Janssen Research & Development *

Clinical Protocol

A Phase 2 Randomized, Open-label, Parallel-group, Multicenter Study to Assess Intrahepatic and Peripheral Changes of Immunologic and Virologic Markers in Response to Combination Regimens Containing JNJ-73763989 and Nucleos(t)ide Analog With or Without JNJ-56136379 in Patients With Chronic Hepatitis B Virus Infection

The INSIGHT Study

Protocol 73763989HPB2003; Phase 2
AMENDMENT 2

JNJ-73763989 and JNJ-56136379

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

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	This document
Amendment 1	10 April 2020
Original Protocol	12-February-2020

Amendment 1 (This document)

Overall Rationale for the Amendment: Following Health Authority (HA) feedback the protocol was amended as specified below

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis, 9.3 Populations for Analyses	An additional population (mITT) was added.	Per HA request, the modified ITT (mITT) analysis set, restricted to participants with biopsy data at both Baseline and Week 40, was defined as the primary analysis population for consistency with the planned observed cases analysis of the primary efficacy endpoint described in section 9.4.1.1.
9.4.1 Analysis of Efficacy and Antiviral Activity, 9.4.1.1 Analysis of the Primary Endpoint, 9.4.1.2 Analysis of Secondary Endpoints, 9.4.1.3 Analysis of Exploratory Endpoints	The mITT analysis set was added to the ITT set for the purpose of the efficacy analyses.	Per HA request, in order to evaluate the potential bias in using complete case analysis, both mITT as primary analysis set and ITT as secondary analysis set will be used.
Title page and footer	Updated confidentiality statement	In line with the latest protocol template

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 2 Randomized, Open-label, Parallel-group, Multicenter Study to Assess Intrahepatic and Peripheral Changes of Immunologic and Virologic Markers in Response to Combination Regimens Containing JNJ-73763989 and Nucleos(t)ide Analog With or Without JNJ-56136379 in Patients With Chronic Hepatitis B Virus Infection

JNJ-73763989 (JNJ-3989) is a liver-targeted antiviral therapeutic for subcutaneous (SC) 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 RNA (pgRNA), the precursor of viral relaxed circular deoxyribonucleic acid (DNA). The RNAi triggers in JNJ-3989, JNJ-73763976 (JNJ-3976) and JNJ-73763924 (JNJ-3924), 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.[35]

JNJ-56136379 (JNJ-6379) is an orally administered capsid assembly modulator (CAM) that is being developed for the treatment of chronic HBV infection. JNJ-6379 binds to 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.

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

OBJECTIVES AND ENDPOINTS

The study will be conducted in 3 phases for all participants: a screening phase (4 weeks), an open-label study intervention phase (48 weeks), and a follow-up phase (48 weeks).

The following objectives and endpoints will be assessed overall, by study panel, and by intervention arm:

Objectives	Endpoints
Primary	
• To assess changes in intrahepatic HBsAg between baseline and on-treatment liver biopsy in response to JNJ-3989-based combination treatment	• Changes in the proportion of HBsAg positive hepatocytes between baseline and on-treatment Week 40
Secondary	
• To assess changes in intrahepatic immune response between baseline and on-treatment liver biopsy	• Changes between baseline and on-treatment liver biopsy in intrahepatic immune response CCI [redacted] in terms of proportion of cells, cell types, and spatial redistribution

Objectives	Endpoints
• To assess changes in intrahepatic viral nucleic acids and proteins between baseline and on-treatment liver biopsy	• Changes from baseline in intrahepatic viral parameters (such as cccDNA, pgRNA, intrahepatic RNA, or HBsAg in terms of copy number, or number of positive cells) • Changes from baseline in intrahepatic cccDNA levels and transcriptional activity (pgRNA/cccDNA ratio)
• To evaluate the efficacy of the study intervention as measured in the periphery	• The proportion of participants during the study intervention and follow-up phases with: – HBsAg seroclearance at Week 72 (ie, 24 weeks after completion of all study interventions at Week 48) without restarting NA treatment. – (Sustained) Reduction, suppression, and/or seroclearance considering single and multiple markers (such as HBsAg, HBeAg, HBV DNA and ALT) – HBsAg and HBeAg seroconversion – Flares (virologic, biochemical, and clinical) • Time to first HBsAg seroclearance
• To evaluate the frequency of virologic breakthrough during study intervention	• Proportion of participants with virologic breakthrough
• To assess HBV-specific T-cell responses	• Changes from baseline in HBV-specific peripheral blood T-cell responses during the study intervention and follow-up phases
• To evaluate the safety and tolerability of the study intervention	• 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 plasma PK of JNJ-3989 (ie, JNJ-3976 and JNJ-3924), JNJ-6379, and optionally of NA, as applicable	• Plasma PK parameters of JNJ-3976, JNJ-3924, JNJ-6379, and optionally of NA, as applicable
CCI [redacted]	[redacted]

Objectives	Endpoints
CCI	

* Only applicable to participants who are enrolled at a site with an on-site Fibroscan device.

Hypothesis

As this is an exploratory study, no hypothesis will be tested.

OVERALL DESIGN

This is a Phase 2 randomized, open-label, multicenter, parallel-group study to assess intrahepatic and peripheral changes of immunologic and virologic markers in response to two combination regimens containing JNJ-3989 and NA, with or without JNJ-6379, in chronic HBV-infected participants.

A target of 24 chronic HBV-infected male and female participants, 18-65 years (inclusive) of age will be enrolled in 2 panels, approximately 12 participants in each panel. Panel 1 will consist of participants who are HBeAg positive and not currently treated and Panel 2 will consist of participants who are HBeAg

negative and virologically suppressed by entecavir (ETV), tenofovir disoproxil, or tenofovir alafenamide (TAF) treatment.

The study will be conducted in 3 phases for all participants: a screening phase (4 weeks), an open-label 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 1:1 ratio within each panel to receive one of the following interventions (ie, treatments) for 48 weeks:

- Intervention arm 1, combination regimen JNJ-3989+JNJ-6379+NA (target of 12 participants):
  - CCI JNJ-3989 (SC injection once every 4 weeks [Q4W], with the last injection at Week 44), AND
  - CCI JNJ-6379 (tablets once daily [qd]), AND
  - NA: ETV, tenofovir disoproxil, or TAF (tablets qd)
- Intervention arm 2, combination regimen JNJ-3989+NA (target of 12 participants):
  - CCI JNJ-3989 (SC injection Q4W, with the last injection at Week 44), AND
  - NA: ETV, tenofovir disoproxil, or TAF (tablets qd)

All participants will complete treatment with JNJ-3989 (and JNJ-6379) after a fixed duration of 48 weeks. If the NA treatment completion criteria (see "Study Intervention Completion at Week 48") are met based on clinical laboratory tests performed at Week 44, treatment with NA will also be completed at Week 48. In participants not meeting these criteria, NA treatment will continue during the follow-up phase.

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 substudy (optional) will undergo intensive PK sampling at Week 4.

After stopping all study interventions, all 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 mentioned below.

Randomization within each panel will be stratified by Fibroscan score (<7 kPa vs ≥7 kPa).

A participant will be considered to have completed the study if he or she has completed the assessments at Follow-up Week 48.

An Independent Flare Expert Panel (IFLEP) will be appointed for this study.

Study Intervention Completion at Week 48

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

CCI

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

Participants who do not meet the above criteria at Week 48 should continue NA treatment during the 48-week follow-up phase.

NA Re-treatment Criteria During Follow-up

Participants who meet the NA treatment completion criteria (as described above) will be monitored closely during the follow-up phase and should re-start NA treatment immediately in the event of:

CCI

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

NUMBER OF PARTICIPANTS

A target of 24 chronic HBV-infected adult male and female participants will be randomized.

Description of Interventions

Intervention name	JNJ-3989	JNJ-6379	Entecavir (ETV) monohydrate	Tenofovir disoproxil	Tenofovir alafenamide (TAF)**
Type	Drug	Drug	Drug	Drug	Drug
Dosage formulation	Solution for injection	Tablets	Film-coated tablets	Film-coated tablets	Film-coated tablets
Unit dose strength(s)	CCI vial	CCI	0.5 mg	245 mg	25 mg
Dosage level	CCI once every 4 weeks (Q4W)	CCI once daily (qd)	Nucleoside-naïve patients: 0.5 mg qd Lamivudine-refractory patients: 1 mg* qd (but should preferably be treated with tenofovir disoproxil or TAF instead) Other indications: 1 mg* qd (must be agreed upon by the sponsor)	245 mg qd	25 mg qd
Route of administration	Subcutaneous injection in the abdomen	Oral	Oral	Oral	Oral
Use	Investigational intervention	Investigational intervention	Background intervention	Background intervention	Background intervention
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Each unit will be labeled with unique medication ID number	Each unit will be labeled with unique medication ID number	Commercial supplies will be sourced. Each unit will be labeled with unique medication ID number	Commercial supplies will be sourced. Each unit will be labeled with unique medication ID number	Commercial supplies will be sourced. Each unit will be labeled with unique medication ID number
		In child-resistant packaging	In child-resistant packaging	In child-resistant packaging	In child-resistant packaging
	Labels will contain information to meet the applicable regulatory requirements.				
Food/Fasting instructions	Regardless of food intake	Regardless of food intake	Per prescribing information	Per prescribing information	Per prescribing information

Q4W: once every 4 weeks; qd: once daily
* 2 tablets of 0.5 mg
** In countries where TAF is available, it will be one of the NA treatment options.

CCI [redacted]

Following local standard practice the biopsy location will be identified with ultrasound (which will also be used to rule out contraindicating conditions for a biopsy) and after application of local anesthesia CCI [redacted] liver biopsy samples will be collected.

The liver biopsy procedure should be preceded and followed by standard medical monitoring according to local medical practice. This may include an overnight stay at the investigator's discretion.

CCI [redacted]

BLOOD EFFICACY ASSESSMENTS

Qualitative and quantitative HBsAg and HBeAg, and quantitative HBcrAg as well as antibodies against HBsAg and HBeAg 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 discretion.

Hepatitis B virus 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 discretion.

Hepatitis B virus DNA, HBsAg, HBeAg, anti-HBs, and anti-HBe antibody testing results will be provided to the investigator and the sponsor from screening until the end of follow-up.

In participants enrolled at a site with an on-site Fibroscan device, Fibroscan assessments will be performed 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.

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

BLOOD IMMUNE ASSESSMENTS

Peripheral Blood Mononuclear Cell Immune Analyses

Samples for PBMC immune analyses will be collected during the study intervention and follow-up phases 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. CCI [redacted]

CCI [redacted] Leftover 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.

Leukapheresis (Optional With Separate Consent)

Leukapheresis allows to selectively collect higher quantities of PBMCs from participants without withdrawing large volumes of blood.

Leukapheresis will only be performed for participants who consent separately to this component of the study. Participants may withdraw such consent at any time without affecting their participation in other aspects of the study.

Leukapheresis may be done at least 1 week (and up to 3 weeks) after the liver biopsies (see Schedule of Activities). Prior to the procedure, the participant's wellbeing will be checked and leukapheresis will only

be offered if there is no clinical reason against it. If a participant has had a recent febrile illness, the leukapheresis should be postponed until body temperature is normal for at least 72 hours.

The leukapheresis procedure should mainly follow local standard procedures. Additional guidelines will be provided via a separate manual in order to standardize this process across sites.

One leukapheresis session is expected to last between 1.5 - 5 hours.

During the procedure, the participant will receive intravenous saline infusions and citrate-based anticoagulant. Use of heparin for anticoagulation is not allowed. A specialized leukapheresis trained research nurse or physician will be in attendance and in charge of the participant's immediate medical care to monitor the leukapheresis.

After completion of the leukapheresis procedure, participants will stay at the site for at least 30 minutes to monitor for any relevant safety events. Additional safety procedures may be performed at the discretion of the site staff. Participants are advised to refrain from exercise and strenuous activities for 3 day after the leukapheresis visit.

SAFETY EVALUATIONS

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

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

PHARMACOKINETIC EVALUATIONS

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

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 substudy (optional) will undergo intensive PK sampling at Week 4. If necessary (eg, for operational reasons), this visit may be scheduled at Week 8, 12, or 16.

Plasma concentration-time data for JNJ-3976, JNJ-3924, JNJ-6379 and, optionally, NA will be analyzed via noncompartmental methods for all participants who underwent intensive PK sampling. The main PK parameter will be area under the plasma concentration-time curve over 24 hours (AUC_{24h}), C_{max}, t_{max}, plasma trough concentration (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 data from a selection of Phase 1 and 2 studies via population PK modelling. Individual estimates of PK parameters may be generated from the population PK analysis for potential use in exposure-response analysis.

PHARMACOKINETIC/PHARMACODYNAMIC EVALUATIONS

Relationships of individual PK parameters for CCI [redacted]

HOST GENETICS

A pharmacogenomic blood sample will be collected (preferably at baseline) to allow for the identification of genetic factors that may influence the efficacy, safety, or PK of the study intervention, to identify genetic factors associated with HBV infection, or to develop assays for the study intervention or HBV infection.

A blood sample will be taken for human leukocyte antigen (HLA) typing. In addition, host DNA blood samples to allow for epigenetic analyses will be collected.

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.

CCI [redacted]

STATISTICAL METHODS

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

Given the exploratory nature of the study and the limited sample size per intervention arm per panel, no statistical testing will be performed. All data will be summarized descriptively including 90% confidence intervals as appropriate.

Statistical Hypotheses

As this is an exploratory study, no hypothesis will be tested.

Sample Size Determination

This study aims to enroll approximately 24 participants in total, ie, 12 participants per study panel and 6 participants per intervention arm within each panel. Due to the exploratory nature of the study, the sample size was determined based on clinical and feasibility considerations related to the liver biopsy procedures performed multiple times during the study, rather than a formal statistical calculation.

Analyses of Efficacy and Antiviral Activity

To evaluate the efficacy and antiviral activity in blood and liver, the primary analysis set will be the modified intent-to-treat (mITT) population and the secondary one will be the ITT population.

All efficacy summaries will be presented with descriptive statistics overall, by study panel (combining intervention arms), and by intervention arm (within and across study panels).

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.

Graphic displays will also be used to summarize the data and to visualize trends by intervention arm and/or study panel.

Where applicable, additional specifics for analyses of primary, secondary, and exploratory endpoints are detailed below.

Analysis of the Primary Endpoint

The primary endpoint is the change between baseline and on-treatment liver biopsy in terms of the proportion of HBsAg positive hepatocytes and will be analyzed descriptively using the general considerations outlined above.

Analysis of Secondary Endpoints

Changes in Intrahepatic Immune Response

CCI [redacted] will be assessed at Week 40 and compared to baseline overall, by study panel, and intervention arm.

The functional characterization of major cell populations will be assessed by transcriptomics and/or proteomics for major cell populations of interest at Week 40 and compared to baseline similarly.

Changes in Intrahepatic Viral Nucleic Acids and Proteins

Changes from baseline in cccDNA level and/or transcriptional activity will be assessed using the general considerations outlined above.

Furthermore, the difference in the level of infected hepatocytes at baseline will be assessed by comparing cccDNA level and/or transcriptional activity.

Analyses of other viral markers will be performed descriptively. Statistical analyses will depend on the assay technology applied and the scope of the analyses.

Analysis of Exploratory Endpoints

The association between CCI [redacted] will be explored both at baseline and on-treatment by study panel and intervention arms using graphical displays and relevant correlation's coefficient.

Impact CCI [redacted] will also be evaluated using similar methods.

CCI [redacted] Impact of treatment on different blood and hepatic markers will also be evaluated.

Safety Analyses

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

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 (number of participants, mean, SD, coefficient of variation, geometric mean, median, minimum, and maximum) will be calculated for the plasma concentrations of JNJ-3976, JNJ-3924, JNJ-6379 and, optionally, NA, as applicable, and for the derived plasma PK parameters (noncompartmental analysis).

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.

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

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

Individual estimates of PK parameters may be generated from the population PK analysis for potential use in exposure-response analysis.

Pharmacokinetic/Pharmacodynamic Analyses

Relationships of CCI [redacted] may be evaluated and graphically displayed.

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 may be investigated. Other biomarkers may be explored at the sponsor's discretion.

Resistance Analysis

The results of HBV viral sequencing will be evaluated by the sponsor virologist. Relevant changes in 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.

Pharmacogenomic Analyses

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

Host Exploratory Biomarker Analyses

Statistical approaches to explore associations between treatment response/clinical outcome and blood and liver biomarkers vary and depend on the different data types of the applied technology platforms, as well

as on the extent of observed differences between participants. Analyses will be conducted at the sponsor's discretion, will always be under the sponsor's supervision, and results will be presented either in the clinical study report or a separate report.

Interim Analysis

Two interim analyses (IAs) may be performed: when all participants have completed Week 20 in the intervention phase (or discontinued earlier) and when they have completed Week 72 in the follow-up phase (ie, Follow-up Week 24) (or discontinued earlier). These IAs will be performed by the sponsor to support interactions with health authorities, as well as to support internal decisions about additional studies and/or investigation of other combination regimens.

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 Flare Expert Panel

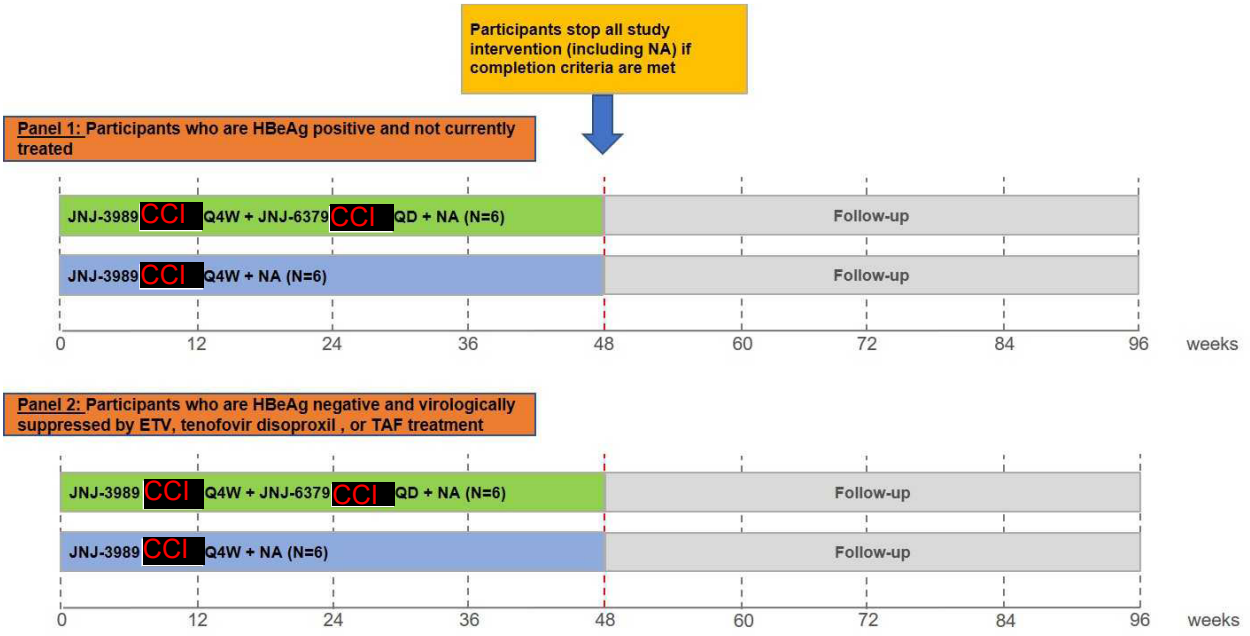
An IFLEP will be appointed for this study. The IFLEP is composed of 3 independent medical experts with experience and expertise in hepatitis B and its treatment. The IFLEP will monitor ALT flares and will make recommendations regarding flare management based on an analysis of aggregate data.

In order to allow for an unbiased assessment, members of the IFLEP will not serve as study investigators.

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

1.2. Schema

Figure 1: Schematic Overview of the Study



NA=nucleos(t)ide analog; Q4W: once every 4 weeks; qd: once daily

1.3. Schedule of Activities

1.3.1. Schedule of Activities - Screening and Study Intervention Phase

Phase	Screening		Open-label Study Intervention[a]																
		W-1													+/CCI				
Visit Day (D)/Week (W)	W-4 to 0[b]	Biopsy	D1[c]	W2	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	Pre-biopsy Visit	Biopsy	Post-biopsy Visit	W44	W48/ WD[d]
Study Day (Window)	-28 to -1	-7 to -1	1	15 (+/-3d)	29 (+/-3d)	57 (+/-3d)	85 (+/-3d)	113 (+/-3d)	141 (+/-3d)	169 (+/-3d)	197 (+/-3d)	225 (+/-3d)	253 (+/-3d)	281 (+/-3d)	<7d Prior to Biopsy	281 (+/-4w)	≥1w-≤3w After Biopsy	309 (+/-3d)	337 (+/-3d)
Screening/Administrative																			
ICF[e]	X																		
ICF for optional CCI	(X)																		
Inclusion/exclusion criteria[g]	X	X																	
Prestudy therapy (including prior anti-HBV therapy)	X																		
Medical/surgical history and demographics[h]	X																		
Preplanned surgery/procedure(s)	X																		
Fibroscan[i,j]	X																		(X)
Ultrasound	X[k]									X[l]									X[l]
Study Intervention																			
Randomization			X																
Administer JNJ-3989			X		X	X	X	X	X	X	X	X	X	X				X	
Intake of JNJ-6379 and NA[n,o]			X		X	X	X	X	X	X	X	X	X	X				X	X
Dispense JNJ-6379 and NA (for at home use)[n,o]			X		X	X	X	X	X	X	X	X	X	X				X	(X)[p]
Oral study intervention accountability					X	X	X	X	X	X	X	X	X	X				X	X
Safety Assessments																			
Complete physical examination[q]	X									X									X
Symptom-directed physical examination, including body weight		X	X	X	X	X	X	X	X		X	X	X	X				X	
Vital signs[r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X	X
Triplicate 12-lead ECG[s]	X		X	X	X		X			X			X						X
Injection site reactions				X	X	X	X	X	X	X	X	X	X	X				X	X

Phase	Screening		Open-label Study Intervention[a]																
		W-1													+/-W40				
Visit Day (D)/Week (W)	W-4 to 0[b]	Biopsy	D1[c]	W2	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	Pre-biopsy Visit	Biopsy	Post-biopsy Visit	W44	W48/ WD[d]
Study Day (Window)	-28 to -1	-7 to -1	1	15 (+/-3d)	29 (+/-3d)	57 (+/-3d)	85 (+/-3d)	113 (+/-3d)	141 (+/-3d)	169 (+/-3d)	197 (+/-3d)	225 (+/-3d)	253 (+/-3d)	281 (+/-3d)	<7d Prior to Biopsy	281 (+/-4w)	≥1w-≤3w After Biopsy	309 (+/-3d)	337 (+/-3d)
Clinical Laboratory Tests																			
Hematology	X		X	X	X	X	X	X	X	X	X	X	X	X	X[m]			X	X
Blood chemistry (including liver function tests)[t,u,v]	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[m]			X	X
Urinalysis[w]	X		X	X	X	X	X	X	X	X	X	X	X	X				X	X
Urine chemistry[x]	X		X	X	X	X	X	X	X	X	X	X	X	X				X	X
CCI																			
Serum IgM anti-HBc antibody test	X																		
Testing for hepatitis A, B, C, D, and E virus, HIV-1 and -2	X																		
FSH test (postmenopausal women only)[z]	X																		
AFP[v]	X									X									X
Hemoglobin A1c	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
HBV genotype[aa]			X																
Liver Biopsy																			
CCI																			
Efficacy Assessments																			
HBV Virology																			
Blood sampling for HBV DNA	CCI																		
Blood sampling for HBV RNA[bb]																			
Sampling for viral genome sequencing[cc]																			

Phase	Screening		Open-label Study Intervention[a]																
		W-1													+/-W40				
Visit Day (D)/Week (W)	W-4 to 0[b]	Biopsy	D1[c]	W2	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	Pre-biopsy Visit	Biopsy	Post-biopsy Visit	W44	W48/ WD[d]
Study Day (Window)	-28 to -1	-7 to -1	1	15 (+/-3d)	29 (+/-3d)	57 (+/-3d)	85 (+/-3d)	113 (+/-3d)	141 (+/-3d)	169 (+/-3d)	197 (+/-3d)	225 (+/-3d)	253 (+/-3d)	281 (+/-3d)	<7d Prior to Biopsy	281 (+/-4w)	≥1w-≤3w After Biopsy	309 (+/-3d)	337 (+/-3d)
HBV Serology																			
Blood sampling for:																			
Anti-HBs and anti-HBe	CCI																		
HBsAg (qualitative)																			
HBeAg (qualitative)[dd]																			
HBsAg (quantitative)																			
HBeAg (quantitative)[ee]																			
HBcrAg[bb]																			
Exploratory serology[ff]																			
Clinical Pharmacology Assessments																			
Blood sampling for sparse PK of JNJ-3989, JNJ-6379, and/or NA[gg]			X[hh]		X[hh]		X[hh]			X[hh]									X[ii]
Blood sampling for intensive PK of JNJ-3989, JNJ-6379, and/or NA (PK substudy)[jj]					X														
Exploratory Host Biomarkers																			
CCI																			
Immune Monitoring																			
Leukapheresis (optional)[kk]			(X)														(X)		
Immune cells (PBMCs)[ll]	CCI																		
Pharmacogenomics (Host DNA)																			
HLA typing			X																
Exploratory host genotyping[mm]	CCI																		
Epigenetic research			X							X									X
Ongoing Participant Review																			
Concomitant therapy[nn]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[nn]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CRF: case report form; CT: computed tomography; D/d: day; DBP: diastolic blood pressure; DNA: deoxyribonucleic acid; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; FSH: follicle-stimulating hormone; HBc: hepatitis B core protein; HBe(Ag): hepatitis B e (antigen); HBcrAg: hepatitis B core-related antigen; HBs(Ag): hepatitis B surface (antigen); HBV: hepatitis B virus; HCC hepatocellular carcinoma; HIV-1 (-2): human immunodeficiency virus type 1 (type 2); HLA: human leukocyte antigen; ICF: informed consent form; IgM: immunoglobulin M; MRI: magnetic resonance imaging; NA: nucleos(t)ide analog; PBMC: peripheral blood mononuclear cell; PK: pharmacokinetic; RNA: ribonucleic acid; SBP: systolic blood pressure; ULN: upper limit of normal; W/w: week; WD: withdrawal.

a. All study visits are to be scheduled relative to the baseline (Day 1) visit date.
b. If necessary (eg, for operational reasons), the screening phase may be extended up to a maximum of 6 weeks in agreement with the sponsor.
c. Day 1 samples are to be collected before the first dose of study intervention.
d. End of study intervention. If NA treatment completion criteria are not met at Week 48 (see Section 6.6), participants will continue NA treatment during the follow-up phase. Participants who discontinue study intervention early will have an early WD visit and will enter follow-up (see the Schedule of Activities - Follow-up Phase) 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.
e. The ICF must be signed before the first study-related activity.
f. If participants agree to undergo an optional liver biopsy, they must sign a separate ICF at screening or at any time prior to the optional liver biopsy (which may take place at Follow-up Week 24, or at any time during the study when clinically indicated). Refusal to give consent for these optional liver biopsy samples does not exclude a participant from participation in the study.
g. Minimum criteria for the availability of documentation supporting the eligibility criteria will be described in Section 10.3, Appendix 3, Regulatory, Ethical and Study Oversight Considerations. Clinical status will be checked at screening and again before the first liver biopsies at Week -1 and before the first dose of study intervention. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after the start of screening but before the first liver biopsies at Week -1 or 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. Retesting to assess eligibility will be allowed once, using an unscheduled visit during the screening period.
h. Medical history also includes mode of HBV transmission, stage of liver fibrosis, and alcohol consumption. Historical HBV DNA data and available data on previous HBV genotype assessments will be recorded in the CRF. Historical HBsAg, HBeAg, and ALT data, if available, will be recorded in the source document.
i. Liver disease staging assessments will be performed based on Fibroscan obtained within 6 months prior to screening or at the time of screening.
j. Only applicable to participants who are enrolled at a site with an on-site Fibroscan device.
k. Participants must have absence of signs of cirrhosis or portal hypertension (absence of nodules, smooth liver contour, normal portal vein, spleen size <12 cm), absence of signs of HCC or clinically relevant renal abnormalities on an abdominal ultrasound performed within 6 months prior to screening or at the time of screening. In case of suspicious findings on conventional ultrasound the participant may still be eligible if HCC or clinically relevant renal abnormalities have been ruled out by a more specific imaging procedure (contrast enhanced ultrasound, CT or MRI). Additional ultrasound assessments may be performed when clinically indicated.
l. A liver ultrasound is recommended approximately every 24 weeks for HCC screening.
m. Following local standard practice the biopsy location will be identified with ultrasound (which will also be used to rule out contraindicating conditions for a biopsy) and after application of local anesthesia the CCI liver biopsy samples will be collected. Prior to any on-treatment biopsy, a recent (≤ 1 week) coagulation and hematology panel, and a platelet aggregation test are required (pre-biopsy visit). Prior to the off-treatment biopsies, blood coagulation and platelets will be assessed according to local practice. On-treatment (pre)biopsy can either occur during a regularly scheduled visit or an unscheduled visit.
n. In between study visits, participants will take oral study intervention at home. Participants will be requested to bring their study intervention with them to each study visit. At study visits, the study intervention should be taken on site.
o. Intake and dispensing of JNJ-6379 only applicable for participants randomized to receive JNJ-3989 and JNJ-6379 in combination with NA.

p. 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.
q. Complete physical examination, including height (only at screening), body weight, skin examination, and other body systems (see Section 8.4.1).
r. Vital signs include supine SBP, DBP, pulse rate, and body temperature.
s. All ECGs will be read centrally; ECGs should be completed before any tests, procedures or other consultation for that visit.
t. Biochemistry samples must be taken after fasting for at least 10 hours for measurement of phosphate, calcium, creatinine, and lipids. Participants should bring their oral study intervention with them to each visit and have that day's intake at the site with breakfast.
u. Creatinine clearance (eGFR calculated by the CKD-EPI formula) will be assessed.
v. 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 8.5.6.1 and Section 10.6.
w. 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).
x. Urine chemistry sample (quantitative measurement): creatinine, sodium, phosphate, glucose, protein, and albumin.
y. Urine sample for selected renal biomarkers including retinol binding protein and beta-2-microglobulin.
z. 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.
aa. HBV genotype will be determined at baseline using standard genotyping assay if HBV DNA levels are sufficiently high. For participants with low HBV DNA levels, available historical data on previous HBV genotype assessment will be collected in the CRF. Exploratory genotyping assays might be performed.
bb. 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.
cc. Samples may be sequenced based on the sponsor virologist's request, considering the HBV DNA levels.
dd. Participants with undocumented (ie, no lab report) HBeAg status as part of their medical history must first complete HBeAg testing and have results reviewed by the investigator to confirm if they qualify for study participation. Documented HBeAg status within 12 months prior to screening is acceptable.
ee. Quantitative HBeAg assessment will only be performed in participants who become HBeAg positive post-baseline based on a qualitative HBeAg assay.
ff. Exploratory serology samples may be analyzed at the sponsor's discretion. Samples may be used to assess virologic or serologic markers of HBV.
gg. 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 and NA), the date and time of the previous JNJ-3989 administration, and the date and time of PK sampling should be recorded.
hh. One sample at any time between 2 and 8 hours after JNJ-3989 dosing. Before leaving the study site, the participant's wellbeing should be confirmed.
ii. Only in case of early withdrawal.
jj. All participants who consent to participate in the intensive PK subgroup (optional) will undergo intensive PK sampling at Week 4. If necessary (eg, for operational reasons), this visit may be scheduled at Week 8, 12, or 16. The study intervention should be taken on site and time of dosing should be recorded. Pharmacokinetic samples will be taken predose and 15 minutes, 30 minutes, 1, 2, 3, 4, 6, 8,* 10,* and 24 hours postdose (*the 8 and 10 hours postdose samples are optional). All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within 20% of the nominal time from dosing (eg, +/- 12 minutes of a 60-minute time point) will not be captured as a protocol deviation if the exact time of the sample collection is noted on the source document and CRF.

kk. Leukapheresis is optional and will only be performed for participants who provided separate consent for this procedure. Refusal to give consent for leukapheresis does not exclude a participant from participation in the study. The leukapheresis procedure will be performed at least 1 week (and up to 3 weeks) after the liver biopsies; this can either occur during a regularly scheduled visit or an unscheduled visit. Prior to the procedure, the participant's wellbeing will be checked and leukapheresis will only be offered if there is no clinical reason against it. If a participant has had a recent febrile illness, the leukapheresis should be postponed until body temperature is normal for at least 72 hours. One leukapheresis session is expected to last between 1.5 - 5 hours. During the procedure, the participant will receive intravenous saline infusions and citrate-based anticoagulant. Use of heparin for anticoagulation is not allowed. After completion of the leukapheresis procedure, participants will stay at the site for at least 30 minutes to monitor for any relevant safety events. Participants are advised to refrain from exercise and strenuous activities for 3 days after the leukapheresis visit.

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

mm. The pharmacogenomic (DNA) sample should preferably be collected at baseline.

nn. Adverse events and concomitant medications will be monitored from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure.

1.3.2. Schedule of Activities - Follow-up Phase

Phase	Follow-up[a,b]												
								+/-FU W24					
Follow-up (FU) Week (W)	FU W2	FU W4	FU W8[c]	FU W12	FU W16[c]	FU W20[c]	FU W24	Optional Biopsy	Post-biopsy Visit	FU W30[c]	FU W36	FU W42[c]	FU W48 EOS
FU Study Day (Window)	15 (+/-4d)	29 (+/-4d)	57 (+/-4d)	85 (+/-4d)	113 (+/-4d)	141 (+/-4d)	169 (+/-4d)	169 (+/-4w)	≥1w-≤3w After Biopsy	211 (+/-4d)	253 (+/-4d)	295 (+/-4d)	337 (+/-4d)
Study Intervention Administration													
Administer/Dispense NA, as applicable[d]	(X)	(X)	(X)	(X)	(X)	(X)	(X)			(X)	(X)	(X)	(X)
NA accountability, as applicable	(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)
Safety Assessments													
Symptom-directed physical examination, including body weight (if applicable)	X	X	X	X	X	X	X			X	X	X	X
Vital signs[f]	X	X	X	X	X		X			X		X	X
Triplicate 12-lead ECG[g]		X											
Liver ultrasound[h]							X						X
Clinical Laboratory Tests													
Hematology	X	X	X	X	X		X			X		X	X
Blood chemistry (including liver function tests)[j,k,l]	X	X	X[m]	X	X[m]	X[m]	X			X[m]	X	X	X
Blood coagulation	X	X		X			X				X	X	X
Urinalysis[n]		X[p]	(X)	(X)	(X)	(X)	(X)			(X)	(X)	(X)	X
Urine chemistry[o]		X[p]	(X)	(X)	(X)	(X)	(X)			(X)	(X)	(X)	X
Urine pregnancy test (women of childbearing potential only)		X	X	X	X	X	X[q]			X[q]	X[q]	X[q]	X
Liver Biopsy													
CCI													
Efficacy Assessments													
Fibroscan[r]							(X)						(X)
HBV Virology													
Blood sample collection for HBV DNA and HBV RNA[s]	CCI												
Sampling for viral genome sequencing[t]													

Phase	Follow-up[a,b]												
								+/-FU W24					
Follow-up (FU) Week (W)	FU W2	FU W4	FU W8[c]	FU W12	FU W16[c]	FU W20[c]	FU W24	Optional Biopsy	Post-biopsy Visit	FU W30[c]	FU W36	FU W42[c]	FU W48 EOS
FU Study Day (Window)	15 (+/-4d)	29 (+/-4d)	57 (+/-4d)	85 (+/-4d)	113 (+/-4d)	141 (+/-4d)	169 (+/-4d)	169 (+/-4w)	≥1w-≤3w After Biopsy	211 (+/-4d)	253 (+/-4d)	295 (+/-4d)	337 (+/-4d)
HBV Serology													
Blood sample collection for:	CCI												
Anti-HBs and anti-HBe													
CCI (qualitative)													
HBeAg (qualitative)													
HBsAg (quantitative)													
HBeAg (quantitative)													
HBcrAg[s]													
Exploratory serology[u]													
Exploratory Host Biomarkers													
CCI													
Immune Monitoring													
Leukapheresis[v]									(X)				
Immune cells (PBMCs)[w]	CCI												
Pharmacogenomics (Host DNA)													
Epigenetic research													
Ongoing Participant Review													
Concomitant therapy[x]	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[x]	X	X	X	X	X	X	X	X	X	X	X	X	X

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; d: days; DBP: diastolic blood pressure; DNA: deoxyribonucleic acid; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; EOS: end of study; 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; NA: nucleos(t)ide analog; PBMC: peripheral blood mononuclear cells; 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. 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.
c. Visit is optional for participants who continue NA treatment.

d. An optional liver biopsy [redacted] may be performed at Follow-up Week 24 or at any time during the study if the participant provided consent.
e. No JNJ-3989/JNJ-6379 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 (Section 6.6), or for those who met the NA re-treatment criteria (Section 6.7). In between study visits, participants will take NA treatment at home. Participants will be requested to bring their NA treatment with them to each study visit. At study visits, the NA treatment should be taken on site.
f. Vital signs include supine SBP, DBP, pulse rate, and body temperature.
g. All ECGs will be read centrally; ECGs should be completed before any tests, procedures or other consultation for that visit.
h. A liver ultrasound is recommended approximately every 24 weeks for HCC screening.
i. Following local standard practice the biopsy location will be identified with ultrasound (which will also be used to rule out contraindicating conditions for a biopsy) and after application of local anesthesia the [redacted] biopsy samples will be collected. Prior to the biopsy, blood coagulation and platelets will be assessed according to local practice. The (pre)biopsy visit can either occur during a regularly scheduled visit or an unscheduled visit.
j. Biochemistry samples must be taken after fasting for at least 10 hours for measurement of phosphate, calcium, creatinine, and lipids.
k. Creatinine clearance (eGFR calculated by the CKD-EPI formula) will be assessed.
l. ALT/AST elevations (ie, ALT and/or AST ≥3x ULN and ≥3x nadir [ie, lowest value during study participation]), should trigger an assessment of confounding factors (alcohol intake, change in concomitant medication, and comorbidities) and a confirmatory visit, to be scheduled preferably within 7 days of the receipt of the initial ALT/AST results, to repeat laboratory testing of AFP, ALT, AST, ALP, bilirubin (total and direct), INR, albumin, and HBV DNA. Additional tests should be considered based on clinical judgement. For more details and further management guidance refer to Section 8.5.6.1 and Section 10.6.
m. Liver function tests only.
n. 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).
o. Urine chemistry sample (quantitative measurement): creatinine, sodium, phosphate, glucose, protein, and albumin.
p. 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.
q. Urine pregnancy tests will be provided to the participants for testing at home. Results will be reported at the next visit.
r. Only applicable to participants who are enrolled at a site with an on-site Fibroscan device.
s. 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.
t. 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.
u. Exploratory serology samples may be analyzed at the sponsor's discretion. Samples may be used to assess virologic or serologic markers of HBV.
v. Leukapheresis is optional and will only be performed for participants who provided separate consent for this procedure and for the optional biopsy during Follow-up. Refusal to give consent for these optional procedures does not exclude a participant from participation in the study. The leukapheresis procedure will be performed at least 1 week (and up to 3 weeks) after the liver biopsy; this can either occur during a regularly scheduled visit or an unscheduled visit. Prior to the procedure, the participant's wellbeing will be checked and leukapheresis will only be offered if there is no clinical reason against it. If a participant has had a recent febrile illness, the leukapheresis should be postponed until body temperature is normal for at least 72 hours. One leukapheresis session is expected to last between 1.5 - 5 hours. During the procedure, the participant will receive intravenous saline infusions and citrate-based anticoagulant. Use of heparin for anticoagulation is not allowed. After completion of the leukapheresis procedure, participants will stay at the site for at least 30 minutes to monitor for any relevant safety events. Participants are advised to refrain from exercise and strenuous activities for 3 days after the leukapheresis visit.

w. Additional PBMC samples may be taken in case of ALT flare, upon discussion with the sponsor, and may require an unscheduled visit.
x. Adverse events and concomitant medications will be monitored from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure.

2. INTRODUCTION

Chronic Hepatitis B Infection

Hepatitis B virus (HBV) is a small deoxyribonucleic acid (DNA) virus that specifically infects the human liver. It consists of a nucleocapsid in which the viral DNA is packed with hepatitis B core protein (HBc) and a membraneous envelope containing hepatitis B surface antigen (HBsAg). The acute phase of the infection (less than 6 months) is either followed by an immune controlled state (spontaneous cure from the infection) or progresses to chronic hepatitis B (more than 6 months). Chronic HBV infection may lead to serious illnesses such as liver cirrhosis and decompensation, and hepatocellular carcinoma (HCC), often with fatal outcome.[33]

The worldwide estimated prevalence of chronic HBV infection is 4.9% with about 292 million people affected.[28] Despite the availability of an efficacious prophylactic vaccine, yearly rates of new infections remain high. Approximately 680,000 people per year worldwide die from cirrhosis and HCC due to chronic HBV infection.[31]

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

Table 1: Various Stages of HBV Infection – Terminology and Characteristics (EASL 2017)[5]

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

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

According to the EASL treatment guidelines, the primary treatment goal for patients with chronic HBV infection is to improve survival and quality of life by preventing progression of liver disease, particularly to cirrhosis, liver failure, and HCC.

Irrespective of the hepatitis B e antigen (HBeAg) status, antiviral therapy is recommended for all patients with signs of active chronic hepatitis.[2,5,30,33] Approved therapies for chronic HBV infection are pegylated interferon alpha (PEG-IFN-α) and nucleos(t)ide analog (NA) inhibitors (ie, NA

treatment) of the HBV polymerase/reverse transcriptase, the enzyme synthesizing HBV DNA from pre-genomic ribonucleic acid (pgRNA).

Oral treatment with NAs is effective at suppressing viral DNA formation and lowering virus concentration in the blood to levels below the lower limit of quantification (LLOQ) of the HBV DNA assays commonly used. This is associated with normalization of liver enzymes and reduced or halted progression of liver disease to cirrhosis and/or decompensation and even with regression of cirrhotic transformation.[4,18,22,25,36] While the risk of HCC development is reduced as well, it is not eliminated.[18,22,25]

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

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

With the low rate of functional cure with current treatments, and persistently high global prevalence of HBV-associated mortality,[5,33] there is a medical need for more effective finite treatment options that lead to sustained seroclearance of HBsAg and HBV DNA off treatment ("functional cure"). In order to achieve an effective finite treatment, combination of therapies with different mechanisms of action, as is standard of care for other chronic viral infections like hepatitis C virus (HCV) and human immunodeficiency virus (HIV), is deemed required.

A challenge for the clinical development of novel HBV agents is that while blood markers are used to assess their efficacy and immune response induced by these agents, their target organ is the liver. Although some of the efficacy blood markers are very well established from a clinical perspective, questions remain on how good these markers correlate with intrahepatic events, such as HBV covalently closed circular DNA (cccDNA) level and transcriptional activity. In addition, the immune response measured in the periphery is known to insufficiently reflect the situation in the liver. For example, the frequency of HBV-specific T-cells as well as liver resident immune cells cannot be adequately assessed by measuring immune response in the periphery. CCI [redacted] A wide range of methods are currently available, such as polymerase chain reaction (PCR) based methods, single cell analyses and high multiplex fluorescence-based methods.

JNJ-73763989 (JNJ-3989) is a liver-targeted antiviral therapeutic for SC injection designed to treat chronic HBV infection via a ribonucleic acid interference (RNAi) mechanism. JNJ-6379 consists of two RNAi triggers, CCI [redacted] Hence, engagement of the cellular RNAi machinery by JNJ-3989 results in specific cleavage of HBV

ribonucleic acid (RNA) transcripts, thereby reducing the levels of HBV proteins and the pgRNA, the precursor of viral relaxed circular DNA. The RNAi triggers in JNJ-3989 injection are designed to target all HBV RNA transcripts derived from cccDNA, as well as transcripts derived from integrated viral DNA. The latter has been suggested to be a significant source of HBsAg in HBeAg negative patients or patients on long term treatment with NAs, the current standard of care.[35]

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

The term “study intervention” throughout the protocol, refers to JNJ-3989, 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

This liver biopsy study is primarily performed to assess changes in intrahepatic viral and host immune markers in response to JNJ-3989-based combination treatment. This analysis can be used to characterize mode of action (MoA) of the treatment. CCI [redacted] Hepatic and peripheral viral and immune markers and their correlations will be assessed. In addition, changes in liver histology may be assessed. The totality of results may be used to inform on the optimal use of therapeutics in current or future combinations. This study aims to assess intrahepatic events in the context of a full (48-week) treatment regimen as used in 2 ongoing Phase 2b studies in a similar HBV population to facilitate comparison of the results across studies.

The efficacy and safety of finite treatment duration will be assessed with a fixed 48-week treatment duration for JNJ-3989 (and JNJ-6379), in combination with NA treatment. Participants meeting pre-defined response criteria (outlined in Section 6.6) will also complete NA treatment after 48 weeks.

2.2. Background

For the most comprehensive nonclinical and clinical information regarding JNJ-3989 and JNJ-6379, refer to the latest version of the Investigator's Brochure (IB) and addendum.[14-16]

2.2.1. Nonclinical Studies

2.2.1.1. JNJ-3989 and JNJ-6379

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 months studies).

JNJ-3989

CCI [redacted]

The nonclinical safety profile of JNJ-3989 has been evaluated through a series of in vitro and in vivo studies. Repeat-dose SC toxicity studies of 2 weeks up to 24 or 37 weeks were conducted in rat and monkey, respectively. CCI [redacted]

CCI

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 SC injection of CCI JNJ-3989 in human volunteers (Study AROHBV1001) (Table 2).

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

CCI

CCI [redacted]

Table 3: Animal/Human Ratios at the NOAEL in Rat and Dog CCI [redacted]

CCI [redacted]

Combination of JNJ-3989 and JNJ-6379

A 1-month repeat-dose combination toxicity study of JNJ-6379 and JNJ-3989 was conducted in male and female Sprague-Dawley rats. CCI [redacted]

[redacted]

CCI

[redacted]

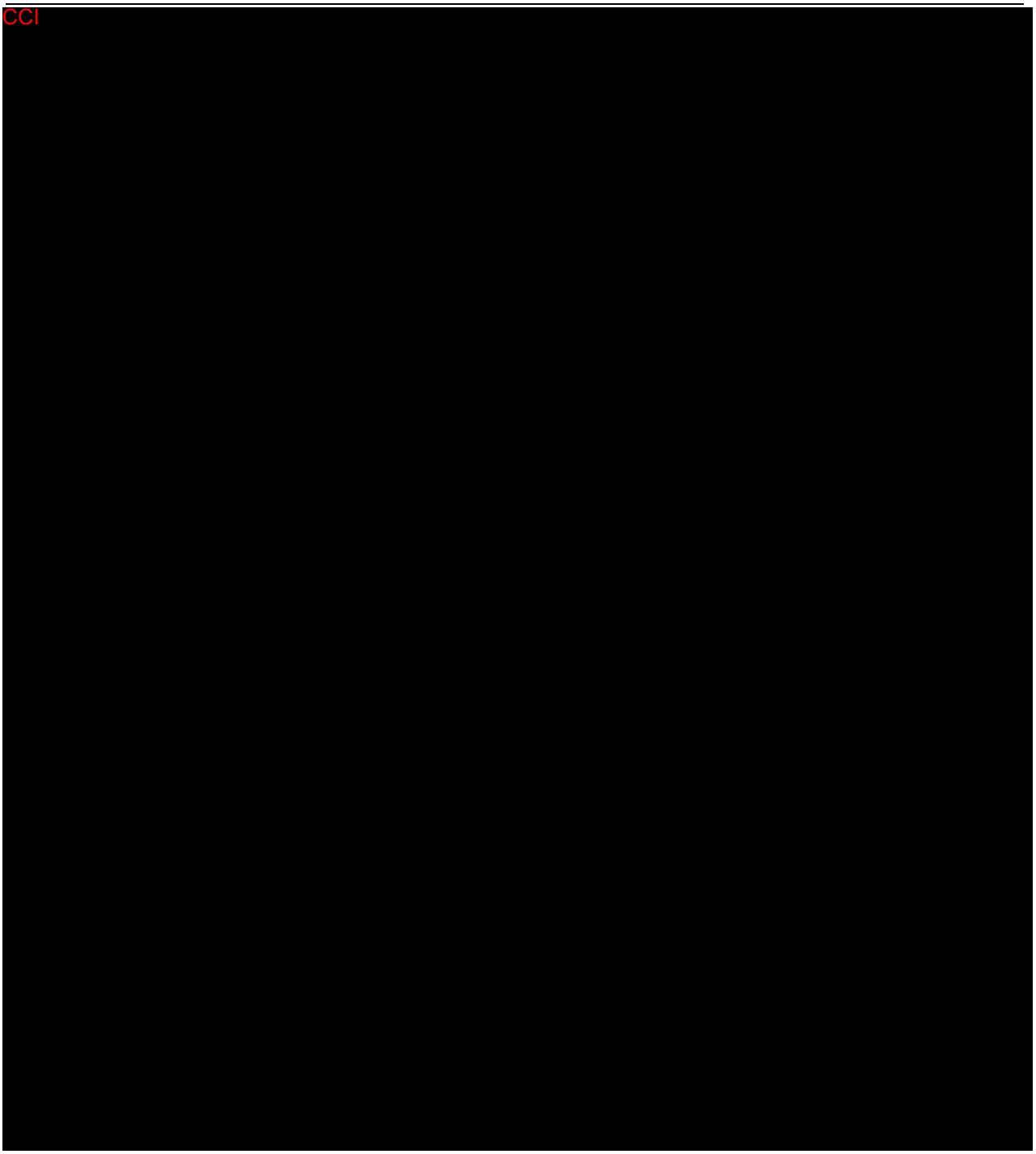
A 3-month combination toxicity study of JNJ-3989 and JNJ-6379 is ongoing, CCI

[redacted]

CCI

[redacted]

CCI



2.2.1.2. Combination of JNJ-3989 or JNJ-6379 with Entecavir, Tenofovir Disoproxil, or Tenofovir Alafenamide

CCI

CCI

[redacted]

CCI

[redacted]

2.2.2. Clinical Studies

2.2.2.1. JNJ-3989 and JNJ-6379

JNJ-3989

Clinical data on pharmacokinetics (PK), efficacy, and safety of JNJ-3989 are available from the ongoing Phase 1/2a AROHBV1001 study with a data cut-off date of 29 October 2019. All dosing with JNJ-3989 has been completed and ongoing participants are in the follow-up. Twenty adult healthy participants have received single SC injections of JNJ-3989 (35, 100, 200, 300, and 400 mg) and 84 adult chronic HBV-infected participants have received multiple doses of JNJ-3989 (25, 50, 100, 200, 300, and 400 mg), administered as 3 SC injections separated by either 7-day, 14-day, or 28-day intervals. All participants either continued or started ETV or tenofovir disoproxil 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 chronic HBV-infected 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 incidents and resolved while on study intervention.

Antiviral-activity data were available for 56 chronic HBV-infected participants who received 3 SC injections of 25 to 400 mg JNJ-3989 every 4 weeks (Q4W).[8,37] In general, mean HBsAg declines reached nadir at Day 113 (ie, 8 weeks after last JNJ-3989). Mean HBsAg levels remained suppressed (below baseline levels) at least until Day 392 (ie, 9 months after last dose) in a substantial proportion of patients.

JNJ-6379

At the time of protocol writing, 126 adult healthy and 41 chronic HBV-infected participants have been dosed with JNJ-6379 in 5 completed Phase 1 studies (56136379HPB1001, 56136379HPB1002, 56136379HPB1003, 56136379HPB1004, and 56136379HPB1005). In addition, data are available from 148 adult chronic HBV-infected 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 ($AUC_{0\text{-}24h}$) 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 ($AUC_{0\text{-}last}$) 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.

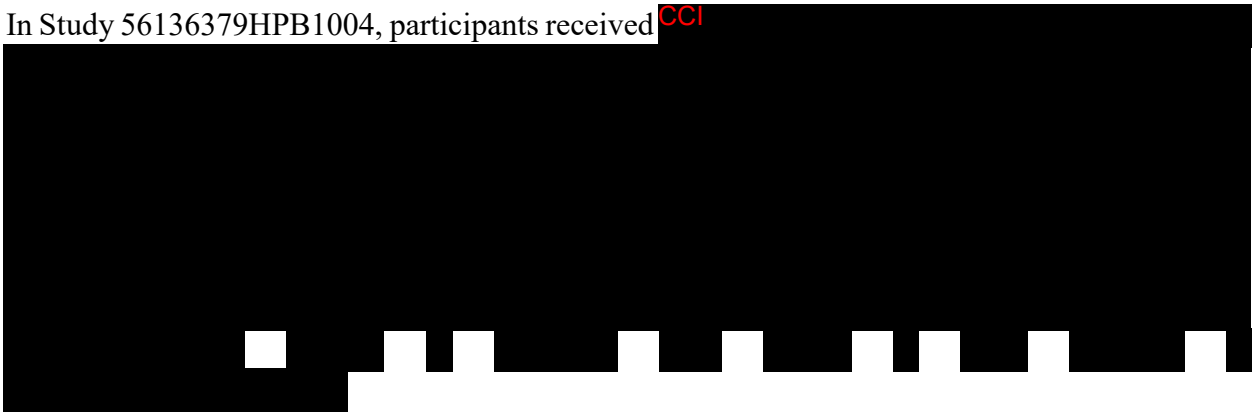
In Study 56136379HPB1002, study intervention exposure levels using a novel tablet formulation, containing CCI [redacted] were similar to exposure levels observed in study 56136379HPB1001 using the original formulation, both in fed conditions. The relative bioavailability of new 25-mg oral tablets of 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. CCI [redacted]

CCI [redacted]

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 CCI



Multiple Dose Studies in chronic HBV-infected Participants

In Sessions 8, 9, 10, 11, and A of Study 56136379HPB1001, treatment-naïve chronic HBV-infected-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 chronic HBV-infected participants. Mean JNJ-6379 exposures in chronic HBV-infected participants could be predicted from data in healthy participants. The PK data show that exposure of JNJ-6379 in chronic HBV-infected 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

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 chronic HBV-infected 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 chronic HBV-infected 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 chronic HBV-infected 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 $\log_{10}$ International Units Per Milliliter (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. Hepatitis B virus 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 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. Nucleos(t)ide analog 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 5 completed Phase 1 studies (56136379HPB1001, 56136379HPB1002, 56136379HPB1003, 56136379HPB1004, and 56136379HPB1005) in healthy and chronic HBV-infected participants (N=126 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 chronic HBV-infected 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.

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 alanine aminotransferase (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.

Combination of JNJ-3989 and JNJ-6379

Clinical data of triple combination treatment of JNJ-3989, JNJ-6379, and NA are available from the ongoing Phase 1/2a AROHBV1001 study (Cohort 12). Twelve adult chronic HBV mono-infected participants have received 3 SC injections of JNJ-3989 (200 mg Q4W) in combination with oral JNJ-6379 (250 mg qd) and oral NA treatment (ETV or tenofovir disoproxil).

Up to the interim analysis (IA) cut-off date of 29 October 2019, no deaths, SAEs, or treatment-emergent adverse events (TEAEs) leading to study intervention discontinuation were reported. Two (16.7%) participants reported at least 1 TEAE during the treatment phase. The TEAEs (upper respiratory tract infection and hypertension) were of mild severity and considered not related to the study intervention by the investigator.

The triple combination treatment of JNJ-3989, JNJ-6379, and NA is currently being investigated in chronic HBV mono-infected participants in the ongoing Phase 2 clinical studies 73763989HPB2001 (REEF-1, 90 participants in triple combination Arm 1) and 73763989PAHPB2002 (REEF-2, 80 participants in triple combination Arm 1).

2.2.2.2. Combination of JNJ-3989 and JNJ-6379 with Entecavir, Tenofovir Disoproxil, or Tenofovir Alafenamide

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

CCI [redacted]

Tenofovir disoproxil (available in several salt forms including tenofovir disoproxil fumarate and tenofovir disoproxil maleate) is a first-generation oral prodrug of the NA tenofovir that is indicated for the treatment of chronic HBV infection in adult and pediatric patients at least 12 years of age. In addition, tenofovir disoproxil in combination with other antiretrovirals is indicated for the treatment of HIV type 1 (HIV-1) infection in adult and pediatric patients at least 2 years of age. The most common adverse reactions (≥10% of participants) are abdominal pain, nausea, insomnia, pruritus, vomiting, dizziness, and pyrexia.

TAF is an ester prodrug of the NA tenofovir that is indicated for the treatment of chronic HBV-infected in adults and that is characterized by a better safety profile than tenofovir disoproxil. The most common adverse reaction (≥10% of participants) is headache.

CCI

[redacted]

Overall Assessment of the Combination Therapy

CCI

[redacted]

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 and addendum.[14-16]

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

2.3.1. Benefits for Study Participation

2.3.1.1. Known Benefits

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

2.3.1.2. Potential Benefits

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

The combination of JNJ-6379 and JNJ-3989 on a background of NAs would target different stages of the viral life cycle. While NA treatment reduces HBV DNA to levels close to or below the LLOQ of the HBV DNA assay, HBV replication is not completely inhibited, resulting in replenishment of the cccDNA pool. The addition of JNJ-6379, which targets the HBV capsid assembly ("primary" 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 responses.[7,20,34] By acting on both viral replication and by reducing barriers to the host immune-responses, 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.

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.

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

2.3.2.2.1. Potential Risks for JNJ-3989

CCI

[redacted]

Viral Resistance

Treatment with JNJ-3989 may 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 or tenofovir is expected to minimize the risk of emerging resistant viral variants.

2.3.2.2.2. Potential Risks for JNJ-6379

CCI

[redacted]

CCI [redacted]

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 tenofovir 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 2.2.2.1 for the results of the IAs).

Drug-drug Interactions

CCI [redacted]

2.3.2.3. Risks Due to Study Procedures

2.3.2.3.1. Potential Risks and Inconvenience Associated with the Liver Biopsy Procedures

CCI [redacted] and CCI [redacted] will be performed during this study for research purposes.

The risks and complications related to these procedures will be described in the informed consent form (ICF) and may include:

- Pain and discomfort located at or near the puncture site and radiating upwards toward the right shoulder region, which may last for up to a few hours or rarely days after the procedure.
- Bleeding at the biopsy site.
- Infection and internal bleeding and/or puncture of other internal organs (gall bladder, lung, intestine or kidney) which can lead to serious complications (uncommon – 1 in 1000 to 1 in 100) including the need for emergency surgery, blood transfusion, or removal of organs. Deaths directly related to liver biopsy occur rarely (approximately 1 in every 10,000 biopsies).

2.3.2.3.2. Potential Risks and Inconvenience Associated with the Optional Leukapheresis Procedure

Participants who provide separate consent may undergo leukapheresis. The risks and complications related to this procedure will be described in the ICF and may include:

- Frequent side effects (~5% of participants): chills, reactions to the citratebased anticoagulant (eg, prolonged bleeding for up to 20 minutes after the procedure), numbness or tingling of the lips, face, or on the fingertips, muscle cramps, abnormal heart rhythm, or metallic taste in the mouth
- Occasional side effects (<5% of participants): bruising or discomfort at the injection sites, pain/numbness in the arm (usually of short duration), tiredness the day following the procedure, weakness, nausea/vomiting, fainting due to decreased blood pressure, pink or red coloration of urine, hemolysis
- Rare side effects (≤1% of participants): superficial inflammation of the vein in the arm that is being used for the procedure which may result in pain, heat, and redness, pulmonary embolism, rapid breathing, chest pain, or cough

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 1/2a Study AROHBV1001 (see Section 2.2.2). 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 2.2.2).
- 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, hematological abnormalities, and events related to cholesterol increase (Section 8.5.6 and Section 8.4.4). In addition, the following toxicities will also be carefully monitored: rash and acute systemic allergic reactions (Section 8.5.6).
- 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).
  - Utilization of withdrawal criteria (see Section 7). If a participant drops out due to withdrawal of consent, he/she retains the option to participate in the safety follow-up procedures.

- Following local standard practice the biopsy location will be identified with ultrasound (which will also be used to rule out contraindicating conditions for a biopsy). At the off-treatment biopsy, blood coagulation and platelets will be assessed according to local practice. Prior to the on-treatment biopsy, a recent (≤ 1 week) coagulation and hematology panel and a platelet aggregation test are required, to ensure normal count and function of platelets and normal coagulation parameters. Site selection will be based on their experience in the performance CCI liver biopsies CCI
- Participants will be monitored closely during the optional leukapheresis. In case of serious complications, the leukapheresis procedure will be stopped immediately. Participants will stay on site for at least 30 minutes after leukapheresis to monitor for potential side effects. Additional safety-related assessments may be performed at the discretion of the investigator and may include additional laboratory tests after the procedure to measure hematologic parameters.
- At regular time points throughout the study (see Schedule of Activities), blood samples for biochemistry, blood coagulation, and hematology and urine samples for urinalysis, urine chemistry, and renal biomarkers will be collected. Vital signs (systolic and diastolic blood pressure [SBP and DBP]), pulse rate, and 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 8.3, Safety Assessments). Events of Special Interest will be closely monitored (Section 8.5.6, Adverse Events of Special Interest).
- An Independent Flare Expert Panel (IFLEP) will be appointed to characterize and adjudicate each ALT flare (see Section 9.6).
- 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).
- JNJ-3989 will be administered using a proper SC technique to decrease the risk of ISRs. Injection site reactions will be managed as outlined in Section 8.5.6.
- 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

The following objectives and endpoints will be assessed overall, by study panel, and by intervention arm:

Objectives	Endpoints
Primary	
• To assess changes in intrahepatic HBsAg between baseline and on-treatment liver biopsy in response to JNJ-3989-based combination treatment	• Changes in the proportion of HBsAg positive hepatocytes between baseline and on-treatment Week 40

Objectives	Endpoints
Secondary	
• To assess changes in intrahepatic immune response between baseline and on-treatment liver biopsy	• Changes between baseline and on-treatment liver biopsy in intrahepatic immune response [redacted] in terms of proportion of cells, cell types, and spatial redistribution
• To assess changes in intrahepatic viral nucleic acids and proteins between baseline and on-treatment liver biopsy	• Changes from baseline in intrahepatic viral parameters (such as cccDNA, pgRNA, intrahepatic RNA, or HBsAg in terms of copy number, or number of positive cells) • Changes from baseline in intrahepatic cccDNA levels and transcriptional activity (pgRNA/cccDNA ratio)
• To evaluate the efficacy of the study intervention as measured in the periphery	• The proportion of participants during the study intervention and follow-up phases with: – HBsAg seroclearance at Week 72 (ie, 24 weeks after completion of all study interventions at Week 48) without restarting NA treatment. – (Sustained) Reduction, suppression, and/or seroclearance considering single and multiple markers (such as HBsAg, HBeAg, HBV DNA and ALT) – HBsAg and HBeAg seroconversion – Flares (virologic, biochemical, and clinical) • Time to first HBsAg seroclearance
• To evaluate the frequency of virologic breakthrough during study intervention	• Proportion of participants with virologic breakthrough
• To assess HBV-specific T-cell responses	• Changes from baseline in HBV-specific peripheral blood T-cell responses during the study intervention and follow-up phases
• To evaluate the safety and tolerability of the study intervention	• 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 plasma PK of JNJ-3989 (ie, JNJ-3976 and JNJ-3924), JNJ-6379, and optionally of NA, as applicable	• Plasma PK parameters of JNJ-3976, JNJ-3924, JNJ-6379, and optionally of NA, as applicable

Objectives	Endpoints
CCI	

* Only applicable to participants who are enrolled at a site with an on-site Fibroscan device.

Refer to Section 8 for evaluations related to endpoints.

HYPOTHESIS

As this is an exploratory study, no hypothesis will be tested.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2 randomized, open-label, multicenter, parallel-group study to assess intrahepatic and peripheral changes of immunologic and virologic markers in response to two combination regimens containing JNJ-3989 and NA, with or without JNJ-6379, in chronic HBV-infected participants.

A target of 24 chronic HBV-infected male and female participants, 18-65 years (inclusive) of age will be enrolled in 2 panels, approximately 12 participants in each panel. Panel 1 will consist of participants who are HBeAg positive and not currently treated and Panel 2 will consist of participants who are HBeAg negative and virologically suppressed by ETV, tenofovir disoproxil, or TAF treatment.

The study will be conducted in 3 phases for all participants: a screening phase (4 weeks), an open-label 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 1:1 ratio within each panel to receive one of the following interventions (ie, treatments) for 48 weeks:

- Intervention arm 1, combination regimen JNJ-3989+JNJ-6379+NA (target of 12 participants):
  - CCI JNJ-3989 (SC injection Q4W, with the last injection at Week 44), AND
  - CCI JNJ-6379 (tablets qd), AND
  - NA: ETV, tenofovir disoproxil, or TAF (tablets qd)
- Intervention arm 2, combination regimen JNJ-3989+NA (target of 12 participants):
  - CCI JNJ-3989 (SC injection Q4W, with the last injection at Week 44), AND
  - NA: ETV, tenofovir disoproxil, or TAF (tablets qd)

All participants will complete treatment with JNJ-3989 (and JNJ-6379) after a fixed duration of 48 weeks. If the NA treatment completion criteria (outlined in Section 6.6) are met based on clinical laboratory tests performed at Week 44, treatment with NA will also be completed at Week 48. In participants not meeting these criteria, NA treatment will continue during the follow-up phase.

After stopping all study interventions, all 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 for more details).

Randomization within each panel will be stratified by Fibroscan score (<7 kPa vs ≥7 kPa).

Safety and tolerability, including (S)AEs, laboratory assessments, ECGs, vital signs, and physical examination, will be assessed throughout the study from the time of signing the ICF until completion of the last study-related activity (see Section 8.4 and Section 8.5).

At Week-1 and Week 40, CCI biopsy samples will be taken. CCI

Efficacy will be evaluated using different parameters including HBsAg and HBeAg (see Section 8.2).

Samples for HBV genome sequencing will be taken at the time points indicated in the Schedule of Activities (see Section 8.2.1). 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.

Peripheral blood mononuclear cell (PBMC) samples for immune analyses will be collected at the time points indicated in the Schedule of Activities (see Section 8.3).

The study includes collection of blood samples for exploratory analysis of viral markers (see Section 8.1) and host blood biomarkers at the host RNA, protein, and cell level (see Section 8.10).

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 substudy (optional) will undergo intensive PK sampling at Week 4.

A population PK analysis may be performed based on the available data for JNJ-6379, JNJ-3989, 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 will be calculated via noncompartmental methods.

Pharmacokinetic/pharmacodynamic relations may be explored (see Section 8.8).

Host DNA samples will be collected to allow for the identification of genetic factors (see Section 8.9). In addition, host DNA blood samples to allow for epigenetic analyses will be collected.

Human leukocyte antigen (HLA) typing will be performed as indicated in the Schedule of Activities.

In case of premature discontinuation of investigational intervention (before Week 48), follow-up assessments should be obtained until 48 weeks after EOSI unless the participant withdraws consent.

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.

An IFLEP will be appointed for this study (see Section 9.6).

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

4.2. Scientific Rationale for Study Design

Study Population

Patients with chronic HBV infection will be eligible if (1) they are HBeAg positive and not currently being treated or (2) if they are HBeAg negative and virologically suppressed by NA treatment.

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

Randomization, Stratification Factors and Blinding

Within each of the two study panels (ie, HBeAg positive patients who are not currently being treated and HBeAg negative patients being virologically suppressed by NA treatment), randomization will be used to minimize bias in the assignment of participants to intervention arms, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across intervention groups, and to enhance the validity of statistical comparisons across intervention arms.

Randomization within each panel will be stratified by Fibroscan score (<7 kPa vs ≥7 kPa).

As this is an exploratory study, participants will be treated in an open-label fashion. In addition, most relevant assessments will be based on objective markers (biopsy and peripheral immunology) and are not subject to bias from the participants or observers.

Criteria for Completion of NA Treatment

To explore the possibility of finite treatment, all participants who completed the 48-week study intervention will stop all study interventions including NAs at Week 48 if they meet NA treatment completion criteria (described in Section 6.6). The treatment completion criteria which take ALT, HBV DNA, HBeAg and HBsAg levels into consideration, have been selected to ensure that only participants with a chance of sustained off-treatment response are allowed to complete all study intervention. CCI [redacted]

CCI [redacted]

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, for more details).

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 until stabilization.

Increases in ALT and HBV DNA are frequently seen in patients after discontinuation of NA treatment. These ALT elevations can be reflecting an activation of the host cellular immune response and can as such lead to functional cure. Cases of fulminant HBV reactivation with fatal outcome were described after cessation of NA treatment, but the vast majority of such cases were described in patients with decompensated liver disease at the time of NA discontinuation. These patients are not eligible to participate in the study. Still, a vigilant follow-up of patients during this phase of the study is critical to ensure patient safety. Increases in ALT that are accompanied by signs of decreased liver function will trigger immediate re-initiation of NA treatment based on protocol-defined NA re-treatment criteria (see Section 6.7).

However, in the absence of signs of decompensation, the decision to re-start NA treatment should take into account that a too early re-initiation might reduce the chances of achieving functional cure. CCI [redacted]

Liver Biopsy

HBV is a hepatropic virus, with the liver being the site of its replication which requires a modulation of intrahepatic immune response to allow the establishment of a chronic persistent infection. Although some of the viral blood markers are well established from a clinical perspective, questions remain on the relationship of these markers with intrahepatic events, such as expression of viral proteins (eg, HBsAg), HBV pgRNA, DNA and cccDNA level and transcriptional activity in the liver, ie, the target organ of HBV infection. Similarly, while assessment of peripheral immune response can provide insights into the HBV related immune response, it is well accepted that a large proportion of the relevant immune responses are enriched and/or restricted to the liver environment.[10,11,29] For example, many HBV specific CD8+ T-cells have a tissue-resident phenotype and innate-like populations such as mucosal associated invariant T (MAIT) cells and Natural Killer cells are enriched with the latter having also a specialized liver-resident component.[11,29]

Collecting liver biopsy samples will allow to perform critical assessments of intrahepatic virologic and immune events occurring in response to treatment with JNJ-3989, JNJ-6379 and NA, and to correlate the findings in the liver with treatment response and to viral and immune blood markers. In addition, these analyses are expected to improve the understanding of the molecular mechanisms of the treatment interventions and to provide important insight into the HBV pathology.

CCI [redacted] The cryopreserved core biopsies will allow characterization of the infected hepatocytes compartment and phenotyping of the major immune cell populations (proportion of cells and spatial distribution). The liver tissue will be used to assess changes from baseline in the proportion of HBsAg positive hepatocytes under therapy. In addition, the liver tissue will also be used to assess other HBV markers in the liver such as, but not limited to, pgRNA, total intracellular HBV RNA and DNA, and HBc. Changes in the quantity and potentially changes in the spatial distribution of these markers (including HBsAg) under JNJ-3989 and JNJ-6379 containing therapy or NA treatment will be assessed. Viral genome (RNA or DNA) sequencing of the samples as well as assessment of HBV viral transcripts and HBV DNA integrants in the host genome may be performed. This will also allow to compare viral parameters assessed in the liver with viral parameters in the blood compartment.

From an immune perspective, both, the innate and adaptive intrahepatic immune compartment will be characterized. CCI [redacted]

[redacted]

Remaining samples may be used for determination of liver JNJ-3989 (ie, JNJ-3976 and JNJ-3924) and/or JNJ-6379 concentrations and/or research on viral and host biomarkers and immune markers at the viral and/or host RNA/DNA, protein, and cell level.

Host DNA and Biomarker Collection

It is recognized that genetic variation can be an important contributory factor to interindividual differences in intervention distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond

differently to an intervention. The goal of the pharmacogenomic component is to collect DNA to allow the identification of genetic factors that may influence the efficacy, safety, or PK of JNJ-3989 and JNJ-6379, to identify genetic and epigenetic factors associated with HBV infection, or to develop assays for the study intervention or HBV infection.

Biomarker samples will be collected to evaluate the MoA of JNJ-3989 and JNJ-6379 in combination with NA, help to explain interindividual variability in clinical outcomes, or may help to identify population subgroups that respond differently to an intervention. CCI [redacted]

Host DNA (pharmacogenomic) and biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, CCI [redacted]

4.2.1. Study-Specific Ethical Design Considerations

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

CCI [redacted] will be performed during this study for research purposes. The risks and complications related to these procedures are described in Section 2.3.2.3. These risks and complications will be described in the ICF and will be clearly explained to potential participants prior to enrollment.

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

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

4.3. Justification for Dose

The proposed dose and treatment duration are selected to maximize the chance for patients to achieve functional cure and are supported by scientific understanding of available data. For both compounds, doses are selected that are currently being tested in ongoing Phase 2b studies

REEF-1(73763989HPB2001) and REEF-2 (73763989PAHPB2002) CCI [redacted]

4.3.1. JNJ-3989

Clinical data on PK, efficacy, and safety of JNJ-3989 are available from the ongoing Phase 1/2a AROHBV1001 study with a data cut-off date of 29 October 2019. All dosing with JNJ-3989 has been completed and ongoing participants are in the follow-up phase. Twenty adult healthy participants have received single SC injections of JNJ-3989 (35, 100, 200, 300, and 400 mg) and 84 adult chronic HBV-infected participants have received multiple doses of JNJ-3989 (25, 50, 100, 200, 300, and 400 mg), administered as 3 SC injections separated by either 7 day, 14-day, or 28-day intervals. All participants either continued or started on ETV or tenofovir disoproxil on Day 1.

JNJ-3989 was generally safe and well tolerated at all doses. No clinically relevant safety signal was identified.

Antiviral activity data were available for 56 chronic HBV-infected participants who received 3 SC injections of 25 to 400 mg JNJ-3989 Q4W. In general, mean HBsAg declines reached nadir at Day 113 (ie, 8 weeks after last JNJ-3989). Mean HBsAg levels remained suppressed (below baseline levels) at least until Day 392 (ie, 9 months after last dose) in a substantial proportion of patients.[8,37]

A dose of CCI [redacted] JNJ-3989 Q4W is chosen based on the observed decline in HBsAg in study AROHBV1001 at this dose over 3 injections, and the lack of a substantial incremental efficacy response at higher doses.

CCI [redacted]

4.3.2. JNJ-6379

A dose of CCI [redacted] JNJ-6379 qd is chosen for this study.

CCI [redacted]

CCI

4.4. End of Study Definition

End of Study Definition

The end of study (EOS) is considered as the last visit (Follow-up Week 48 or early discontinuation) 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.

Study Completion Definition

A participant will be considered to have completed the study if he or she has completed the assessments at Follow-up Week 48.

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.

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.

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

For a discussion of the statistical considerations of participant selection, refer to Section 9.2.

5.1. Inclusion Criteria

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

1. Adult 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.

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

3. 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 positivity 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. If none of the above are available, the following ways of documenting chronicity are acceptable at the time of screening: absence of marker for acute infection such as immunoglobulin M (IgM) anti-HBs and anti-HBc antibodies, which can be tested at screening.

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

    a. be HBeAg positive, AND

    b. have serum HBV DNA at screening ≥20,000 IU /mL, AND

    c. have ALT levels at screening <10x ULN, AND

    d. have indication for NA treatment according to local standard practice.

5. Virologically suppressed participants should:

    a. be HBeAg negative, AND

    b. be on stable HBV treatment, defined as currently receiving NA treatment (ETV, tenofovir disoproxil, or TAF) for at least 6 months prior to screening and have been on the same NA treatment regimen (at the same dose) for at least 3 months at the time of screening, AND

    c. have serum HBV DNA <60 IU/mL on 2 measurements at least 3 months apart (one of which is at screening), AND

    d. have documented ALT values <2.0x ULN on 2 measurements at least 3 months apart (one of which is at screening).

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

7. 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.

8. Participants must have fibroscan liver stiffness measurement ≤9.0 kPa within 6 months 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 (eg, conventional liver ultrasound, computed tomography [CT] or magnetic resonance imaging [MRI]) and serum marker panels are not allowed to rule out severe fibrosis or cirrhosis.

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

10. A woman must be (as defined in Section 10.8, Appendix 8, Contraceptive and Barrier Guidance and Collection of Pregnancy Information):

    a. not of childbearing potential

    b. of childbearing potential and practicing a highly effective, preferably user-independent method of contraception (failure rate of <1% per year when used consistently and correctly) for at least 30 days prior to screening and agrees 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 located 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.

11. 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 period and until 90 days after last dose of study intervention.
12. Female participants must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study intervention period and until 90 days after last dose of study intervention.
13. Male participants must agree not to donate sperm for the purpose of reproduction during the study intervention phase and until 90 days after last dose of study intervention.
14. Participants must sign an ICF indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.
15. Participants must separately consent if he or she agrees to undergo optional study procedures (ie, leukapheresis, intensive PK, and/or optional biopsy). Refusal to give consent to one or all of these optional study procedures does not exclude from participation in the study.
16. In the investigator's opinion, the participant is able to understand and comply with protocol requirements, instructions, and study restrictions and is likely to complete the procedures as planned for this this study.

5.2. Exclusion Criteria

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

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

   Note: 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.

   Note: Participants with a positive IgM antibody test for HEV infection may be enrolled after discussion with the sponsor if an active HEV infection can be ruled out by documentation of negative anti-HEV IgG.

2. Participants with any of the following laboratory abnormalities within 12 months prior to screening or at the time of screening:
   a. Total bilirubin >1.5x ULN, OR
   b. Direct bilirubin >1.2x ULN, OR
   c. Serum albumin <3.2 g/dL,
3. History or evidence of clinical signs/symptoms of hepatic decompensation including but not limited to: portal hypertension, ascites, hepatic encephalopathy, esophageal varices.
4. Participants with evidence of liver disease of non-HBV etiology. This includes but is not limited to hepatitis virus infections mentioned in exclusion criterion 1, drug- or alcohol related liver disease, autoimmune hepatitis, hemochromatosis, Wilson's disease, α-1 antitrypsin deficiency, primary biliary cholangitis, primary sclerosing cholangitis, Gilbert's syndrome (mild cases are allowed, see exclusion criterion 2a), or any other non-HBV liver disease considered clinically significant by the investigator.
5. Participants with history or signs of cirrhosis or portal hypertension (nodules, no smooth liver contour, no normal portal vein, spleen size ≥12 cm), signs of HCC or clinically relevant renal abnormalities on an abdominal ultrasound performed within 6 months prior to screening or at the time of screening.

   Note: 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).
6. 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:
   a. Estimated glomerular filtration rate (eGFR) ≥grade 3 (<60 mL/min/1.73m²), 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 (AFP) >100 ng/mL;

      Note: Participants with AFP >ULN but ≤100 ng/mL may be eligible if HCC can be ruled out based on a sensitive imaging study (eg, contrast enhanced ultrasound, CT, or MRI) during screening.
   g. Any other laboratory abnormality considered to be clinically significant by the investigator.

7. Participants with presence of coagulopathy or bleeding disorder as indicated by:

   a. International normalized ratio (INR) ≥1.1 x ULN;

   b. Partial thromboplastin time > 1.1 x ULN;

   c. Any signs of prolonged bleeding (>10 minutes).

8. Participants with presence of hemoglobinopathy (including sickle cell disease, thalassemia).

9. Participants who had a liver biopsy performed prior to screening that led to complications and that in the opinion of the investigator would prohibit another liver biopsy.

10. Participants with history of amyloidosis.

11. Participant refusal to accept blood transfusions.

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

13. Participants with a history of malignancy within 5 years prior to 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).

14. 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.

15. 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.

16. 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.

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

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

19. Participants with clinically relevant drug or alcohol abuse within 12 months before screening.

20. Participants with history of clinically relevant drug rash.

21. Participants who have taken any disallowed therapies as noted in Section 6.5 before the planned first dose of study intervention.

22. 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.

23. 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.

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

25. Participants who had major surgery (eg, requiring general anesthesia), excluding diagnostic surgery, within 12 weeks before screening; or who have not fully recovered from surgery; or have 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.

26. 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.

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

28. Participants with known allergies, hypersensitivity, or intolerance to JNJ-3989 and JNJ-6379 or their excipients (refer to the IBs and addendum).[14-16]

29. Participants with contraindications to the use of ETV, tenofovir disoproxil, or TAF per local prescribing information.

30. For participants undergoing optional leukapheresis: contraindications to the use of citrate-based anticoagulation per local prescribing information.

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 Week -1 liver biopsy or before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. The required source documentation to support meeting the enrollment criteria are noted in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

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

1. Agree to follow all requirements as outlined in Section 6.5 (details 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 (eg, contraceptive requirements).

5.4. Screen Failures

NOTE: Retesting of abnormal laboratory values that may lead to exclusion will be allowed once. Retesting will take place during an unscheduled visit in the screening phase.

Participant Identification, Enrollment, and Screening Logs

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

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant

identification and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

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

6. STUDY INTERVENTION

6.1. Study Intervention(s) Administered

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 CCI mL of JNJ-3989 (containing the two RNAi triggers, JNJ-3976 and JNJ-3924) for SC injection, CCI

The JNJ-6379 supplied for this study is formulated as oral tablets containing 25 mg (CCI and 100 mg (CCI 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 and addendum for a list of excipients.[14-16]

The NAs ETV, tenofovir disoproxil, and TAF formulated as oral film-coated tablets of 0.5-mg, 245-mg, and 25-mg strength, respectively, will be provided by the sponsor.

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, JNJ-6379, and the NAs will be done in an open label way. Commercial supplies of NAs 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 will be dispensed in child-resistant packaging. Nucleos(t)ide analog 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 injections will be administered SC in the abdomen at the study site.

In between study visits, participants will take their oral study intervention (JNJ-6379/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.

During the study, virologically suppressed 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, tenofovir disoproxil, or TAF prior to screening, they should be treated with one of the other two NAs during this study.

Participants who are not receiving any HBV treatment at screening will receive tenofovir disoproxil at start of intervention.

If clinically indicated, switching from one NA treatment (ETV, tenofovir disoproxil, or TAF) to another NA treatment (ETV, tenofovir disoproxil, 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 8.6.

Description of Interventions

Intervention name	JNJ-3989	JNJ-6379	Entecavir (ETV) monohydrate	Tenofovir disoproxil	Tenofovir alafenamide (TAF)**
Type	Drug	Drug	Drug	Drug	Drug
Dosage formulation	Solution for injection	Tablets	Film-coated tablets	Film-coated tablets	Film-coated tablets
Unit dose strength(s)	CCI vial	CCI	0.5 mg	245 mg	25 mg
Dosage level	CCI once every 4 weeks (Q4W)	CCI once daily (qd)	Nucleoside-naïve patients: 0.5 mg qd Lamivudine-refractory patients: 1 mg* qd (but should preferably be treated with tenofovir disoproxil or TAF instead) Other indications: 1 mg* qd (must be agreed upon by the sponsor)	245 mg qd	25 mg qd
Route of administration	Subcutaneous injection in the abdomen	Oral	Oral	Oral	Oral
Use	Investigational intervention	Investigational intervention	Background intervention	Background intervention	Background intervention
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Each unit will be labeled with unique medication ID number	Each unit will be labeled with unique medication ID number	Commercial supplies will be sourced. Each unit will be labeled with unique medication ID number	Commercial supplies will be sourced. Each unit will be labeled with unique medication ID number	Commercial supplies will be sourced. Each unit will be labeled with unique medication ID number
		In child-resistant packaging	In child-resistant packaging	In child-resistant packaging	In child-resistant packaging
	Labels will contain information to meet the applicable regulatory requirements.				

Intervention name	JNJ-3989	JNJ-6379	Entecavir (ETV) monohydrate	Tenofovir disoproxil	Tenofovir alafenamide (TAF)**
Food/Fasting instructions	Regardless of food intake	Regardless of food intake	Per prescribing information	Per prescribing information	Per prescribing information

Q4W: once every 4 weeks; qd: once daily
* 2 tablets of 0.5 mg
** In countries where TAF is available, it will be one of the NA treatment options.

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 study intervention 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 oral study intervention to the participant, and the return of oral study intervention from the participant (if applicable), must be documented on the intervention accountability form. Participants must be instructed to return all original containers, whether empty or containing oral study intervention. The JNJ-3989 injections administered to the participant must be documented on the intervention accountability form. All study intervention will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study intervention containers.

Study intervention must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention, and oral 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.

Potentially hazardous materials containing hazardous liquids, such as used ampules, needles, syringes and vials, should be disposed of immediately in a safe manner and therefore will not be retained for intervention accountability purposes.

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 participating in the study. Returned study intervention must not be dispensed again, even to the same participant. Whenever a participant brings his or her oral study intervention to the study site for pill count, this is not seen as a return of supplies. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual.

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 within each panel to 1 of 2 intervention arms in a 1:1 ratio (Arm 1 [JNJ-3989+JNJ-6379+NA]:Arm 2 [JNJ-3989+NA]) 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 within each panel by Fibroscan score (<7 kPa vs ≥7 kPa). The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant participant details to uniquely identify the participant.

Blinding

As this is an open label study, blinding procedures are not applicable.

6.4. Study Intervention Compliance

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

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 study interventions as indicated in the Schedule of Activities.

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

- If an injection of JNJ-3989 was missed, the injection should be given as soon as possible but within 3 weeks after the scheduled time. Otherwise, the injection should be skipped and the next injection should be given at the next scheduled time point per the initial injection schedule.

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

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

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

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

Concomitant therapies must be recorded throughout the study, from signing of the ICF until completion of the participant's last study-related procedure. Concomitant therapies should also be recorded beyond the last study-related procedure only in conjunction with new or worsening S(AE)s.

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

An overview of disallowed medication is provided in Table 4.

Table 4: Disallowed Medication

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

Disallowed from 1 month prior to screening until end of follow-up:
• Moderate and potent inhibitors of CYP3A4 (eg, azole anti-fungals, macrolide antibiotics, diltiazem, verapamil). • Moderate and potent inducers of CYP3A4 (anti-epileptics: eg, carbamazepine, oxcarbazepine, [fos]phenytoin, and phenobarbital; anti-tuberculosis drugs: rifabutin, rifampin, and rifapentine; other: bosentan, modafinil). • Inhibitors of P-glycoprotein transporter (eg, amiodarone, azithromycin clarithromycin, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, quinidine, ritonavir, verapamil). • Inhibitors of breast cancer resistance protein (BCRP) transporter (eg, curcumin, cyclosporin A, eltrombopag). • Any medication that reduces renal function or competes for active tubular secretion (eg cimetidine, probenecid, quinidine). • Anticoagulants and antiplatelet agents. ***Note:*** The use of citrate-based anticoagulant is allowed for participants during the leukapheresis procedure. Use of heparin for anticoagulation is not allowed. ***Note:*** The use of ibuprofen or paracetamol is allowed.
Disallowed from screening until end of follow-up:
• Products containing *Hypericum perforatum* (St. John's wort). • Any anti-HBV drug (including vaccines) other than the study intervention taken in the context of this study. ***Note:*** NA standard of care treatment is allowed for virologically suppressed participants. • 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.

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

Table 5: Concomitant Medication to be Used With Caution

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

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

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

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

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

Medications requiring SC injection (other than JNJ-3989; eg, insulin) should be administered away from the JNJ-3989 injection sites.

6.6. Study Intervention Completion at Week 48

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

CCI

[redacted]

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

Participants who do not meet the above criteria at Week 48 should continue NA treatment during the 48-week follow-up phase.

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

6.7. NA Re-treatment Criteria During Follow-up

Participants who meet the NA treatment completion criteria outlined in Section 6.6 will be monitored closely during the follow-up phase and should re-start NA treatment immediately in the event of:

CCI

[redacted]

6.8. Intervention After the End of the Study

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

7. DISCONTINUATION OF INVESTIGATIONAL INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's investigational intervention (JNJ-3989 and, if applicable, JNJ-6379) must be discontinued if any of the criteria listed below apply. In those cases, NA treatment may be continued or, in consultation with the sponsor or discontinued based on investigator judgement.

- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue JNJ-3989 (and, if applicable, JNJ-6379).
- The participant becomes pregnant.
- The participant has a ≥grade 3 rash (see Section 10.5, Appendix 5, Rash Management) or allergic reaction (see Section 8.5.6.4).
- The participant has signs of hepatic decompensation (ie, clinical evidence of ascites, bleeding varices, or hepatic encephalopathy).
- The participant has a confirmed ≥grade 3 eGFR abnormality and a drop from baseline of >10 mL/min/1.73 m2, considered at least possibly related to JNJ-3989 (or JNJ-6379). Change of NA treatment should be considered anytime, according to the prescribing information (see Section 8.5.6.5).
- The participant has a confirmed QTcF prolongation (defined as a QTcF value of >500 ms, or an increase from baseline of >60 ms) at any given time point.
- The participant requires ≥7 days of treatment with any of the disallowed medications listed in Section 6.5 and does not intend to discontinue treatment with the disallowed medication.
- The participant has confirmed HBV virologic breakthrough (ie, confirmed on-treatment HBV DNA increase by >1 $\log_{10}$ IU/mL from nadir or confirmed on-treatment HBV DNA level >200 IU/mL in participants who had HBV DNA level <LLOQ of the HBV DNA assay). In case of virologic breakthrough, 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 8.5.6.1 and Schedule of Activities), changing the NA should be considered in consultation with the sponsor.
- The participant has ALT/AST elevations, as described in Section 8.5.6.1.
- The participant has confirmed ≥grade 3 hematologic abnormalities as described in Section 8.5.6.6.

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

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

In case a participant withdraws consent for the second biopsy, the study participant may continue the study intervention and visit schedule as outlined in the Schedule of Activities.

7.2. Participant Discontinuation/Withdrawal From the Study

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

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

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

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the CRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent then no additional assessments are allowed. No additional participants will be enrolled in case a participant withdraws from the study.

Withdrawal of Consent

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

7.2.1. Withdrawal From the Use of Research Samples

Withdrawal From the Use of Samples in Future Research

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

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to randomization attempts should be made to obtain contact information from each participant, eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

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

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

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participants to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

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

If applicable, ECGs should be completed before any tests, procedures, or other consultations for that visit. Blood collections for PK and PD assessments should be kept as close to the specified time as possible. 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 CRF. Other measurements may be done earlier than specified time points if needed. Actual dates and times of assessments will be recorded in the source documentation and CRF.

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

The amount of blood drawn from each participant over the entire course of this study will be approximately 1053 mL.

During the leukapheresis procedure, WBCs will be separated from the blood, while the rest of the blood is returned to circulation. This process typically yields approximately 200 ml of cells. For participants undergoing all 3 optional leukapheresis procedures, approximately 600 ml will be collected.

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

Sample Collection and Handling

The actual dates and times of sample collection, as well as the actual start and stop times of the leukapheresis procedure, must be recorded in the CRF or laboratory requisition form.

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

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

Study-specific Materials

The investigator will be provided with the following supplies:

- IB and any addenda for JNJ-3989 and JNJ-6379,
- Prescribing Information for ETV, tenofovir disoproxil, and TAF,
- Pharmacy manual/study site investigational product and procedures manual,
- Laboratory manuals,
- IWRS Manual,
- CRF Completion Guidelines,
- Sample ICF,
- Contact information page(s).

8.1. Liver Biopsy

CCI [redacted] liver biopsies CCI [redacted] will be performed at the time points indicated in the Schedule of Activities. CCI [redacted]

Following local standard practice the biopsy location will be identified with ultrasound (which will also be used to rule out contraindicating conditions for a biopsy) and after application of local anesthesia the CCI [redacted] liver biopsy samples will be collected.

The liver biopsy procedure should be preceded and followed by standard medical monitoring according to local medical practice. This may include an overnight stay at the investigator's discretion.

CCI [redacted]

CCI

[redacted]

8.2. Blood Efficacy Assessments

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

Qualitative and quantitative HBsAg and HBeAg, and quantitative HBcrAg as well as antibodies against HBsAg and HBeAg 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 discretion.

Hepatitis B virus 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 discretion.

Hepatitis B virus DNA, HBsAg, HBeAg, anti-HBs, and anti-HBe antibody testing results will be provided to the investigator and the sponsor from screening until the end of follow-up.

It is the responsibility of the investigator:

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

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

8.2.1. 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.

8.3. Blood Immune Assessments

8.3.1. Peripheral Blood Mononuclear Cell Immune Analyses

Samples for PBMC immune analyses will be collected during the study intervention and follow-up phases 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. CCI [redacted] Leftover 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 flare, upon discussion with the sponsor, which may require an unscheduled visit.

8.3.2. Leukapheresis (Optional With Separate Consent)

Leukapheresis allows to selectively collect higher quantities of PBMCs from participants without withdrawing large volumes of blood.

Leukapheresis will only be performed for participants who consent separately to this component of the study. Participants may withdraw such consent at any time without affecting their participation in other aspects of the study.

Leukapheresis may be done at least 1 week (and up to 3 weeks) after the liver biopsies (see Schedule of Activities).Prior to the procedure, the participant's wellbeing will be checked and leukapheresis will only be offered if there is no clinical reason against it. If a participant has had a recent febrile illness, the leukapheresis should be postponed until body temperature is normal for at least 72 hours.

The leukapheresis procedure should mainly follow local standard procedures. Additional guidelines will be provided via a separate manual in order to standardize this process across sites.

One leukapheresis session is expected to last between 1.5 - 5 hours.

During the procedure, the participant will receive intravenous saline infusions and citrate-based anticoagulant. Use of heparin for anticoagulation is not allowed. A specialized leukapheresis trained research nurse or physician will be in attendance and in charge of the participant's immediate medical care to monitor the leukapheresis.

After completion of the leukapheresis procedure, participants will stay at the site for at least 30 minutes to monitor for any relevant safety events. Additional safety procedures may be performed at the discretion of the site staff. Participants are advised to refrain from exercise and strenuous activities for 3 day after the leukapheresis visit.

8.4. Safety Assessments

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

Adverse events will be reported and followed by the investigator as specified in Section 8.5 and Section 10.4, Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

Specific toxicity management plans in line with the known pharmacological profile of the study intervention (and the drug classes) evaluated in this study are implemented (Section 8.5.6).

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

Details regarding the IFLEP are provided in Section 9.6 and in the Committees Structure in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

8.4.1. Physical Examinations

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

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

8.4.2. Vital Signs

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

Blood pressure and pulse rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

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

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

8.4.3. Electrocardiograms

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

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

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

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

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

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

8.4.4. Clinical Safety Laboratory Assessments

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

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

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

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

8.5. Adverse Events and Serious Adverse Events

Special attention will be paid to those participants who discontinue the study for an AE, or who experience an AE of at least grade 3, or an SAE. The grades are based on the DAIDS Toxicity Grading Scale (Section 10.9, Appendix 9, DAIDS Table).

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

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

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

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

All Adverse Events

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

Serious Adverse Events

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

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

8.5.2. Method of Detecting Adverse Events and Serious Adverse Events

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

Solicited Adverse Events

Solicited AEs are predefined local (at the injection site) for which the participant is specifically questioned. Information on ISRs (Section 8.5.6.2) will be solicited.

Unsolicited Adverse Events

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

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

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

8.5.4. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

8.5.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the SAE Form. Any participant who becomes pregnant during the study must discontinue further investigational intervention (JNJ-3989 [and JNJ-6379, if applicable]).

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

8.5.6. 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, hematological abnormalities, and events related to cholesterol increase (Section

8.4.4, Clinical Safety Laboratory Assessments). In addition, the following toxicities will also be carefully monitored: rash and acute systemic allergic reactions.

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

8.5.6.1. Intervention-emergent ALT/AST Elevations

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

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

Any intervention-emergent elevation of ALT and/or AST ≥3x ULN and ≥3x nadir (ie, lowest value during study participation) should trigger an assessment of confounding factors (alcohol intake, change in concomitant medication, and comorbidities) and should trigger a confirmatory study visit to repeat laboratory testing of ALT, AST, ALP, AFP, bilirubin (total and direct), INR, albumin, and HBV DNA. Additional tests should be considered based on clinical judgement (refer to Section 10.6, Appendix 6, Intervention-emergent ALT/AST Elevations). The confirmatory visit should be scheduled as soon as possible, preferably within 7 days of the receipt of the initial ALT/AST results. In case the repeat laboratory testing shows an isolated ALT/AST elevation (ie, with stable albumin, bilirubin [total and direct], and INR) the participant may continue study intervention. In case of confirmed ALT elevation >1,000 U/L and ≥3x the baseline value, investigational intervention (JNJ-3989 [and JNJ-6379, if applicable]) should be discontinued. In both cases, NA treatment should be continued. The participant will be monitored on a weekly basis (laboratory testing of ALT, AST, ALP, AFP, bilirubin [total and direct], INR, albumin, and HBV DNA) until ALT and/or AST levels have returned to 50% of the maximal value.

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

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

the participant should discontinue investigational intervention (JNJ-3989 [and JNJ-6379, if applicable]) and should be monitored on a weekly basis or as per good clinical practice until ALT and/or AST levels have returned to 50% of the maximal value and, if present, liver-related symptoms have improved. NA treatment should be continued. Additional tests should be

considered based on clinical judgement (refer to Section 10.6, Appendix 6, Intervention-emergent ALT/AST Elevations).

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

8.5.6.2. Rash

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

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

Monitoring of the evolution of rash events will be performed as described in Table 6 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, RBC count, WBC count, differential count [neutrophils, lymphocytes, monocytes, eosinophils, and basophils], and platelet count), and creatinine. The values of the local laboratory assessments need to be transcribed in the CRF by the study site personnel.

The participant may be treated symptomatically until the rash resolves. Oral antihistamines (eg, cetirizine, levocetirizine) and/or topical corticosteroids may provide symptomatic relief but effectiveness of these measures has not been established. If systemic corticosteroids exceeding 5 mg of prednisolone equivalent/day are required for treatment of rash, the investigational intervention (JNJ-3989 [and JNJ-6379, if applicable]) needs to be permanently discontinued. NA treatment can be continued. If the rash is considered to be most likely due to concomitant illness or non-study interventions, standard management, including discontinuation of the likely causative agent, should be undertaken.

Injection Site Reactions

At the time points specified in the Schedule of Activities or at an unscheduled visit if needed, an evaluation of the injection site will be performed based on participant's description and/or physical examination. Evaluations will be recorded in the source documents and 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) should 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.

8.5.6.3. Complications From Liver Biopsy

Participants should be closely monitored for liver biopsy complications. Infection and internal bleeding and/or puncture of other internal organs (gall bladder, lung, intestine or kidney) can lead to serious complications (uncommon – 1 in 1000 to 1 in 100) including the need for emergency surgery, blood transfusion or removal of organs. Deaths directly related to liver biopsy occur rarely (approximately 1 in every 10,000 biopsies). Criteria for participant selection and laboratory assessments are in place to minimize these risks. Additional investigations can be performed at the investigator's discretion. Participants must be treated as clinically appropriate.

8.5.6.4. 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, if applicable). 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, if applicable). 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.

8.5.6.5. Renal Complications

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

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

8.5.6.6. Hematologic Abnormalities

CCI

[redacted]

CCI [redacted] any relevant abnormalities in hematologic parameters will be carefully monitored as described below:

- Platelet counts: <100, 000 cells/mm^3 (at least Grade 2 [DAIDS]) or <100 GI/L or reduction from baseline by at least 50% baseline
- Hemoglobin: Decrease from baseline of at least 2 g/dL from baseline or at least Grade 2 (DAIDS)
- Reticulocyte count: 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 intervention (JNJ-3989 [and JNJ-6379, if applicable]) should be considered. In case of discontinuation, NA treatment should be continued.

8.6. 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, tenofovir disoproxil, or TAF) greater than the prescribed dose will be considered an overdose. The sponsor does not recommend specific therapeutic 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 or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.7. Pharmacokinetics

Plasma samples will be used to evaluate the PK of JNJ-3989 (ie, JNJ-3976 and JNJ-3924), JNJ-6379, and, optionally, NA, as applicable. Serum collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these samples. Participant confidentiality will be maintained.

8.7.1. Evaluations

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

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 substudy (optional) will undergo intensive PK sampling at Week 4. If necessary (eg, for operational reasons), this visit may be scheduled at Week 8, 12, or 16.

8.7.2. Analytical Procedures

Pharmacokinetics

Plasma samples will be analyzed to determine concentrations of JNJ-3976 and JNJ-3924 using a validated, specific, and sensitive liquid chromatography-fluorescence hybridization method under the supervision of the sponsor.

At the sponsor's discretion, plasma samples may be analyzed to determine concentrations of JNJ-6379 and/or NA using a validated, specific, and sensitive liquid chromatography-mass spectrometry method under the supervision of the sponsor.

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

8.7.3. Pharmacokinetic Parameters and Evaluations

Parameters

Plasma concentration-time data for JNJ-3989 (ie, JNJ-3976 and JNJ-3924), JNJ-6379 and, optionally, NA will be analyzed via noncompartmental methods for all participants who underwent intensive PK sampling. The main PK parameter will be area under the plasma concentration-time curve over 24 hours (AUC_{24h}), C_{max}, t_{max}, plasma trough concentration (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 data from a selection of Phase 1 and 2 studies via population PK modelling. Individual estimates of PK parameters may be generated from the population PK analysis for potential use in exposure-response analysis.

8.8. Pharmacokinetics/Pharmacodynamics

Relationships of individual PK parameters for JNJ-3976, JNJ-3924, JNJ-6379, and, optionally, NA, with selected liver and blood biomarkers, and/or with selected safety endpoints may be evaluated.

8.9. Host Genetics

A pharmacogenomic blood sample will be collected (preferably at baseline) to allow for the identification of genetic factors that may influence the efficacy, safety, or PK of the study intervention, to identify genetic factors associated with HBV infection, or to develop assays for the study intervention or HBV infection.

A blood sample will be taken for HLA typing as indicated in the Schedule of Activities. In addition, host DNA blood samples to allow for epigenetic analyses will be collected.

8.10. Host Biomarkers

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

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

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

8.11. Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

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.

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

9.1. Statistical Hypotheses

As this is an exploratory study, no hypothesis will be tested.

9.2. Sample Size Determination

This study aims to enroll approximately 24 participants in total, ie, 12 participants per study panel and 6 participants per intervention arm within each panel. Due to the exploratory nature of the study, the sample size was determined based on clinical and feasibility considerations related to the liver biopsy procedures performed multiple times during the study, rather than a formal statistical calculation.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Randomized	All participants who were randomized in the study
Intent-to-treat (ITT)	All participants who were randomly assigned to an intervention arm and received at least 1 dose of study intervention. Participants will be analyzed according to the study intervention they were randomly assigned to.
Modified intent-to-treat (mITT)	All participants who were randomly assigned to an intervention arm, received at least 1 dose of study intervention, and have biopsy data at both baseline and Week 40. 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. Participants will be analyzed according to the study intervention they actually received.

9.4. Statistical Analyses

The Statistical Analysis Plan will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

Given the exploratory nature of the study and the limited sample size per intervention arm per panel, no statistical testing will be performed. All data will be summarized descriptively including 90% confidence intervals as appropriate.

9.4.1. Analysis of Efficacy and Antiviral Activity

To evaluate the efficacy and antiviral activity in blood and liver, the primary analysis set will be the mITT population and the secondary one will be the ITT population.

All efficacy summaries will be presented with descriptive statistics overall, by study panel (combining intervention arms), and by intervention arm (within and across study panels).

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.

Graphic displays will also be used to summarize the data and to visualize trends by intervention arm and/or study panel.

Where applicable, additional specifics for analyses of primary, secondary, and exploratory endpoints are detailed below.

9.4.1.1. Analysis of the Primary Endpoint

The primary endpoint is the change between baseline and on-treatment liver biopsy in terms of the proportion of HBsAg positive hepatocytes and will be analyzed descriptively using the general considerations outlined above.

No imputation rule will be applied for the analysis on the mITT population since only complete cases will be considered. In addition, the treatment policy strategy will be followed to account for the occurrence of intercurrent events, such as treatment discontinuation prior to Week 40, ie, all biopsies collected at Week 40 will be used, regardless of occurrence of treatment discontinuation prior to Week 40. This strategy is supported by the small sample size, the exploratory nature of the study and ethical considerations.

Furthermore, a secondary analysis will be performed on the ITT population using a similar treatment policy strategy as described above. In addition, a sensitivity analysis on the ITT population will be combining a treatment policy strategy with the Baseline Observation Carried Forward (BOCF) approach.

9.4.1.2. Analysis of Secondary Endpoints

Secondary endpoints will be analyzed on both the mITT and the ITT population.

Changes in Intrahepatic Immune Response

CCI [redacted] will be assessed at Week 40 and compared to baseline overall, by study panel, and intervention arm.

The functional characterization of major cell populations will be assessed by transcriptomics and/or proteomics for major cell populations of interest at Week 40 and compared to baseline similarly.

Changes in Intrahepatic Viral Nucleic Acids and Proteins

Changes from baseline in cccDNA level and/or transcriptional activity will be assessed using the general considerations outlined above.

Furthermore, the difference in the level of infected hepatocytes at baseline will be assessed by comparing cccDNA level and/or transcriptional activity.

Analyses of other viral markers will be performed descriptively. Statistical analyses will depend on the assay technology applied and the scope of the analyses.

9.4.1.3. Analysis of Exploratory Endpoints

CCI [redacted]

CCI

[redacted]

9.4.2. Safety Analyses

All safety analyses will be made on the Safety Population (Section 9.3).

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.

Adverse Events

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

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

Adverse Events Related to the Applied Study Procedures

Summaries, listings, datasets, or participant narratives will be provided, as appropriate, for those enrolled participants who die, or who experience an AE or a severe or a serious AE related to the applied study procedures.

All AE's linked to the study procedure will be evaluated in conjunction with other systemic symptoms and laboratory abnormalities: information on time of onset, duration of events, time to resolution, concomitant therapies, and relationship to study procedures (eg, liver biopsies, blood collection and leukapheresis) will be summarized and described in the report.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point by intervention arm and study phase. A graphical presentation of changes from baseline over time in selected laboratory tests will be also used by intervention arm.

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

Electrocardiogram

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

The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and QTcF.13

Descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled time point. The percentage of participants with QTc interval >450 milliseconds, >480 milliseconds, or >500 milliseconds will be summarized, as will the percentage of participants with QTc interval increases from baseline >30 milliseconds or >60 milliseconds. Shifts in QTc interval categories will be cross-tabulated by intervention arm and study phase.

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

Vital Signs

Vital signs including temperature, pulse rate, and supine blood pressure (SBP and DBP) will be summarized over time, using descriptive statistics and/or graphically. The percentage of participants with values beyond clinically important limits will be summarized by intervention arm.

Physical Examinations

Physical examination findings will be summarized at each scheduled time point. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

9.4.3. Other Analyses

Pharmacokinetic Analyses

Descriptive statistics (number of participants, mean, SD, coefficient of variation, geometric mean, median, minimum, and maximum) will be calculated for the plasma concentrations of JNJ-3976, JNJ-3924, JNJ-6379 and, optionally, NA, as applicable, and for the derived plasma PK parameters (noncompartmental analysis).

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.

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

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

Individual estimates of PK parameters may be generated from the population PK analysis for potential use in exposure-response analysis.

Pharmacokinetic/Pharmacodynamic Analyses

Relationships of PK parameters for JNJ-3976, JNJ-3924, JNJ-6379, and, optionally, NA with selected efficacy and with selected safety endpoints may be evaluated and graphically displayed.

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 may be investigated. Other biomarkers may be explored at the sponsor's discretion.

Resistance Analysis

The results of HBV viral sequencing will be evaluated by the sponsor virologist. Relevant changes in 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.

Pharmacogenomic Analysis

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 Exploratory Biomarker Analysis

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

9.5. Interim Analysis

Two IAs may be performed: when all participants have completed Week 20 in the intervention phase (or discontinued earlier) and when they have completed Week 72 in the follow-up phase (ie, Follow-up Week 24) (or discontinued earlier). These IAs will be performed by the sponsor to support interactions with health authorities, as well as to support internal decisions about additional studies and/or investigation of other combination regimens.

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.

9.6. Independent Flare Expert Panel

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

In order to allow for an unbiased assessment, members of the committee will not serve as study investigators.

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

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Definitions of Terms

AE	adverse event
AFP	alpha-fetoprotein
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{0\text{-}xh}$	area under the plasma concentration-time curve from administration to x h
$AUC_{0\text{-}last}$	area under the plasma concentration-time curve from administration to last quantifiable sampling point
AUC_{τ}	area under the plasma concentration-time curve over the dose interval (tau) at steady-state
AUC_{∞}	area under the plasma concentration-time curve to last sampling point from time zero extrapolated to infinity
bpm	beats per minute
CAM	capsid assembly modulator
cccDNA	covalently closed circular deoxyribonucleic acid
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	total apparent oral clearance
C_{max}	maximum plasma concentration
CRF	case report form
CT	computed tomography
CYP	cytochrome P450
DAIDS	Division of Acquired Immunodeficiency Syndrome
DBP	diastolic blood pressure
DDI	drug-drug interaction
DNA	deoxyribonucleic acid
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
eDC	electronic data capture
EFD	embryofetal development
eGFR	estimated glomerular filtration rate
ELISpot	enzyme-linked immunospot
EOS	end of study
EOSI	end of study intervention
ETV	entecavir
CCI	[redacted]
FSH	Follicle-stimulating hormone
FU Wx	Follow-up Week x
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBc	hepatitis B core protein
HBcrAg	hepatitis B core-related antigen
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBs	hepatitis B surface
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
HEV	hepatitis E virus
HIV-1(-2)	human immunodeficiency virus type 1 (type 2)
HLA	human leukocyte antigen
HRT	hormonal replacement therapy

IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ICS	intracellular cytokine staining
IEC	Independent Ethics Committee
IFLEP	Independent Flare Expert Panel
IFN	interferon
IFN-γ	gamma interferon
IgM	immunoglobulin M
IL	interleukin
INR	International Normalized Ratio
IRB	Institutional Review Board
ISR	injection site reaction
ITT	Intent-to-treat
IU/mL	International Units Per Milliliter
IWRS	interactive web response system
LLN	lower limit of normal
LLOQ	lower limit of quantification
MoA	mode of action
MRI	magnetic resonance imaging
NA	nucleos(t)ide analog
NOAEL	no observed adverse effect level
(q)PCR	(quantitative) polymerase chain reaction
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PBMC	peripheral blood mononuclear cell
pgRNA	pre-genomic ribonucleic acid
PQC	Product Quality Complaint
Q4W	once every 4 weeks
qd	once daily
QTcF	QT interval corrected for heart rate according to Fridericia
RBC	red blood cell
RNA	ribonucleic acid
RNAi	ribonucleic acid interference
SAE	serious adverse event
SBP	systolic blood pressure
SC	subcutaneous
SD	standard deviation
siRNA	small interfering RNA
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2term}$	terminal half-life
t_{max}	time to reach the maximum plasma concentration
TAF	tenofovir alafenamide
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
ULN	upper limit of normal
WBC	white blood cell

Definitions of Terms

Study intervention	JNJ-73763989 (JNJ-3989), JNJ-56136379 (JNJ-6379) and NA (either ETV, tenofovir disoproxil, or TAF)
Functional cure	HBsAg seroclearance 24 weeks after end of treatment
HBsAg or HBeAg seroclearance	HBsAg or HBeAg negativity, respectively, based on the assay used
HBsAg or HBeAg seroconversion	HBsAg or HBeAg negativity and anti-HBs or anti-HBe antibody positivity, respectively
Virologic breakthrough	Confirmed on-treatment HBV DNA increase by >1 $\log_{10}$ IU/mL from nadir or confirmed on-treatment HBV DNA level >200 IU/mL in participants who had HBV DNA level <LLOQ of the HBV DNA assay
ALT/AST nadir	Lowest ALT/AST value during study participation

10.2. Appendix 2: Clinical Laboratory Tests

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

Protocol-Required Safety Laboratory Assessments

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

Note: Reflex testing of pancreatic amylase should be done in case of amylase or lipase increase from screening onwards.</td></tr>
<tr><td>Routine Urinalysis</td><td colspan="2"><u>Dipstick</u>
Specific gravity
pH
Glucose
Protein
Blood
Ketones
Bilirubin
Urobilinogen
Nitrite
Leukocyte esterase</td><td><u>Sediment (if dipstick result is abnormal)</u>
RBCs
WBCs
Epithelial cells
Crystals
Casts
Bacteria</td></tr>
</table>

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

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

REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

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

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

Protocol Amendments

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

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

Regulatory Approval/Notification

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

Required Prestudy Documentation

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

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

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

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

Independent Ethics Committee or Institutional Review Board

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

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)

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

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

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

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

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

- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

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

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

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

Country Selection

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

Other Ethical Considerations

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

FINANCIAL DISCLOSURE

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

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

INFORMED CONSENT PROCESS

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

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of his or her disease. Participants will

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

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

Where local regulations require, a separate ICF may be used for the required DNA component of the study.

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

DATA PROTECTION

Privacy of Personal Data

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

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

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

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

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

LONG-TERM RETENTION OF SAMPLES FOR ADDITIONAL FUTURE RESEARCH

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

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

COMMITTEES STRUCTURE

Independent Flare Expert Panel

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

In order to allow for an unbiased assessment, members of the committee will not serve as study investigators

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

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

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

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of JNJ-3989 and JNJ-6379, and thus may

be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

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

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

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

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

DATA QUALITY ASSURANCE

Data Quality Assurance/Quality Control

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

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

The sponsor will review CRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

CASE REPORT FORM COMPLETION

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in CRF. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the participant's source documents. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

All participative measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the electronic data capture (eDC) tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

SOURCE DOCUMENTS

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; dates of blood collection, date and time of start and end of leukapheresis, results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of investigational intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the CRF and will be considered source data:

- Race
- Blood pressure and pulse/heart rate
- Height and weight
- Details of physical examination

The minimum source documentation requirements for Section 5.1 and Section 5.2 that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for

use by the sponsor. If eSource is utilized, references made to the CRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the CRF.

MONITORING

The sponsor will use a combination of monitoring techniques (central, remote, or on-site monitoring) to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

ON-SITE AUDITS

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a

regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

RECORD RETENTION

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

STUDY AND SITE START AND CLOSURE

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

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

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per ICH)

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to All Adverse Events under Section 8.5.1 for time of last AE recording).

Serious Adverse Event

A SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For JNJ-3989 and JNJ-6379, the expectedness of an adverse event will be determined by whether or not it is listed in the IB. For ETV, tenofovir disoproxil, and TAF with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the package insert.

ATTRIBUTION DEFINITIONS

Assessment of Causality

The causal relationship to study intervention is determined by the Investigator. The following selection should be used to assess all AEs.

Related

There is a reasonable causal relationship between study intervention administration and the AE.

Not Related

There is not a reasonable causal relationship between study intervention administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

SEVERITY CRITERIA

An assessment of severity grade will be made by the investigator using the general categorical descriptors outlined in the DAIDS Toxicity Grading Scale (see Section 10.9, Appendix 9, DAIDS Table).

SPECIAL REPORTING SITUATIONS

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Medication error, intercepted medication error, or potential medication error involving a sponsor medicinal product (with or without patient exposure to the sponsor medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study intervention from breastfeeding

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a SAE should be recorded on the SAE page of the CRF.

PROCEDURES

All Adverse Events

All adverse events, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

In the context of this study, AEs and SAEs associated with/triggered by the liver biopsies, leukapheresis, or blood collection procedures are to be reported to the sponsor.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as a SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

The cause of death of a participant in a study, whether or not the event is expected or associated with the study intervention, is considered an SAE.

CONTACTING SPONSOR REGARDING SAFETY

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 8.5.1). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

10.5. Appendix 5: Rash Management

Table 6: Management of Rash Events by Severity Grade

	Definition	Study Intervention Action	Activities by Day[a]	Referral to Dermatologist and Dermatology Activities
Grade 1 rash (with or without pruritus)[b]	Erythema	Study intervention intake may be continued at the investigator's discretion	Day 0: optional on site visit for initial rash evaluation may be performed at the investigator's discretion. Safety laboratory assessments may be performed at the investigator's discretion (recommended if visit occurs). Digital pictures* of skin lesions may be taken at the investigator's discretion. Determine if participant was adhering to the recommended sun-protective measures. If appropriate, provide sun protection counseling. Day 1 and thereafter: appropriate follow-up visits at the investigator's discretion until resolution of rash. Safety laboratory assessments and photography (digital pictures* of skin lesions) may be performed at the investigator's discretion. * Digital pictures to be taken at the clinical site upon consent of the participant.	Not required
Grade 2 rash (with or without pruritus)[b]	Diffuse, maculopapular rash, or dry desquamation	Study intervention intake may be continued at the investigator's discretion	Day 0: required on-site visit (if a visit is not possible, telephone contact with the participant should take place to collect information and give advice on the necessary measures to be taken). Safety laboratory assessments may be performed at the investigator's discretion (recommended). Digital pictures* of skin lesions may be taken at the investigator's discretion. Digital pictures* of skin lesions are recommended in case consultation of a dermatologist is required. Determine if participant was adhering to the recommended sun-protective measures. If appropriate, provide sun protection counseling. Day 1 and thereafter: appropriate follow-up visits at the investigator's discretion until resolution of rash or until clinical stability is reached.	Referral to dermatologist at the discretion of the investigator[c] Biopsy not required, but may be performed at the dermatologist's discretion

Table 6: Management of Rash Events by Severity Grade

	Definition	Study Intervention Action	Activities by Day[a]	Referral to Dermatologist and Dermatology Activities
			Safety laboratory assessments are required on Day 1 and are required thereafter only if the previous values were abnormal (but may be performed at the investigator's discretion). If the rash progresses to a higher grade, safety laboratory assessments of the higher grade should be followed. Digital pictures* of skin lesions may be taken at the investigator's discretion. * Digital pictures to be taken at the clinical site upon consent of the participant.	
Grade 3 rash[b]	Vesiculation, moist desquamation, or ulceration OR Any cutaneous event with 1 of the following: - Elevations in AST/ALT >2×baseline value - Fever >38°C or 100°F - Eosinophils >1.00×10^3/μL - Serum sickness-like reaction	Must permanently discontinue JNJ-3989 and JNJ-6379; no rechallenge allowed NA treatment may be discontinued based on investigator judgement in consultation with the sponsor	Day 0: required on-site visit. Safety laboratory assessments required to be performed. Digital pictures* of skin lesions may be taken at the investigator's discretion (recommended). Determine if participant was adhering to the recommended sun-protective measures. If appropriate, provide sun protection counseling. Day 1: required on-site visit. Safety laboratory assessments required to be performed. Digital pictures* of skin lesions may be taken at the investigator's discretion (recommended). Further visit(s): appropriate follow-up required until resolution of rash or until clinical stability is reached. Safety laboratory assessments and photography (digital pictures* of skin lesions) are recommended to be performed until the rash severity resolves to grade 2 or grade 1. * Digital pictures to be taken at the clinical site upon consent of the participant.	Required[c] Biopsy not required, but may be performed at the dermatologist's discretion.

Table 6: Management of Rash Events by Severity Grade

	Definition	Study Intervention Action	Activities by Day[a]	Referral to Dermatologist and Dermatology Activities
Grade 4 rash	Exfoliative dermatitis OR Mucous membrane involvement in at least 2 distinct sites OR Erythema multiforme major OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis OR Necrosis requiring surgery	Must permanently discontinue JNJ-3989 and JNJ-6379; no rechallenge allowed NA treatment may be discontinued based on investigator judgement in consultation with the sponsor	Day 0: required on-site visit. Safety laboratory assessments required to be performed. Digital pictures* of skin lesions may be taken at the investigator's discretion (recommended). Determine if participant was adhering to the recommended sun-protective measures. If appropriate, provide sun protection counseling. Day 1: required on-site visit. Safety laboratory assessments required to be performed. Digital pictures* of skin lesions may be taken at the investigator's discretion (recommended). Further visit(s): appropriate follow-up required until resolution of rash or until clinical stability is reached. Safety laboratory assessments and photography (digital pictures* of skin lesions) are recommended to be performed until the rash severity resolves to grade 2 or grade 1. * Digital pictures to be taken at the clinical site upon consent of the participant.	Required[c] Biopsy required and to be performed as soon as possible after the onset of the rash.

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; NA: nucleos(t)ide analog.

[a] Day 0 of the rash is the first day of investigator assessment and not the first day of rash as reported by the participant. The initial visit should be conducted as soon as possible after the participant contacts the investigator to report the AE (ie, preferably on Day 0). The initial visit and subsequent visits to manage the rash may require unscheduled visit(s).

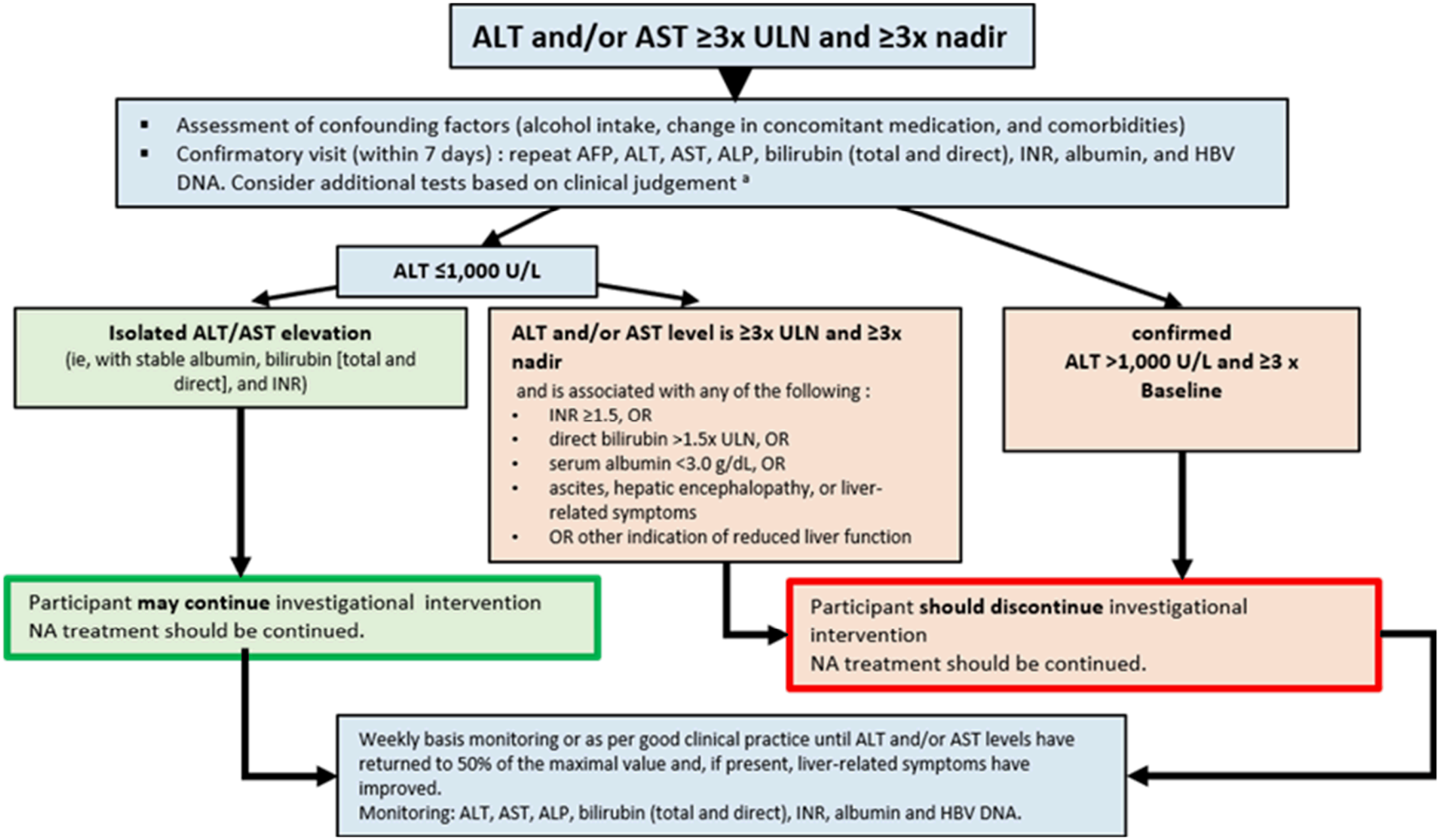
[b] The participant should be advised to contact the investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms appear, or if mucosal involvement develops. In case the rash evolves to a higher grade than that first observed, management of the rash should follow the guidelines indicated for the higher grade.

[c] If applicable, dermatologist visit should occur preferably within 24 hours after onset of rash.

Notes:

- Local laboratory assessments are to be used for rash management. The values of the local laboratory assessments need to be transcribed in the eCRF by the study site personnel.
- Digital pictures that are collected, dermatological consultation reports or biopsy reports that become available, should be de-identified and provided to the sponsor.

10.6. Appendix 6: Intervention-emergent ALT/AST Elevations



[a]Additional tests may be considered based on clinical judgement in case of confirmed ALT flares:

- Hepatitis A, D, C, E: IgM anti-HAV; delta IgM, IgG & PCR, HCV RNA, IgM & IgG anti-HEV, HEV RNA
- CMV, HSV, EBV infection: IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV, PCR
- HIV
- Ig-electrophoresis

10.7. Appendix 7: Cardiovascular Safety Abnormalities

ECG

All important abnormalities from the ECG readings will be listed.

Abnormality Code	ECG parameter			
	Heart Rate	**PR**	**QRS**	**$QT_{corrected}$**
Abnormalities on actual values				
Abnormally low	<45 bpm	NAP	-	-
Abnormally high	≥120 bpm	>220 ms	≥120 ms	-
Borderline prolonged QT	-	-	-	450 ms < QTc ≤480 ms
Prolonged QT	-	-	-	480 ms < QTc ≤500 ms
Pathologically prolonged QT	-	-	-	QTc >500 ms
Abnormalities on changes from baseline (ΔQTc)				
Normal QTc change	-	-	-	ΔQTc <30 ms
Borderline QTc change	-	-	-	30 ms ≤ ΔQTc ≤60 ms
Abnormally high QTc change	-	-	-	ΔQTc >60 ms

ECG: electrocardiogram; NAP = not applicable
For absolute QTc parameters the categories are defined based on the ICH E14 GuidanceF[a]

Vital Signs[b]

The following abnormalities will be defined for vital signs:

Abnormality Code	Vital Signs parameter		
	Pulse	**DBP**	**SBP**
Abnormalities on actual values			
Abnormally low	≤45 bpm	≤50 mmHg	≤90 mmHg
Grade 1 or mild	-	>90 mmHg - <100 mmHg	>140 mmHg - <160 mmHg
Grade 2 or moderate	-	≥100 mmHg - <110 mmHg	≥160 mmHg - <180 mmHg
Grade 3 or severe	-	≥110 mmHg	≥180 mmHg
Abnormally high	≥120 bpm	-	-

DBP: diastolic blood pressure; SBP: systolic blood pressure

[a] The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs CHMP/ICH/2/04, May 2005.

[b] The classification of AEs related to hypotension and hypertension will be done according to the DAIDS grading scale.

10.8. Appendix 8: Contraceptive and Barrier Guidance 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 8.5.5 and Section 10.4, Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone

• Lactational amenorrhea method (LAM)
a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention. c) Male condom and female condom should not be used together (due to risk of failure with friction).

10.9. Appendix 9: DAIDS Table

DIVISION OF AIDS (DAIDS) TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS, VERSION 2.1, PUBLISH DATE: JULY, 2017

The DAIDS grading table is a descriptive terminology to be utilized for AE reporting in this study. A grading (severity) scale is provided for each AE term.

General Instructions

Grading Adult and Pediatric Adverse Events

When a single parameter is not appropriate for grading an AE in both adult and pediatric populations, separate parameters with specified age ranges are provided. If there is no distinction between adult and pediatric populations, the listed parameter should be used for grading an AE in both populations.

Determining Severity Grade for Parameters Between Grades

If the severity of an AE could fall under either 1 of 2 grades (eg, the severity of an AE could be either grade 2 or grade 3), sites should select the higher of the 2 grades.

Laboratory normal ranges should be taken into consideration to assign gradings to a laboratory value.

Definitions

Basic self-care functions	Adults: activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding Young children: activities that are age and culturally appropriate (eg, feeding self with culturally appropriate eating implements)
Usual social & functional activities	Activities which adults and children perform on a routine basis and those which are part of regular activities of daily living, for example: Adults: adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, or pursuing a hobby Young Children: activities that are age and culturally appropriate (eg, social interactions, play activities, learning tasks)
Intervention	Medical, surgical, or other procedures recommended or provided by a healthcare professional for the treatment of an AE.

Estimating Severity Grade for Parameters not Identified in the Grading Table

The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical AE **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

NOTE: Laboratory abnormalities may have their grading defined in the DAIDS table below, however, all laboratory abnormalities do not necessarily represent an AE. If a laboratory abnormality is considered an AE, the AE need not have the same grade as the laboratory abnormality itself. The AE grade for a laboratory abnormality should be defined by the table above.

MAJOR CLINICAL CONDITIONS				
CARDIOVASCULAR				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities[a] ***Hypertension*** *(with the lowest reading taken after repeat testing during a visit)* *aged ≥18 years*	140 to <160 mmHg systolic OR 90 to <100 mmHg diastolic	≥160 to <180 mmHg systolic OR ≥100 to <110 mmHg diastolic	≥180 mmHg systolic OR ≥110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (eg, malignant hypertension) OR Hospitalization indicated
aged <18 years	>120/80 mmHg	≥95th to <99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (eg, malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only 1*	NAP	NAP	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction

ECG: electrocardiogram; IV: intravenous; NAP: not applicable

[a] Blood pressure norms for children aged <18 years can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Pediatrics 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.

MAJOR CLINICAL CONDITIONS				
CARDIOVASCULAR				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (eg, hypoxemia) OR Intervention indicated (eg, oxygen)	Life-threatening consequences OR Urgent intervention indicated (eg, vasoactive medications, ventricular assist device, heart transplant)
Hemorrhage (with significant acute blood loss)	NAP	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of >2 units packed RBCs (for children, packed RBCs >10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only 1* *aged >16 years*	PR interval 0.21 to <0.25 seconds	PR interval ≥0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥3.0 seconds	Complete AV block
aged ≤16 years	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥3.0 seconds	Complete AV block
Prolonged QTc Interval as per Fridericia's formula[b]	0.45 to 0.47 seconds	>0.47 to 0.50 seconds	>0.50 seconds OR ≥0.06 seconds above baseline	Life-threatening consequences (eg, TdP, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only 1*	NAP	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (eg, pulmonary embolism, thrombus)

AV: atrioventricular; NAP: not applicable; RBC: red blood cell; TdP: Torsades de Pointes
[b] Modified by the sponsor.

DERMATOLOGIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Alopecia (scalp only)	Detectable by participant, representative, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NAP	NAP
Bruising	Localized to 1 area	Localized to more than 1 area	Generalized	NAP
Cellulitis	NAP	Nonparenteral treatment indicated (eg, oral antibiotics, antifungals, antivirals)	IV treatment indicated (eg, IV antibiotics, antifungals, antivirals)	Life-threatening consequences (eg, sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NAP	NAP
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NAP	NAP
Petechiae	Localized to 1 area	Localized to more than 1 area	Generalized	NAP
Pruritus[c] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NAP
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae OR superficial ulcerations of mucous membrane limited to 1 site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving 2 or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

IV: intravenous; NAP: not applicable

[c] For pruritus associated with injections or infusions, refer to the SITE REACTIONS TO INJECTIONS AND INFUSIONS section.

ENDOCRINE AND METABOLIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (eg, ketoacidosis, hyperosmolar nonketotic coma, end organ failure)
Gynecomastia	Detectable by participant, representative, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NAP
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, myxedema coma)
Lipoatrophy[d]	Detectable by participant, representative, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NAP
Lipohypertrophy[e]	Detectable by participant, representative, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NAP

NAP: not applicable

[d] A disorder characterized by fat loss in the face, extremities, and buttocks.

[e] A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

GASTROINTESTINAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (eg, tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (eg, diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only 1*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NAP
Cholecystitis	NAP	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis, perforation)
Constipation	NAP	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea *aged ≥1 year*	Transient or intermittent episodes of unformed stools OR Increase of ≤3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
aged <1 year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (eg, liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia *Report only 1 and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (eg, hypotensive shock)

IV: intravenous; NAP: not applicable

GASTROINTESTINAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Mucositis or Stomatitis *Report only 1 and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (eg, aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (<24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for >48 hours OR Rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Pancreatitis	NAP	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (eg, circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NAP	NAP	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (eg, perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NAP	NAP
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)

IV: intravenous; NAP: not applicable

MUSCULOSKELETAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NAP	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[f] *aged ≥30 years*	BMD t-score -2.5 to -1	NAP	NAP	NAP
aged <30 years	BMD z-score -2 to -1	NAP	NAP	NAP
Osteoporosis[f] *aged ≥30 years*	NAP	BMD t-score <-2.5	Pathologic fracture (eg, compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
aged <30 years	NAP	BMD z-score <-2	Pathologic fracture (eg, compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

BMD: bone mineral density; NAP: not applicable

[f] Bone mineral density t- and z-scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

NEUROLOGIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Acute CNS Ischemia	NAP	NAP	Transient ischemic attack	Cerebral vascular accident (eg, stroke with neurological deficit)
Altered Mental Status (for Dementia, refer to *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Developmental Delay *Specify type, if applicable* *aged <18 years*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function

CNS: central nervous system; NAP: not applicable

NEUROLOGIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures ***New Onset Seizure*** *aged ≥18 years*	NAP	NAP	1 to 3 seizures	Prolonged and repetitive seizures (eg, status epilepticus) OR Difficult to control (eg, refractory epilepsy)
aged <18 years (includes new or pre-existing febrile seizures)	Seizure lasting <5 minutes with <24 hours postictal state	Seizure lasting 5 to <20 minutes with <24 hours postictal state	Seizure lasting ≥20 minutes OR >24 hours postictal state	Prolonged and repetitive seizures (eg, status epilepticus) OR Difficult to control (eg, refractory epilepsy)
Pre-existing Seizure	NAP	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (eg, severity or focality)	Prolonged and repetitive seizures (eg, status epilepticus) OR Difficult to control (eg, refractory epilepsy)
Syncope	Near syncope without loss of consciousness (eg, pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NAP

NAP: not applicable

PREGNANCY, PUERPERIUM, AND PERINATAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Stillbirth (report using mother's participant ID) *Report only 1*	NAP	NAP	Fetal death occurring at ≥20 weeks gestation	NAP
Preterm Birth (report using mother's participant ID)	Live birth at 34 to <37 weeks gestational age	Live birth at 28 to <34 weeks gestational age	Live birth at 24 to <28 weeks gestational age	Live birth at <24 weeks gestational age
Spontaneous Abortion or Miscarriage[g] (report using mother's participant ID) *Report only 1*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NAP

ID: identity, NAP: not applicable

[g] A pregnancy loss occurring at <20 weeks gestational age.

PSYCHIATRIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NAP
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only 1*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

NAP: not applicable

RESPIRATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥70% to <80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50% to <70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25% to <50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow <25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only 1*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90% to <95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry <90%	Respiratory failure with ventilator support indicated (eg, CPAP, BPAP, intubation)

BPAP: biphasic positive airway pressure; CPAP: continuous positive airway pressure; NAP: not applicable

SENSORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hearing Loss *aged ≥12 years*	NAP	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (>80 dB at 2 kHz and above) OR Nonserviceable hearing (ie, >50 dB audiogram and <50% speech discrimination)
aged <12 years (based on a 1, 2, 3, 4, 6, and 8 kHz audiogram)	>20 dB hearing loss at ≤4 kHz	>20 dB hearing loss at >4 kHz	>20 dB hearing loss at ≥3 kHz in 1 ear with additional speech-language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech-language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NAP
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

dB: decibel; kHz: kilohertz; NAP: not applicable

SYSTEMIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NAP
Cytokine Release Syndrome[h]	Mild signs and symptoms AND Therapy (ie, antibody infusion) interruption not indicated	Therapy (ie, antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (eg, requiring pressor or ventilator support)
Fatigue or Malaise *Report only 1*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0°C to <38.6°C or 100.4°F to <101.5°F	≥38.6°C to <39.3°C or ≥101.5°F to <102.7°F	≥39.3°C to <40.0°C or ≥102.7°F to <104.0°F	≥40.0°C or ≥104.0°F
Pain[i] (not associated with study intervention injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated
Serum Sickness[j]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (eg, antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (eg, steroids or IV fluids)	Life-threatening consequences (eg, requiring pressor or ventilator support)

IV: intravenous; NAP: not applicable

[h] A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.

[i] For pain associated with injections or infusions, refer to the SITE REACTIONS TO INJECTIONS AND INFUSIONS section.

[j] A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.

SYSTEMIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Underweight[k] *aged >5 to 19 years*	WHO BMI z-score <-1 to -2	WHO BMI z-score <-2 to -3	WHO BMI z-score <-3	WHO BMI z-score <-3 with life-threatening consequences
aged 2 to 5 years	WHO Weight-for-height z-score <-1 to -2	WHO Weight-for-height z-score <-2 to -3	WHO Weight-for-height z-score <-3	WHO Weight-for-height z-score <-3 with life-threatening consequences
aged <2 years	WHO Weight-for-length z-score <-1 to -2	WHO Weight-for-length z-score <-2 to -3	WHO Weight-for-length z-score <-3	WHO Weight-for-length z-score <-3 with life-threatening consequences
Unintentional Weight Loss (excludes postpartum weight loss)	NAP	5% to <9% loss in body weight from baseline	≥9% to <20% loss in body weight from baseline	≥20% loss in body weight from baseline OR Aggressive intervention indicated (eg, tube feeding, total parenteral nutrition)

BMI: body mass index; NAP: not applicable; WHO: World Health Organization

[k] WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants aged >5 to 19 years and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those aged ≤5 years.

URINARY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Urinary Tract Obstruction	NAP	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

NAP: not applicable

SITE REACTIONS TO INJECTIONS AND INFUSIONS				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Injection Site Pain or Tenderness *Report only 1*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness[1] *Report only 1* *aged >15 years*	2.5 to <5 cm in diameter OR 6.25 to <25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥5 to <10 cm in diameter OR ≥25 to <100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥10 cm in diameter OR ≥100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (eg, abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
aged ≤15 years	≤2.5 cm in diameter	>2.5 cm in diameter with <50% surface area of the extremity segment involved (eg, upper arm or thigh)	≥50% surface area of the extremity segment involved (eg, upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (eg, abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only 1* *aged >15 years*	Same as for **Injection Site Erythema or Redness**, *aged >15 years*	Same as for **Injection Site Erythema or Redness**, *aged >15 years*	Same as for **Injection Site Erythema or Redness**, *aged >15 years*	Same as for **Injection Site Erythema or Redness**, *aged >15 years*
aged ≤15 years	Same as for **Injection Site Erythema or Redness**, *aged ≤15 years*	Same as for **Injection Site Erythema or Redness**, *aged ≤15 years*	Same as for **Injection Site Erythema or Redness**, *aged ≤15 years*	Same as for **Injection Site Erythema or Redness**, *aged ≤15 years*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in <48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NAP

NAP: not applicable

[1] Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

LABORATORY VALUES[m]				
CHEMISTRIES				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Acidosis	NAP	pH ≥7.3 to <LLN	pH <7.3 without life-threatening consequences	pH <7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to <LLN *30 to <LLN*	≥2.0 to <3.0 *≥20 to <30*	<2.0 *<20*	NAP
ALP, High	1.25 to <2.5×ULN	2.5 to <5.0×ULN	5.0 to <10.0×ULN	≥10.0×ULN
Alkalosis	NAP	pH >ULN to ≤7.5	pH >7.5 without life-threatening consequences	pH >7.5 with life-threatening consequences
ALT or SGPT, High *Report only 1*	1.25 to <2.5×ULN	2.5 to <5.0×ULN	5.0 to <10.0×ULN	≥10.0×ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only 1*	1.1 to <1.5×ULN	1.5 to <3.0×ULN	3.0 to <5.0×ULN	≥5.0×ULN
AST or SGOT, High *Report only 1*	1.25 to <2.5×ULN	2.5 to <5.0×ULN	5.0 to <10.0×ULN	≥10.0×ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to <LLN *16.0 to <LLN*	11.0 to <16.0 *11.0 to <16.0*	8.0 to <11.0 *8.0 to <11.0*	<8.0 *<8.0*
Bilirubin ***Direct Bilirubin,[n] High*** *aged >28 days*	NAP	NAP	>ULN with other signs and symptoms of hepatotoxicity	>ULN with life-threatening consequences (eg, signs and symptoms of liver failure)
aged ≤28 days	ULN to ≤1 mg/dL	>1 to ≤1.5 mg/dL	>1.5 to ≤2 mg/dL	>2 mg/dL
Total Bilirubin, High *aged >28 days*	1.1 to <1.6×ULN	1.6 to <2.6×ULN	2.6 to <5.0×ULN	≥5.0×ULN
aged ≤28 days	Refer to Appendix A[o]	Refer to Appendix A[o]	Refer to Appendix A[o]	Refer to Appendix A[o]

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LLN: lower limit of normal; mEq: milliequivalent; NAP: not applicable; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamate-pyruvate transaminase; ULN: upper limit of normal

[m] Reminder: An asymptomatic abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited time frame unless it meets protocol-specific reporting requirements.

[n] Direct bilirubin >1.5 mg/dL in a participant aged <28 days should be graded as grade 2, if <10% of the total bilirubin.

[o] Appendix A "Total Bilirubin Table for Term and Preterm Neonates" is provided together with the DAIDS table corrected version 2.1 at the following URL: https://rsc niaid nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf. Appendix A is not applicable for this study.

LABORATORY VALUES				
CHEMISTRIES				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Calcium, High (mg/dL; *mmol/L*)				
aged ≥7 days	10.6 to <11.5 *2.65 to <2.88*	11.5 to <12.5 *2.88 to <3.13*	12.5 to <13.5 *3.13 to <3.38*	≥13.5 *≥3.38*
aged <7 days	11.5 to <12.4 *2.88 to <3.10*	12.4 to <12.9 *3.10 to <3.23*	12.9 to <13.5 *3.23 to <3.38*	≥13.5 *≥3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	>ULN to <6.0 *>ULN to <1.5*	6.0 to <6.4 *1.5 to <1.6*	6.4 to <7.2 *1.6 to <1.8*	≥7.2 *≥1.8*
Calcium, Low (mg/dL; *mmol/L*)				
aged ≥7 days	7.8 to <8.4 *1.95 to <2.10*	7.0 to <7.8 *1.75 to <1.95*	6.1 to <7.0 *1.53 to <1.75*	<6.1 *<1.53*
aged <7 days	6.5 to <7.5 *1.63 to <1.88*	6.0 to <6.5 *1.50 to <1.63*	5.50 to <6.0 *1.38 to <1.50*	<5.50 *<1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	<LLN to 4.0 *<LLN to 1.0*	3.6 to <4.0 *0.9 to <1.0*	3.2 to <3.6 *0.8 to <0.9*	<3.2 *<0.8*
Cardiac Troponin I, High	NAP	NAP	NAP	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to <6×ULN	6 to <10×ULN	10 to <20×ULN	≥20×ULN
Creatinine, High *Report only* [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* [p]	NAP	<90 to 60 ml/min or ml/min/1.73 m^2 OR 10% to <30% decrease from participant's baseline	<60 to 30 ml/min or ml/min/1.73 m^2 OR 30% to <50% decrease from participant's baseline	<30 ml/min or ml/min/1.73 m^2 OR ≥50% decrease from participant's baseline or dialysis needed
Glucose (mg/dL; *mmol/L*)				
Fasting, High	110 to 125 *6.11 to <6.95*	>125 to 250 *6.95 to <13.89*	>250 to 500 *13.89 to <27.75*	>500 *≥27.75*
Nonfasting, High	116 to 160 *6.44 to <8.89*	>160 to 250 *8.89 to <13.89*	>250 to 500 *13.89 to <27.75*	>500 *≥27.75*
Glucose, Low (mg/dL; *mmol/L*)				
aged ≥1 month	55 to 64 *3.05 to <3.55*	40 to <55 *2.22 to <3.05*	30 to <40 *1.67 to <2.22*	<30 *<1.67*
aged <1 month	50 to 54 *2.78 to <3.00*	40 to <50 *2.22 to <2.78*	30 to <40 *1.67 to <2.22*	<30 *<1.67*
Lactate, High	ULN to <2.0×ULN without acidosis	≥2.0×ULN without acidosis	Increased lactate with pH <7.3 without life-threatening consequences	Increased lactate with pH <7.3 with life-threatening consequences

eGFR: estimated glomerular filtration rate; LLN: lower limit of normal; NAP: not applicable; ULN: upper limit of normal

[p] Reminder: Choose the method that selects for the higher grade.

[q] Use the applicable formula (ie, Cockcroft-Gault in mL/min or Schwartz, modification of diet in renal disease study [MDRD], or Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] in mL/min/1.73m^2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.

LABORATORY VALUES				
CHEMISTRIES				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Lipase, High	1.1 to <1.5×ULN	1.5 to <3.0×ULN	3.0 to <5.0×ULN	≥5.0×ULN
Lipid Disorders (mg/dL; *mmol/L*) ***Cholesterol, Fasting, High*** *aged ≥18 years*	200 to <240 *5.18 to <6.19*	240 to <300 *6.19 to <7.77*	≥300 *≥7.77*	NAP
aged <18 years	170 to <200 *4.40 to <5.15*	200 to <300 *5.15 to <7.77*	≥300 *≥7.77*	NAP
LDL, Fasting, High *aged ≥18 years*	130 to <160 *3.37 to <4.12*	160 to <190 *4.12 to <4.90*	≥190 *≥4.90*	NAP
aged >2 to <18 years	110 to <130 *2.85 to <3.34*	130 to <190 *3.34 to <4.90*	≥190 *≥4.90*	NAP
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to 1,000 *>5.7 to 11.4*	>1,000 *>11.4*
Magnesium[r], Low (mEq/L; *mmol/L*)	1.2 to <1.4 *0.60 to <0.70*	0.9 to <1.2 *0.45 to <0.60*	0.6 to <0.9 *0.30 to <0.45*	<0.6 *<0.30*
Phosphate, Low (mg/dL; *mmol/L*) *aged >14 years*	2.0 to <LLN *0.65 to <LLN*	1.4 to <2.0 *0.45 to <0.65*	1.0 to <1.4 *0.32 to <0.45*	<1.0 *<0.32*
aged 1 to 14 years	3.0 to <3.5 *0.97 to <1.13*	2.5 to <3.0 *0.81 to <0.97*	1.5 to <2.5 *0.48 to <0.81*	<1.5 *<0.48*
aged <1 year	3.5 to <4.5 *1.13 to <1.45*	2.5 to <3.5 *0.81 to <1.13*	1.5 to <2.5 *0.48 to <0.81*	<1.5 *<0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to <6.0 *5.6 to <6.0*	6.0 to <6.5 *6.0 to <6.5*	6.5 to <7.0 *6.5 to <7.0*	≥7.0 *≥7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to <3.4 *3.0 to <3.4*	2.5 to <3.0 *2.5 to <3.0*	2.0 to <2.5 *2.0 to <2.5*	<2.0 *<2.0*
Sodium, High (mEq/L; *mmol/L*)	146 to <150 *146 to <150*	150 to <154 *150 to <154*	154 to <160 *154 to <160*	≥160 *≥160*
Sodium, Low (mEq/L; *mmol/L*)	130 to <135 *130 to <135*	125 to <130 *125 to <130*	120 to <125 *120 to <125*	<120 *<120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to <10.0 *0.45 to <0.59*	10.0 to <12.0 *0.59 to <0.71*	12.0 to <15.0 *0.71 to <0.89*	≥15.0 *≥0.89*

LDL: low-density lipoprotein; LLN: lower limit of normal; mEq: milliequivalent; NAP: not applicable; ULN: upper limit of normal

[r] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

LABORATORY VALUES				
HEMATOLOGY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Absolute CD4+ Count, Low (cells/mm³; *cells/L*) *aged >5 years (not HIV-infected)*	300 to <400 *0.300×10⁹ to <0.400×10⁹*[s]	200 to <300 *0.200×10⁹ to <0.300×10⁹*[s]	100 to <200 *0.100×10⁹ to <0.200×10⁹*[s]	<100 *<0.100×10⁹*[s]
Absolute Lymphocyte Count, Low (cells/mm³; *cells/L*) *aged >5 years (not HIV-infected)*	600 to <650 *0.600×10⁹ to <0.650×10⁹*	500 to <600 *0.500×10⁹ to <0.600×10⁹*	350 to <500 *0.350×10⁹ to <0.500×10⁹*	<350 *<0.350×10⁹*
Absolute Neutrophil Count, Low (cells/mm³; *cells/L*) *aged >7 days*	800 to 1,000 *0.800×10⁹ to 1.000×10⁹*	600 to 799 *0.600×10⁹ to 0.799×10⁹*	400 to 599 *0.400×10⁹ to 0.599×10⁹*	<400 *<0.400×10⁹*
aged 2 to 7 days	1,250 to 1,500 *1.250×10⁹ to 1.500×10⁹*	1,000 to 1,249 *1.000×10⁹ to 1.249×10⁹*	750 to 999 *0.750×10⁹ to 0.999×10⁹*	<750 *<0.750×10⁹*
aged ≤1 day	4,000 to 5,000 *4.000×10⁹ to 5.000×10⁹*	3,000 to 3,999 *3.000×10⁹ to 3.999×10⁹*	1,500 to 2,999 *1.500×10⁹ to 2.999×10⁹*	<1,500 *<1.500×10⁹*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to <200 *1.00 to <2.00* OR 0.75 to <1.00×LLN	75 to <100 *0.75 to <1.00* OR ≥0.50 to <0.75×LLN	50 to <75 *0.50 to <0.75* OR 0.25 to <0.50×LLN	<50 *<0.50* OR <0.25×LLN OR Associated with gross bleeding
Hemoglobin[t], Low (g/dL; *mmol/L*)[u] *aged ≥13 years (male only)*	10.0 to 10.9 *6.19 to 6.76*	9.0 to <10.0 *5.57 to <6.19*	7.0 to <9.0 *4.34 to <5.57*	<7.0 *<4.34*
aged ≥13 years (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to <9.5 *5.25 to <5.88*	6.5 to <8.5 *4.03 to <5.25*	<6.5 *<4.03*
aged 57 days to <13 years (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to <9.5 *5.25 to <5.88*	6.5 to <8.5 *4.03 to <5.25*	<6.5 *<4.03*
aged 36 to 56 days (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to <8.5 *4.32 to <5.26*	6.0 to <7.0 *3.72 to <4.32*	<6.0 *<3.72*
aged 22 to 35 days (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to <9.5 *4.94 to <5.88*	6.7 to <8.0 *4.15 to <4.94*	<6.7 *<4.15*
aged 8 to ≤21 days (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to <11.0 *5.57 to <6.81*	8.0 to <9.0 *4.96 to <5.57*	<8.0 *<4.96*
aged ≤7 days (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to <13.0 *6.19 to <8.05*	9.0 to <10.0 *5.59 to <6.19*	<9.0 *<5.59*

HIV: human immunodeficiency virus; LLN: lower limit of normal

[s] Revised by the sponsor.

[t] Male and female sex are defined as sex at birth. For transgender participants aged ≥13 years who have been on hormone therapy for more than 6 consecutive months, grade hemoglobin based on the gender with which they identify (ie, a transgender female should be graded using the female sex at birth hemoglobin laboratory values).

[u] The most commonly used conversion factor to convert g/dL to mmol/L is 0.6206. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for the particular laboratory.

LABORATORY VALUES				
HEMATOLOGY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
INR, High (not on anticoagulation therapy)	1.1 to <1.5×ULN	1.5 to <2.0×ULN	2.0 to <3.0×ULN	≥3.0×ULN
Methemoglobin (% hemoglobin)	5.0% to <10.0%	10.0% to <15.0%	15.0% to <20.0%	≥20.0%
PTT, High (not on anticoagulation therapy)	1.1 to <1.66×ULN	1.66 to <2.33×ULN	2.33 to <3.00×ULN	≥3.00×ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to <125,000 *100.000×10^9 to <125.000×10^9*	50,000 to <100,000 *50.000×10^9 to <100.000×10^9*	25,000 to <50,000 *25.000×10^9 to <50.000×10^9*	<25,000 *<25.000×10^9*
PT, High (not on anticoagulation therapy)	1.1 to <1.25×ULN	1.25 to <1.50×ULN	1.50 to <3.00×ULN	≥3.00×ULN
WBC, Decreased (cells/mm^3; *cells/L*)				
aged >7 days	2,000 to 2,499 *2.000×10^9 to 2.499×10^9*	1,500 to 1,999 *1.500×10^9 to 1.999×10^9*	1,000 to 1,499 *1.000×10^9 to 1.499×10^9*	<1,000 *<1.000×10^9*
aged ≤7 days	5,500 to 6,999 *5.500×10^9 to 6.999×10^9*	4,000 to 5,499 *4.000×10^9 to 5.499×10^9*	2,500 to 3,999 *2.500×10^9 to 3.999×10^9*	<2,500 *<2.500×10^9*

INR: International Normalized Ratio; NAP: not applicable; PT: prothrombin time; PTT: partial thromboplastin time; ULN: upper limit of normal; WBC: white blood cell

LABORATORY VALUES				
URINALYSIS				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤250 mg	2+ or >250 to ≤500 mg	>2+ or >500 mg	NAP
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to <10 RBCs per high power field	≥10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NAP

NAP: not applicable; RBC: red blood cell

10.10. Appendix 10: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 1 (10 April 2020)

Overall Rationale for the Amendment: Following Health Authority (HA) feedback the protocol was amended as specified below

Section Number and Name	Description of Change	Brief Rationale
9.4.1.1 Analysis of the Primary Endpoint	Methods for handling missing data were added to the protocol.	Per HA request the approach to handle missing data in the primary analysis of the primary endpoint was added.
2.3.2.3.1 Potential Risks and Inconvenience Associated with the Liver Biopsy Procedures 8.5.6.3 Complications From Liver Biopsy	The risk language regarding possible serious complications of liver biopsies has been updated.	Per HA request the complications from a liver biopsy are now described in the protocol.
1.3.1 Schedule of Activities - Screening and Study Intervention Phase Schedule of Activities - Follow-up Phase	Additional timepoints were added for whole blood single cell profiling.	Correction

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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): [redacted]

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
[redacted]	07-May-2020 15:48:37 (GMT)	Document Approval