Study Intervention With JNJ-73763989+JNJ-56136379+Nucleos(t)ide Analog (NA) Regimen Compared to NA Alone in e Antigen-negative Virologically Suppressed Participants With Chronic Hepatitis B Virus Infection

REEF-2 Study

Protocol 73763989PAHPB2002; Phase 2b
AMENDMENT 4

JNJ-73763989 and JNJ-56136379

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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	This document
Amendment 3	30-September-2021
Amendment 2	27-January-2020
Amendment 1	26-Sept-2019
Original Protocol	31-Jul-2019

Amendment 4 (This document)

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 and Monitoring After Stopping of NA 10.13 Appendix 13: NA Re-treatment and Monitoring After Stopping of NA

Description of Change	Brief Rationale	Section Number and Name
Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted	Throughout the protocol

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1. PROTOCOL SUMMARY

1.1. Synopsis

Clinical Protocol 73763989PAHPB2002: A Randomized, Double-blind, Placebo-controlled Phase 2b Study to Evaluate Efficacy, Pharmacokinetics, and Safety of 48-week Study Intervention With JNJ-73763989+JNJ-56136379+Nucleos(t)ide Analog (NA) Regimen Compared to NA Alone in e Antigen-negative Virologically Suppressed Participants With Chronic Hepatitis B Virus Infection. Protocol 73763989PAHPB2002 is an intervention-specific appendix (ISA) to Master Protocol PLATFORMPAHPB2001.

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 (JNJ-73763976 [JNJ-3976] and JNJ-73763924 [JNJ-3924]) in JNJ-3989 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 for JNJ-3989, JNJ-6379 or placebo for JNJ-6379, and NA.

OBJECTIVES AND ENDPOINTS

Below is the list of objectives and endpoints that will be evaluated in this study, delineating the details in alignment with the general objectives listed in the Master Protocol PLATFORMPAHPB2001. The details specific for this ISA are highlighted (colored fill).

Objectives	Endpoints
Primary	
• To evaluate the efficacy of 48-week study intervention with JNJ-3989+JNJ-6379+NA regimen compared to NA alone.	• Proportion of participants with HBsAg seroclearance at Week 72 (ie, 24 weeks after completion of all study interventions at Week 48) without restarting NA treatment.
Secondary	
• To evaluate the safety and tolerability of the study intervention throughout the study.	• Safety and tolerability including but not limited to the proportion of participants with (serious) adverse events ([S]AEs) and abnormalities in clinical laboratory tests (including hematology, blood biochemistry, blood coagulation,

Objectives	Endpoints
	urinalysis, urine chemistry, and renal biomarkers), 12-lead electrocardiograms (ECGs), vital signs, and physical examinations throughout the study.
• To evaluate the efficacy of the study intervention at the end of treatment.	• Proportion of participants with HBsAg seroclearance at Week 48. • Proportion of participants with HBV DNA <lower limit of quantification (LLOQ) at Week 48.
• To evaluate the efficacy as measured by blood markers (such as HBsAg, HBV DNA, and alanine aminotransferase [ALT]) during study intervention and follow-up.	• Proportion of participants with HBsAg seroclearance at Week 96 (ie, 48 weeks after completion of all study interventions at Week 48) without restarting NA treatment. • Proportion of participants with HBsAg seroclearance 24 weeks after stopping all study interventions without restarting NA treatment. • Proportion of participants with HBsAg seroclearance 48 weeks after stopping all study interventions without restarting NA treatment. • Proportion of participants with (sustained) reduction, suppression, and/or seroclearance considering single and multiple markers (such as HBsAg, HBV DNA and ALT). • Proportion of participants with HBsAg seroconversion. • Change from baseline over time in HBsAg and HBV DNA. • Time to achieve first HBsAg 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 participants with HBV DNA levels and/or changes from baseline below/above different cut-offs (eg, <LLOQ of the assay). • Proportion of participants with flares (virologic, biochemical and clinical).

Objectives	Endpoints
• To evaluate the frequency of virologic breakthrough during study intervention.	• Proportion of participants with virologic breakthrough.
• To evaluate the proportion of participants requiring NA re-treatment during follow-up.	• Proportion of participants who meet the NA re-treatment criteria.
• To identify baseline and on-treatment markers associated with sustained off-treatment response.	• Correlation of baseline characteristics and baseline/on-treatment viral blood markers (such as baseline NA treatment duration, age, and baseline/on-treatment HBsAg levels) with selected off-treatment efficacy variables.
• To evaluate the pharmacokinetics (PK) of JNJ-3989 (JNJ-3976 and JNJ-3924), JNJ-6379, and NA, as applicable.	• Population PK parameters of JNJ-3989 (JNJ-3976 and JNJ-3924), JNJ-6379, and NA, as applicable.
Exploratory	
• To evaluate the efficacy of NA re-treatment during follow-up.	• Proportion of participants with decline in HBV DNA, ALT and/or HBsAg levels after restart of NA treatment during follow-up.
• To explore changes in the severity of liver disease.	• Changes in fibrosis (according to Fibroscan liver stiffness measurements) at end-of-study intervention and end of follow-up versus baseline.
• To explore the efficacy in terms of changes in HBV RNA and hepatitis B core-related antigen (HBcrAg) levels.	• Changes from baseline in HBV RNA and HBcrAg levels during study intervention and follow-up.
• To explore the impact of study intervention on participants' self-stigma and health-related quality of life using patient-reported outcomes (PROs) during study intervention and follow-up and to assess the psychometric properties of the HBV-specific self-stigma scale.	• Changes over time in score on the HBV-specific self-stigma scale. • Psychometric properties of the HBV-specific self-stigma scale. • Changes over time in the 5-Level EuroQol 5-Dimension (EQ-5D-5L) Visual Analog Scale (VAS) score and Index score.
• To explore the relationship of PK with selected pharmacodynamic (PD) parameters of efficacy and safety.	• Relationship of various PK parameters with selected efficacy and safety endpoints.
• To explore the HBV genome sequence during study intervention and follow-up.	• Assessment of intervention-associated mutations.
• To explore HBV-specific T-cell responses during study intervention and follow-up.*	• Changes from baseline in HBV-specific peripheral blood T-cell responses.

* Peripheral blood mononuclear cell (PBMC) samples for immune analyses will be collected at selected sites only.

Hypothesis

The primary hypothesis of this study is that the combination regimen of JNJ-3989+JNJ-6379+NA is more efficacious than NA treatment alone, as measured by the primary efficacy endpoint, the proportion of participants with HBsAg seroclearance at Week 72 (ie, 24 weeks after completion of all study interventions at Week 48) without restarting NA treatment.

OVERALL DESIGN

This ISA describes a Phase 2b study of JNJ-3989 and JNJ-6379. It is a companion document to the Master Protocol PLATFORMPAHPB2001, which describes the common design elements of the Platform study in participants with chronic hepatitis B (CHB). This ISA describes specific and/or additional protocol elements applicable to this intervention cohort, in which participants will be treated with the study intervention, JNJ-3989 and JNJ-6379 or placebos, in combination with NA.

The study described in this ISA is a Phase 2b, multicenter, randomized, double-blind, placebo-controlled, 2 parallel-group study to evaluate the efficacy of 48-week study intervention with a JNJ-3989+JNJ-6379+NA regimen compared to NA treatment alone, assessed by HBsAg seroclearance at Week 72 (ie, 24 weeks after completion of all study interventions at Week 48) without restarting NA treatment in HBeAg-negative virologically suppressed CHB-infected participants who received NA treatment for at least 2 years prior to screening. All participants will stop all study interventions including NAs at Week 48 and will be followed up until Week 96. After completing this study, participants may have the option to enroll into a long-term follow-up study.

The study will be conducted in 3 phases: a screening phase (4 weeks), a study intervention phase (48 weeks), and a follow-up phase (48 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. The duration of individual participation will be up to 102 weeks.

A target of 120 participants will be randomized in a 2:1 ratio to one of the following intervention arms and will receive study intervention for 48 weeks:

- Intervention Arm 1 (N=80): 200 mg JNJ-3989 (injection once monthly) +
  250 mg JNJ-6379 (tablets once daily [qd]) +
  NA* qd;
- Intervention Arm 2 (N=40): placebo for JNJ-3989 (injection once monthly) +
  placebo for JNJ-6379 (tablets qd) +
  NA* qd.

* NA: entecavir (ETV), tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF)

All participants who complete 48-week study intervention should stop all study interventions including NAs at Week 48. Any relevant change in participant baseline status with regards to ALT, HBV DNA levels and/or HBeAg status or any other event that in the opinion of the investigator could prevent stopping NA should be discussed with the sponsor. After stopping all study interventions, participants will be monitored closely during the 48-week follow-up phase and should restart NA treatment in accordance with the NA re-treatment criteria (see Section 'NA Re-treatment Criteria and Monitoring After Stopping of NA' for more details).

The investigator should consider to re-start NA treatment per local standard of care at the EOS visit (Follow-up Week 48) for participants who discontinued NA treatment at Week 48, 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.

The investigators and participants will remain blinded to intervention allocation until all participants have reached Week 72 (or discontinued earlier), while the sponsor's central study team will be unblinded at the time of the Week 48 interim analysis (IA). Details on the central study team will be provided in the Independent Data Monitoring Committee (IDMC) charter.

All participants who consent to participate in the intensive PK subgroup (optional) will undergo intensive PK sampling (minimally 18 participants).

Participants will be considered to have completed the study if they have completed the assessments of the end-of-study visit Follow-up Week 48 (Week 96).

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

NA Re-treatment Criteria and Monitoring After Stopping of NA

After completing treatment with JNJ-3989, JNJ-6379 (or their matching placebos) and NA at Week 48 (or after premature discontinuation), participants 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, alkaline phosphatase (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 restart 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 collected 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.

NUMBER OF PARTICIPANTS

A target of 120 HBeAg-negative virologically suppressed CHB-infected male and female participants, 18-65 years (inclusive) of age will be randomized in a 2:1 ratio to receive either JNJ-3989 and JNJ-6379 in combination with NA (N=80) or their respective placebos in combination with NA (N=40). Randomization will be stratified by screening HBsAg level (<1,000 IU/mL or ≥1,000 IU/mL), race (Asian versus non-Asian) and type of NA (TDF/TAF versus ETV).

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	200 mg once every 4 weeks	1 mL once every 4 weeks	250 mg qd	qd	Lamivudine-refractory patients: 1 mg* qd (but should preferably be treated with TDF or TAF instead) Other indications: 1 mg* qd (must be agreed upon by the sponsor)	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

All efficacy assessments will be performed at predefined time points as specified 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 validated 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 request.

HBV DNA and HBV RNA will be quantified at central laboratories using validated assays 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 request.

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

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 evaluate mutations associated with the study intervention.

Patient-reported Outcomes

The impact of HBV treatment on participants will be assessed using PROs at predefined time points. The following PRO instruments will be used: HBV-specific self-stigma scale and EQ-5D-5L questionnaire. The content validity of the HBV-specific self-stigma scale is currently being evaluated and the data collected in this study will be used to assess the psychometric properties of this scale.

SAFETY ASSESSMENTS

Safety and tolerability (AEs, clinical safety laboratory assessments, ECGs, vital signs and physical examinations) will be evaluated as described in Section 8.2 of the Master Protocol PLATFORMPAHPB2001 and at predefined time points as specified in the Schedule of Activities. In addition, urine samples for urine chemistry and renal biomarkers will be collected.

Specific toxicity management plans are in place for follow-up of rash, injection site reactions, acute systemic allergic reactions, ALT/aspartate aminotransferase elevations, and renal complications.

PHARMACOKINETICS

Plasma samples will be used to evaluate the PK of the study intervention. Samples collected for analyses of the study intervention's plasma concentrations may additionally be used to evaluate safety or efficacy aspects.

All participants will have sparse PK sampling on Day 1 and at Weeks 4, 12, and 24 (and at early withdrawal). All participants who consent to participate in the intensive PK subgroup (optional) will undergo intensive PK sampling at Week 4 (minimally 18 participants). If necessary (eg, for operational reasons), this visit may be scheduled at Week 8, 12, or 16.

Plasma concentration-time data for JNJ-3989 (ie, JNJ-3976 and JNJ-3924), JNJ-6379 and, optionally, NA will be analyzed via population PK for all participants. Area under the plasma concentration-time curve

over 24 hours (AUC_{24h}) and plasma trough concentrations (C_{0h}) will be estimated using empiric Bayes estimation.

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 parameters will be AUC_{24h}, maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), C_{0h}, plasma concentration at the end of the dosing interval (τ) (C_τ), and minimum plasma concentration (C_{min}). 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.

PHARMACOKINETIC/PHARMACODYNAMIC EVALUATIONS

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

IMMUNE EVALUATIONS

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.

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 (host DNA) blood sample should be collected at baseline to allow for host pharmacogenomic research, where local regulations permit. In addition, host DNA blood samples to allow for epigenetic analyses will be collected. These samples could for example be used to assess changes in frequencies of immune cells such as myeloid derived suppressor cells. These samples will only be collected from participants who consent separately to this component of the study.

In addition, other samples may be used for exploratory genetic or epigenetic 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. These samples can only be used to investigate the potential association of genetic or epigenetic factors with efficacy, safety, or PK of the study intervention, or HBV infection, or may be used to develop tests/assays related to the study intervention or HBV infection.

EXPLORATORY 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 when all participants have completed Week 72 or discontinued earlier. The final analysis will be performed when all participants have completed the last study visit (Week 96) or discontinued earlier.

Sample Size Determination

The total study sample size is 120 participants who will be randomly assigned to one of the two intervention arms in a 2:1 ratio (JNJ-3989+JNJ-6379+NA: placebo+placebo+NA). Statistical power to test the primary hypothesis was assessed using the Mantel-Haenszel test with a 1-sided Type 1 error rate of 0.05, assuming the observed percentage of participants with HBsAg seroclearance at Week 72 in the placebo+placebo+NA arm to be 5%. The sample size of 80 participants in the investigational arm and 40 participants in the control arm provides >91% statistical power to detect a ≥20% difference in the primary endpoint.

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 an intervention arm and who received at least 1 dose of study intervention within this ISA will be included in the ITT population. Participants will be analyzed according to the study intervention they were randomly assigned to.

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

Primary Efficacy Endpoint (HBsAg Seroclearance 24 Weeks After Completion of All Study Interventions at Week 48)

The proportion of participants who achieved HBsAg seroclearance at Week 72 (24 weeks after completion of 48 weeks of treatment with study intervention) without restarting NA treatment will be compared between intervention arms at a 1-sided 0.05 alpha. The primary endpoint will be compared between intervention arms using the stratum-adjusted Mantel-Haenszel difference in proportions, where the stratification factors screening HBsAg level (<1,000 IU/mL or ≥1,000 IU/mL), race (Asian versus non-Asian) and type of NA (TDF/TAF versus ETV) determine the strata. The associated 90% confidence interval for the difference in proportions will also be calculated.

All participants who do not achieve HBsAg seroclearance at Week 72 and/or require NA re-treatment between Week 48 and Week 72 are considered treatment non-responders for the purpose of the primary endpoint analysis.

Secondary and Exploratory Efficacy Endpoints

Descriptive statistics will be used for all efficacy endpoints which will be summarized by intervention arm and study phase. Comparisons between 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.

Resistance Analyses

The results of HBV viral sequencing will be evaluated by the sponsor virologist. Relevant changes of amino acid and/or nucleic acid variations (eg, substitutions) in the HBV genome will be tabulated and described.

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

Patient-reported Outcomes

The PRO 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 (Weeks 48, 72, 96) and between Week 48 and later time points for different subgroups: participants with HBsAg seroclearance 24 weeks and 48 weeks after completion of all study interventions at Week 48 without restarting NA treatment versus those without HBsAg seroclearance at those time points.

The data collected in this study will be used to assess the psychometric properties of the HBV-specific self-stigma scale. The psychometric analyses will be described in a separate document and results will be presented in a separate report.

Safety Analyses

Safety analyses will be based on the safety population and are specified in Section 9.4.3 of the Master Protocol PLATFORMPAHPB2001. All participants who received at least 1 dose of study intervention within this ISA will be included in the safety population. Participants will be analyzed according to the study intervention they actually received.

Safety will be evaluated by means of descriptive summaries of AEs including AEs of special interest to any of the study interventions, clinical laboratory tests, ECGs, vital signs, and physical examinations. The safety analysis will be done by study phase. Results will be presented in tabular format and/or graphically by intervention arm and over time, as appropriate.

Other Analyses

Pharmacokinetic Analyses

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

For each participant with intensive PK sampling, plasma concentration-time data of JNJ-6379, JNJ-3976, JNJ-3924, and, optionally, 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. Plasma PK parameters in participants undergoing intensive PK sampling will be calculated via noncompartmental methods for JNJ-6379, JNJ-3976, JNJ-3924, and, optionally, NA, as applicable. The PK parameters will be C_{max}, C_{τ}, and AUC_{24h}. The PK parameters will be subjected to an exploratory graphical analysis, including various transformations, to get a general overview.

Special attention will be paid to the plasma concentrations and PK parameters of those participants who discontinued the study for an AE, or who experienced an AE ≥grade 3 or an SAE.

Population PK analysis of plasma concentration-time data of JNJ-6379, JNJ-3976, JNJ-3924 and, optionally, NA will be performed using nonlinear mixed-effects modeling. Data may be combined with previous Phase 1 and/or 2 studies to support a relevant structural model. Available baseline characteristics (eg, demographics, laboratory variables, genotypes) will be included in the model as necessary. 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-6379, JNJ-3976, JNJ-3924, 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 will be given in a population PK analysis plan and results of the population PK analysis will be presented in a separate report.

Pharmacokinetic/Pharmacodynamic Analyses

Relationships of PK parameters for JNJ-6379, JNJ-3976, JNJ-3924 and, optionally, NA (ETV, tenofovir, and/or TAF) with selected efficacy and safety endpoints will be evaluated and graphically displayed. Details will be described in the Statistically Analysis Plan.

Modeling of key PD parameters (eg, HBsAg, HBV DNA) may be performed using population PK/PD. If PK/PD modeling of key efficacy endpoints is performed, treatment effect and possible covariates such as disease progression will be investigated. Other biomarkers may be explored at the sponsor's discretion. Details of the PK/PD analyses will be described in a population PK/PD analysis plan and results will be presented in a separate report.

Immune Analyses

Descriptive statistics (n, mean, SD, CV, geometric mean, median, minimum, and maximum) will be used to describe the magnitude of the gamma interferon (IFN-γ) T-cell response or the CD4+ and CD8+ T-cell responses (expressing at least 1 cytokine such as interleukin [IL]-2, tumor necrosis factor [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, including epigenetic analyses, 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 interindividual variability. 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

An IA will be conducted to assess safety and evaluate the time course of different disease markers to support the sponsor's interactions with health authorities, as well as to inform internal decisions about additional studies and/or investigation of other treatment combinations. The IA is planned when all

participants have completed Week 48 or discontinued earlier. The sponsor's central study team will be unblinded at this IA. Details on this team will be provided in the IDMC charter.

Up to two additional IAs may be performed by the sponsor between Week 48 and the primary analysis at Week 72, to support interactions with health authorities.

Both primary and interim analyses will be based on all data available at the predefined cut-off time points, and may include data at later time points for those participants who have reached subsequent visits.

Independent Data Monitoring Committee

At the analysis time points specified above and at regular intervals, an IDMC will meet and review unblinded data to ensure the continuing safety of the participants enrolled in the study. In addition, at the analysis time points specified above, the IDMC will also review the unblinded results of selected efficacy parameters measured by different HBV disease blood markers (eg, HBV DNA, HBsAg, etc).

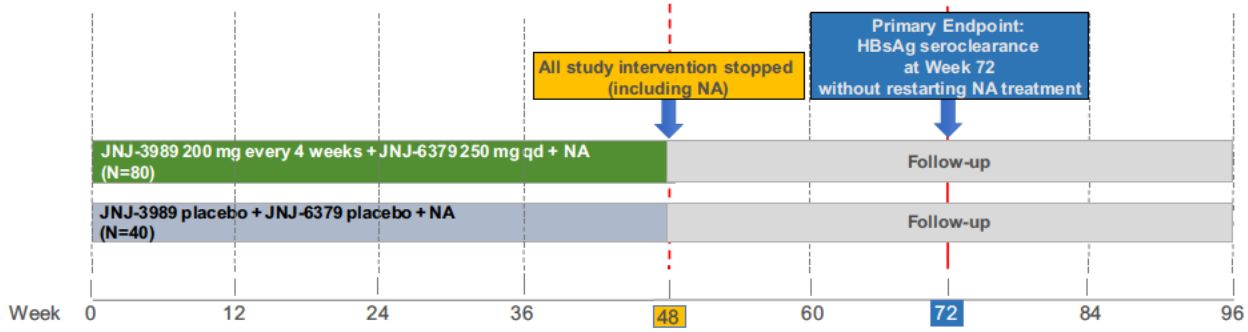
Possible recommendations of the IDMC include, but are not limited to, stopping the study for safety concerns, or study amendments.

Independent Flare Expert Panel

An IFLEP will be appointed. The IFLEP is composed of 3 independent medical experts with experience and expertise in HBV and its treatment. The responsibilities of the IFLEP include: conduct regular review of all relevant and available individual participant blinded study data related to ALT flares; determine and adjudicate each ALT flare; and provide documentation of the final decision to IDMC.

1.2. Schema

Figure 1: Schematic Overview of the Study



ETV: entecavir; NA: nucleos(t)ide analog; qd: once daily; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate
NA: ETV, TDF, or TAF; qd dosing according to the prescribing information

All participants who complete 48-week study intervention should stop all study interventions including NAs at Week 48. After stopping all study interventions, participants will be monitored closely during the follow-up phase and should restart NA treatment in accordance with the NA re-treatment criteria (see Section 'NA Re-treatment Criteria and Monitoring After Stopping of NA' for more details).

1.3. Schedule of Activities

Below are comprehensive schedules of activities that will be performed in this study, including those from the Master Protocol PLATFORMPAHPB2001. All differences with the Master Protocol PLATFORMPAHPB2001 (including the ISA-specific activities) are highlighted (colored fill).

1.3.1. Schedule of Activities – Screening and Study Intervention Phase

Phase	Screening	Double-blind Study Intervention[a]													
Study Week (W)	W 4 to 0[c]	W0[d]	W2	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48/WD[b]
Study Day (Window)	28	1	15 (+/ 2d)	29 (+/ 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[e]	X														
ICF for optional pharmacogenomic samples	X														
Inclusion/exclusion criteria[f]	X														
Prestudy therapy (including prior anti HBV therapy)	X														
Medical/surgical history and demographics[g]	X														
Preplanned surgery/procedure(s)	X														
Fibroscan or liver biopsy[h]	X														
Abdominal ultrasound[i]	X														
Serum IgM anti HBc antibody test	X														
Study Intervention															
Randomization to intervention arm within this ISA		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[j]		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)[k]
Oral study intervention accountability			X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Assessments															
Complete physical examination[l]	X								X						X
Symptom directed physical examination, including body weight		X	X	X	X	X	X	X		X	X	X	X	X	
Vital signs[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Triplicate 12 lead ECG[n]	X	X		X		X			X			X			X
Injection site reactions		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Liver ultrasound[o]		X							X						X

Phase	Screening	Double-blind Study Intervention[a]													
Study Week (W)	W 4 to 0[c]	W0[d]	W2	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48/WD[b]
Study Day (Window)	28	1	15 (+/ 2d)	29 (+/ 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
Blood chemistry (including liver function tests)[p,q,r]	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[s]	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Urine chemistry[t]	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Renal biomarkers[u]		X				X			X			X			X
Testing for hepatitis A, B, C, D, and E virus, HIV 1 and 2[r]	X														
FSH test (postmenopausal women only)[v]	X														
Alpha fetoprotein[r]	X								X						X
Hemoglobin A1c test	X														
Serum pregnancy test (women of childbearing potential only)	X														
Urine pregnancy test (women of childbearing potential only)		X		X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Assessments															
Fibroscan[w]		(X)													(X)
HBV Virology															
Blood sampling for HBV DNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sampling for HBV RNA[x]	X	X	X	X	X	X	X	X	X		X		X		X
Sampling for viral genome sequencing[y]	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 (qualitative)	X	X							X					X	X
HBsAg (quantitative)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBeAg (quantitative)[z]				X	X	X			X					X	X
HBcrAg[x]	X	X	X	X	X	X		X	X		X		X	X	X
Exploratory serology[aa]	X	X	X	X	X	X	X	X	X		X		X	X	X

Phase	Screening	Double-blind Study Intervention[a]													
Study Week (W)	W -4 to 0[c]	W0[d]	W2	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48/WD[b]
Study Day (Window)	28	1	15 (+/- 2d)	29 (+/- 2d)	57 (+/- 2d)	85 (+/- 2d)	113 (+/- 3d)	141 (+/- 3d)	169 (+/- 3d)	197 (+/- 3d)	225 (+/- 3d)	253 (+/- 3d)	281 (+/- 3d)	309 (+/- 3d)	337 (+/- 3d)
Clinical Pharmacology Assessments															
Blood sampling for sparse PK of JNJ 3989, JNJ 6379, and/or NA[bb]		X[cc]		X[cc]		X[cc]			X[cc]						X[dd]
Blood sampling for intensive PK of JNJ 3989, JNJ 6379, and/or NA (PK subgroup)[ee]				X											
Exploratory Host Biomarkers															
Whole blood RNA gene expression		X				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		X		X
Antidrug antibodies (to JNJ 3989)		X			X		X		X		X		X		
Immune Monitoring															
Immune cells (PBMCs) (selected sites only)[ff]		X							X						X
Pharmacogenomics (Host DNA)															
Exploratory host genotyping and epigenetic research (optional)[gg]		X							X						X
PRO Evaluations															
HBV specific self stigma scale	X	X							X						X
EQ 5D 5L		X							X						X
Ongoing Participant Review															
Concomitant therapy[hh]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[hh]	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: days; DBP: diastolic blood pressure; DNA: deoxyribonucleic acid; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; EQ-5D-5L: 5-Level EuroQol 5-Dimension; FSH: follicle-stimulating hormone; HBc: hepatitis B core protein; HBe(Ag): hepatitis B e (antigen); HBcrAg: hepatitis B core-related antigen; 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; ISA: intervention-specific appendix; MRI: magnetic resonance imaging; NA: nucleos(t)ide analog; PBMC: peripheral blood mononuclear cells; PK: pharmacokinetic; PRO: patient-reported outcome; RNA: ribonucleic acid; SBP: systolic blood pressure; ULN: upper limit of normal; W: Week; WD: withdrawal.

a. All study visits are to be scheduled relative to the baseline (Day 1) visit date.
b. Participants who discontinue study intervention early will have an early WD visit and will enter follow-up (see the follow-up Schedule of Activities in Section 1.3.2) unless they withdraw consent. Participants who withdraw consent will be offered an optional safety follow-up visit. For the optional safety follow-up visit, assessments are at the investigator's discretion and could be similar to the early WD visit.
c. If necessary (eg, for operational reasons), the screening phase may be extended up to a maximum of 6 weeks in agreement with the sponsor.
d. Day 1 samples are to be collected before the first dose of study intervention.

e. Both the Platform Master ICF and the ISA ICF must be signed before the first study-related activity.
f. Minimum criteria for the availability of documentation supporting the eligibility criteria are described in the Source Documents section in Attachment 3 of the Master Protocol PLATFORMPAHPB2001. Clinical status will be checked at screening and 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.
g. Medical history also includes mode of HBV transmission, stage of liver fibrosis, and alcohol consumption. Historical HBV DNA, HBsAg, HBeAg, and ALT data, if available, will be recorded in the CRF and/or the source document. Available historical data on a previous HBV genotype assessment will also be collected in the CRF.
h. Liver disease staging assessments will be performed based on Fibroscan or liver biopsy results, obtained within 6 months (in case of Fibroscan) or within 2 years (in case of liver biopsy) prior to screening or at the time of screening.
i. Participants must have absence of signs of cirrhosis or portal hypertension (absence of nodules, smooth liver contour, normal portal vein, spleen size <12 cm) and absence of signs of HCC on an abdominal ultrasound performed within 6 months prior to screening or at the time of screening or clinically relevant renal abnormalities. 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).
j. 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.
k. NA will be dispensed at Week 48 for intake during the follow-up phase in case the participant cannot stop NA treatment at Week 48.
l. Complete physical examination, including height (only at screening), body weight, skin examination, and other body systems.
m. Vital signs include supine SBP, DBP, pulse rate, and body temperature.
n. All ECGs will be read centrally. Only on Day 1, an ECG will be collected and assessed locally prior to dosing.
o. A liver ultrasound is recommended every 6 months 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). The liver ultrasound does not need to be repeated at baseline if it was done within 6 months prior to screening or at the time of screening.
p. Biochemistry samples must be taken after fasting for at least 10 hours for measurement of phosphate, calcium, creatinine, and lipids. If applicable, participants should bring their study intervention with them to each visit and have that day's intake at the site with breakfast.
q. Creatinine clearance (eGFR calculated by the CKD-EPI formula) will be assessed.
r. 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 8.3.6.3, Intervention-emergent ALT/AST Elevations and Section 10.6, Appendix 6, Intervention-emergent ALT/AST Elevations.
s. Urinalysis by dipstick: specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic analysis if needed. The dipstick reading should be done as soon as possible and in accordance with the manufacturer's recommendation. In case of a positive dipstick result, a urine sample will be set aside for additional examination of the positive parameter (eg, quantification as applicable).
t. Urine chemistry sample (quantitative measurement): creatinine, sodium, phosphate, glucose, protein, and albumin.
u. Urine sample for selected renal biomarkers including retinol binding protein and beta-2-microglobulin.
v. 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 (see Section 10.8 Appendix 8: Contraceptive and Barrier Guidance and Collection of Pregnancy Information).

w. 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.
x. HBcrAg and HBV RNA samples may be batched and only selected samples may be tested at the sponsor's request. Samples can be used for assessment of other serologic/virologic markers of HBV.
y. Samples may be sequenced based on the sponsor virologist's request, considering the HBV DNA levels.
z. Quantitative HBeAg assessment will only be performed in participants who become HBeAg-positive post baseline based on a qualitative HBeAg assay.
aa. Exploratory serology samples may be analyzed at the sponsor's discretion. Samples may be used to assess virologic or serologic markers of HBV.
bb. All participants will have sparse PK sampling. For all samples, the date and time of the preceding 2 intakes of oral study intervention (JNJ-6379/placebo and NA), the date and time of the previous JNJ-3989/placebo administration, and the date and time of PK sampling should be recorded. For participants in the intensive PK subgroup, the sparse PK sample does not need to be collected at the time of an intensive PK visit.
cc. 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.
dd. Only in case of early withdrawal.
ee. All participants who consent to participate in the intensive PK subgroup (optional) will undergo intensive PK sampling at Week 4 (minimally 18 participants). 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, +/- 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 data collection record (eg, CRF).
ff. 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, and may require an unscheduled visit.
gg. These samples are optional and will only be collected from participants who consent separately to this component of the study.
hh. Adverse events and concomitant medications will be monitored from the time a signed and dated ISA ICF is obtained until completion of the participant's last ISA-related procedure.

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). Participants who could not stop NAs or who have re-started NA treatment during the follow-up period, provided that their HBV DNA and ALT values are stable, will have less frequent visits (at least every 12 weeks).

Phase			**Follow-up**[a,b]										
Follow up (FU) Week (W)	FU W2	FU W4	FU W8	FU W12	FU W16	FU W20	FU W24	FU W28	FU W32	FU W36	FU W40	FU W44	FU W48 EOS
FU Study Day (Window)	15 (+/ 4d)	29 (+/ 4d)	57 (+/ 4d)	85 (+/ 4d)	113 (+/ 4d)	141 (+/ 4d)	169 (+/ 4d)	197 (+/ 4d)	225 (+/ 4d)	253 (+/ 4d)	281 (+/ 4d)	309 (+/ 4d)	337 (+/ 4d)
Visits in case all treatments including NA stopped	X	X	X	X	X	X	X	X	X	X	X	X	X
Visits in case NA is not stopped or NA re-started, provided that their HBV DNA and ALT values are stable				X			X			X			X
Study Intervention Administration													
Administer/Dispense NA, as applicable[c]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)[v]
NA accountability, as applicable	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Assess NA re treatment criteria, as applicable	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Safety Assessments													
Symptom directed physical examination, including body weight (if applicable)	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Triplicate 12 lead ECG[e]		X											
Liver ultrasound[f]							X						X
Clinical Laboratory Tests													
Hematology	X	X	X	X	X		X	X		X		X	X
Blood chemistry (including liver function tests)[g,h,i]	X	X	X[j]	X	X[j]	X[j]	X	X[j]	X[j]	X	X[j]	X[j]	X
Blood coagulation	X	X		X			X			X		X	X
Urinalysis[k]		X[m]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X
Urine chemistry[l]		X[m]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X
Urine pregnancy test (women of childbearing potential only)		X	X	X	X	X	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X
Alpha fetoprotein[i]							X						X
Efficacy Assessments													
Fibroscan[o]							(X)						(X)
HBV Virology													
Blood sample collection for HBV DNA and HBV RNA[p, w]	X	X	X	X	X	X	X	X	X	X	X	X	X
Sampling for viral genome sequencing[q]		X		X		X		X	X		X		X

Phase			Follow-up[a,b]										
Follow up (FU) Week (W)	FU W2	FU W4	FU W8	FU W12	FU W16	FU W20	FU W24	FU W28	FU W32	FU W36	FU W40	FU W44	FU W48 EOS
FU Study Day (Window)	15 (+/ 4d)	29 (+/ 4d)	57 (+/ 4d)	85 (+/ 4d)	113 (+/ 4d)	141 (+/ 4d)	169 (+/ 4d)	197 (+/ 4d)	225 (+/ 4d)	253 (+/ 4d)	281 (+/ 4d)	309 (+/ 4d)	337 (+/ 4d)
Visits in case all treatments including NA stopped	X	X	X	X	X	X	X	X	X	X	X	X	X
Visits in case NA is not stopped or NA re-started, provided that their HBV DNA and ALT values are stable				X			X			X			X
HBV Serology													
Blood sample collection for:													
Anti HBs and anti Hbe		X		X			X			X			X
HBsAg and HBeAg (qualitative)				X			X						X
HBsAg (quantitative)	X	X	X	X	X	X	X	X	X	X	X	X	X
HBeAg (quantitative)	X	X	X	X	X	X	X	X	X	X	X	X	X
HBcrAg[p]		X		X			X			X			X
Exploratory serology[r]	X	X	X	X	X	X	X			X			X
Exploratory Host 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)[s]	X		X	X			X						X
Pharmacogenomics (Host DNA)													
Exploratory host genotyping and epigenetic research (optional)[t]	X			X			X						X
PRO Evaluations													
HBV specific self stigma				X			X			X			X
EQ 5D 5L				X			X			X			X
Ongoing Participant Review													
Concomitant therapy[u]	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[u]	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: days; DBP: diastolic blood pressure; DNA: deoxyribonucleic acid; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; EOS: end of study; EQ-5D-5L: 5-Level EuroQol 5-Dimension; FU: follow-up; HBcrAg: hepatitis B core-related antigen; HBe(Ag): hepatitis B e (antigen); HBs(Ag): hepatitis B surface (antigen); HBV: hepatitis B virus; HCC: hepatocellular carcinoma; ICF: informed consent form; ISA: intervention-specific appendix; NA: nucleos(t)ide analog; PBMC: peripheral blood mononuclear cells; PRO: patient-reported outcome; RNA: ribonucleic acid; SBP: systolic blood pressure; ULN: upper limit of normal; W: Week.

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. No JNJ-3989/JNJ-6379/placebo will be administered or dispensed during follow-up. Administration/Dispensation of NA is only applicable for participants who could not stop NA treatment at Week 48, 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.
d. Vital signs include supine SBP, DBP, pulse rate, and body temperature.
e. All ECGs will be read centrally.
f. A liver ultrasound is recommended every 6 months 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).
g. Biochemistry samples must be taken after fasting for at least 10 hours for measurement of phosphate, calcium, creatinine, and lipids.
h. Creatinine clearance (eGFR calculated by the CKD-EPI formula) will be assessed.
i. 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 8.3.6.3, Intervention-emergent ALT/AST Elevations and Section 10.6, Appendix 6, Intervention-emergent ALT/AST Elevations.
j. Liver function tests only.
k. Urinalysis by dipstick: specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic analysis if needed. The dipstick reading should be done as soon as possible and in accordance with the manufacturer's recommendation. 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).
l. Urine chemistry sample (quantitative measurement): creatinine, sodium, phosphate, glucose, protein, and albumin.
m. A urinalysis and urine chemistry sample will be taken at Follow-up Week 4. In case of abnormalities, the tests should be repeated at the following visits.
n. Urine pregnancy tests will be provided to the participants for testing at home as urine pregnancy test should be done at least every 4 weeks. Results will be reported at the next visit. If urine pregnancy test is positive, the investigator needs to be informed immediately by the participant.
o. Only applicable to participants who are enrolled at a site with an on-site Fibroscan device.
p. HBcrAg and HBV RNA samples may be batched and only selected samples may be tested at the sponsor's request. Samples can be used for assessment of other serologic/virologic markers of HBV.
q. Samples may be sequenced based on the sponsor virologist's request, considering the HBV DNA levels. A sample for viral genome sequencing will be taken at an unscheduled visit for confirmation of virologic relapse.
r. Exploratory serology samples may be analyzed at the sponsor's discretion. Samples may be used to assess virologic or serologic markers of HBV.
s. 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, and may require an unscheduled visit.

t. These samples are optional and will only be collected from participants who consent separately to this component of the study.
u. Adverse events and concomitant medications will be monitored from the time a signed and dated ISA ICF is obtained until completion of the participant's last ISA-related procedure.
v. The investigator should consider to re-start NA treatment per local standard of care at the EOS visit (Follow-up Week 48) for participants who discontinued NA treatment at Week 48, 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.
w. 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 10.13, Appendix 13, for guidance after stopping NA treatment.

2. INTRODUCTION

This intervention-specific appendix (ISA) describes a Phase 2b study of JNJ-73763989 (JNJ-3989) and JNJ-56136379 (JNJ-6379) in combination with a nucleos(t)ide analog (NA). It is a companion document to the Master Protocol PLATFORMPAHPB2001, which describes the common design elements of the Platform study in participants with chronic hepatitis B (CHB). This ISA describes specific and/or additional protocol elements applicable to this intervention cohort, in which participants will be treated with the study intervention, JNJ-3989 and JNJ-6379 or placebos, in combination with a NA (see Section 2.2.2).

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 (JNJ-73763976 [JNJ-3976] and JNJ-73763924 [JNJ-3924]) in JNJ-3989 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 NAs, the current standard of care.[37]

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 hepatitis B core protein (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)[14,15] and Addendum.[16]

An introduction on HBV and the current treatment options is provided in Section 2 of the Master Protocol PLATFORMPAHPB2001.

The term "study intervention" throughout the protocol, refers to JNJ-3989 or placebo for JNJ-3989, JNJ-6379 or placebo for JNJ-6379, 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 hepatocellular carcinoma [HCC]) in chronically infected HBV patients under long-term NA therapy.

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".[24] With currently available NA treatment strategies the rate of HBsAg seroclearance remains very low (around 3%), even under long-term treatment.[5] To maintain suppression of HBV replication and reduce liver injury, life-long treatment with HBV NAs is necessary in most patients, but this approach is associated with potential non-adherence, possibly triggering relapse of symptomatic hepatitis as well as emergence of drug resistance with limited re-treatment options.[6,9,21,22,30,31,36]

The development of new HBV regimens such as JNJ-3989 and JNJ-6379 with different mechanisms of action seems a promising approach in increasing HBV functional cure, but development of these agents requires appropriate comparison with current standard of care and would need to be assessed prospectively in the setting of patients discontinuing NA therapy.

Recent studies explored the concept of stopping NAs in long-term suppressed patients. In some of these studies, increased incidence of HBsAg seroclearance has been observed in HBeAg-negative HBV patients off NA therapy (Reveal cohort).[19] The landmark study of Hadziyannis in 33 HBeAg-negative patients showed that 39% of the patients who stopped 4-5 years of adefovir therapy, had HBsAg loss during the follow-up period of 5.5 years.[10] Other European studies have reported that cessation of NA therapy can lead to HBsAg loss over time. In the FINITE study, the percentage of patients with HBsAg loss increased from 11% (2 of 18) after 48 weeks to 31% (4 of 13) after 144 weeks after stopping therapy.[1] Similar results were reported after stopping 4 years or more of entecavir (ETV) or tenofovir disoproxil fumarate (TDF), with cumulative rates of HBsAg loss reported to be 5% after 6 months, 16% after 12 months, and 25% after 18 months.[28] A recent prespecified analysis of 2 TDF randomized controlled studies evaluated the outcome after withdrawal of TDF and reported HBsAg loss in 5 (5%) of the 106 HBeAg-negative patients who entered the 24-week treatment follow-up period.[3]

In a recent systematic review that included 25 studies mainly from Asia, identification of predictors of virologic relapse and HBsAg loss after stopping NA led to conflicting results, partly due to the heterogeneity of the studies and low rate of HBsAg loss (2%).[29] Lower baseline HBsAg level was the only statistical baseline factor for off-therapy HBsAg seroclearance in a large cohort of 1075 HBeAg-negative patients in Taiwan.[18] Studies conducted in Asia have reported a lower estimated annual incidence of 1.78% of HBsAg loss highlighting potential differences among Asians and Caucasians.[18] A recent European retrospective, observational cohort study that included 198 NA-treated CHB patients who stopped NA treatment after HBeAg seroconversion showed 7-fold higher annual HBsAg seroclearance rates in Caucasian patients compared to non-Caucasians.[34]

After stopping NA treatment, it is expected that most of the patients will have rebound of HBV DNA. This was reported in the Hadziyannis study where all patients had an initial rebound of HBV DNA and 76% showed an alanine aminotransferase (ALT) flare suggesting that virologic relapse might be an important trigger for immune response that could lead to subsequent HBsAg loss. This was also reported in a recent prospective study showing that level of HBV DNA after stopping NA was the most important factor for subsequent HBsAg decline.[13] Therefore factors that may influence virologic relapse should be taken into consideration. Some recent studies have reported that patients treated with TDF experience virologic relapse significantly earlier than those receiving ETV. In a randomized study of 220 HBeAg-negative Asian patients who stopped treatment, 71% (47 of 66) treated with TDF had virologic relapse by Week 12, whereas 4.5% of patients (7 of 154) treated with ETV had virologic relapse in the same period ($p < 0.0001$), while the overall virologic relapse rate was similar.[12] Similarly, in a retrospective study that included 234 HBeAg-negative Asian patients who stopped treatment, median time to virologic relapse was 18 weeks (TDF) versus 33 weeks (ETV).[20]

Given the reported influence of race (Asian versus non-Asian), type of NAs (TDF/tenofovir alafenamide [TAF] versus ETV) and baseline HBsAg level on virologic relapse and subsequently HBsAg seroclearance, those 3 elements will be included as stratification factors in the current study.

The main goal of this Phase 2b study is to evaluate the efficacy of 48-week study intervention with a JNJ-3989+JNJ-6379+NA regimen compared to NA alone, assessed by HBsAg seroclearance at Week 72 (ie, 24 weeks after completion of all study interventions at Week 48) without restarting NA treatment in HBeAg-negative virologically suppressed CHB-infected participants who received NA treatment for at least 2 years prior to screening.

This study is also aiming at identifying baseline and on-treatment markers associated with sustained off-treatment response.

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 also for their combination (up to 3-month studies).

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 studies 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.[17] 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.[17] 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 human exposures after a single subcutaneous injection of 200 mg JNJ-3989 in human volunteers (Study AROHBV1001) (Table 1).

Table 1: 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]			1,315	20,136	-	-
24-week rat[c]	M		41,100	437,000	31.3	21.7
	F		43,100	270,000	32.8	13.4
37-week monkey[d]	M		73,200	1,230,000	55.7	61.1
	F		65,800	988,000	50.0	49.1
JNJ-3924						
Human exposure[a]			363	4,605		
24-week rat[c]	M		25,200	271,000	69.4	58.8
	F		26,200	163,000	72.2	35.4
37-week monkey[d]	M		21,600	383,000	59.5	83.2
	F		23,000	392,000	63.4	85.1

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; F: female; M: male; NOAEL: no observed adverse effect level.

[a] Single dose of 200 mg JNJ 3989 in healthy volunteers via subcutaneous injection (Study AROHBV1001; based on recent clean dataset with data cutoff 29 October 2019. Clinical PK update will be included in next revision of the IB.).

[b] $AUC_{0\text{-}last}$ for human exposure; $AUC_{0\text{-}24h}$ for animal exposures

[c] Once weekly dosing for 4 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

JNJ-6379

Following 6 months of treatment in rats, the kidney and female reproductive tract (irregular estrous 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 estrous cycle, from which they recovered at the end of the 9-week treatment-free period. These irregular estrous 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 2.

Table 2: Animal/Human Ratios at the NOAEL in Rat and Dog (Human Exposure at 250 mg JNJ-6379 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	-	-		
6M rat	M		7,540	93,100	0.6	0.4	0.9	0.6
	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 pharmacokinetic (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 is ongoing 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, 2 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.

In the 1-month rat study, JNJ-3989 was administered weekly via subcutaneous 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. Control animals received both vehicles via the respective routes. JNJ-6379 was administered daily via oral gavage at a dose level of 100 mg/kg.

No treatment-related mortality occurred during the study. Also, no relevant clinical signs were noted. Body weights and body weight gain were slightly decreased during the last weeks of treatment in males at ≥30/100 mg/kg and in females at 180/100 mg/kg, with correlating lower food intake at the high dose.

JNJ-3989 at 180 mg/kg presented vacuolation and basophilic granules in tubular epithelium of the kidney. At 30 mg/kg no kidney changes were noted.

There were no differences in kidney morphologic alterations between rats dosed with the single compound JNJ-3989, compared to the group dosed with the combination of the 2 compounds.

Crystals were observed in the urine of animals dosed with JNJ-6379 at 100 mg/kg, either alone or in combination, with mainly males being affected, and correlating with significant amounts of drug-related material in the urine (predominantly M7 but also unchanged drug).

No histopathology kidney findings were seen with JNJ-6379 at 100 mg/kg.

No drug-drug interaction (DDI) was seen in this study as well as in the previous study where the 2 compounds were given for 7 days.

In conclusion, daily oral administration of JNJ-6379 at 100 mg/kg in combination with weekly subcutaneous injection with JNJ-3989 at 30 or 180 mg/kg 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 dosed with JNJ-6379 at 100 mg/kg (per os) alone or with JNJ-3989 at 180 mg/kg (subcutaneous) alone. There were no additive or synergistic changes noted in the kidneys or in clinical pathology.

Preliminary results of a 3-month combination toxicity study with JNJ-6379 an 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.

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).

For further information, refer to the IB Addenda.[41,42]

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 2 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 ETV or 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 in pronounced mean HBsAg declines which were 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 is still emerging. 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 adult participants is also completed and clinical study report writing is currently ongoing (56136379HPB1005). In addition, data are available from 148 adult CHB 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 the JNJ-6379 25-mg and 600-mg dose levels. 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_{τ}) 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, data from Study 56136379HBP1002 with a 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 170 mg JNJ-6379 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 25 to 250 mg JNJ-6379 qd for 28 days, unblinded). Available antiviral activity data for 4 weeks of treatment with JNJ-6379 in this study 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 (cut-off date: 8 February 2019) 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 also includes 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 (cut-off date: 7 March 2019) 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 (23.8%) of 21 participants on JNJ-6379 experienced a mean reduction from baseline in HBV RNA of >2 $\log_{10}$ IU/mL versus 1 (14.3%) of 7 participants on placebo. HBV RNA levels at Week 24 were undetectable for 21 (100.0%) of 21 participants on JNJ-6379 and 4 (57.1%) of 7 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 virologic 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 lower limit of quantification (LLOQ) of the HBV DNA assay. All 5 participants with virologic 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 virologic 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 virologic 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 virologic 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 futility rule mentioned above.

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, Tenofovir Disoproxil Fumarate, or Tenofovir Alafenamide

Entecavir monohydrate is an HBV NA reverse transcriptase inhibitor indicated for the treatment of CHB 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 the NA tenofovir that is indicated for the treatment of CHB 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 human immunodeficiency virus 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 is an ester prodrug of the NA tenofovir that is indicated for the treatment of CHB in adults and that is characterized by a better safety profile than TDF. The most common adverse reactions (≥10% of participants) is headache.

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

There is no common target organ between JNJ-6379 or JNJ-3989 and ETV.[27]

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.[11,17] 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).[4,32] 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, renal tubular epithelial karyomegaly was observed in rats, dogs, and monkeys.[26] 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.[7]

Overall Nonclinical Assessment of the Combination Therapy

Based on the points listed below, no clinically relevant DDIs and no specific concerns about additive or synergistic toxicities are expected in kidney 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
- available clinical data with JNJ-6379 (Jade study [56136379HPB2001]) up to 24 weeks treatment on the absence of 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. [41,42]

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.[14,15,16]

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

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 block HBV replication more profoundly 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.[8,23,35] 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 and JNJ-3989 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. JNJ-3989 showed no effects on fertility in rats.

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 also lead to viral resistance, but resistance to JNJ-3989 is not anticipated to impact treatment with other small interfering RNAs (siRNAs). Using these agents in combination, especially in combination with ETV, TDF, or TAF 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-6379 was not genotoxic in the in vitro and in vivo tests.

JNJ-6379 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. All 5 participants with virologic breakthrough in the Jade study who received 75 mg JNJ-6379 monotherapy, had an emerging core amino acid mutation T33N, which is known to confer reduced JNJ-6379 activity in vitro (see Section 2.2.1 for the results of the IAs).

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 adult 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 ISRs, ALT/AST elevations, renal complications, hematologic abnormalities, and events related to cholesterol increase (Section 8.3.6, Adverse Events of Special Interest 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, Adverse Events of Special Interest).
- Continued careful assessment of the safety, efficacy, and PK during treatment is included in this study.

- To minimize potential risk and stress to participants, the following measures are in place:

  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, pulse rate, and body temperature), height (only at screening), body 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, Adverse Events of Special Interest).

  An Independent Data Monitoring Committee (IDMC) 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 9.6, Independent Data Monitoring Committee). In addition, an Independent Flare Expert Panel (IFLEP) will be appointed to characterize and adjudicate each ALT flare (see Section 9.7, Independent Flare Expert Panel).

  After stopping treatment with NA and JNJ-3989 and JNJ-6379, participants will be monitored closely during the follow-up phase, with frequent follow-up visits and pre-defined NA re-treatment criteria in case of flares (Section 6.7, NA Re-treatment Criteria and Monitoring After Stopping of NA).

  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 (see 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, Adverse Events of Special Interest.

  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

Below is the list of objectives and endpoints that will be evaluated in this study, delineating the details in alignment with the general objectives listed in the Master Protocol PLATFORMPAHPB2001. The details specific for this ISA are highlighted (colored fill).

Objectives	Endpoints
Primary	
• To evaluate the efficacy of 48-week study	• Proportion of participants with HBsAg

Objectives	Endpoints
intervention with JNJ-3989+JNJ-6379+NA regimen compared to NA alone.	seroclearance at Week 72 (ie, 24 weeks after completion of all study interventions at Week 48) without restarting NA treatment.
Secondary	
• To evaluate the safety and tolerability of the study intervention throughout the study.	• Safety and tolerability including but not limited to the 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, vital signs, and physical examinations throughout the study.
• To evaluate the efficacy of the study intervention at the end of treatment.	• Proportion of participants with HBsAg seroclearance at Week 48. • Proportion of participants with HBV DNA <LLOQ at Week 48.
• To evaluate the efficacy as measured by blood markers (such as HBsAg, HBV DNA, and ALT) during study intervention and follow-up.	• Proportion of participants with HBsAg seroclearance at Week 96 (ie, 48 weeks after completion of all study interventions at Week 48) without restarting NA treatment. • Proportion of participants with HBsAg seroclearance 24 weeks after stopping all study interventions without restarting NA treatment. • Proportion of participants with HBsAg seroclearance 48 weeks after stopping all study interventions without restarting NA treatment. • Proportion of participants with (sustained) reduction, suppression, and/or seroclearance considering single and multiple markers (such as HBsAg, HBV DNA and ALT). • Proportion of participants with HBsAg seroconversion. • Change from baseline over time in HBsAg and HBV DNA. • Time to achieve first HBsAg seroclearance. • Proportion of participants with HBsAg levels and/or changes from baseline below/above different cut-offs (eg,

Objectives	Endpoints
	HBsAg <100 IU/mL or >1 log_{10} IU/mL reduction in HBsAg from baseline). • 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 flares (virologic, biochemical, and clinical).
• To evaluate the frequency of virologic breakthrough during study intervention.	• Proportion of participants with virologic breakthrough.
• To evaluate the proportion of participants requiring NA re-treatment during follow-up.	• Proportion of participants who meet the NA re-treatment criteria.
• To identify baseline and on-treatment markers associated with sustained off-treatment response.	• Correlation of baseline characteristics and baseline/on-treatment viral blood markers (such as baseline NA treatment duration, age, and baseline/on-treatment HBsAg levels) with selected off-treatment efficacy variables.
• To evaluate the PK of JNJ-3989 (JNJ-3976 and JNJ-3924), JNJ-6379, and NA, as applicable.	• Population PK parameters of JNJ-3989 (JNJ-3976 and JNJ-3924), JNJ-6379, and NA, as applicable.
Exploratory	
• To evaluate the efficacy of NA re-treatment during follow-up.	• Proportion of participants with decline in HBV DNA, ALT and/or HBsAg levels after restart of NA treatment during follow-up.
• To explore changes in the severity of liver disease.	• Changes in fibrosis (according to Fibroscan liver stiffness measurements) at end-of-study intervention (EOSI) and end of follow-up versus baseline.
• To explore the efficacy in terms of changes in HBV RNA and HBcrAg levels.	• Changes from baseline in HBV RNA and HBcrAg levels during study intervention and follow-up.
• To explore the impact of study intervention on participants' self-stigma and health-related quality of life using patient-reported outcomes (PROs) during study intervention and follow-up and to assess the psychometric properties of the HBV-specific self-stigma scale.	• Changes over time in score on the HBV-specific self-stigma scale. • Psychometric properties of the HBV-specific self-stigma scale. • Changes over time in the 5-Level EuroQol 5-Dimension (EQ-5D-5L) Visual Analog Scale (VAS) score and Index score.
• To explore the relationship of PK with selected pharmacodynamic (PD) parameters of efficacy	• Relationship of various PK parameters with selected efficacy and safety

Objectives	Endpoints
and safety.	endpoints.
• To explore the HBV genome sequence during study intervention and follow-up.	• Assessment of intervention-associated mutations.
• To explore HBV-specific T-cell responses during study intervention and follow-up.*	• Changes from baseline in HBV-specific peripheral blood T-cell responses.

* 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 the definitions of terms, refer to Section 10.1, Appendix 1, Abbreviations and Definitions of Terms.

HYPOTHESIS

The primary hypothesis of this study is that the combination regimen of JNJ-3989+JNJ-6379+NA is more efficacious than NA treatment alone, as measured by the primary efficacy endpoint, the proportion of participants with HBsAg seroclearance at Week 72 (ie, 24 weeks after completion of all study interventions at Week 48) without restarting NA treatment.

4. STUDY DESIGN

4.1. Overall Design

This ISA describes a Phase 2b study of JNJ-3989 and JNJ-6379. It is a companion document to the Master Protocol PLATFORMPAHPB2001, which describes the common design elements of the Platform study in participants with CHB. This ISA describes specific and/or additional protocol elements applicable to this intervention cohort, in which participants will be treated with the study intervention, JNJ-3989 and JNJ-6379 or placebos, in combination with NA.

The study described in this ISA is a Phase 2b, multicenter, randomized, double-blind, placebo-controlled, 2 parallel-group study to evaluate the efficacy of 48-week study intervention with a JNJ-3989+JNJ-6379+NA regimen compared to NA treatment alone, assessed by HBsAg seroclearance at Week 72 (ie, 24 weeks after completion of all study interventions at Week 48) without restarting NA treatment in HBeAg-negative virologically suppressed CHB-infected participants who received NA treatment for at least 2 years prior to screening. All participants will stop all study interventions including NAs at Week 48 and will be followed up until Week 96. After completing this study, participants may have the option to enroll into a long-term follow-up study.

A target of 120 HBeAg-negative virologically suppressed CHB-infected male and female participants, 18-65 years (inclusive) of age, who received NA treatment for at least 2 years prior to screening will be randomized in a 2:1 ratio to receive either JNJ-3989 and JNJ-6379 in combination with NA or their respective placebos in combination with NA.

The study will be conducted in 3 phases: a screening phase (4 weeks), a study intervention phase (48 weeks), and a follow-up phase (48 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. The duration of individual participation will be up to 102 weeks.

Participants will be randomized in a 2:1 ratio to one of the following intervention arms and will receive study intervention for 48 weeks:

- Intervention Arm 1 (N 80): 200 mg JNJ-3989 (injection once monthly) +
  250 mg JNJ-6379 (tablets qd) +
  NA* qd;
- Intervention Arm 2 (N 40): placebo for JNJ-3989 (injection once monthly) +
  placebo for JNJ-6379 (tablets qd) +
  NA* qd.

* NA: ETV, TDF, or TAF

All participants who complete 48-week study intervention should stop all study interventions including NAs at Week 48 (see Section 6.6, Study Intervention Completion at Week 48). After stopping all study interventions, participants will be monitored closely during the 48-week follow-up phase and should restart NA treatment in accordance with the NA re-treatment criteria (see Section 6.7, NA Re-treatment Criteria and Monitoring After Stopping of NA, for more details).

Randomization will be stratified by screening HBsAg level (<1,000 IU/mL or ≥1,000 IU/mL), race (Asian versus non-Asian) and type of NA (TDF/TAF versus ETV).

The investigators and participants will remain blinded to intervention allocation until all participants have reached Week 72 (or discontinued earlier), while the sponsor's central study team will be unblinded at the time of the Week 48 IA. Details on the central study team will be provided in the IDMC charter.

Both the Platform Master informed consent form (ICF) and the ISA ICF must be signed before the first study-related activity.

Safety and tolerability, including AEs, laboratory assessments, ECGs, vital signs, and physical examination, will be assessed throughout the study from the time that the ISA ICF is signed until the completion of the last study-related activity (see Section 8.2, Safety Assessments, and Section 8.3, Adverse Events and Serious Adverse Events).

Samples for HBV genome sequencing will be taken at the time points indicated in the Schedule of Activities (see Section 8.1.1, Sequencing). Sequencing of samples obtained may be triggered by the sponsor's virologist based on changes in HBV DNA levels observed in each individual participant and the limits of the sequencing assay.

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

A population PK analysis will be performed based on the available data for JNJ-6379, JNJ-3976, JNJ-3924 and, optionally, NA, potentially in combination with data from a selection of Phase 1 and/or 2 studies. PK parameters in participants undergoing intensive PK sampling (minimally 18 participants) will be calculated via noncompartmental methods (see Section 8.5, Pharmacokinetics).

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

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

Two PRO instruments (the HBV-specific self-stigma scale and EQ-5D-5L questionnaire) will be used to explore the impact of HBV treatment on participants (see Section 8.1.2, Patient-reported Outcomes).

Participants will be considered to have completed the study if they have completed the assessments of the end-of-study visit Follow-up Week 48 (Week 96).

If a participant discontinues study intervention before the end of the 48-week study intervention phase, follow-up assessments should be obtained until 48 weeks after EOSI unless the participant withdraws consent. NA treatment (either ETV, TDF or TAF as per local practice) should be continued at this time as per local treatment guidelines.

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

The Schedule of Activities summarizes the frequency and timing of efficacy, safety, and other assessments applicable to the Master Protocol PLATFORMPAHPB2001 and this ISA.

An IDMC will be commissioned for this study (Section 9.6, Independent Data Monitoring Committee). In addition, an IFLEP will be appointed (Section 9.7, Independent Flare Expert Panel).

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 are currently on NA treatment and are HBeAg negative.

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 regimen evaluated in this study will first be established in patients without liver cirrhosis prior to initiating studies in patients with more advanced liver disease.

Control Arm

The safety and tolerability of the investigational combination arm (Intervention Arm 1) will be compared to those of standard of care NA (Intervention Arm 2).

The analysis of the primary efficacy endpoint and other secondary endpoints will be based on comparison of the investigational combination arm with the control arm (see Section 9.4, Statistical Analyses).

Randomization

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 treatment arms, and to enhance the validity of statistical comparisons across intervention arms.

Stratification Factors

Randomization will be stratified by screening HBsAg level (<1,000 IU/mL or ≥1,000 IU/mL), race (Asian versus non-Asian), and type of NA (TDF/TAF versus ETV) in order to provide a reasonably balanced representation of the 3 baseline factors across the 2 intervention arms.

Blinding

The investigators and participants will remain blinded to intervention allocation until all participants have reached Week 72 (or discontinued earlier), while the sponsor's central study team will be unblinded at the time of the Week 48 IA.

Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

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), and weekly visits for patients with ALT/AST ≥3x upper limit of normal (ULN) and ≥3x nadir (ie, lowest value during study participation) 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. 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, NA Re-treatment Criteria and Monitoring After Stopping of NA).

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 and monitoring after stopping of NA are presented graphically in Section 10.13, Appendix 13.

Host DNA and Exploratory Host Biomarker Collection

Refer to Section 4.2 of the Master Protocol PLATFORMPAHPB2001.

4.2.1. Study-specific Ethical Design Considerations

Refer to Section 4.2.1 of the Master Protocol PLATFORMPAHPB2001.

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.[38]

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. The injections were separated by either 7-day intervals (100, 200, and 300 mg doses), 14-day intervals (100 mg dose), or 28-day intervals (all doses tested). 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 in pronounced mean HBsAg declines which were 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 these doses. A reduced mean decline was observed at the lower dose of 25 mg. Data on the 50 mg dose is still emerging.

A dose of 200 mg JNJ-3989 once monthly is chosen for the combination treatment regimen of JNJ-3989+JNJ-6379+NA based on the observed decline in HBsAg in AROHBV1001 at this dose over 3 injections, and the lack of dose response observed at higher doses.

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 maximum effect (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

4.4.1. Participant Completion

A participant will be considered to have completed the study if he or she has completed assessments at the final follow-up visit.

4.4.2. Study Completion (End of Study Definition)

The study is considered completed with the last visit for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant visit at that study site, in the time frame specified in the Clinical Trial Agreement.

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. Refer to Section 5.4, Screen Failures of the Master Protocol PLATFORMPAHPB2001 for conditions under which the repeat of any screening procedures is allowed.

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.

Each potential participant must satisfy all inclusion and exclusion criteria from the Master Protocol PLATFORMPAHPB2001 (numbering prefixed by "M" in the list below) and all additional intervention-specific inclusion and exclusion criteria (numbering prefixed by "A"). The latter inclusion and exclusion criteria are highlighted (colored fill). For the few criteria from the Master Protocol that are specified or more restricted in this ISA, the additional text is also highlighted (colored fill).

5.1. Inclusion Criteria

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

M01/ A01. Male or female participants ≥18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place) to ≤65 years of age.

M02. Participant must be medically stable based on 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.

M03/ A02. Participants must have HBV infection documented by serum HBsAg positivity at screening. In addition, chronicity must be documented by any of the following at least 6 months prior to screening: serum HBsAg positivity, HBeAg or HBV DNA positivity, ALT elevation above ULN without another cause than HBV infection, documented transmission event, liver biopsy with changes consistent with chronic HBV, or should be documented by absence of marker for acute infection such as positive immunoglobulin M (IgM) anti-hepatitis B surface (HBs) and anti-HBc antibodies, which can be tested at screening.

The participants should be virologically suppressed. They should:

- Be HBeAg-negative,
- Be on stable HBV treatment, defined as currently receiving NA treatment (ETV, TDF, or TAF) for at least 24 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
- Have serum HBV DNA <60 IU/mL on 2 sequential measurements at least 6 months apart (one of which is at screening), AND
- Have documented ALT values <2.0x ULN on 2 sequential measurements at least 6 months apart (one of which is at screening).

M04. Participants must have a body mass index (weight in kg divided by the square of height in meters) between 18.0 and 35.0 kg/m^2, extremes included.

M05/ Participant must sign a Master ICF (specific for the Master Protocol PLATFORMPAHPB2001) and an ICF specific for this ISA indicating that he or she

A03. understands the purpose of, and procedures required for, the study and is willing to participate in the study.

M06. Participant must sign a separate ICF if he or she agrees 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.

M07/A04. Criterion modified per Amendment 2.

M07/A04.1. Female participants must be (as defined in Section 10.8 Appendix 8: Contraceptive and Barrier Guidance and Collection of Pregnancy Information):

a. Not of childbearing potential, OR

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 must agree to remain on a highly effective method while receiving study intervention and until 90 days after last dose of study intervention. Examples of highly effective methods of contraception are provided in Section 10.8 Appendix 8: Contraceptive and Barrier Guidance and Collection of Pregnancy Information.

Note: 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.

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.

M08. 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.

M09. In the investigator's opinion, the participant is able to understand and comply with protocol requirements, instructions, and study restrictions (Section 5.3, Lifestyle Considerations) and is likely to complete the study as planned in this ISA (including the

procedures outlined in the Master Protocol PLATFORMPAHPB2001).

A05. Participants must have HBsAg >100 IU/mL at screening.

A06. 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 2 years 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 with absence of signs of portal hypertension.

Note: Conventional imaging procedures alone (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.

A07/ M10. Male participants must agree to wear a condom when engaging in any activity that allows for passage of ejaculate to another person during the study intervention phase and until 90 days after last dose of study intervention.

A08. Female participants must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study intervention phase and until 90 days after last dose of study intervention.

A09. Male participants must agree not to donate sperm for the purpose of reproduction during the study intervention phase and until 90 days after the last dose of study intervention.

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

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from this ISA:

M01/ A01. Criterion modified per Amendment 2.

M01.1/A01.1. Participants with evidence of hepatitis A virus infection (hepatitis A antibody IgM), hepatitis C virus (HCV) infection (HCV antibody), hepatitis D virus (HDV) infection (HDV antibody), hepatitis E virus (HEV) 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.

M02. Criterion modified per Amendment 2.

M02.1. Participants with evidence of hepatic decompensation at any time point prior to or at the time of screening:

a. Total bilirubin >1.5xULN,
b. Direct bilirubin >1.2xULN, OR
c. Prothrombin time >1.3xULN (unless caused by anticoagulation therapy or vitamin K deficiency), OR
d. Serum albumin <3.2 g/dL, OR
e. History of clinical symptoms of hepatic decompensation (eg, ascites, jaundice, hepatic encephalopathy or coagulopathy, especially if resulting in a Child-Pugh classification B or C at the time clinical symptoms present or at screening).

M03. History or evidence of clinical signs or symptoms of hepatic decompensation, including but not limited to: portal hypertension, ascites, hepatic encephalopathy, esophageal varices.

M04. Participants with evidence of liver disease of non-HBV etiology. This includes but is not limited to hepatitis infections mentioned in exclusion criterion M01/A01, 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 M02a) or any other non-HBV liver disease considered clinically significant by the investigator.

M05/A02. Criterion modified per Amendment 2.

M05.1/A02.1. Participants with history or signs of cirrhosis or portal hypertension (nodules, no smooth liver contour, no normal portal vein, spleen size ≥12 cm) or signs of HCC on an abdominal ultrasound performed within 6 months prior to screening or at the time of screening or clinically relevant renal abnormalities. 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).

M06/A03. Criterion modified per Amendment 2.

M06.1/A03.1. 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 creatinine clearance ≥grade 3 (<60 mL/min) at screening, calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula;

b. Pancreatic lipase elevation ≥grade 3;

c. Pancreatic amylase 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 >100 ng/mL;

Note: Participants with alpha-fetoprotein >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.

g. Any other laboratory abnormality considered to be clinically significant by the investigator (also see inclusion criterion M03/A02).

Note: Retesting of abnormal laboratory values that may lead to exclusion will be allowed once without prior approval from the sponsor. Retesting will take place at an unscheduled visit during the screening phase. Participants with a normal value at retest may be included.

M07. Participants with hemoglobin A1c >8% at screening.

M08. 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 are considered cured with minimal risk of recurrence).

M09. Criterion modified per Amendment 2.

M09.1 Participants with abnormal sinus rhythm (heart rate <45 or >100 beats per minute [bpm]); QT interval corrected for heart rate according to Fridericia's formula (QTcF) >450 ms for males and >470 ms for females; QRS interval ≥120 ms; PR interval >220 ms; abnormal conduction; or any other clinically significant abnormalities on a 12-

lead ECG at screening.

Note: Retesting of an abnormal ECG that may lead to exclusion will be allowed once without prior asking approval from the sponsor. Retesting will take place during an unscheduled visit in the screening phase. Participants not meeting the above exclusion criterion at retest may be included.

M10. Participants with a history of or current cardiac arrhythmias (eg, extrasystole, 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 and/or coronary heart disease), moderate to severe valvular disease, or uncontrolled hypertension at screening.

M11. 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.

M12. Participants who have received an organ transplant (except for skin, hair, or cornea transplants).

M13. Participants with any history of or current clinically significant skin disease requiring regular or periodic treatment.

M14. Participants with clinically relevant alcohol or drug abuse within 12 months of screening.

M15. Participants with history of clinically relevant drug rash.

M16/ A04. Participants who have taken any disallowed therapies as noted in Section 6.5, Concomitant Therapy before the planned first dose of study intervention.

M17. Participants having used any invasive investigational medical device within 3 months, or having received an investigational intervention or a biological product, immunoglobulin or other blood product not intended for the treatment of HBV within 6 months or 5 half-lives (whichever is longer), before the planned first dose of study

intervention, or is currently enrolled in an interventional clinical study with an investigational product.

M18/ A05. 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.

M19/ A06. Male participants who plan to father a child while enrolled in this study or within 90 days after the last dose of study intervention.

M20. 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 has surgery planned during the time of expected participation in the study.

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

M21. Participant is an employee 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, as well as family members of the employees or the investigator.

M22. Criterion modified per Amendment 2.

M22.1. Vulnerable participants (eg, incarcerated individuals, individuals under a legal protection measure).

A07. Participants with known allergies, hypersensitivity, or intolerance to JNJ-3989 and JNJ-6379 or their excipients or to placebo content (refer to the IB).[14,15,16,40]

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 the 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 Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

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 the inclusion and exclusion Criteria of the Master Protocol PLATFORMPAHPB2001 and of this ISA (Section 5.1, Inclusion Criteria and 5.2, Exclusion Criteria in both documents) (eg, contraceptive requirements).

5.4. Screen Failures

Refer to Section 5.4 of the Master Protocol PLATFORMPAHPB2001 for handling of screen failures.

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	200 mg once every 4 weeks	1 mL once every 4 weeks	250 mg qd	qd	Lamivudine-refractory patients: 1 mg* qd (but should preferably be treated with TDF or TAF instead) Other indications: 1 mg* qd (must be agreed upon by the sponsor)	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.[14,15,16]

The placebo for JNJ-3989 will be a solution for subcutaneous injection [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 and the CRF.

JNJ-3989/placebo injections will be administered subcutaneously (preferably in the abdomen) 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. Investigators should follow guidance detailed in the respective prescribing information, including special warnings and precaution for use.

During the study, participants will continue the same NA treatment they were receiving at time of screening (and during at least 3 months prior to screening). 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.

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 interventions 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. 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. 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, not 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 in the study.

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 in a 2:1 ratio to 1 of 2 intervention arms (JNJ-3989+JNJ-6379+NA:placebo+placebo+NA). 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 screening HBsAg level (<1,000 IU/mL or ≥1,000 IU/mL), race (Asian versus non-Asian) and type of NA (TDF/TAF versus ETV).

For more information on the interactive web response system (IWRS), refer to Section 6.3 of the Master Protocol PLATFORMPAHPB2001.

Blinding

The investigators and participants will remain blinded to intervention allocation until all participants have reached Week 72 (or discontinued earlier), while the sponsor's central study team will be unblinded at the time of the Week 48 IA.

Under normal circumstances, the blind should not be broken until all participants have completed Week 72 or discontinued earlier. The investigator may in an emergency determine the identity of the study intervention by contacting the IWRS. While the responsibility to break the study 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, time, and reason for the unblinding must be documented by the IWRS, in the appropriate section of the CRF, and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

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.

Participants who have had their study intervention assignment unblinded should continue study intervention intake (unless instructed otherwise) and should return for scheduled evaluations.

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

For more information on blinding, refer to Section 6.3 of the Master Protocol PLATFORMPAHPB2001.

6.4. Study Intervention Compliance

JNJ-3989/placebo will be administered at the study site as a subcutaneous injection by qualified study-site personnel to assure compliance with study requirements.

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.

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 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.

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.

6.5. Concomitant Therapy

Overviews of ISA-specific disallowed medication and concomitant medications that should be used with caution are provided in Table 3 and Table 4, respectively. For general concomitant therapy considerations, refer to Section 6.5 of the Master Protocol PLATFORMPAHPB2001.

Table 3: Disallowed Medication

Disallowed at any time prior to screening until end of follow-up:
• Any CAM and oligonucleotide-based HBV 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:
• Any systemically (eg, intravenously, intramuscularly, orally, subcutaneously) administered medication that directly or indirectly interferes with immune responses (eg, cyclosporine, interleukins, IFN, programmed death-[ligand] 1 inhibitors, 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 breast cancer resistance protein (BCRP) transporter (eg, curcumin, cyclosporine A, eltrombopag) or P-glycoprotein transporter (eg, amiodarone, azithromycin clarithromycin, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, quinidine, ritonavir, verapamil). • Any medication that reduces renal function or competes for active tubular secretion (eg cimetidine, probenecid, quinidine).
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. ***Note:*** NA standard of care treatment is allowed. • 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 EOSI:
• Ethinylestradiol-containing contraceptives with an ethinylestradiol content >20 µg. ***Note:*** Starting treatment with ethinylestradiol-containing contraceptives during the study is not allowed.

Table 4: Concomitant Medications 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.
- Anticoagulants.
  Note: aspirin and other antiplatelet agents are allowed.

Note: The list of disallowed concomitant medication and medication to be used with caution is 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 prescribing information for ETV, TDF, and TAF should be consulted for any additional prohibited medication.

Medications requiring subcutaneous injection (other than JNJ-3989/placebo; eg, insulin) should be administered away from the JNJ-3989 injection site.

6.6. Study Intervention Completion at Week 48

All participants should stop all study interventions (JNJ-3989, JNJ-6379, and NA or both placebos and NA) at Week 48.

Any relevant change in participant baseline status with regards to ALT, HBV DNA levels and/or HBeAg status or any other event that in the opinion of the investigator could prevent stopping NA should be discussed with the sponsor.

For participants who cannot stop NA treatment, follow-up assessments will be obtained until Week 96.

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

After completing treatment with JNJ-3989, JNJ-6379 (or their matching placebos) and NA at Week 48 (or after premature discontinuation), participants 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, alkaline phosphatase (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 restart 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 collected 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.

Management of intervention-emergent ALT/AST elevations is discussed in Section 8.3.6.3, Intervention-emergent ALT/AST Elevations.

NA re-treatment criteria and monitoring after stopping of NA are presented graphically in Section 10.13, Appendix 13.

6.8. Intervention After the End of the Study

Refer to Section 6.7 of the Master Protocol PLATFORMPAHPB2001.

The investigator should consider to re-start NA treatment per local standard of care at the EOS visit (Follow-up Week 48) for participants who discontinued NA treatment at Week 48, 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

If a participant discontinues study intervention for any reason before Week 48, the participant will have an early withdrawal visit and will enter follow-up unless he/she withdraws consent. If the reason for withdrawal from the study is withdrawal of consent, then the participant 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.

7.1. Discontinuation of Study Intervention

JNJ-3989 and JNJ-6379 (or matching placebos) must be discontinued before Week 48 for all reasons listed in Section 7.1 of the Master Protocol PLATFORMPAHPB2001 and for all additional intervention-specific reasons. All the discontinuation criteria are listed below and the intervention-specific criteria are highlighted (colored fill). For the few criteria from the Master Protocol that are specified or more restricted in this ISA, the changes compared to the Master Protocol are also highlighted (colored fill). When JNJ-3989 or JNJ-6379 (or the matching placebos) are discontinued, NA treatment may be continued or, in consultation with the sponsor, discontinued based on investigator judgement.

The discontinuation criteria are:

- The investigator believes that for safety or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue JNJ-3989 and JNJ-6379 (or matching placebos).
- The participant becomes pregnant.
- The participant has a ≥grade 3 rash or allergic reaction.
- 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 according to the prescribing information.
- The participant has a 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, the investigator in consultation with the sponsor should consider changing the NA (to an NA that is not cross-resistant to the current NA, after evaluation of all data available). In case of virologic breakthrough, the same assessments will be done at an unscheduled visit as will be done in case of an ALT flare, but no PBMC sample will be taken (see Section 8.3.6.3 and Schedule of Activities).
- The participant has ALT/AST elevations, as described in Section 8.3.6.3, Intervention-emergent ALT/AST Elevations.

Note: The grades are based on the DAIDS Toxicity Grading Scale (see Section 10.9, Appendix 9, DAIDS Table).

7.2. Participant Discontinuation/Withdrawal From the Study

In case a participant is withdrawn from the study intervention cohort for any of the reasons listed in Section 7.2 of the Master Protocol PLATFORMPAHPB2001, additional participants will not be entered.

7.2.1. Withdrawal From the Use of Research Samples

Refer to Section 7.2.1 of the Master Protocol PLATFORMPAHPB2001.

7.3. Lost to Follow-up

Refer to Section 7.3 of the Master Protocol PLATFORMPAHPB2001.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

Refer to Section 8 of the Master Protocol PLATFORMPAHPB2001.

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

The total blood volume to be collected from each participant during planned assessments for the entire study will be approximately 1200 mL. In addition, PBMC samples (at selected sites only; approximately 300 mL), optional exploratory host genotyping and epigenetic research samples (approximately 60 mL) and optional intensive PK samples (approximately 66 mL) may 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).

Sample Collection and Handling

Refer to Section 8 of the Master Protocol PLATFORMPAHPB2001.

Study-specific Materials

In addition to the items described in Section 8 of the Master Protocol PLATFORMPAHPB2001, the investigator will be provided with the following supplies:

- A binder with the PRO instruments,
- Prescribing Information for ETV, TDF, and TAF,
- Contact information page(s).

8.1. Efficacy Assessments

All efficacy assessments will be performed at predefined time points as specified in the Schedule of Activities.

Qualitative and quantitative HBsAg and HBeAg, and quantitative HBcrAg as well as anti-HBs and anti-hepatitis B e (HBe) antibodies will be determined using validated 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 request.

HBV DNA and HBV RNA will be quantified at central laboratories using validated assays 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 request.

HBeAg 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). HBsAg and anti-HBs testing results from the Week 44 visit onwards will be provided for each participant to the investigator from FU Week 2 onwards. 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. Note that screening and Day 1 predose results are not blinded. HBV DNA results will be provided to the investigator and the sponsor from screening until the end of follow-up. 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 JNJ-3989 and JNJ-6379 (or the matching placebos) are discontinued in participants with confirmed virologic breakthrough (see Section 7.1, Discontinuation of Study Intervention),
- To assess if NA treatment cannot be stopped at Week 48 due to any relevant change in participant baseline status with regards to ALT, HBV DNA levels and/or HBeAg status or any other event (see Section 6.6, Study Intervention Completion at Week 48),
- To assess whether restart of NA treatment during follow-up is needed (see Section 6.7, NA Re-treatment Criteria and Monitoring After Stopping of NA).

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

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 evaluate mutations associated with the study intervention.

Sequencing of the HBV genome will be performed to monitor HBV variants present at the time points indicated in the Schedule of Activities. The sequencing of samples 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 the HBV infection and efficacy of the study intervention, including viral genotypic and phenotypic assessments.

8.1.2. Patient-reported Outcomes

The impact of HBV treatment on participants will be assessed using PROs at predefined time points (see Schedule of Activities). The following PRO instruments will be used: HBV-specific self-stigma scale and EQ-5D-5L questionnaire.

The PRO assessments will be performed by all participants. 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, and instructed how 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.

HBV-specific Self-stigma Scale, Version 1.0

The HBV-specific self-stigma scale is an HBV-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.[33,39]

The HBV-specific self-stigma scale version 1.0 is provided in Section 10.10, Appendix 10, HBV-specific Self-stigma Scale.

5-Level EuroQol 5-Dimension Questionnaire

The EQ-5D-5L questionnaire is a brief, 2-page, generic health-related quality-of-life assessment that evaluates a subject's self-rated health state on 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Additionally, a VAS records the subject's self-rated health on a vertical VAS where the endpoints are labelled 'best imaginable health state' (100) and 'worst imaginable health state' (0). This information can be used as a quantitative measure of health outcome as judged by the subject. EQ-5D scores include the following:

- EQ-5D Valuation Index score (a weighted scoring of the 5 dimension scores with a possible range from 0 to 1);
- EQ-5D VAS score (with a possible range from 0 [worst imaginable health] to 100 [best imaginable health]);
- EQ-5D descriptive system scores (5 scores reflecting each of the 5 dimensions ranging from 0 [no limitation] to 4 [incapacity]).

It takes about 2 minutes to complete the EQ-5D-5L questionnaire.

A representative example of the EQ-5D-5L questionnaire is provided in Section 10.11, Appendix 11, 5-Level EuroQol 5-Dimension Questionnaire (EQ-5D-5L).

8.2. Safety Assessments

Safety and tolerability (AEs, clinical safety laboratory assessments, ECGs, vital signs and physical examinations) will be evaluated as described in Section 8.2 of the Master Protocol PLATFORMPAHPB2001 and at predefined time points as specified in the Schedule of Activities.

Additional clinical safety laboratory assessments specific for this protocol are described in Section 10.2, Appendix 2, Clinical Laboratory Tests.

8.2.1. Physical Examinations

Refer to Section 8.2.1 of the Master Protocol PLATFORMPAHPB2001.

8.2.2. Vital Signs

Refer to Section 8.2.2 of the Master Protocol PLATFORMPAHPB2001.

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

8.2.3. Electrocardiograms

Refer to Section 8.2.3 of the Master Protocol PLATFORMPAHPB2001.

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

8.2.4. Clinical Safety Laboratory Assessments

Refer to Section 8.2.4 of the Master Protocol PLATFORMPAHPB2001.

In addition, urine samples for urine chemistry and renal biomarkers will be collected as noted in Section 10.2, Appendix 2, Clinical Laboratory Tests.

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

8.3. Adverse Events and Serious Adverse Events

Adverse events and SAEs will be evaluated as described in Section 8.3 of the Master Protocol PLATFORMPAHPB2001, including handling of pregnancy described in Section 8.3.5.

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 Attachment 4 of the Master Protocol PLATFORMPAHPB2001.

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

Refer to Section 8.3.1 of the Master Protocol PLATFORMPAHPB2001.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Refer to Section 8.3.2 of the Master Protocol PLATFORMPAHPB2001.

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

Refer to Section 8.3.3 of the Master Protocol PLATFORMPAHPB2001.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

Refer to Section 8.3.4 of the Master Protocol PLATFORMPAHPB2001.

8.3.5. Pregnancy

Refer to Section 8.3.5 of the Master Protocol PLATFORMPAHPB2001.

8.3.6. Adverse Events of Special Interest

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 ISRs, ALT/AST elevations, renal complications, and events related to cholesterol increase (Section 8.2.4, Clinical Safety Laboratory Assessments). In addition, the following toxicities will also be carefully monitored: rash and acute systemic allergic reactions.

For participants reporting rash, ISRs, acute systemic allergic reactions, ALT/AST elevations, 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. 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 5 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, JNJ-3989 and JNJ-6379 (or placebos) need to be permanently discontinued. NAs can be continued. 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.

8.3.6.1.1. 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.

8.3.6.2. 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 (or placebos). 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 (or placebos). 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.

8.3.6.3. 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 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 baseline value, JNJ-3989 and JNJ-6379 (or their matching placebos) 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 <5x ULN and HBV DNA is <20,000 IU/mL.

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 JNJ-3989 and JNJ-6379 (or their matching placebos) and should be monitored on a weekly basis or as per good clinical practice until ALT and/or AST levels have returned to <5x ULN and HBV DNA is <20,000 IU/mL 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 and monitoring after stopping of NA are presented in Section 6.7.

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 (or placebos) if considered at least possibly related to JNJ-3989 or JNJ-6379 and should be followed appropriately until resolution of the 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.

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 weeks of 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; any dose of NA (ETV, TDF or TAF) greater than the prescribed dose 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 the study intervention. Samples collected for analyses of the study intervention's plasma concentrations may additionally be used to evaluate safety or efficacy aspects.

All participants will have sparse PK sampling on Day 1 and at Weeks 4, 12, and 24 (and at early withdrawal). All participants who consent to participate in the intensive PK subgroup (optional) will undergo intensive PK sampling at Week 4 (minimally 18 participants). If necessary (eg, for operational reasons), this visit may be scheduled at Week 8, 12, or 16.

Plasma concentration-time data for JNJ-3989 (ie, JNJ-3976 and JNJ-3924), JNJ-6379 and, optionally, NA will be analyzed via population PK for all participants. Area under the plasma concentration-time curve over 24 hours (AUC_{24h}) and plasma trough concentrations (C_{0h}) will be estimated using empiric Bayes estimation.

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 parameters will be AUC_{24h}, C_{max}, t_{max}, C_{0h}, plasma concentration at the end of the dosing interval (τ) (C_{τ}), and minimum plasma concentration (C_{min}). 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.

8.6. Pharmacokinetic/Pharmacodynamic Evaluations

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

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 (host DNA) blood sample should be collected at baseline to allow for host pharmacogenomic research, where local regulations permit. In addition, host DNA blood samples to allow for epigenetic analyses will be collected. These samples could for example be used to assess changes in frequencies of immune cells such as myeloid derived suppressor cells. These samples will only be collected from participants who consent separately to this component of the study. Complete host genomic testing may be done to search for links of specific genes to (HBV-related) liver disease or to the PK, PD, efficacy, safety, or tolerability of the study intervention. Only host DNA research related to the study interventions under this protocol or to chronic HBV infection will be performed. Further, a participant may withdraw such consent at

any time without affecting their participation in other aspects of the study, or their future participation in the Platform study (see Section 7.2.1 of the Master Protocol PLATFORMPAHPB2001).

In addition, other samples may be used for exploratory genetic or epigenetic 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. These samples can only be used to investigate the potential association of genetic or epigenetic factors with efficacy, safety, or PK of the study intervention, or HBV infection, or may be used to develop tests/assays related to the study intervention or HBV infection.

These analyses will be performed at the sponsor's discretion, will always be under the sponsor's supervision, and may be reported separately.

8.9. Exploratory 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 at the time points indicated in the Schedule of Activities. Leftovers of other samples might also be used for exploratory research of host and viral markers.

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.

These analyses will be performed at the sponsor's discretion, will always be under the sponsor's supervision, and may be reported separately from the main study report.

More information is provided in Section 8.8 of the Master Protocol PLATFORMPAHPB2001.

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).

9.1. Statistical Hypothesis

The primary hypothesis of this study is that the combination regimen of JNJ-3989+JNJ-6379+NA is more efficacious than NA treatment alone, as measured by the primary efficacy endpoint, the proportion of participants with HBsAg seroclearance at Week 72 (ie, 24 weeks after completion of all study interventions at Week 48) without restarting NA treatment.

9.2. Sample Size Determination

The total study sample size is 120 participants who will be randomly assigned to one of the two intervention arms in a 2:1 ratio (JNJ-3989+JNJ-6379+NA: placebo+placebo+NA). Statistical power to test the primary hypothesis was assessed using the Mantel-Haenszel test with a 1-sided Type 1 error rate of 0.05, assuming the observed percentage of participants with HBsAg seroclearance at Week 72 in the placebo+placebo+NA arm to be 5%. The sample size of 80 participants in the investigational arm and 40 participants in the control arm provides >91% statistical power to detect a ≥20% difference in the primary endpoint.

The 2:1 randomization ratio (N 80:40, JNJ-3989+JNJ-6379+NA:placebo+placebo+NA) was chosen to balance statistical and clinical considerations as it provides adequate evidence of efficacy and safety, with the benefit of offering study participants a higher chance to receive investigational treatment. Safety will be compared between arms descriptively only, and no inferential testing is planned.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Screened	All participants who signed the ICF for the Master Protocol and this ISA
Enrolled	All participants who were randomly assigned to an intervention arm in this ISA
Intent-to-treat (ITT)	All participants who were randomly assigned to an intervention arm and who received at least 1 dose of study intervention within this ISA. Participants will be analyzed according to the study intervention they were randomly assigned to.
Safety	All participants who received at least 1 dose of study intervention within this ISA. Participants will be analyzed according to the study intervention they actually received.

9.4. Statistical Analyses

9.4.1. Efficacy Analyses

The primary efficacy analysis will be performed when all participants have completed Week 72 or discontinued earlier. The final analysis will be performed when all participants have completed the last study visit (Week 96) or discontinued earlier.

To evaluate the efficacy, the primary analysis set will be the Intent-to-treat (ITT) population (defined in Section 9.3).

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, range and interquartile 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,

screening HBsAg level (<1,000 IU/mL or ≥1,000 IU/mL), race (Asian versus non-Asian) and type of NA (TDF/TAF versus ETV).

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

9.4.1.1. Primary Efficacy Endpoint (HBsAg Seroclearance 24 Weeks After Completion of All Study Interventions at Week 48)

The proportion of participants who achieved HBsAg seroclearance at Week 72 (24 weeks after completion of 48 weeks of treatment with study interventions) without restarting NA treatment will be compared between intervention arms at a 1-sided 0.05 alpha. The primary endpoint will be compared between intervention arms using the stratum-adjusted Mantel-Haenszel difference in proportions,[25] where the stratification factors screening HBsAg level (<1,000 IU/mL or ≥1,000 IU/mL), race (Asian versus non-Asian) and type of NA (TDF/TAF versus ETV) determine the strata. The associated 90% confidence interval (CI) for the difference in proportions will also be calculated.

All participants who do not achieve HBsAg seroclearance at Week 72 and/or require NA re-treatment between Week 48 and Week 72 are considered treatment non-responders for the purpose of the primary endpoint analysis. In addition, participants who withdraw from treatment prior to Week 48 or from the study prior to Week 72 will be defined as non-responder. If the HBsAg value at Week 72 is missing, the non-missing value closest to Week 72 within the window of Weeks 60-84 (12 weeks prior/after Week 72) will be used.

Additional analyses may be performed on the primary efficacy endpoint using the Bayesian methodology to leverage the Platform framework. Posterior probabilities will be calculated for the treatment difference in the primary efficacy endpoint. This Bayesian analysis may incorporate historical data and/or data from other ISAs that may enter the Platform study in the future. Details on the Bayesian approach will be provided in the Modelling and Simulation Report.

9.4.1.2. Secondary and Exploratory Efficacy Endpoints

Descriptive statistics will be used for all efficacy endpoints which will be summarized by intervention arm and study phase. Comparisons between 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. Details will be described in the SAP.

To evaluate the efficacy at the end of treatment, the proportion of participants with HBsAg seroclearance and the proportion of participants with HBV DNA <LLOQ at Week 48, respectively, will be tabulated by study intervention arm. Between arm comparisons for both endpoints will be evaluated using the stratum-adjusted Mantel-Haenszel difference in

proportions, where the stratification factors screening HBsAg level (<1,000 IU/mL or ≥1,000 IU/mL), race (Asian versus non-Asian) and type of NA (TDF/TAF versus ETV) determine the strata and corresponding 90% cIs.

The efficacy of the study intervention during the follow-up phase will also be evaluated. The proportion of participants with HBsAg seroclearance at Week 96 without restarting NA treatment, the proportion of participants with HBV DNA <LLOQ at Weeks 72 and 96, respectively, the proportion of participants achieving partial response (HBV suppression without restarting NA treatment) at different time points during follow-up, the proportion of participants with flares (virologic, biochemical, and clinical), and the proportion of participants requiring NA re-treatment during follow-up will be tabulated by intervention arm. The comparison between the intervention arms will be done using the stratum-adjusted Mantel-Haenszel difference in proportions, as described above. A similar analysis will be conducted for the proportion of participants with HBsAg seroclearance 24 and 48 weeks, respectively, after stopping all study interventions without restarting NA treatment.

The proportion of participants who reach HBV DNA <LLOQ and/or ALT normalization after restart of NA treatment during follow-up will also be tabulated by intervention arm and the comparison between the intervention arms will be done using the Mantel-Haenszel test for difference in proportions as described above.

The blood markers (such as HBsAg, HBV DNA, and ALT) during study intervention and follow-up will also be summarized by intervention arm over time and plotted. The proportion of participants with virologic breakthrough (on treatment) and the proportion of participants with (sustained) reduction, suppression, and/or seroclearance during follow-up considering single and multiple markers (such as HBsAg, HBV DNA, and ALT) will be summarized by intervention arm. The proportion of participants with HBsAg seroconversion will be tabulated by intervention arm. Descriptive statistics on values and changes from baseline over time in HBsAg and HBV DNA will be summarized by intervention arm. Additional summaries will be provided by the randomization stratification factors (screening HBsAg level [<1,000 IU/mL or ≥1,000 IU/mL], race [Asian versus non-Asian] and type of NA [TDF/TAF versus ETV]).

The time to achieve first HBsAg seroclearance will be summarized based on Kaplan-Meier estimates in tables and graphs and compared between study interventions using the log rank test. The proportion of participants with HBsAg 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.

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 screening HBsAg level [<1,000 IU/mL or ≥1,000 IU/mL], race [Asian versus

non-Asian] and type of NA [TDF/TAF versus ETV], 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.

9.4.1.3. Resistance Analyses

The results of HBV viral sequencing will be evaluated by the sponsor virologist. Relevant changes of amino acid and/or nucleic acid variations (eg, substitutions) in the HBV genome will be tabulated and described.

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

9.4.1.4. Patient-reported Outcomes

The PRO 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 (Weeks 48, 72, 96) and between Week 48 and later time points for different subgroups: participants with HBsAg seroclearance 24 weeks and 48 weeks after completion of all study interventions at Week 48 without restarting NA treatment versus those without HBsAg seroclearance at those time points. Further details will be provided in the SAP.

The data collected in this study will be used to assess the psychometric properties of the HBV-specific self-stigma scale. The psychometric analyses will be described in a separate document and results will be presented in a separate report.

9.4.2. Safety Analyses

The safety analyses will be based on the safety population (defined in Section 9.3) and are specified in Section 9.4.3 of the Master Protocol PLATFORMPAHPB2001.

Safety will be evaluated by means of descriptive summaries of AEs including AEs of special interest to any of the study interventions, clinical laboratory tests, ECGs, vital signs, and physical examinations. The safety analysis will be done by study phase. Results will be presented in tabular format and/or graphically by intervention arm and over time, as appropriate.

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-6379, JNJ-3976, JNJ-3924, and NA (ETV, tenofovir, and/or TAF), as applicable, and for the derived plasma PK parameters for both noncompartmental and population PK analyses.

For each participant with intensive PK sampling, plasma concentration-time data of JNJ-6379, JNJ-3976, JNJ-3924, and, optionally, 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. Plasma PK parameters in participants undergoing intensive PK sampling will be calculated via noncompartmental methods for JNJ-6379, JNJ-3976, JNJ-3924, and, optionally, NA, as applicable. The PK parameters will be C_{max}, C_{τ}, and AUC_{24h}. The PK parameters will be subjected to an exploratory graphical analysis, including various transformations, to get a general overview.

Special attention will be paid to the plasma concentrations and PK parameters of those participants who discontinued the study for an AE, or who experienced an AE ≥grade 3 or an SAE.

Population PK analysis of plasma concentration-time data of JNJ-6379, JNJ-3976, JNJ-3924 and, optionally, NA will be performed using nonlinear mixed-effects modeling. Data may be combined with previous Phase 1 and/or 2 studies to support a relevant structural model. Available baseline characteristics (eg, demographics, laboratory variables, genotypes) will be included in the model as necessary. 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-6379, JNJ-3976, JNJ-3924, 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 will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

Pharmacokinetic/Pharmacodynamic Analyses

Relationships of PK parameters for JNJ-6379, JNJ-3976, JNJ-3924 and, optionally, NA (ETV, tenofovir, and/or TAF) with selected efficacy and safety endpoints will be evaluated and graphically displayed. Details will be described in the SAP.

Modeling of key PD parameters (eg, HBsAg, HBV DNA) may be performed using population PK/PD. If PK/PD modeling of key efficacy endpoints is performed, treatment effect and possible covariates such as disease progression will be investigated. Other biomarkers may be explored at the sponsor's discretion. Details of the PK/PD analyses will be described in a population PK/PD analysis plan and results will be presented in a separate report.

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, including epigenetic analyses, 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 interindividual variability. 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

An IA will be conducted to assess safety and evaluate the time course of different disease markers to support the sponsor's interactions with health authorities, as well as to inform internal decisions about additional studies and/or investigation of other treatment combinations. The IA is planned when all participants have completed Week 48 or discontinued earlier. The sponsor's central study team will be unblinded at this IA. Details on this team will be provided in the IDMC charter.

Up to two additional IAs may be performed by the sponsor between Week 48 and the primary analysis at Week 72, to support interactions with health authorities.

Both primary and interim analyses will be based on all data available at the predefined cut-off time points, and may include data at later time points for those participants who have reached subsequent visits.

More details are provided in Section 9.5 of the Master Protocol PLATFORMPAHPB2001.

9.6. Independent Data Monitoring Committee

At the analysis time points specified above and at regular intervals, an IDMC will meet and review unblinded data to ensure the continuing safety of the participants enrolled in the study. In addition, at the analysis time points specified above, the IDMC will also review the unblinded results of selected efficacy parameters measured by different HBV disease blood markers (eg, HBV DNA, 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). Possible recommendations of the IDMC include, but are not

limited to, stopping the study for safety concerns, or study amendments. 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.

More details are provided in Section 9.6 of the Master Protocol PLATFORMPAHPB2001.

9.7. Independent Flare Expert Panel

An IFLEP will be appointed. The IFLEP is composed of 3 independent medical experts with experience and expertise in HBV and its treatment. The responsibilities of the IFLEP include: conduct regular review of all relevant and available individual participant blinded study data related to ALT flares; determine and adjudicate each ALT flare; and provide documentation of the final decision to IDMC. Adjudication review cycles will match IDMC schedule and will be set up ideally 2 weeks before IDMC.

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

Abbreviations

AE	adverse event
A/H	animal/human ratio
AFP	Alpha-fetoprotein
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 hours
$AUC_{0\text{-}last}$	area under the plasma concentration-time curve from administration to last quantifiable sampling point
AUC_{∞}	area under the plasma concentration-time curve to last sampling point from time zero extrapolated to infinity
AUC_{τ}	area under the plasma concentration-time curve over the dosing interval (τ)
bpm	beats per minute
C_{0h}	plasma trough concentration
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
C_{min}	minimum plasma concentration
CRF	case report form
CT	computed tomography
C_{τ}	plasma concentration at the end of the dosing interval (τ)
CV	coefficient of variation
CYP	cytochrome P450
DAIDS	Division of Acquired Immunodeficiency Syndrome
DBP	diastolic blood pressure
DDI	drug-drug interaction
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EFD	embryofetal development
eGFR	estimated glomerular filtration rate
ELISpot	enzyme-linked immunospot
E_{max}	maximum effect
EOSI	end-of-study intervention
EQ-5D-5L	5-Level EuroQol 5-Dimension
ETV	entecavir
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBc	hepatitis B core protein
HBcrAg	hepatitis B core-related antigen
HBe(Ag)	hepatitis B e (antigen)
HBs(Ag)	hepatitis B surface (antigen)
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
HEV	hepatitis E virus

HIV(-1/2)	human immunodeficiency virus (type 1/2)
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICS	intracellular cytokine staining
IDMC	Independent Data Monitoring Committee
IFLEP	Independent Flare Expert Panel
IFN-γ	gamma interferon
IgG	immunoglobulin G
IgM	immunoglobulin M
IL	Interleukin
INR	International Normalized Ratio
ISA	intervention-specific appendix
ISR	injection site reaction
ITT	Intent-to-treat
IWRS	interactive web response system
LLN	lower limit of normal
LLOQ	lower limit of quantification
MoA	mode of action
MRI	magnetic resonance imaging
NA	nucleos(t)ide analog
NOAEL	no observed adverse effect level
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
pgRNA	pre-genomic ribonucleic acid
PK	pharmacokinetic(s)
PRO	patient-reported outcome(s)
qd	once daily
QTcF	QT interval corrected for heart rate according to Fridericia's formula
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
siRNA	small interfering ribonucleic acid
$t_{1/2term}$	terminal half-life
TAF	tenofovir alafenamide
t_{max}	time to reach C_{max}
TDF	tenofovir disoproxil fumarate
TNF	tumor necrosis factor
ULN	upper limit of normal
VAS	Visual Analog Scale
WBC	white blood cell

Definitions of Terms

ALT/AST nadir	Lowest ALT/AST value during study participation
End-of-study intervention (EOSI)	Time of the last administration of study intervention
HBsAg seroclearance	HBsAg negativity based on the assay used
HBsAg seroconversion	HBsAg negativity and anti-HBs antibody positivity
Intervention cohort	Cohorts of adult participants with chronic hepatitis B virus infection who receive a

	specific study intervention within this Platform study, and in whom the efficacy and safety of that intervention is evaluated
Study intervention	JNJ-73763989 or placebo, JNJ-56136379 or placebo, and NA (either ETV, TDF, or TAF)
Study intervention phase	48-week phase from randomization to last administration of study intervention
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

10.2. Appendix 2: Clinical Laboratory Tests

The clinical laboratory tests will be performed by the selected laboratory according to the Schedule of Activities. The tests to be performed are discussed in Section 8.2.4 of the Master Protocol PLATFORMPAHPB2001.

In addition, the following assessments will be performed specifically for this ISA:

Laboratory Assessments	Parameters	
Urine Chemistry (quantitative measurement)	Creatinine Sodium Phosphate	Glucose Protein Albumin
Renal Biomarkers	Retinol binding protein Beta-2-microglobulin	
Other optional tests in response to ALT flare (refer to Section 10.6, Appendix 6)	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

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

FINANCIAL DISCLOSURE

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

INFORMED CONSENT PROCESS

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

DATA PROTECTION

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

LONG-TERM RETENTION OF SAMPLES FOR ADDITIONAL FUTURE RESEARCH

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

COMMITTEES STRUCTURE

Independent Data Monitoring Committee

At the analysis time points specified above and at regular intervals, an IDMC will meet and review unblinded data to ensure the continuing safety of the participants enrolled in the study. In addition, at the analysis time points specified above, the IDMC will also review the unblinded results of selected efficacy parameters measured by different HBV disease blood markers (eg, HBV DNA, 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). Possible recommendations of the IDMC include, but are not limited to, stopping the study for safety concerns, or study amendments. 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.

More details are provided in Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

Independent Flare Expert Panel

An IFLEP will be appointed. The IFLEP is composed of 3 independent medical experts with experience and expertise in HBV and its treatment. The responsibilities of the IFLEP include: conduct regular review of all relevant and available individual participant blinded study data related to ALT flares; determine and adjudicate each ALT flare; and provide documentation of

the final decision to IDMC. Adjudication review cycles will match IDMC schedule and will be set up ideally 2 weeks before IDMC.

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

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

DATA QUALITY ASSURANCE

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

CASE REPORT FORM COMPLETION

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

SOURCE DOCUMENTS

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

MONITORING

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

ON-SITE AUDITS

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

RECORD RETENTION

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

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

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Refer to Attachment 4 of the Master Protocol PLATFORMPAHPB2001.

ATTRIBUTION DEFINITIONS

Refer to Attachment 4 of the Master Protocol PLATFORMPAHPB2001.

SEVERITY CRITERIA

Refer to Attachment 4 of the Master Protocol PLATFORMPAHPB2001.

SPECIAL REPORTING SITUATIONS

Refer to Attachment 4 of the Master Protocol PLATFORMPAHPB2001.

PROCEDURES

Refer to Attachment 4 of the Master Protocol PLATFORMPAHPB2001.

CONTACTING SPONSOR REGARDING SAFETY

Refer to Attachment 4 of the Master Protocol PLATFORMPAHPB2001.

PRODUCT QUALITY COMPLAINT HANDLING

Refer to Attachment 4 of the Master Protocol PLATFORMPAHPB2001.

10.5. Appendix 5: Rash Management

Table 5: 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[c] 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[c] of skin lesions) may be performed at the investigator's discretion.	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). Safety laboratory assessments may be performed at the investigator's discretion (recommended). Digital pictures[c] of skin lesions may be taken at the investigator's discretion. Digital pictures[c] 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	Referral to dermatologist at the discretion of the investigator[d] Biopsy not required, but may be performed at the dermatologist's discretion

Table 5: Management of Rash Events by Severity Grade

	Definition	Study Intervention Action	Activities by Day[a]	Referral to Dermatologist and Dermatology Activities
			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[c] of skin lesions may be taken at the investigator's discretion.	
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 (or placebos); 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[c] 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[c] 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[c] of skin lesions) are recommended to be performed until the rash severity resolves to grade 2 or grade 1.	Required[d] Biopsy not required, but may be performed at the dermatologist's discretion.

Table 5: 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 (or placebos); 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[c] 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[c] 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[c] of skin lesions) are recommended to be performed until the rash severity resolves to grade 2 or grade 1.	Required[d] 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 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.

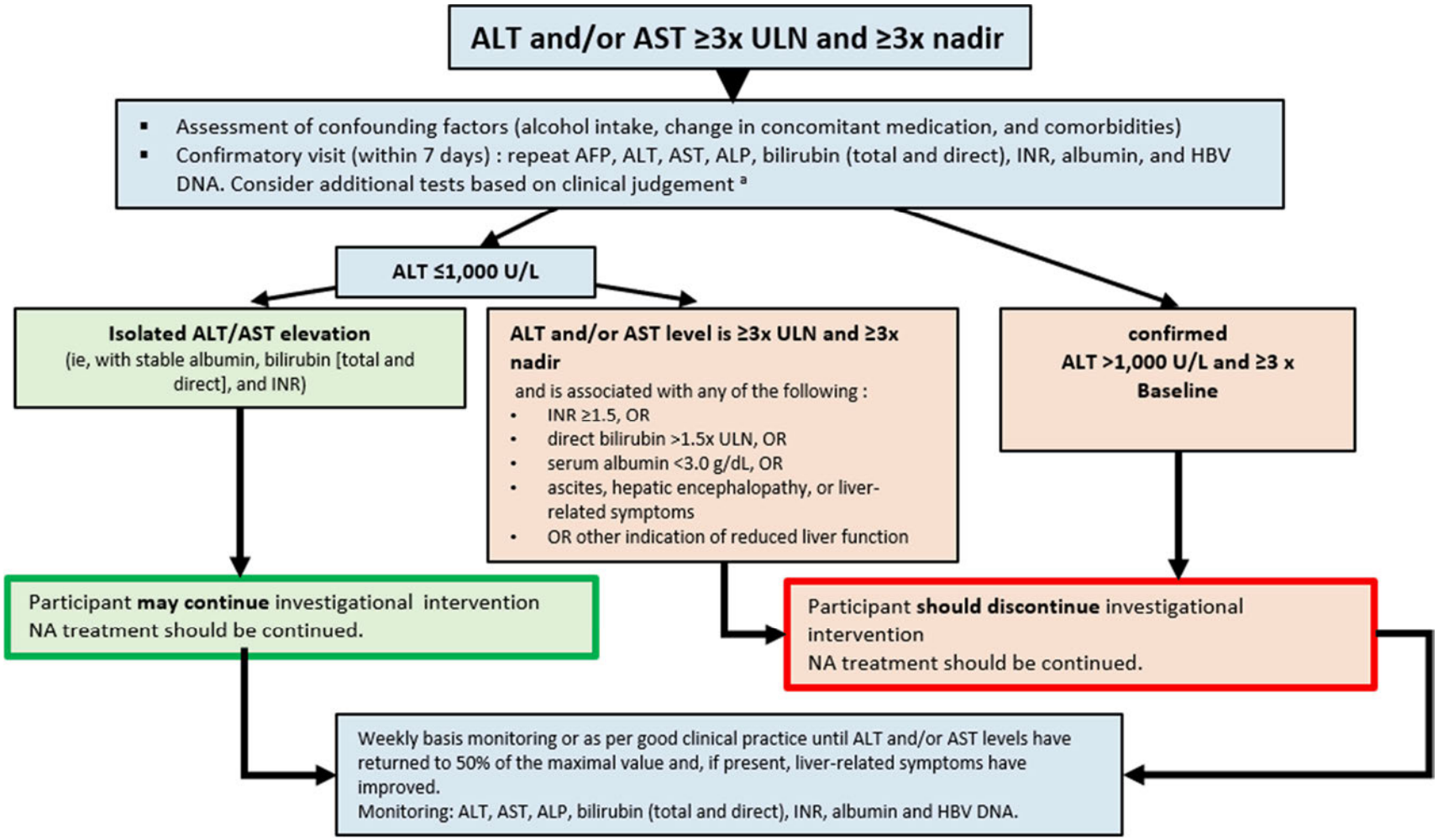
[c] Digital pictures to be taken at the clinical site upon consent of the participant.

[d] 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 CRF by the study site personnel.*
- *If a copy of the dermatologist's report, biopsy, and/or digital pictures are required, they should be deidentified and will be provided to 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 and PCR, HCV RNA, IgM and IgG anti-HEV, HEV RNA
- CMV, HSV, EBV infection: IgM and IgG anti-CMV, IgM and IgG anti-HSV; IgM and 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 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (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 and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1. Pregnancy information will be collected and reported as noted in Section 8.3.5.

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 follicle-stimulating hormone (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 to confirm a woman is not of childbearing potential. 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, or 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.

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
• Intrauterine device (IUD)

• Intrauterine hormone-releasing system (IUS)
• Tubal closure (eg, bilateral tubal occlusion, bilateral tubal ligation)
• Azoospermic partner *(vasectomized or due to medical cause)* *(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 oral intravaginal transdermal injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation 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.)*
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.

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/mm^3; *cells/L*)				
aged >5 years (not HIV infected)	300 to <400 *0.300×10^9 to $<0.400\times10^9$*[s]	200 to <300 *0.200×10^9 to $<0.300\times10^9$*[s]	100 to <200 *0.100×10^9 to $<0.200\times10^9$*[s]	<100 *$<0.100\times10^9$*[s]
Absolute Lymphocyte Count, Low (cells/mm^3; *cells/L*)				
aged >5 years (not HIV infected)	600 to <650 *0.600×10^9 to $<0.650\times10^9$*	500 to <600 *0.500×10^9 to $<0.600\times10^9$*	350 to <500 *0.350×10^9 to $<0.500\times10^9$*	<350 *$<0.350\times10^9$*
Absolute Neutrophil Count, Low (cells/mm^3; *cells/L*)				
aged >7 days	800 to 1,000 *0.800×10^9 to 1.000×10^9*	600 to 799 *0.600×10^9 to 0.799×10^9*	400 to 599 *0.400×10^9 to 0.599×10^9*	<400 *$<0.400\times10^9$*
aged 2 to 7 days	1,250 to 1,500 *1.250×10^9 to 1.500×10^9*	1,000 to 1,249 *1.000×10^9 to 1.249×10^9*	750 to 999 *0.750×10^9 to 0.999×10^9*	<750 *$<0.750\times10^9$*
aged ≤1 day	4,000 to 5,000 *4.000×10^9 to 5.000×10^9*	3,000 to 3,999 *3.000×10^9 to 3.999×10^9*	1,500 to 2,999 *1.500×10^9 to 2.999×10^9*	<1,500 *$<1.500\times10^9$*
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: HBV-specific Self-stigma Scale

Note: This appendix provides a representative example of the questionnaire that will be used in this study. The site should always use the most recently provided version of the questionnaire.

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	❑	❑	❑	❑	❑

10.11. Appendix 11: 5-Level EuroQol 5-Dimension Questionnaire (EQ-5D-5L)

Note: This appendix provides a representative example of the questionnaire that will be used in this study. The site should always use the most recently provided version of the questionnaire.

Health Questionnaire

English version for the UK

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

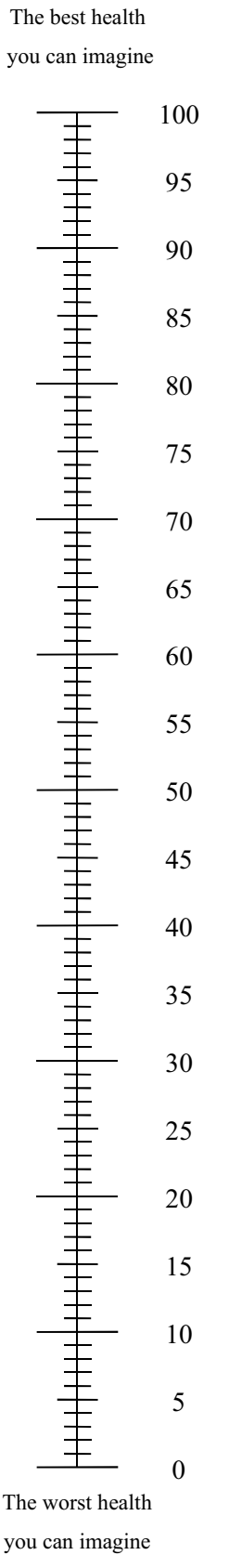
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY ☐



10.12. Appendix 12: 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 NA re-treatment criterion and to include more frequent monitoring for participants who discontinued NA treatment at Week 48 or during follow-up.

A severe clinical alanine aminotransferase (ALT) flare following discontinuation of NA treatment was reported in a virologically suppressed 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 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[5]. 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.	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 6.7 NA Re-treatment Criteria During Follow-up 8.3.6.3 Intervention-emergent ALT/AST Elevations 6.8 Intervention After the End of the Study 10.13 Appendix 13: NA Re-treatment During Follow-up
Participants who discontinued NA treatment at Week 48 , 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 8 STUDY ASSESSMENTS AND PROCEDURES
Clarifications were made to the urine pregnancy testing during follow-up.	Clarification.	1.3.2 Schedule of Activities – Follow-up Phase
Clarifications were made	Clarification.	1.3.2 Schedule of Activities – Follow-up Phase

Description of Change	Brief Rationale	Section Number and Name
concerning the optional safety follow-up visit for participants who withdraw consent during follow-up.		
The contraceptive guidance from the Master Protocol was replaced by ISA-specific contraceptive guidance, which includes the following updates versus the Master Protocol version: the list of examples which are not allowed as sole method of contraception during the study and the footnote concerning possible interaction between hormonal contraception and the study intervention have been removed. Additional clarifications were also made.	Upon Health Authority request and to align with the latest version of the sponsor's protocol template.	1.3.1 Schedule of Activities – Screening and Study Intervention Phase 5.1 Inclusion Criteria 10.8 Appendix 8: Contraceptive and Barrier Guidance and Collection of Pregnancy Information
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 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	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 SC at 60 mg/kg related to bone marrow depletion with pancytopenia including marked thrombocytopenia.

Clarifications, Additions and Corrections		
1.3.1 Schedule of Activities – Screening and Study Intervention Phase	Addition of HBeAg (qualitative) assessment at Week 44	Negative HBeAg status needs to be confirmed at Week 48 before stopping NA treatment based on the Week 44 result using the qualitative HBeAg assay
8.1 Efficacy Assessments	Blinding of post-baseline (Day1) HBsAg results to investigators and participants until follow-up Week 2	All participants who complete the Week 48 visit, should stop all study interventions including NAs at Week 48. HBsAg level is part of the primary endpoint. In order to avoid any bias, HBsAg results will be made available after stopping NA and from FU Week 2 visit onwards.
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	Addition of Alpha-fetoprotein measurement every 24 weeks and in case 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.
1.3.1 Schedule of Activities –	Language was added for participants in the intensive PK	To avoid unnecessary duplication of PK sampling for participants in the intensive PK subgroup.

Screening and Study Intervention Phase	subgroup, such that the sparse PK sample does not need to be collected at the time of an intensive PK visit.	
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 order of assessments in case of multiple assessments at the same time point was removed (refer to Master protocol PLATFORMPAHPB2001 amendment 2).	For more flexibility in timing of the assessments. The PRO assessment and ECGs should be prioritized, but the order of the other assessments is of less importance.
1.3.1 Schedule of Activities – Screening and Study Intervention Phase, 5.2 Exclusion Criteria	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.	Additional safety measure.
1.3.1 Schedule of Activities – Screening and Study Intervention Phase	Updated footnote for liver ultrasound assessment at baseline	Liver ultrasound is performed every 6 months to monitor for development of HCC in participants with increased risk for HCC. No need to repeat liver ultrasound assessment at baseline if done within 6 months
1.3.2 Schedule of Activities – Follow-up Phase	Visit windows for follow-up Week 2 and Week 4 were updated	Visit windows for follow-up Week 2 and Week 4 were increased from +/-2 days to +/-4 days to allow sufficient time for laboratory results to come in, especially HBeAg results, in order to assess re-treatment criteria.
5.1 Inclusion Criteria	A timeframe was added for female participants of childbearing potential to use a highly effective method of contraception for at least 30 days prior to screening.	The minimum time period for contraceptive use prior to screening ensures adequate protection of females of childbearing potential.
5.2 Exclusion Criteria	The note in exclusion criterion M01/A01 was modified to allow participants with positive HCV, HDV or HEV antibody test to enroll if an active infection can be ruled out (refer to Master protocol PLATFORMPAHPB2001 amendment 2).	To only exclude patients with active infection. Some patients may carry antibodies after an acute infection, which never developed into a chronic infection.
5.2 Exclusion Criteria	Exclusion criterion M02 was modified to include 'total bilirubin >1.5x ULN'. In addition, the reference to benign cause such as Gilbert's disease was removed for 'direct bilirubin' (refer to Master protocol PLATFORMPAHPB2001 amendment 2).	For clarification as no threshold for total bilirubin was included. For correction as Gilbert's syndrome is often associated with increased indirect bilirubin, not direct bilirubin.
5.2 Exclusion Criteria	Pancreatic amylase elevation ≥grade 3 was added in exclusion criterion M06/A03 (refer to Master protocol	Additional safety measure.

	PLATFORMPAHPB2001 amendment 2).	
5.2 Exclusion Criteria	Exclusion criterion M09 was updated to exclude participants with PR interval >220 ms instead of >200 ms	To align with ongoing HBV protocols with JNJ-3989 where a less restrictive cutoff was selected.
1.1 Synopsis/ Description of Interventions 6.1 Study Intervention(s) Administered	Specification on which NA treatments are available for the study was adapted.	To account for import restrictions with regards to tenofovir alafenamide (TAF) in some participating countries as well as indications other than lamivudine-resistant for ETV 1 mg.
6.4 Study Intervention Compliance	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.
6.5 Concomitant Therapy	Over-the-counter products, herbal medications and dietary supplements were removed from the disallowed concomitant medication list.	For clarification. Only products containing *Hypericum perforatum* are disallowed.
7.1 Discontinuation of Study Intervention	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.
8.3.6.3 Intervention-emergent ALT/AST Elevations 10.2 Appendix 2: Clinical Laboratory Tests 10.6 Appendix 6: Intervention-emergent ALT/AST Elevations	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
8.3.6.1.1 Injection Site Reactions 10.5 Appendix 5: Rash Management	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.	To protect the participant's privacy. To clarify that the pictures are optional and explain the proper steps to follow.

6.3 Measures to Minimize Bias: Randomization and Blinding	Added language explaining that persons involved in PK and viral load modeling will have access to the PK and viral load data before formal unblinding, while persons involved in trial conduct, data management and statistics will not have access to these data.	To allow the sponsor to make informed portfolio decisions for further development of the compound while protecting the blind prior to the primary analysis.
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
6.5 Concomitant Therapy – Table 3	NA standard of care treatment is not part of "any anti HBV drug that are disallowed from screening until end of follow-up"	Clarification
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 are not part of eligibility criteria assessed after screening.	Clarification
1.1 Synopsis/ Description of Interventions 6.1 Study Intervention(s) Administered	Subcutaneous injection of JNJ-3989 is now unambiguously described to be administered in the abdomen, instead of by preference.	For clarification and consistency in approach.
1.1 Synopsis/ Description of Interventions 1.2 Schema 6.1 Study Intervention(s) Administered	"Once monthly" in the dosage regimen of JNJ-3989 was replaced by "once every 4 weeks".	For clarification
7.1 Discontinuation of Study Intervention 8.3.6.4 Renal Complications	The relationship for discontinuation criterion for a confirmed ≥grade 3 eGFR abnormality and a drop from baseline of >10 mL/min/1.73 m^2 was clarified to refer specifically to JNJ-3989 and JNJ-6379 instead of investigational intervention.	For clarification
8.3.6.1.1 Injection Site Reactions	Wording was modified such that all ISRs will need to be reported in the CRF, but not by default as an AE.	For clarification
5.1 Inclusion Criteria	Update alphanumeric code IC A07/M09 to A07/M10 as male contraception requirement is IC 10 in Master Platform Protocol	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 2.3.2.2.2 Potential Risks for JNJ-6379	Potential risk on viral resistance to JNJ-3989 was moved to Section 2.3.2.2.1 as appropriate.	Correction
8 STUDY ASSESSMENTS AND PROCEDURES	Approximations of total blood volumes were modified. A note was added with regards to total blood volume.	Correction To clarify that the total blood volume to be collected from each participant may vary.
1.3.1 Schedule of Activities – Screening and Study Intervention Phase	A time window was added for intensive PK sampling.	For completeness
2.2.1 JNJ-3989 and JNJ-6379	Clarification of fertility study	For completeness
5.2 Exclusion Criteria	Individuals under a legal protection measure were added to criterion #M22 as an additional example of vulnerable participants (refer to Master protocol PLATFORMPAHPB2001 amendment 2).	For completeness
1.1 Synopsis/ Description of Interventions 6.1 Study Intervention(s) Administered	The volume of the placebo for JNJ-3989 was added to the dosage regimen.	For completeness
1.3.1 Schedule of Activities – Screening and Study Intervention Phase 2.3.2.2.1 Potential Risks for JNJ-3989 6.1 Study Intervention(s) Administered 6.5 Concomitant Therapy 7.1 Discontinuation of Study Intervention 10.1 Appendix 1: Abbreviations and Definitions of Terms 10.9 Appendix 9: DAIDS Table	Minor grammatical, formatting, or spelling changes were made.	Minor errors corrected.

Amendment 1 (26 September 2019)

Overall Rationale for the Amendment: Following Health Authority (HA) feedback under the Voluntary Harmonisation Procedure, the protocol was amended as specified below.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis, 9.4.1.1 Primary Efficacy Endpoint (HBsAg Seroclearance 24 Weeks After Completion of All Study Interventions at Week 48)	Methods for handling missing data were added to the protocol.	Per HA request, instead of referring to the SAP, the approach to handle missing data in the primary analysis of the primary efficacy endpoint was added.
5.1 Inclusion Criteria	Numbering of the inclusion criteria was updated due to addition of an inclusion criterion to the master protocol.	Formatting
5.2 Exclusion Criteria, 11 REFERENCES	Exclusion criterion #7 was amended to also include known allergies, hypersensitivity, or intolerance to placebo content.	Per HA feedback, exclusion criterion #7 was corrected to also include placebo content.
6.1 Study Intervention(s) Administered	It was clarified that during treatment with ETV, TDF or TAF, guidance per the respective prescribing information should be followed, in particular with reference to special warnings and precautions for use.	For consistency and completeness and per HA feedback, reference to the prescribing information of ETV, TDF, and TAF was added for guidance during NA treatment.
6.3 Measures to Minimize Bias: Randomization and Blinding	Wording on unblinding was updated to clarify that the investigator will contact the sponsor before unblinding but only if this does not delay action with respect to treatment in case of emergency.	The protocol currently recommends the investigator contact the sponsor before breaking the blind if possible. The text was updated to emphasize participant safety per HA feedback.
6.5 Concomitant Therapy	More general recommendation to consider alternative medications or adjusted doses was provided in Table 4 (Concomitant Medications to be Used With Caution).	As JNJ-6379 is a mild inducer of CYP3A, CYP3A substrates are included in the table of concomitant medications to be used with caution (Table 4). More general recommendation to consider alternative medications or adjusted doses was provided in this table per HA request.

10.13. Appendix 13: 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.

11. REFERENCES

1. Berg T, Simon K-G, Mauss S, Schott E, Heyne R, Klass DM, et al. Long-term response after stopping tenofovir disoproxil fumarate in non-cirrhotic HBeAg-negative patients—FINITE study. J Hepatol. 2017;67:918-924.
2. Brooks ST, Whitely E, Egger M, Smith GD, Mulheran PA, Peters TJ. Subgroup analyses in randomized trials: risks of subgroup-specific analyses; power and sample size for the interaction test. J Clin Epidemiol. 2004;57(3):229-236.
3. Buti M, Wong DK, Gane E, et al. Safety and efficacy of stopping tenofovir disoproxil fumarate in patients with chronic hepatitis B following at least 8 years of therapy: a prespecified follow-up analysis of two randomized trials. Lancet Gastroenterol Hepatol. 2019;4(4):296-304.
4. Cohen SM, Johansson SL, Arnold LL, Lawson TA. Urinary tract calculi and thresholds in carcinogenesis. Food and Chem Tox. 2002;40:793-799.
5. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67:370–398.
6. European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. J Hepatol. 2012;57(1):167–185.
7. European Medicines Agency (EMA). Assessment report Vemlidy (Tenofovir alafenamide). https://www.ema.europa.eu/documents/assessment-report/vemlidy-epar-public-assessment-report en.pdf. 10 November 2016. Accessed 29 January 2019.
8. Fang Z, Li J, Yu X, et al. Polarization of monocytic myeloid-derived suppressor cells by hepatitis B surface antigen is mediated via ERK/IL-6/STAT3 signaling feedback and restrains the activation of T cells in chronic hepatitis B virus infection. J Immunol. 2015;195(10):4873-4483.
9. Ford N, Scourse R, Lemoine M, et al. Adherence to Nucleos(t)ide Analogue Therapies for Chronic Hepatitis B Infection: A systematic review and meta-analysis. Hepatol Commun. 2018;2(10):1160-1116.
10. Hadziyannis SJ, Sevastianos,V, Rapti I, Vassilopoulos D, Hadziyannis E. Sustained responses and loss of HBsAg in HBeAg-negative patients with chronic hepatitis B who stop longterm treatment with adefovir. Gastroenterology. 2012;143:629-636.
11. Henry SP, Johnson M, Zanardi TA, Fey R, Auyeung D, Lappin PB, Levin AA. Renal uptake and tolerability of a 2'-O-methoxyethyl modified antisense oligonucleotide (ISIS 113715) in monkey. Toxicology. 2012;301(1-3):13-20.
12. Höner Zu Siederdissen C, Hui AJ, Sukeepaisarnjaroen W, et al. Contrasting timing of virological relapse after discontinuation of tenofovir or entecavir in hepatitis B e antigen–negative patients. J Infect Dis. 2018;218(9):1480-1484.
13. Höner Zu Siederdissen C, Rinker F, Maasoumy B, et al. Viral and host responses after stopping long-term nucleos(t)ide analogue therapy in HBeAg-negative chronic hepatitis B. J Infect Dis. 2016;214(10):1492-1497.
14. Investigator's Brochure: JNJ-73763989 Edition 3. Janssen Research & Development (May 2019).
15. Investigator's Brochure: JNJ-56136379 Edition 4. Janssen Research & Development (Feb 2019).
16. Investigator's Brochure: JNJ-56136379 Edition 4, Addendum 1. Janssen Research & Development (May 2019).
17. Janas MM, Harbison CE, Perry VK, et al. The nonclinical safety profile of GalNac-conjugated RNAi therapeutics in subacute studies. Toxicologic Pathology. 2018;46(7):735-745.
18. Jeng WJ, Chen YC, Chien RN, Sheen IS, Liaw YF. Incidence and predictors of hepatitis B surface antigen seroclearance after cessation of nucleos(t)ide analogue therapy in hepatitis B e antigen-negative chronic hepatitis B. Hepatology. 2018;68(2):425-434.
19. Jeng W-J, Yang H-I, Chen Y-C, et al. Increased incidence of HBsAg seroclearance in HBeAg negative chronic hepatitis B patients discontinued Nuc therapy comparing to natural course – a propensity score matched study. J Hepatol. 2018;68 Suppl 1:S88.
20. Kuo MT, Hu TH, Hung CH, et al. Hepatitis B virus relapse rates in chronic hepatitis B patients who discontinue either entecavir or tenofovir. Aliment Pharmacol Ther. 2019;49(2):218-228.

21. Lee M, Keeffe EB. Study of adherence comes to the treatment of chronic hepatitis B. J Hepatol. 2011;54:6–8.

22. Lesmana LA, Leung NWY, Mahachai V, et al. Hepatitis B: Overview of the burden of disease in the Asia-Pacific region. Liver International. 2006;26:3–10.

23. Li H, Zhai N, Wang Z, et al. Regulatory NK cells mediated between immunosuppressive monocytes and dysfunctional T cells in chronic HBV infection. Gut. 2018;67(11):2035-2044.

24. Lok AS, Zoulim F, Dusheiko G, Ghany MG. Hepatitis B cure: from discovery to regulatory approval. J Hepatol. 2017;67(4):847-861.

25. Mantel N and Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959;22:719-748.

26. Memorandum to Advisory Committee Members and Guests from Tenofovir Review Team. Background Package for NDA 21-356: VIREAD (tenofovir disoproxil fumarate), 6 September 2001.

27. Memorandum to Advisory Committee Members and Guests from Entecavir Review Team. Briefing document for NDA 21-797, entecavir 0.5 and 1 mg tablets and NDA 21-798, entecavir oral solution 0.05 mg/mL, 10 February 2005.

28. Papatheodoridis GV, Rigopoulou EI, Papatheodoridi M, et al. DARING-B: discontinuation of effective entecavir or tenofovir disoproxil fumarate long-term therapy before HBsAg loss in non-cirrhotic HBeAg-negative chronic hepatitis B. Antivir Ther. 2018;23(8):677-685.

29. Papatheodoridis G, Vlachogiannakos I, Cholongitas E, et al. Discontinuation of oral antivirals in chronic hepatitis B: a systematic review. Hepatology. 2016;63(5):1481-1492.

30. Scaglione SJ, Lok AS. Effectiveness of hepatitis B treatment in clinical practice. Gastroenterology. 2012;142:1360-1368.

31. Sorrell MF, Belongia EA, Costa J, et al. National Institutes of Health Consensus Development Conference Statement: Management of hepatitis B. Ann Intern Med. 2009;150:104–110.

32. Tannehill-Gregg SH, Dominick MA, Reisinger AJ, et al. Strain-related Differences in Urine Composition of Male Rats of Potential Relevance to Urolithiasis. Toxicol Pathol. 2009;37:293-305.

33. US Food and Drug Administration. Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. 2019. Available on: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measure-use-medical-product-development-support-labeling-claims. Accessed on 4 June 2019.

34. Van Hees S, Chi H, Hansen B, et al. Sustained off-treatment viral control is associated with high hepatitis B surface antigen seroclearance rates in Caucasian patients with nucleos(t)ide analogue–induced HBeAg seroconversion. J Viral Hepat. 2019;26(6):766–769.

35. Wang S, Chen Z, Hu C, et al. Hepatitis B virus surface antigen selectively inhibits TLR2 ligand-induced IL-12 production in monocytes/macrophages by interfering with JNK activation. J Immunol. 2013;190(10):5142-5151.

36. Woo G, Tomlinson G, Nishikawa Y, et al. TDF and ETV are the most effective antiviral agents for chronic hepatitis B: A systematic review and Bayesian meta-analyses. Gastroenterology. 2010;139:1218–1229.

37. Wooddell CI, Yuen MF, Chan HL, et al. RNAi-based treatment of chronically infected patients and chimpanzees reveals that integrated hepatitis B virus DNA is a source of HBsAg. Sci Transl Med. 2017;9(409).

38. World Health Organization. WHO Requirements for the Collection, Processing and Quality Control of Blood, Blood Components and Plasma Derivatives. WHO Technical Report Series No. 840, Annex 2 (Adopted by ECBS 1992). Available from: https://www.who.int/bloodproducts/publications/WHO TRS 840 A2.pdf. Accessed 10 July 2019.

39. Zumbo BD, Chan EKH. Validity and Validation in Social, Behavioral, and Health Sciences. Springer Press; 2014.

40. Investigator's Brochure: JNJ-56136379 Edition 4, Addendum 2. Janssen Research & Development (Sep 2019).

41. Investigator's Brochure: JNJ-73763989 Edition 3, Addendum 1. Janssen Research & Development (January 2020).

42. Investigator's Brochure: JNJ-56136379 Edition 4, Addendum 3. Janssen Research & Development (January 2020).

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it, in conjunction with the accompanying Master Protocol, 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	26-Nov-2021 15:32:04 (GMT)	Document Approval

Janssen Research & Development *

Clinical Protocol

COVID-19 Appendix

Intervention-specific Appendix 2 to Master Protocol PLATFORMPAHPB2001

A Randomized, Double blind, Placebo-controlled Phase 2b Study to Evaluate Efficacy, Pharmacokinetics, and Safety of 48-week Study Intervention With JNJ-73763989+JNJ-56136379+Nucleos(t)ide Analog (NA) Regimen Compared to NA Alone in e Antigen-negative Virologically Suppressed Participants With Chronic Hepatitis B Virus Infection

REEF-2 study

Protocol 73763989PAHPB2002; 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: 2019-002674-31

Status: Approved
Date: 25 May 2020
Prepared by: Janssen Research & Development, a division of Janssen Pharmaceutica NV
EDMS number: EDMS-RIM-66038, 2.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL 73763989PAHPB2002 (EDMS-ERI-188471315)

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.

Screening and Randomization:

- Enrollment of new participants may continue based on the investigator's assessment of risks versus benefits, depending on the situation at a particular site, and the ability to monitor participant safety.
- Baseline visits for participants recently screened for this study should be postponed if the current situation does not allow for an orderly conduct of the study.

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	26-May-2020 06:49:59 (GMT)	Document Approval