Janssen Research & Development *

Clinical Protocol

Intervention-specific Appendix 4 to Clinical Protocol PLATFORMPAHPB2001 A Phase 2, Open-label, Single-arm, Multicenter Study to Assess Efficacy, Safety, Tolerability, and Pharmacokinetics of Treatment With JNJ-73763989, JNJ-56136379, Nucleos(t)ide Analogs, and Pegylated Interferon Alpha-2a in Virologically Suppressed Patients With Chronic Hepatitis B Virus Infection

The PENGUIN Study

Protocol 73763989PAHPB2006; Phase 2
Amendment 4

JNJ-73763989 and JNJ-56136379

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 4	This document
Amendment 3	04 October 2021
Amendment 2	07 May 2021
Amendment 1	10 March 2021
Original Protocol	02 October 2020

Amendment 4 (This document)

Overall Rationale for the Amendment: The primary reason for this amendment is to update the criteria for post-treatment monitoring and for nucleos(t)ide analog (NA) re-treatment for participants who discontinued NA treatment at follow-up Week 2.

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

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

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

Description of Change	Brief Rationale	Section Number and Name
Update of criteria for post-treatment monitoring and for NA re-treatment.	In further off-treatment analysis of REEF-2 with all participants having reached at least 12 weeks of follow-up post stopping NA, some participants show a pattern of fast increase of HBV DNA followed by significant elevations of ALT that improved after re-starting of NA treatment. Based on these observations it was decided to implement more conservative rules for post-treatment monitoring and re-treatment criteria for all participants who met NA treatment completion criteria and stopped NA treatment.	1.1 Synopsis 1.3 Schedule of Activities 2.3.3 Benefit-Risk Assessment for Study Participation 4.2 Scientific Rationale for Study Design 6.7.1 NA Re-treatment Criteria and Monitoring After Stopping of NA 10.12 Appendix 12: NA Re-treatment and Monitoring After Stopping of NA
Minor errors were corrected.	Correction	1.1 Synopsis 1.3 Schedule of Activities 2.1 Study Rationale 6.8 Continued Access to Study Intervention After the End of the Study

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1. PROTOCOL SUMMARY

1.1. Synopsis

Clinical Protocol 73763989PAHPB2006: A Phase 2, Open-label, Single-arm, Multicenter Study to Assess Efficacy, Safety, Tolerability, and Pharmacokinetics of Treatment With JNJ-73763989, JNJ-56136379, Nucleos(t)ide Analogs, and Pegylated Interferon Alpha-2a in Virologically Suppressed Patients With Chronic Hepatitis B Virus Infection.
Protocol 73763989PAHPB2006 is an intervention-specific appendix (ISA) to Master Protocol PLATFORMPAHPB2001.

JNJ-73763989 (JNJ-3989) is a liver-targeted antiviral therapeutic for subcutaneous injection designed to treat chronic hepatitis B virus (HBV) infection via a ribonucleic acid interference (RNAi) mechanism. Engagement of the cellular RNAi machinery by JNJ-3989 results in specific cleavage of HBV RNA transcripts, thereby reducing the levels of HBV proteins and the pre-genomic ribonucleic acid (pgRNA), the precursor of viral relaxed circular deoxyribonucleic acid (rcDNA). The small interfering RNA (siRNA) triggers in JNJ-3989, JNJ-73763976 (JNJ-3976) and JNJ-73763924 (JNJ-3924), are designed to target all HBV ribonucleic acid (RNA) transcripts derived from covalently closed circular deoxyribonucleic acid (cccDNA), as well as transcripts derived from integrated HBV deoxyribonucleic acid (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 (Wooddell 2017).

JNJ-56136379 (JNJ-6379) is an orally administered Class N capsid assembly modulator (CAM-N) interfering with the capsid assembly and disassembly during HBV replication. 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 with normal shape but which are devoid of HBV DNA or RNA (non-functional capsids; Class N), 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. JNJ-6379 was initially part of the study intervention for participants enrolled before Protocol Amendment 3 was in effect, but has been removed as study intervention with the implementation of an urgent safety measure, as described in Protocol Amendment 3.

As of Protocol Amendment 3: The term “study intervention” throughout the protocol, refers to JNJ-3989, NA, and pegylated interferon alpha-2a (PegIFN-α2a).

OBJECTIVES AND ENDPOINTS

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

Objectives	Endpoints
Primary	
• To evaluate the efficacy in terms of HBsAg levels of the study intervention (ie, JNJ-3989 + JNJ-6379[d] + NA and PegIFN-α2a).	• Proportion of participants with a reduction of at least 2 $\log_{10}$ IU/mL in HBsAg levels from baseline to Week 24 (end of study intervention [EOSI]).
Secondary	
• To evaluate the safety and tolerability of the study intervention.	• Safety and tolerability including but not limited to the proportion of participants with (serious) adverse events ([S]AEs) and abnormalities in clinical laboratory tests (including hematology,

Objectives	Endpoints
	blood biochemistry, blood coagulation, urinalysis, urine chemistry, renal biomarkers), 12-lead electrocardiograms (ECGs), vital signs, and ophthalmic and physical examinations throughout the study.
• To evaluate the efficacy of the study intervention at the end of the 24-week treatment period.	• Proportion of participants meeting the protocol-defined NA treatment completion criteria at EOSI.
• To evaluate the efficacy of the study intervention as measured by blood markers (such as HBsAg, HBeAg[a], HBV DNA, and alanine aminotransferase [ALT]) during the study intervention and follow-up (FU) period.	• Proportion of participants with HBeAg[a], HBsAg, HBV DNA, and ALT levels below/above different cut-offs. • Proportion of participants with HBsAg and/or HBeAg[a] seroconversion. • Change from baseline over time in HBsAg, HBeAg[a], and/or HBV DNA. • Time to achieve HBsAg and/or HBeAg[a] seroclearance/seroconversion, and/or HBV DNA < lower limit of quantification (LLOQ).
• To evaluate the frequency of virologic breakthrough[b] during the 24-week treatment period, as well as during the FU period for participants who continue treatment with NA.	• Proportion of participants with virologic breakthrough[b].
• To evaluate the efficacy of the study intervention during the FU period.	• Proportion of participants with HBsAg seroclearance at Week 48 (ie, 24 weeks after completion of all study interventions at Week 24) without re-starting NA treatment. • Proportion of participants with HBV DNA <LLOQ at Week 48 (ie, 24 weeks after completion of all study interventions at Week 24) without re-starting NA treatment. • Frequency of virologic and/or biochemical flares. • Proportion of participants requiring NA re-treatment.
• To evaluate the pharmacokinetics (PK) of JNJ-3989 (JNJ-3924 and JNJ-3976) and optionally of JNJ-6379, NA and PegIFN-α2a.	• PK parameters of JNJ-3989 (JNJ-3924 and JNJ-3976). • Optionally, PK parameters of JNJ-6379, NA and/or PegIFN-α2a compared to historical data.
Exploratory	
• To explore host and viral baseline and on-treatment markers associated with end of treatment and/or off-treatment response.	• Association of baseline characteristics and baseline/on-treatment host and viral blood markers (such as age and HBsAg levels) with selected on or off-treatment efficacy variables.

Objectives	Endpoints
• To explore changes in the severity of liver disease.	• Changes in fibrosis (according to Fibroscan liver stiffness measurements) at EOSI and the end of the FU period versus baseline.
• To explore efficacy of the study intervention in terms of changes in HBV RNA and hepatitis B core-related antigen (HBcrAg) levels during the study intervention and FU period.	• Changes from baseline in HBV RNA and HBcrAg levels over time.
• To explore the relationship of PK with selected pharmacodynamic (PD) parameters of efficacy and safety.	• Relationship of various PK parameters with selected efficacy and safety endpoints.
• To explore the effect of PegIFN-α2a coadministration on the PK of JNJ-3989 (JNJ-3924 and JNJ-3976) and JNJ-6379[e], as applicable (PK substudy).	• Effect of PegIFN-α2a coadministration on the PK of JNJ-3989 (JNJ-3924 and JNJ-3976) and JNJ-6379, as applicable.
• To explore the HBV genome sequence during the study intervention and FU period.	• Assessment of intervention-associated mutations over time.
• To explore HBV-specific T-cell responses during the study intervention and FU period.[c]	• Changes from baseline in HBV-specific peripheral blood T-cell responses over time.[c]
• To explore the efficacy of NA re-treatment in participants who meet the criteria for NA re-treatment.	• Proportion of participants who reach HBV DNA <LLOQ after re-start of NA treatment during the FU period.

[a] In HBeAg-positive participants only.
[b] For the definition of virologic breakthrough, refer to Section 10.1, Appendix 1: Abbreviations and Definitions of Terms.
[c] Peripheral blood mononuclear cell (PBMC) samples for immune analyses will be collected at selected sites only.
[d] As of Protocol Amendment 3, JNJ-6379 has been removed as study intervention and the study will continue with JNJ-3989, NA and PegIFN-α2a only. Participants had to stop JNJ-6379 treatment immediately.
[e] Not all participants completed treatment with JNJ-6379, as JNJ-6379 has been removed as study intervention with the implementation of Protocol Amendment 3.

Hypothesis

As this is an exploratory single-arm study, no formal statistical hypothesis has been formulated.

OVERALL DESIGN

This ISA describes a Phase 2a study of the combination regimen of JNJ-3989, NA, and PegIFN-α2a. Prior to Protocol Amendment 3, the study intervention also included JNJ-6379. It is a companion document to the Master Protocol PLATFORMPAHPB2001, which describes the common design elements of the Platform study in participants with chronic hepatitis B (CHB). This ISA describes specific and/or additional protocol elements applicable to this open-label, single-arm, multicenter, interventional study to evaluate the efficacy, safety, tolerability, and PK of the combination of JNJ-3989, NAs, and PegIFN-α2a in approximately 50 patients with CHB.

Note that as of Protocol Amendment 3, JNJ-6379 has been removed as study intervention and the study will continue with JNJ-3989, NA and PegIFN-α2a only. Participants had to stop JNJ-6379 treatment immediately.

This open-label study will be conducted in 4 periods:

- Screening Period (4 weeks [if necessary, can be extended to a maximum of 8 weeks decided on a case-by-case basis and in agreement with the sponsor]).
- Treatment Period 1 (12 weeks) consisting of combination treatment with JNJ-3989 + NA.
- Treatment Period 2 (12 weeks) adding PegIFN-α2a to the combination treatment regimen of Treatment Period 1.
- Follow-up (FU) Period (48 weeks).

The total duration of individual participation will be up to 76 weeks (including 4 weeks of screening).

Enrolled participants will start Treatment Period 1 with the following combination treatment regimen for a duration of 12 weeks:

200 mg JNJ-3989 (subcutaneous injection every 4 weeks [Q4W]) +

NA (tablets QD): tenofovir disoproxil (245 mg), or tenofovir alafenamide (TAF; 25 mg), or entecavir (ETV; 0.5 mg).

At Week 12, participants who still meet the eligibility criteria for PegIFN-α2a (see Section 5.2, Exclusion Criteria) will start Treatment Period 2 for a duration of 12 weeks:

200 mg JNJ-3989 (subcutaneous injection Q4W) +

NA (tablets QD): tenofovir disoproxil (245 mg), or TAF (25 mg), or ETV (0.5 mg) +

180 µg PegIFN-α2a (subcutaneous injection once weekly).Participants no longer meeting the PegIFN-α2a eligibility criteria at Week 12 will continue with the Period 1 treatment until Week 24.

At Week 24, all participants will stop treatment with JNJ-3989 + PegIFN-α2a and start the FU Period. If the protocol-defined NA treatment completion criteria (HBsAg <10 IU/mL, and HBeAg-negative, and HBV DNA <LLOQ, and ALT <3x upper limit of normal [ULN]) have been met at Week 24, NA will be stopped at the next scheduled visit (ie, FU Week 2), otherwise NA treatment will continue during the complete FU Period. Participants who meet the protocol-defined NA treatment completion criteria will be monitored closely during the 48-week FU Period and should re-start NA treatment immediately if NA re-treatment criteria are met, as specified below.

The investigator should consider to re-start NA treatment per local standard of care at the EOS visit (Follow-up Week 48) for participants who met the NA treatment completion criteria at Week 24, who did not re-start NA treatment during the follow-up phase, and who did not achieve and maintain HBsAg seroclearance. NA will not be provided by the sponsor after the final study visit.

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

Participants will be considered to have completed the study if they have completed all the assessments of the end of study (EOS) visit (ie, FU Week 48).

An internal data review committee (DRC) will be commissioned for monitoring safety of participants enrolled in this study. In addition, an Independent Flare Expert Panel (IFLEP) will be appointed.

NA Re-treatment Criteria and Monitoring After Stopping of NA

Participants who meet the protocol-defined NA treatment completion criteria will be monitored closely during the FU Period.

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

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

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

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

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

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

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

NUMBER OF PARTICIPANTS

Approximately 50 virologically suppressed CHB-infected participants, 18-65 years (inclusive) of age, will be enrolled in this study. Approximately 40% HBeAg-positive participants will be enrolled.

Description of Interventions

Intervention Name	JNJ-3989	JNJ-6379***	PegIFN-α2a	Tenofovir disoproxil	Tenofovir alafenamide (TAF)*	Entecavir (ETV) monohydrate
Type	Drug	Drug	Drug	Drug	Drug	Drug
Dose Formulation	Solution for injection	Tablets	Solution for injection	Film-coated tablets	Film-coated tablets	Film-coated tablets
Unit Dose Strength(s)	200 mg/mL	25 and 100 mg	180 µg/0.5 mL	245 mg	25 mg	0.5 mg
Dosage Level(s)	200 mg once every 4 weeks (Q4W)	250 mg once daily (QD)	180 µg once weekly (QW)	245 mg QD	25 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)
Route of Administration	Subcutaneous injection (in the abdomen)	Oral	Subcutaneous injection (in the thigh or abdomen)	Oral	Oral	Oral
Use	Investigational intervention	Investigational intervention	Investigational intervention	Background intervention	Background intervention	Background intervention
Investigational Medicinal Product (IMP)	Yes	Yes	Yes	Yes	Yes	Yes
Non-investigational Medicinal Product/ Auxiliary Medicinal Product (NIMP/AxMP)	No	No	No	No	No	No
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	Provided centrally by the sponsor

Intervention Name	JNJ-3989	JNJ-6379***	PegIFN-α2a	Tenofovir disoproxil	Tenofovir alafenamide (TAF)*	Entecavir (ETV) monohydrate
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.	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	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 the prescribing information	Per the prescribing information	Per the prescribing information	Per the prescribing information

Q4W: once every 4 weeks; QD: once daily; QW: once weekly.
* In countries where TAF is available, it will be one of the NA treatment options.
** 2 tablets of 0.5 mg.
*** Participants enrolled before Protocol Amendment 3 was in effect, may have received JNJ-6379 as part of their study intervention. As of Protocol Amendment 3: Study intervention includes JNJ-3989, NA and PegIFN-α2a

EFFICACY EVALUATIONS

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

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

HBV DNA and HBV RNA will be assessed at central laboratories using validated assays for the quantification of HBV DNA and HBV RNA. Samples for the determination of HBV DNA will be processed in real-time. Samples for the determination of HBV RNA can be analyzed in batch and at the sponsor's request.

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

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

Sequencing

Viral genome sequence analysis will be performed to evaluate mutations associated with the study intervention.

SAFETY EVALUATIONS

Safety and tolerability (AEs, clinical safety laboratory assessments, ECGs, vital signs and physical examinations) will be evaluated as described in Section 8.2 and Section 8.3 of the Master Protocol PLATFORMPAHPB2001 and at predefined time points as specified in the Schedule of Activities. In addition, ophthalmic examinations will be performed and urine samples for urine chemistry and renal biomarkers will be collected.

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

PHARMACOKINETIC EVALUATIONS

Plasma or serum samples, as applicable, will be used to evaluate the PK of the study intervention. Samples collected for PK may additionally be used to evaluate safety or efficacy aspects.

Venous blood samples will be collected for measurement of plasma or serum (as applicable) concentrations of JNJ-3989 (ie, JNJ-3976 and JNJ-3924) and, optionally, NA and/or PegIFN-α2a, at time points specified in the Schedule of Activities. Bioanalysis of NA and PegIFN-α2a is optional at the discretion of the sponsor. Bioanalysis of JNJ-6379 may also be done on samples collected from participants who received JNJ-6379 prior to Protocol Amendment 3.

All participants will have sparse PK sampling during the treatment periods. Participants who consent to participate in the intensive PK substudy (optional) will also undergo intensive PK sampling at time points specified in the Schedule of Activities.

Concentration-time data for JNJ-3989 (ie, JNJ-3976 and JNJ-3924), and optionally JNJ-6379, NA and/or PegIFN-α2a will be analyzed via noncompartmental methods for all participants who underwent intensive PK sampling. The PK parameters will be maximum plasma concentration (C_{max}), plasma concentration

24 hours after administration (C_{24h}), and area under the plasma concentration-time curve from administration to 24 hours (AUC_{24h}). Additional PK parameters may be calculated if applicable. To assess the effect of PegIFN-α2a on JNJ-6379 (as applicable) and JNJ-3989, the PK parameters of JNJ-6379 (as applicable), JNJ-3976, and JNJ-3924 coadministered with PegIFN-α2a at Week 20 (or 16) will be compared to those of JNJ-6379 (as applicable), JNJ-3976, and JNJ-3924 at Week 4 (or 8) as reference (time points as specified in the Schedule of Activities).

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

PHARMACOKINETIC/PHARMACODYNAMIC EVALUATIONS

Relationships of individual PK parameters for JNJ-3976, JNJ-3924, and optionally JNJ-6379, NA and/or PegIFN-α2a, with selected efficacy and/or safety endpoints may be evaluated, if applicable.

IMMUNE ASSESSMENTS

At selected sites, peripheral blood mononuclear cell (PBMC) samples for immune analyses will be collected during study intervention and follow-up and will be analyzed centrally for HBV-specific responses by enzyme-linked immunospot (ELISpot) and/or intracellular cytokine staining (ICS) after stimulation with HBV-specific antigens.

Additional experiments may be performed to further phenotypically and functionally characterize PBMCs using proliferation or cytotoxic assays or other methods such as cytometry by time of flight to evaluate innate and adaptive immune responses. Leftover PBMC samples may be used at the sponsor's discretion for additional exploratory research (eg, assessment of other immune cells such as natural killer [NK]-cells, myeloid-derived suppressor cells [MDSCs], dendritic cells [DCs], and B-cells) related to HBV infection or study intervention (safety/efficacy).

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

HOST GENETICS

A mandatory sample for human leukocyte antigen (HLA) haplotyping will be collected from all participants.

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

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

EXPLORATORY HOST BIOMARKERS

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

The analyses may include gene expression and cytokine analyses assessing markers such as interferon-stimulated genes (ISGs), alpha interferon (IFN-α), and interferon γ-induced protein 10 (IP-10).

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

Blood samples will be taken at the time points indicated in the Schedule of Activities which can be used to explore immunogenicity of JNJ-3989 and optionally PegIFN-α2a. The emergence of antidrug antibodies to JNJ-3989 and optionally to PegIFN-α2a might be analyzed using assays such as an enzyme-linked immunosorbent assay or functional assays.

STATISTICAL METHODS

The primary efficacy analysis will be performed when all participants have completed Week 24 (EOSI) or discontinued earlier. The final analysis will be performed when all participants have completed the last study visit (FU Week 48) or discontinued earlier.

Sample Size Determination

No formal sample size calculation was performed, as this is a single-arm study for exploratory and proof of concept (PoC) purposes. However, with a sample size of 50 participants having data for the primary efficacy endpoint at Week 24, if at least 25 (50%) participants are responders, it can be concluded with 90% confidence that the true response rate is at least 0.38, with a confidence interval (CI) width of 0.248 (90% CI: 0.376-0.624). With a sample size of 20 participants (for one of the interim analyses [IAs]) the precision of the estimate of the primary efficacy endpoint decreases, as the two-sided 90% CI width increases. For the same assumed proportion of responders of 50% (10 out of 20 participants), the 90% CI width becomes 0.396. The table below shows the 90% CI and the corresponding width for proportion of responders of 0.30, 0.50, 0.70, and 0.90.

	N=20		N=50	
Proportion of responders	**90% CI***	**Width of CI**	**90% CI***	**Width of CI**
0.30	0.140-0.508	0.368	0.195-0.424	0.229
0.50	0.302-0.698	0.396	0.376-0.624	0.248
0.70	0.492-0.860	0.368	0.576-0.805	0.229
0.90	0.717-0.982	0.265	0.801-0.960	0.159

CI: confidence interval.
* Clopper-Pearson exact method is used.

Efficacy Analyses

To evaluate the efficacy, the primary analysis set will be the intent-to-treat (ITT) population (ie, all participants who were enrolled and who received at least 1 dose of study intervention within this ISA).

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

Primary Efficacy Endpoint

The primary endpoint is the proportion of participants with a reduction in HBsAg levels of at least 2 $\log_{10}$ IU/mL from baseline to Week 24. Participants who do not have HBsAg data in the analysis window of Week 24 will be defined as non-responders.

The primary efficacy endpoint will be summarized with the point estimate paired with its 90% CI using the Clopper-Pearson exact method. The same method will apply in a secondary analysis of the primary endpoint to the IFN-ITT analysis set comprising the ITT participants who have received at least 1 dose of PegIFN-α2a.

Secondary Efficacy Endpoints

Descriptive statistics and 90% CIs will be used to summarize all efficacy endpoints.

Specific key selected endpoints may be analyzed using suitable categorical data approaches (eg, Clopper-Pearson interval or logistic regression for proportions or other categorical type of endpoint), longitudinal repeated measures models (eg, for continuous types of variables), or survival analysis based on the Kaplan-Meier estimates (for time-to-event variables), as appropriate.

Resistance Analyses

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

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

Safety Analyses

Safety analyses are specified in Section 9.4.3 of the Master protocol PLATFORMPAHPB2001.

Safety will be evaluated by means of descriptive summaries of (S)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 period. Results will be presented in tabular format and/or graphically over time, as appropriate.

Other Analyses

Pharmacokinetic Analyses

Descriptive statistics (n, mean, standard deviation [SD], coefficient of variation [CV], geometric mean, median, minimum, and maximum) will be calculated for the plasma concentrations of JNJ-3989 (JNJ-3976, and JNJ-3924) and, optionally, of NA, PegIFN-α2a and/or JNJ-6379, and for the derived plasma PK parameters for noncompartmental PK analyses.

For each participant with intensive PK sampling, plasma concentration-time data of JNJ-3976 and JNJ-3924, and, optionally, of NA, PegIFN-α2a and/or JNJ-6379, will be graphically presented. Similarly, graphs of the mean plasma concentration-time profiles and overlay graphs with combined individual plasma concentration-time profiles will be produced. Plasma PK parameters in participants undergoing intensive PK sampling will be calculated via noncompartmental methods for JNJ-3976 and JNJ-3924, and, optionally, NA, PegIFN-α2a and/or JNJ-6379. The PK parameters will be C_{max}, C_{24h}, and AUC_{24h}; other PK parameters may also be calculated. The PK parameters will be subjected to an exploratory graphical analysis, including various transformations, to get a general overview.

To assess the effect of PegIFN-α2a on JNJ-3989, the PK parameters of JNJ-3989 coadministered with PegIFN-α2a at Week 20 (or 16) will be compared to those of JNJ-3989 at Week 4 (or 8) as reference. The primary PK parameters are C_{max} and AUC_{24h} on the logarithmic scale. A mixed effects model will be fitted to log-transformed PK parameters with treatment period as a fixed effect and participant as a random effect.

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

Population PK analysis of plasma concentration-time data of JNJ-3976 and JNJ-3924 may be performed using non-linear 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. If a population PK analysis is conducted, the results will be presented either in the clinical study report or in a separate report.

Pharmacokinetic/Pharmacodynamic Analyses

Relationships of PK parameters for JNJ-3976 and JNJ-3924, and, optionally, of NA, PegIFN-α2a and/or JNJ-6379 with selected efficacy and/or 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 may be investigated. Other biomarkers may be explored at the sponsor's discretion. If conducted, the results will be presented in a separate report.

Immune Analyses

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

Pharmacogenomic Analyses

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

Host Biomarker Analyses

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

Interim Analyses

Interim analyses (IAs) will be conducted to assess safety and efficacy to support the sponsor's interactions with health authorities, as well as to inform internal decisions about additional studies and/or investigation of other treatment combinations. The IAs are planned when:

- Approximately 20 participants have completed Week 24 (EOSI) or discontinued earlier.
- All participants have completed Week 36 (FU Week 12) or discontinued earlier.
- All participants have completed Week 48 (FU Week 24) or discontinued earlier.

An optional IA may be conducted when all participants have completed Week 60 (FU Week 36) or discontinued earlier.

The study is open-label, and the sponsor will conduct the pre-planned IAs. Hence, the study team and the DRC will have access to the IA results, while the investigators and participants will not.

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

Data Review Committee

The internal DRC established for the Platform study will review interim data and formulate recommendations to protect the safety and well-being of the participants. Description of the DRC is provided in Section 9.6 of the Master Protocol PLATFORMPAHPB2001. The possible recommendations and role of the DRC will be further detailed in the DRC charter for this ISA.

Independent Flare Expert Panel

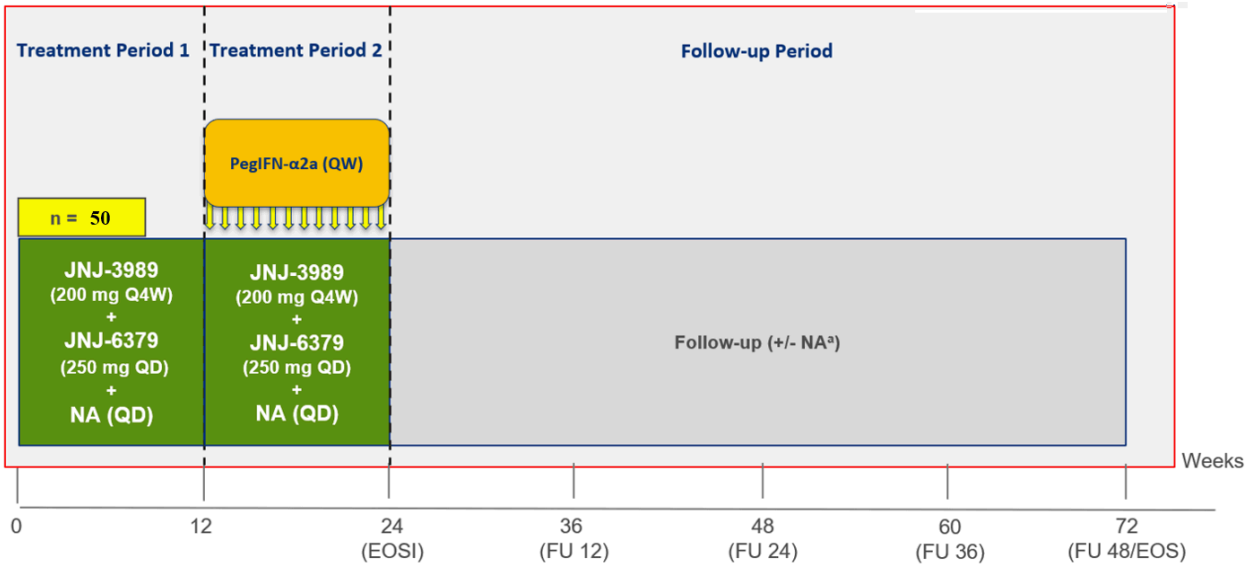
An IFLEP will be appointed. The IFLEP is composed of 3 independent medical experts with experience and expertise in HBV and its treatment. The IFLEP will monitor ALT flares and will make recommendations regarding flare management based on an analysis of aggregate data.

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

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

1.2. Schema

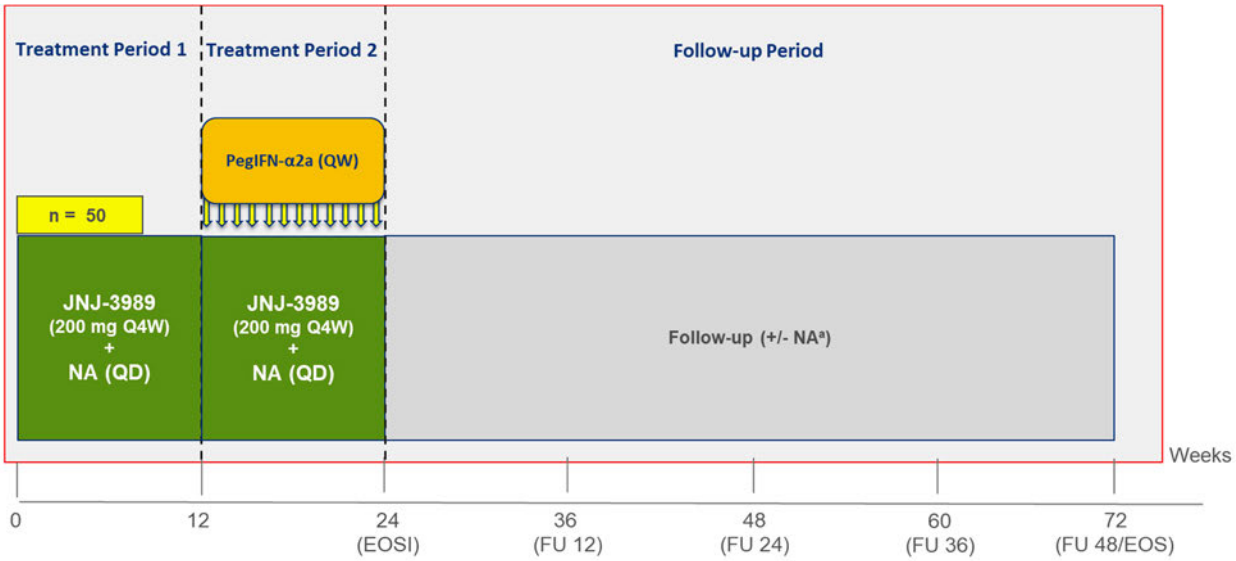
Figure 1: Schematic Overview of the Study – Prior to Protocol Amendment 3



ALT: alanine aminotransferase ; DNA: deoxyribonucleic acid; EOS: end of study; EOSI: end of study intervention; FU: follow-up; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; JNJ-3989: JNJ-73763989; JNJ-6379: JNJ-56136379; LLOQ: lower limit of quantification; n: number of participants; NA: nucleos(t)ide analog; PegIFN-α2a: pegylated interferon alpha-2a; ULN: upper limit of normal; Q4W: every 4 weeks; QD: once daily; QW: once weekly.

[a] If NA treatment completion criteria (HBsAg <10 IU/mL, and HBeAg-negative, and HBV DNA <LLOQ, and ALT <3x ULN) have been met at Week 24, NA will be stopped at the next scheduled visit (ie, FU Week 2), otherwise NA treatment will continue during the complete FU period.

Figure 2: Schematic Overview of the Study – As of Protocol Amendment 3



ALT: alanine aminotransferase ; DNA: deoxyribonucleic acid; EOS: end of study; EOSI: end of study intervention; FU: follow-up; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; JNJ-3989: JNJ-73763989; LLOQ: lower limit of quantification; n: number of participants; NA: nucleos(t)ide analog; PegIFN-α2a: pegylated interferon alpha-2a; ULN: upper limit of normal; Q4W: every 4 weeks; QD: once daily; QW: once weekly.

[a] If NA treatment completion criteria (HBsAg <10 IU/mL, and HBeAg-negative, and HBV DNA <LLOQ, and ALT <3x ULN) have been met at Week 24, NA will be stopped at the next scheduled visit (ie, FU Week 2), otherwise NA treatment will continue during the complete FU period.

1.3. Schedule of Activities

Below is a comprehensive schedule of activities that will be performed in this study, including that from the Master Protocol PLATFORMPAHPB2001. All differences with the Master Protocol PLATFORMPAHPB2001 (including the ISA-specific activities) are highlighted (colored fill). Guidance in the event of disruption to the study conduct is provided in Section 10.10, Appendix 10: Study Conduct During a Natural Disaster.

Study Period	Screening	Treatment Period 1[a,d,e]				Treatment Period 2[a,d,e]					Follow-up[a,e,qq]												
Visit Day (D)/Week (W)	W-4 to 0[b]	D1[c]	W2	W4	W8	W12	W14	W16	W20	W24 /EOSI /WD[e]	FU W2	FU W4	FU W8	FU W12	*FU W16[qq]*	*FU W20[qq]*	FU W24	*FU W28[qq]*	*FU W32[qq]*	FU W36	*FU W40[qq]*	*FU W44[qq]*	FU W48 /EOS /WD[e, aaa]
Study Day (Window)	-28 to 0	1	15 +/-2d	29 +/-2d	57 +/-2d	85 +/-2d	99 +/-3d	113 +/-3d	141 +/-3d	169 +/-3d	15 +/-4d	29 +/-4d	57 +/-4d	85 +/-4d	113 +/-4d	141 +/-4d	169 +/-4d	197 +/-4d	225 +/-4d	253 +/-4d	281 +/-4d	*309 +/-4d*	337 +/-4d
Screening/Administrative																							
ICF (including ICF for optional PK)[f]	X																						
ICF for optional pharmacogenomic samples	X																						
Inclusion/exclusion criteria[g]	X																						
PegIFN-α2a eligibility	X					X[pp]																	
Prestudy therapy (including prior anti-HBV therapy)	X																						
Medical/surgical history and demographics[h]	X																						
Preplanned surgery/procedure(s)	X																						
Fibroscan or liver biopsy[i]	X																						
Ultrasound[j]	X																						
Serum IgM anti-HBc antibody test	X																						
HBV genotype[k]		X																					
Study Intervention																							
Administration of JNJ-3989		X		X	X	X		X	X														
Intake of JNJ-6379[m,tt,zz]		X	X	X	X	X	X	X	X	X[l]													
Intake of NA[m,tt]		X	X	X	X	X	X	X	X	X[l]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)[l]
Dispensation of JNJ-6379[tt,zz]		X		X[xx]	X[xx]	X[xx]		X[xx]	X[xx]														
Dispensation of NA[tt]		X		X	X	X		X	X	X[l]		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	

Study Period	Screening	Treatment Period 1[a,d,e]				Treatment Period 2[a,d,e]					Follow-up[a,e,qq]												
Visit Day (D)/Week (W)	W-4 to 0[b]	D1[c]	W2	W4	W8	W12	W14	W16	W20	W24 /EOSI /WD[e]	FU W2	FU W4	FU W8	FU W12	*FU W16[qq]*	*FU W20[qq]*	FU W24	*FU W28[qq]*	*FU W32[qq]*	FU W36	*FU W40[qq]*	*FU W44[qq]*	FU W48 /EOS /WD[e, aaa]
Study Day (Window)	-28 to 0	1	15 +/-2d	29 +/-2d	57 +/-2d	85 +/-2d	99 +/-3d	113 +/-3d	141 +/-3d	169 +/-3d	15 +/-4d	29 +/-4d	57 +/-4d	85 +/-4d	113 +/-4d	141 +/-4d	169 +/-4d	197 +/-4d	225 +/-4d	253 +/-4d	281 +/-4d	*309 +/-4d*	337 +/-4d
Administration of PegIFN-α2a[m,tt]						X	X	X	X														
Dispensation of PegIFN-α2a[m,tt]						X		X	X														
Provide PegIFN-α2a self-injection tracker[n]						X																	
Review PegIFN-α2a self-injection tracker[o]							X	X	X	X													
Study intervention accountability				X	X	X		X	X	X		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Assess NA treatment completion criteria											X[uu]												
Continuous assessment of NA re-treatment criteria, as applicable												(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Safety Assessments																							
Complete physical examination[p]	X									X													
Symptom-directed physical examination, including body weight		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmic examination (including fundoscopy)	X				X[q]					X[r]													
Vital signs[s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Triplicate 12-lead ECG[t]	X	X		X		X				X		X											
Injection site reactions (for JNJ-3989 and/or PegIFN-α2a)		X	X	X	X	X	X	X	X	X													
Liver ultrasound[u]		(X)								X							X						X
Clinical Laboratory Tests																							
Hematology[w]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X		X		X	X
Blood chemistry (including liver function tests)[v,x,y]	X	X	X	X	X	X	X	X	X	X	X	X	X[rr]	X	X[rr]	X[rr]	X	X[rr]	X[rr]	X	X	X	X
Blood coagulation	X	X		X	X	X	X	X	X	X	X	X		X			X			X		X	X
Urinalysis[z]	X	X		X	X	X	X	X	X	X	X[ww]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X
Urine chemistry[aa]	X	X		X	X	X	X	X	X	X	X[ww]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X

Study Period	Screening	Treatment Period 1[a,d,e]				Treatment Period 2[a,d,e]					Follow-up[a,e,qq]												
Visit Day (D)/Week (W)	W-4 to 0[b]	D1[c]	W2	W4	W8	W12	W14	W16	W20	W24 /EOSI /WD[e]	FU W2	FU W4	FU W8	FU W12	*FU W16[qq]*	*FU W20[qq]*	FU W24	*FU W28[qq]*	*FU W32[qq]*	FU W36	*FU W40[qq]*	*FU W44[qq]*	FU W48 /EOS /WD[e, aaa]
Study Day (Window)	-28 to 0	1	15 +/-2d	29 +/-2d	57 +/-2d	85 +/-2d	99 +/-3d	113 +/-3d	141 +/-3d	169 +/-3d	15 +/-4d	29 +/-4d	57 +/-4d	85 +/-4d	113 +/-4d	141 +/-4d	169 +/-4d	197 +/-4d	225 +/-4d	253 +/-4d	281 +/-4d	*309 +/-4d*	337 +/-4d
Renal biomarkers[bb]		X				X				X													
Testing for hepatitis A, B, C, D, and E virus, HIV-1 and -2[y]	X																						
FSH test (postmenopausal women only)[dd]	X																						
AFP test[y,cc]	X									X							X						X
Hemoglobin A1c test	X																						
Serum pregnancy test (women of childbearing potential only)	X																						
Urine pregnancy test (women of childbearing potential)		X		X	X	X	X	X	X	X		X	X	X[ss]	X[ss]	X	X[ss]	X[ss]	X[ss]	X[ss]	X[ss]	X[ss]	X
TSH and T4	X				X																		
Efficacy Evaluations																							
Fibroscan[ee]		(X)								(X)							(X)						(X)
HBV Virology																							
Blood sampling for HBV DNA[yy]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sampling for HBV RNA[ff]	X	X		X	X	X	X	X	X	X	X	X		X			X						X
Sampling for viral genome sequencing[gg]	X	X				X				X				X		X		X	X		X		X
HBV Serology																							
Blood sampling for:																							
Anti-HBs and anti-HBe	X	X			X					X		X		X			X			X			X
HBsAg and HBeAg (qualitative)	X	X			X					X				X			X						X
HBsAg (quantitative)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBeAg (quantitative)[vv]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBcrAg[ff]	X	X		X	X	X		X	X	X		X		X			X			X			X
Exploratory serology[hh]	X	X		X	X	X	X	X	X	X	X	X	X	X	X		X			X			X

Study Period	Screening	Treatment Period 1[a,d,e]				Treatment Period 2[a,d,e]					Follow-up[a,e,qq]												
Visit Day (D)/Week (W)	W-4 to 0[b]	D1[c]	W2	W4	W8	W12	W14	W16	W20	W24 /EOSI /WD[e]	FU W2	FU W4	FU W8	FU W12	*FU W16[qq]*	*FU W20[qq]*	FU W24	*FU W28[qq]*	*FU W32[qq]*	FU W36	*FU W40[qq]*	*FU W44[qq]*	FU W48 /EOS /WD[e, aaa]
Study Day (Window)	-28 to 0	1	15 +/-2d	29 +/-2d	57 +/-2d	85 +/-2d	99 +/-3d	113 +/-3d	141 +/-3d	169 +/-3d	15 +/-4d	29 +/-4d	57 +/-4d	85 +/-4d	113 +/-4d	141 +/-4d	169 +/-4d	197 +/-4d	225 +/-4d	253 +/-4d	281 +/-4d	*309 +/-4d*	337 +/-4d
Clinical Pharmacology Assessments																							
Blood sampling for sparse PK of JNJ-3989 and optionally NA and PegIFN-α2a[ii]		X[ij]		X[ij,ll]		X[ij]			X[ij,ll]														
Blood sampling for intensive PK of JNJ-3989 and optionally NA and PegIFN-α2a (PK substudy)[kk]				X					X														
Exploratory Host Biomarkers																							
Whole blood RNA gene expression		X				X	X	X		X													X
Whole blood single cell profiling		X			X	X				X		X	X	X			X			X			X
Host serum proteins (eg, cytokines)		X		X	X	X		X	X	X		X	X	X			X			X			X
Antidrug antibodies (to JNJ-3989 and optionally PegIFN-α2a)		X			X			X		X				X			X						X
Immune Monitoring																							
Immune cells (PBMCs) (selected sites only)[mm]		X				X				X		X		X			X						X
Pharmacogenomics (DNA)																							
HLA typing		X																					
Exploratory host genotyping (optional)[nn]		X																					
Epigenetic research (optional)[nn]		X				X				X		X		X			X						X
Ongoing Participant Review																							
Concomitant therapy[oo]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[oo, xx]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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

For Japan only, twice weekly visits are to be scheduled during the first week of treatment with PegIFN-α2a (ie, Week 12), followed by weekly visits up to Week 23, for assessment of safety (injection site reactions, physical examination, ophthalmic examination [when indicated], vital signs), hematology (only up to Week 20), concomitant

therapy and adverse events. During Week 12 (first 2 visits with PegIFN-α2a), the study day visit window is +/-2d. After Week 12, the study day visit window is +/-3d until Week 24.

AFP: alpha-fetoprotein; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CRF: case report form; CT: computed tomography; D/d: day; DAIDS: Division of Acquired Immunodeficiency Syndrome; DBP: diastolic blood pressure; DNA: deoxyribonucleic acid; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; EOS: end of study; EOSI: end of study intervention; FSH: follicle-stimulating hormone; FU: follow-up; GI = giga; 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; INR: International Normalized Ratio; ISA: intervention-specific appendix; MRI: magnetic resonance imaging; NA: nucleos(t)ide analog; PBMC: peripheral blood mononuclear cells; PegIFN-α2a: pegylated interferon alpha-2a; PK: pharmacokinetic; RBC: red blood cell; RNA: ribonucleic acid; SBP: systolic blood pressure; T4: thyroxine; TSH: thyroid stimulating hormone; ULN: upper limit of normal; W: week; WD: withdrawal.

a. All study visits are to be scheduled relative to the baseline (Day 1) visit date. All follow-up study visits are to be scheduled relative to the Week 24/EOSI visit. 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.
b. If necessary (eg, for operational reasons), the Screening Period may be extended up to a maximum of 8 weeks in agreement with the sponsor.
c. Day 1 samples are to be collected before the first dose of study intervention.
d. All assessments (with the exception of the sparse and intensive PK samples) should be performed before administration/intake of JNJ-3989 and NA. If applicable, weekly PegIFN-α2a administration should preferably be done on the same day of the week in the evening by self-injection. If desired, participants can also choose to have the administration of PegIFN-α2a performed on site irrespective of the time of day. For participants in Japan, weekly administration of PegIFN-α2a must be performed at the study site by the investigator or his/her designee.
e. Participants who discontinue study intervention early will have an early WD visit and will enter follow-up unless they withdraw consent. Participants who withdraw consent will be offered an optional safety follow-up visit to occur on the day of consent withdrawal. For the optional safety follow-up visit, assessments are at the investigator's discretion and could be similar to the early WD visit.
f. Both the Platform Master ICF and the ISA ICF must be signed before the first study-related activity. For participants who consent to participation in the intensive PK study (optional), the corresponding checkbox in the ISA ICF must be checked.
g. Minimum criteria for the availability of documentation supporting the eligibility criteria are described in the source documents section in Attachment 3 of the Master Protocol PLATFORMPAHPB2001. Clinical status will be checked and documented at screening and again before first dose of study intervention. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study.
h. Medical history also includes mode of HBV transmission, stage of liver fibrosis, and alcohol consumption. Historical HBV DNA, ALT, HBsAg, and HBeAg data, if available, will be recorded in the CRF and/or source documents. Available historical data on previous HBV genotype assessments will also be collected in the CRF. HBeAg status should also be recorded.
i. Liver disease staging assessments will be performed based on Fibroscan or liver biopsy results, obtained within 6 months prior to screening or at the time of screening (in case of Fibroscan) or within 1 year prior to screening (in case of liver biopsy).
j. Participants must have absence of signs of cirrhosis or portal hypertension (absence of nodules, smooth liver contour, normal portal vein, spleen size <12 cm) and absence of signs of HCC or clinically relevant renal abnormalities on an abdominal ultrasound performed within 3 months prior to screening or at the time of screening. In case of suspicious findings on conventional ultrasound the participant may still be eligible if HCC or clinically relevant renal abnormalities have been ruled out by a more specific imaging procedure (contrast-enhanced ultrasound, CT or MRI).
k. HBV genotype will be determined at baseline using a standard genotyping assay if HBV DNA levels are sufficiently high. Available historical data on a previous HBV genotype assessment will also be collected in the CRF. Exploratory genotyping may be performed.
l. Not applicable for the WD visit.
m. In between study visits, participants will take NA at home and will bring their NA with them to each study visit. At study visits, NA should be taken on site. Weekly PegIFN-α2a administration should preferably be done on the same day of the week in the evening by self-injection. A total of 12 injections should be administered, starting at Week 12, with the last injection during Week 23. If desired, participants can also choose to have the weekly administration of PegIFN-α2a performed on site irrespective of the time of day. For participants in Japan, weekly administration of PegIFN-α2a must be performed at the study site by the investigator or his/her designee.
n. Only applicable in case of self-injection.

o. Participants who are administering PegIFN-α2a by self-injection will be requested to complete a self-injection tracker. Refer to Section 6.4, Study Intervention Compliance, for more details.
p. Complete physical examination, including height (only at screening), body weight, skin examination, and other body systems.
q. For participants with a risk factor (eg, diabetes or hypertension), an ophthalmic examination should be repeated at Week 8 (+/- 3 weeks) at the investigator's discretion in case their condition changes. Any participant experiencing a decrease or loss of vision at any time point during study participation, must have a prompt ophthalmic examination. Medical records of the examination should be collected and assessed by the investigator.
r. A +/- 3-week visit window is allowed for the ophthalmic examination at Week 24.
s. Vital signs include supine SBP, DBP, pulse rate, and body temperature.
t. All ECGs will be read centrally. Only on Day 1, an ECG will be collected and assessed locally prior to dosing. ECGs should be completed before any tests, procedures or other consultations for that visit.
u. The liver ultrasound does not need to be repeated at baseline if it was done at screening or within 3 months prior to screening.
v. Biochemistry samples should be taken after fasting for at least 10 hours (6 hours for Week 2) for measurement of phosphate, calcium, creatinine, and lipids. If applicable, participants should bring their study intervention with them to each visit and have that day's intake at the site with food.
w. The following criteria will trigger additional unscheduled visits: Platelet counts: <100,000 cells/mm^3 or <100 GI/L or reduction from baseline by at least 50%; Hemoglobin: Decrease of at least 2 g/dL from baseline or at least grade 2 (DAIDS); Reticulocytes: Reduction to <0.5% of the RBC count; Neutrophil count: Treatment-emergent reduction to at least grade 2 (DAIDS) (see also Section 8.3.6.6, Hematologic Abnormalities).
In case any 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.
x. Creatinine clearance (eGFR calculated by the CKD-EPI formula) will be assessed.
y. 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). A confirmatory visit should be scheduled as soon as possible 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 10.7, Appendix 7: Intervention-emergent ALT/AST Elevations.
z. 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).
aa. Urine chemistry sample (quantitative measurement): creatinine, sodium, phosphate, glucose, protein, and albumin.
bb. Urine sample for selected renal biomarkers including retinol binding protein and beta-2-microglobulin (other biomarkers might be measured).
cc. Additional samples may be collected for AFP testing in case of ALT flares.
dd. For postmenopausal women only: An FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to confirm a woman is not of childbearing potential (see Section 10.5 Appendix 5: Contraceptive and Barrier Guidance).
ee. Only applicable to participants who are enrolled at a site with an on-site Fibroscan device. A Fibroscan assessment will only be done at baseline if it was not done at screening.
ff. 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.
gg. Samples may be sequenced based on the sponsor virologist's request, considering the HBV DNA levels. In case of a virologic breakthrough/flare, additional samples for viral sequencing may be taken.
hh. Exploratory serology samples may be analyzed at the sponsor's discretion. Samples may be used to assess virologic or serologic markers of HBV.
ii. All participants will have sparse PK sampling for JNJ-3989, NA, and PegIFN-α2a. Bioanalysis of NA and PegIFN-α2a is optional at the discretion of the sponsor. Bioanalysis of JNJ-6379 may also be done on samples collected from participants who received JNJ-6379 prior to Protocol Amendment 3. For all samples, the date and time of the preceding 2 intakes of oral NA, the date and time of the previous JNJ-3989 and PegIFN-α2a administration, as applicable, and the date and time of PK sampling should be recorded.
jj. One sample at any time between 2 and 8 hours after JNJ-3989 dosing. Before leaving the study site, the participant's well-being should be confirmed.
kk. All participants who consent to participate in the intensive PK substudy (optional) will undergo intensive PK sampling at Week 4 and Week 20. If necessary (eg, for operational reasons), this visit may be scheduled at Week 8 or Week 16, respectively. The study intervention (JNJ-3989, NA, and, if applicable, PegIFN-α2a) 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 post JNJ-3989 dose (*the 8 and 10 hours postdose samples are optional). All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within 20% of the nominal time from dosing (eg, +/-12 minutes of a 60-minute time point) will not be captured as a protocol deviation if the exact time of the sample collection is noted on the source document and data collection record (eg, CRF).

ll. Sparse PK sampling is not required for participants with intensive PK sampling at the same visit.

mm. PBMC samples will be collected at selected sites only. Additional PBMC samples may be taken in case of ALT flares, upon discussion with the sponsor, and may require an unscheduled visit.

nn. These samples are optional and will only be collected from participants who consent separately to this component of the study. The exploratory host genotyping sample should preferably be collected at baseline.

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

pp. Exclusion criterion A25 regarding contraindications to the use of PegIFN-α2a needs to be checked and documented again prior to the start of Treatment Period 2. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of PegIFN-α2a is given such that he or she meets exclusion criterion A25, then the participant should continue treatment as planned but without PegIFN-α2a.

qq. Visits at follow-up Week 16, 20, 28, 32, 40, and 44 are optional for participants who continue NA treatment and for participants who have restarted NA treatment during the follow-up period, provided that their HBV DNA and ALT values are stable.

rr. Liver function tests only.

ss. Urine pregnancy tests will be provided to the participants for at home use as necessary to ensure urine pregnancy tests are performed at least every 4 weeks. Participants will report the results to the study site personnel at the next visit, and these will be added to the source documents. If positive, the participant should contact the site immediately.

tt. No JNJ-3989/PegIFN-α2a will be administered or dispensed during follow-up. Administration/Dispensation of NA is only applicable for participants who could not stop NA treatment, or for those who met the NA re-treatment criteria. In between study visits, participants will take NA at home and they will bring their NA treatment with them to each study visit.

uu. If the NA treatment completion criteria are met at Week 24, treatment with NA will be stopped at FU Week 2.

vv. Available historical data on HBeAg status before start of NA treatment will be collected in the CRF.

ww. A urinalysis and urine chemistry sample will be taken at FU Week 2. In case of abnormalities, the tests should be repeated at the following visits.

xx. Includes close monitoring for neuropsychiatric adverse events during the PegIFN-α2a treatment period. Participants who develop a neuropsychiatric adverse event during PegIFN-α2a treatment, will be monitored closely until the neuropsychiatric adverse event resolves, with frequent (at least weekly) follow-up phone calls.

yy. NA treatment should be re-started in accordance with the NA re-treatment criteria (see Section 6.7.1, NA Re-treatment Criteria and Monitoring After Stopping of NA and Section 10.12 Appendix 12, for guidance after stopping NA treatment).

zz. Participants enrolled before Protocol Amendment 3 was in effect, may have received JNJ-6379 as part of their study intervention.

aaa. The investigator should consider to re-start NA treatment per local standard of care at the EOS visit (Follow-up Week 48) for participants who met the NA treatment completion criteria at Week 24, who did not re-start NA treatment during the follow-up phase, and who did not achieve and maintain HBsAg seroclearance. NA will not be provided by the sponsor after the final study visit.

2. INTRODUCTION

This intervention-specific appendix (ISA) describes a Phase 2a study of JNJ-73763989 (JNJ-3989) in combination with a nucleos(t)ide analog (NA) and pegylated interferon alpha-2a (PegIFN-α2a). Prior to Protocol Amendment 3, the study intervention also included JNJ-56136379 (JNJ-6379). It is a companion document to the Master Protocol PLATFORMPAHPB2001, which describes the sponsor's Platform study in participants with chronic hepatitis B (CHB). This ISA describes specific and/or additional protocol elements applicable to this intervention cohort, in which participants will be treated with the study intervention, JNJ-3989 in combination with an NA and PegIFN-α2a (see Section 2.2, Background).

JNJ-3989 is a liver-targeted antiviral therapeutic for subcutaneous injection designed to treat chronic hepatitis B virus (HBV) infection via a ribonucleic acid interference (RNAi) mechanism. Engagement of the cellular RNAi machinery by JNJ-3989 results in specific cleavage of HBV RNA transcripts, thereby reducing the levels of HBV proteins and the pre-genomic ribonucleic acid (pgRNA), the precursor of viral relaxed circular deoxyribonucleic acid (rcDNA). The small interfering RNA (siRNA) triggers in JNJ-3989, JNJ-73763976 (JNJ-3976) and JNJ-73763924 (JNJ-3924), are designed to target all HBV ribonucleic acid (RNA) transcripts derived from covalently closed circular deoxyribonucleic acid (cccDNA), as well as transcripts derived from integrated HBV deoxyribonucleic acid (DNA). The latter has been suggested to be a significant source of hepatitis B surface antigen (HBsAg) in hepatitis B e antigen (HBeAg)-negative patients or patients on long-term treatment with NAs, the current standard of care (Wooddell 2017).

JNJ-6379 is an orally administered Class N capsid assembly modulator (CAM-N) interfering with the capsid assembly and disassembly during HBV replication. 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 with normal shape but which are devoid of HBV DNA or RNA (non-functional capsids; Class N), 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. JNJ-6379 was initially part of the study intervention, but has been removed as study intervention with the implementation of an urgent safety measure, as described in Protocol Amendment 3.

Select NAs and PegIFN-α2a are approved treatments of chronic HBV infection.

For the most comprehensive nonclinical and clinical information regarding JNJ-3989 and JNJ-6379, refer to the latest version of the Investigator's Brochures (IBs) (IB JNJ-3989 2020; IB JNJ-6379 2021). For nonclinical and clinical information regarding NA and PegIFN-α2a, refer to their respective prescribing information.

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

As of Protocol Amendment 3, the term "study intervention" throughout the protocol, refers to JNJ-3989, NA, and PegIFN-α2a, as defined in Section 6.1, Study Intervention(s) Administered.

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

At the time of protocol writing, combination treatment with JNJ-3989, JNJ-6379, and NA was believed to have the potential to specifically decrease HBV viral antigen levels and inhibit viral replication. Since HBsAg is immune suppressive, the direct reduction of HBsAg levels by JNJ-3989 is anticipated to contribute to the restoration of the immune response that is impaired in chronic HBV infection.

This study is designed to assess efficacy and safety of a treatment regimen of JNJ-3989 and NA for 24 weeks with the addition of PegIFN-α2a during the last 12 weeks. Prior to Protocol Amendment 3, the study intervention also included JNJ-56136379 (JNJ-6379).The combination of the treatment regimen of JNJ-3989 + NA with PegIFN-α2a is based on 2 different properties of alpha interferon (IFN-α): a direct antiviral effect and an immune boosting effect. The direct antiviral activity against HBV replication, and in some cases HBsAg production, was demonstrated for PegIFN-α2a (Belloni 2012). In addition, IFN-α is expected to act as immune booster with potential to reactivate natural killer (NK)-cells (Gill 2016).

Virologically suppressed CHB-infected patients will be enrolled with the target to include both HBeAg-positive and negative patients.

The primary objective of the study will be to assess the effect on HBsAg levels at EOSI. In addition, off-treatment efficacy will be explored to evaluate if a treatment duration of 24 weeks, including 12 weeks of combined treatment with PegIFN-α2a, can induce functional cure in patients with CHB.

2.2. Background

JNJ-6379 was initially part of the study intervention, but has been removed as study intervention with the implementation of an urgent safety measure, as described in Protocol Amendment 3. For completeness, background information on JNJ-6379 is still included in this section.

2.2.1. Primary Pharmacology

JNJ-3989

JNJ-3989 is a 2:1 molar mixture of 2 synthetic, double-stranded, N-acetylgalactosamine (GalNac) conjugated RNAi triggers (JNJ-3976 and JNJ-3924, respectively). RNAi is a naturally occurring phenomenon by which short, double-stranded RNA oligonucleotides trigger a sequence-specific down-modulation of gene expression. The RNAi triggers in JNJ-3989 are designed to target all HBV transcripts derived from cccDNA and integrated viral DNA. This is made possible by the

fact that all HBV transcripts expressed from cccDNA, including the RNA transcript (pgRNA) that is used as a template for replication of HBV DNA, are terminated by the same polyadenylation site and share a common sequence region upstream of this site. One RNAi trigger (JNJ-3924) in JNJ-3989 has its target within this common sequence region and thus has the potential to knock down expression of all viral proteins as well as the pgRNA expressed from cccDNA. The second RNAi trigger (JNJ-3976), which targets the HBsAg-encoding region, was designed to knock down expression of HBsAg derived from integrated HBV DNA as well as all viral proteins derived from cccDNA with the exception of HBV x protein. Silencing viral RNA will reduce HBV DNA and viral proteins, including HBsAg.

In mice transiently harboring the human HBV genome, treatment with JNJ-3989 led to dose-dependent reductions of serum HBsAg, HBeAg, and HBV DNA. Multiple doses of JNJ-3989 resulted in additional and prolonged antigen and HBV DNA reductions in a stepwise fashion when compared to a single dose. This was consistent with prolonged liver persistence of antisense strands, which, when loaded into the RNA-induced silencing complex (RISC), exert the pharmacologic RNAi activity. The ability of JNJ-3989 to reduce serum HBV DNA was additive to synergistic with entecavir (ETV). ETV alone had no effect on serum HBsAg levels, and no negative effect on the ability of JNJ-3989 to reduce serum HBsAg was observed when given in combination.

JNJ-6379

JNJ-6379 is an HBV capsid assembly modulator (CAM) with dual mode of action; (1) interfering with capsid assembly, preventing encapsidation of pgRNA and blocking HBV replication, (2) inhibition of the de novo formation of cccDNA. JNJ-6379 binds to the core protein dimer and disrupts the normal viral capsid assembly process, thereby preventing the Pol-pgRNA encapsidation. This results in the formation of HBV capsids, devoid of HBV DNA (non-functional capsids), and ultimately in the inhibition of HBV replication in vitro. 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.

In a stable HBV-replicating HepG2.117 cell line, JNJ-6379 displayed median 50% and 90% effective concentration (EC_{50} and EC_{90}) values of 54 nM (22.6 ng/mL) and 226 nM (94.6 ng/mL), respectively. Addition of human serum proteins had limited effect on JNJ-6379 anti-HBV activity with an approximately 4-fold shift for 40% human serum. Antiviral activity of JNJ-6379 was also assessed in primary human hepatocytes with an EC_{90} of 376 nM for HBV DNA, representing the "primary" mechanism of action of JNJ-6379, ie, interfering with HBV capsid assembly. In addition, JNJ-6379 inhibited the de novo formation of cccDNA with an EC_{90} of 4,019 nM, based on HBV RNA) when compound was added together with viral inoculum ("secondary" mechanism of action).

In cytotoxicity assays, the 50% cytotoxic concentrations (CC_{50}) of JNJ-6379 were ≥29.9 µM across the cell lines tested resulting in selectivity indices of ≥554 (based on the antiviral activity in the stable HBV-replicating HepG2.117 cell line).

In vitro combination studies of JNJ-6379 with either ETV or tenofovir resulted in additive to synergistic anti-HBV activity.

JNJ-6379 remained active against a diverse panel of genotype A to H clinical isolates. Analysis of site-directed mutant (SDMs) identified amino acid substitutions in the CAM-binding pocket at positions 23 (F23Y), 25 (P25G), 30 (L30F), 33 (T33N, T33P), 37 (L37Q), 106 (S106T), 110 (F110I), 118 (Y118F), 124 (V124G), 127 (R127H) and 128 (T128I) reduced anti-HBV activity of JNJ-6379 ranging from 3.0- (S106T) to 85-fold (T33N). All substitutions were rare in a public database of >7,600 HBV core sequences (frequencies 0.01–0.3%). NAs retained full activity against these core SDMs.

2.2.2. Nonclinical Studies

2.2.2.1. 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-month studies).

JNJ-3989

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

The nonclinical safety profile of JNJ-3989 has been evaluated through a series of in vitro and in vivo studies. Repeat-dose subcutaneous toxicity studies of 2 weeks up to 24 or 37 weeks were conducted in rat and monkey, respectively. In the 2-week studies, JNJ-3989 was administered once weekly via subcutaneous injection at 30 up to 300 mg/kg. In the 24- or 37-week studies, JNJ-3989 was administered once weekly for the first month, followed by once monthly thereafter at 30 up to 180 mg/kg. JNJ-3989 was well tolerated in these studies.

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

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

All these changes likely represented the distribution, accumulation, and clearance of JNJ-3989 and were considered not to be adverse due to the nature of the findings and the low severity. These are

commonly described findings for N-acetylgalactosamine-conjugated RNAi (Janas 2018). The no observed adverse effect level (NOAEL) was therefore considered to be the highest dose tested, ie, CCI mg/kg in the 24-week study.

In the 2-week study in monkey, apart from a minimally increased ALP activity which was considered not adverse, no JNJ-3989-related effects were observed. In the 37-week study, JNJ-3989-related target organs were the liver, mandibular and/or mesenteric lymph nodes, and the subcutaneous injection site. Findings included Kupffer cell basophilia/hypertrophy in the liver, vacuolated macrophages in the lymph nodes, and macrophage infiltrates in the injection site. Partial reversibility was observed for these findings. This likely represented the distribution, accumulation, and clearance of JNJ-3989 and was considered not to be adverse due to the low severity and/or nature of the findings. These are commonly described findings for N-acetylgalactosamine conjugated RNAi (Janas 2018). A non-adverse, minimally increased ALP activity was observed at 180 mg/kg without a microscopic correlate. The NOAEL in the monkey was considered to be the highest dose tested, ie, CCI mg/kg in the 37-week study.

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

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

JNJ-3989 was shown to be non-genotoxic when tested in the bacterial reverse mutation assay, and in vitro and in vivo micronucleus test.

Results of the non-Good Laboratory Practice (GLP) in vitro studies demonstrated there is no potential for induction of the innate immune system (cytokine and complement activation), mitochondrial toxicity/cytotoxicity, or platelet aggregation associated with JNJ-3989 exposure at concentrations up to 250 µg/mL.

The animal-to-human exposure ratios were calculated using rat and monkey exposures at NOAEL from the 24-week and 37-week studies, respectively, and human exposures after a single subcutaneous injection of 200 mg JNJ-3989 in human volunteers (Study AROHBV1001) (Table 1).

Table 1: Animal/Human Exposure Ratios at NOAEL for JNJ-3989

		Sex	NOAEL (mg/kg)	C_{max} (ng/mL)	AUC[a] (ng·h/mL)	Ratio Total Concentration C_{max} A/H Ratio	Ratio Total Concentration AUC[a] A/H Ratio
JNJ-73763976	Human exposure[b]		CCI	1,315	20,136	-	-
	24-week rat[c]	M		41,100	437,000	31.3	21.7
		F		43,100	270,000	32.8	13.4
	37-week monkey[d]	M		73,200	1,230,000	55.7	61.1
		F		65,800	988,000	50.0	49.1
JNJ-73763924	Human exposure[b]			363	4,605	-	-
	24-week rat[c]	M		25,200	271,000	69.4	58.8
		F		26,200	163,000	72.2	35.4
	37-week monkey[d]	M		21,600	383,000	59.5	83.2
		F		23,000	392,000	63.4	85.1

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

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

[b] Single dose of 200 mg JNJ-73763989 in healthy participants via subcutaneous injection (Study AROHBV1001; based on recent clean dataset with data cut-off date 29 October 2019).

[c] Once weekly dosing for 5 weeks, followed by once monthly dosing up to a total of 24 weeks.

[d] Once weekly dosing for 5 weeks, followed by once monthly dosing, up to a total of 37 weeks.

JNJ-6379

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

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

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

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

Animal/human ratios at the NOAEL in rat and dog for human exposure at 250 mg JNJ-6379 once daily (QD) for 28 days are displayed in Table 2.

Table 2: Animal/Human Ratios at the NOAEL in Rat and Dog (Human Exposure at 250 mg JNJ-6379 Once Daily for 28 Days [Study 56136379HPB1001])

					Ratio Total Concentration		Ratio Concentration Corrected for Plasma Protein Binding[b]	
	Sex	NOAEL (mg eq./kg/day)	C_{max} (ng/mL)	AUC_{0-24h} (ng.h/mL)	C_{max} A/H Ratio	AUC_{0-24h} A/H Ratio	C_{max} A/H Ratio	AUC_{0-24h} A/H Ratio
Human exposure[a]		CCI	13,798	267,180	-	-		
6M rat	M		7,540	93,100	0.6	0.3	0.9	0.6
	M		13,600[d]	180,000[d]	1.0	0.7	1.7	1.1
	F		19,900	233,000	1.4	0.9	2.4	1.5
9M dog	M		30,000	606,000	2.2	2.3	3.3	3.4
	F		22,500	383,000	1.6	1.4	2.5	2.2

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

[a] 250 mg JNJ-6379 QD for 28 days (Study 56136379HPB1001).

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

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

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

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 (Study TOX13609). JNJ-6379 (in polyethylene glycol 400 + 10% polyvinylpyrrolidone-vinyl acetate) was administered daily via oral gavage at 100 mg/kg, alone or in combination with JNJ-3989 (in CCI saline) which was administered weekly via subcutaneous injections at 30 and 180 mg/kg. In addition, 180 mg/kg JNJ-3989 (subcutaneous, weekly) was dosed as well in a monotherapy group. Control animals received both vehicles via the respective routes.

No treatment-related mortality occurred during the study and no relevant clinical signs were noted. Body weights and body weight gain were slightly decreased during the last weeks of treatment in males at ≥100/30 mg/kg JNJ-6379/JNJ-3989 and in females at 100/180 mg/kg JNJ-6379/JNJ-3989, with correlating lower food intake at the high dose.

JNJ-6379 and/or JNJ-3989 elicited minimal to mild changes in white (WBC) and red blood cell (RBC) parameters, as well as minimal decreases in platelets, fibrinogen and a minimal increase in activated partial thromboplastin time at ≥100/30 mg/kg JNJ-6379/JNJ-3989. Minimal to mild increases in alanine aminotransferase (ALT), ALP, gamma-glutamyl transferase, urea, cholesterol (up to moderate), phospholipids, and triglycerides were observed from the same dose onwards. At 100/180 mg/kg JNJ-6379/JNJ-3989, minimal to mild increases in glutamate dehydrogenase (GLDH) and bilirubin concentrations in females were observed, and a minimal decrease in glucose concentrations in males. The above changes in clinical pathology were considered non-adverse based on the minimal severity observed and were of a similar nature and magnitude as when animals were dosed with the test items alone.

Drug-containing sediment was observed in the urine of animals dosed with JNJ-6379 at 100 mg/kg, either alone or in combination, with mainly males being affected. In the group given JNJ-6379 alone, the drug-containing sediment was studied and correlated with significant amounts of drug-related material in the urine (predominantly M7 but also unchanged drug).

JNJ-6379-related morphological findings at 100 mg/kg/day in males and/or females were considered non-adverse, and were seen in the liver (centrilobular hypertrophy, weight increase), thymus (decreased lymphoid cellularity, weight decrease, small size), spleen (infiltration mononuclear cells in capsule, correlating with pale white focus/irregular surface), adrenal gland (hypertrophy of zona fasciculata correlating with enlargement, weight increase), and thyroid gland (follicular cell hypertrophy).

JNJ-3989-related morphological findings at 30 mg/kg in males and/or females were considered non-adverse and were seen in the liver (increased vacuolation and increased mitosis) and administration site (mixed cell infiltrate, infiltration of vacuolated macrophages with basophilic stippling). Non-adverse findings at 180 mg/kg were seen in the liver (increased vacuolation of hepatocytes and/or Kupffer cells correlating with pale discoloration, prominent lobular pattern; single cell necrosis, increased mitosis, karyomegaly, hypertrophy/hyperplasia of bile ducts), kidney (vacuolation and basophilic granules in tubular epithelium), mesenteric, axillary and/or popliteal lymph nodes (macrophage vacuolation, sinus histiocytosis), and the administration site (mixed cell infiltrate, infiltration of vacuolated macrophages with basophilic stippling).

Differences in morphologic alterations between rats dosed with the single compounds, compared to the groups dosed with the combination of the 2 compounds included a minor increase in incidence and severity of decreased lymphoid cellularity in the thymus with lower thymus weights in females of the 100/180 mg/kg JNJ-6379/JNJ-3989 group. All remaining findings in the groups dosed with the combination of test articles were in line with the findings recorded for the groups dosed with the single compounds. There were no additional target organs or findings identified following the treatment with the combination of JNJ-6379 with JNJ-3989.

No relevant drug-drug interaction (DDI) was seen.

In conclusion, weekly subcutaneous injections with JNJ-3989 at 30 or 180 mg/kg in combination with daily administration of JNJ-6379 at 100 mg/kg (oral) for 1 month were well tolerated with no

clinical signs or treatment-related mortality. Changes in clinical pathology and histopathology were mostly similar to the findings for the monotherapy groups dosed with JNJ-6379 at 100 mg/kg (oral) alone or with JNJ-3989 at 180 mg/kg (subcutaneous) alone. The only synergistic changes included a slight decrease in body weight (gain) at ≥100/30 mg/kg JNJ-6379/JNJ-3989, in food consumption at 100/180 mg/kg JNJ-6379/JNJ-3989, and a further decrease in lymphoid cellularity in the thymus of females at 100/180 mg/kg JNJ-6379/JNJ-3989. These alterations were minor and non-adverse in nature. Based on these results, the NOAEL was considered to be CCI mg/kg JNJ-6379/JNJ-73989. Maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve from administration to 24 hours (AUC_{0-24h}) for JNJ-6379 in males were 13,200 ng/mL and 181,000 ng.h/mL, and for females 15,500 ng/mL and 206,000 ng.h/mL, respectively, after 1 month of treatment. The mean C_{max} and AUC_{0-24h} for analyte JNJ-3924 in males were 20,900 ng/mL and 160,000 ng.h/mL, and for females 21,300 ng/mL and 125,000 ng.h/mL, respectively. For analyte JNJ-3976, the mean C_{max} and AUC_{0-24h} in males were 35,200 ng/mL and 258,000 ng.h/mL, and for females 35,300 ng/mL and 201,000 ng.h/mL, respectively.

A 3-month combination toxicity study of JNJ-3989 and JNJ-6379 was conducted (Study TOX13608). In this study, JNJ-3989 was initially administered weekly (ie, a total of 6 doses) and monthly thereafter, via subcutaneous injections at dose levels of 60 and 180 mg/kg when given in combination with JNJ-6379, and at 180 mg/kg for the monotherapy group. JNJ-6379 was administered daily via oral gavage at a dose level of 100 mg/kg in the monotherapy and combination groups. Control animals received both vehicles via the respective routes.

No test article-related mortalities were noted among animals dosed with JNJ-6379 alone, JNJ-3989 alone, or JNJ-6379/JNJ-3989 at 100/180 mg/kg. One male receiving JNJ-3989 alone at 180 mg/kg died on Day 45, after a rapid change in its clinical condition. The death of this animal was considered to reflect an acute stress response without a relationship to the test article. One accidental death due to a possible gavage error was noted among the toxicokinetic animals in the 100/60 mg/kg JNJ-6379/JNJ-3989 group.

One male rat (No. 48) dosed at 100/60 mg/kg JNJ-6379/JNJ-989 was euthanized on Day 24 after showing severe clinical signs in the morning (decreased activity, erected fur, pallor and cold to touch). No clinical signs were noted for this animal until Day 23, and body weight and weight gain were unaffected during the first 3 weeks of the study. The cause of moribundity was considered to be a markedly decreased hematopoietic cellularity of the bone marrow with pancytopenia including markedly reduced platelet counts and consequent hemorrhages (in a variety of organs and tissues) and blood loss. A relation to the treatment with JNJ-6379 and/or JNJ-3989 cannot be excluded. None of the remaining animals of this study showed decreased cellularity of the bone marrow.

Body weight and weight gain were slightly decreased in the JNJ-6379 monotherapy group, and in both combination groups, with correlating lower food intake. Given the magnitude of the changes and the absence of clinical signs, these findings were considered non-adverse.

JNJ-6379-related changes included increases in lymphocytes, total WBCs, hepatobiliary enzyme activities (ALT, GLDH and/or ALP), cholesterol, and triglycerides. In addition, females showed decreases in glucose, and males had an increased urea concentration. JNJ-3989-related changes included increases in ALP, ALT, GLDH, cholesterol and triglycerides in males and/or females. In one or both combination groups, decreased platelet counts (females), RBC parameters (males), glucose, albumin, globulin and (occasionally) total protein concentrations and increased ALP, ALT, gamma-glutamyl transferase and GLDH activities, and cholesterol levels were observed in one or both sexes. Both sexes showed an increased plasma urea concentration. Based on the magnitude of changes, these were concluded to be non-adverse for either monotherapy or combination therapy groups.

No changes were observed for the urinary biomarkers albumin, β2-microglobulin, Kidney Injury Molecule-1 [KIM-1], Neutrophil Gelatinase Associated Lipocalin [NGAL], cystatin-C, and clusterin in the JNJ-6379 monotherapy group. Precipitate was observed in the urine of animals dosed with JNJ-6379.

JNJ-6379-related morphological findings were observed in the female reproductive tract (included a decreased number of corpora lutea, prominent atretic follicles in the ovary), which was considered adverse. Other findings were observed in the liver (centrilobular hepatocellular hypertrophy), kidney (diffuse dilatation in females), spleen (infiltration of mononuclear cells and/or fibrosis in the capsule), adrenal gland (hypertrophy of the zona fasciculata in females), and thyroid gland (follicular cell hypertrophy in males). All findings were considered non-adverse due to the nature of the findings and the low severity.

JNJ-3989-related morphological findings were observed in the liver (increased vacuolation of hepatocytes and/or Kupffer cells, single cell necrosis, oval cell hyperplasia, basophilic granules, increased mitosis and/or karyocytomegaly), kidney (basophilic granules and vacuolation in tubular epithelium), lymph nodes (macrophage vacuolation and/or sinus histiocytosis), and injection site (infiltration of macrophages with basophilic stippling, mononuclear cell infiltrate, multinucleate giant cells and/or increased incidence and severity of hemorrhage). The findings were usually dose-related in incidence and/or severity, and were considered non-adverse due to the nature of the findings and the low severity.

In the combination groups, differences in morphological alterations versus the monotherapy groups consisted of a minor increase and severity of decreased lymphoid cellularity in the thymus, possibly partly explained by the reduce body weight gain seen in these groups. There were no additional target organs or findings identified.

No DDI was observed.

In conclusion, administration of JNJ-6379 (daily, orally) and JNJ-3989 (intermittent, subcutaneous) in monotherapy groups and in the JNJ-6379/JNJ-3989 100/180 mg/kg group was well tolerated. In the 100/60 mg/kg group, one male rat was euthanized. The cause of moribundity was considered to be a markedly decreased hematopoietic cellularity of the bone marrow with pancytopenia including markedly reduced platelet counts and consequent hemorrhages and blood

loss. A relation to the treatment with JNJ-6379 and/or JNJ-3989 cannot be excluded. In the surviving rats, changes in clinical pathology and histopathology were similar in the monotherapy and combination groups. Synergistic changes at ≥100/60 mg/kg included a dose-related decrease in body weight (gain) and food intake, a moderate decrease in platelet counts in females and a minimal decrease in RBC parameters in males. Microscopically a further decrease in lymphoid cellularly in the thymus was observed. These alterations were mild in nature and considered non-adverse. A NOAEL could not be defined.

Based on the observation of pancytopenia in 1 rat and a mild platelet decrease in the combination groups in the 3-month combination toxicity study, the sponsor is implementing additional monitoring of significant on-treatment hematologic changes in clinical studies with dosing longer than 4 weeks (see Section 8.3.6.6, Hematologic Abnormalities). However, no significant abnormalities of hematologic parameters have been observed in clinical studies to date.

For further information, refer to the latest version of the IBs for JNJ-3989 and JNJ-6379 (IB JNJ-3989 2020; IB JNJ-6379 2021).

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

There is no common target organ between JNJ-6379 or JNJ-3989 and ETV (Memorandum 2005). The single common toxicity target organ between JNJ-6379, JNJ-3989, and tenofovir disoproxil or tenofovir alafenamide (TAF) is the kidney.

In the chronic rat studies with JNJ-3989, slight alteration of the renal tubular epithelium was characterized by basophilic stippling and/or microvacuolation of the cytoplasm of renal tubules in the outer cortex in rats. These findings were not considered toxicologically meaningful since they were related to compound accumulation, there was no evidence of cellular damage (degeneration/necrosis) and there were no correlated clinical pathology indicators of changes in renal function (Henry 2012; Janas 2018). These kidney findings have been observed in both the 2-week and 6-month studies and did not worsen over time. No kidney findings were observed in monkeys.

In the chronic rat study (6 months) with JNJ-6379, retrograde nephropathy, secondary to papillary or pelvic calculi/precipitates, was noted in male rats but not in dogs or female rats. This finding is mainly due to precipitation or calculi formation in distal parts of the kidney/lower urinary tract and is of limited relevance to man, due to differences in urinary composition and functional anatomy between (male) rats and humans. In general, compounds or metabolites of low solubility and high renal clearance may cause concretions in the kidneys/urinary tract, especially at high doses, as the urine concentrates in the distal nephron and supersaturation of the compound can occur. Urinary pH, proteins and osmolality can also influence the formation of urinary concretions. Male rat urine normally has a high concentration of protein and high osmolality. In addition, rats may be predisposed to retrograde nephropathy because they are known to experience spontaneous urine reflux during micturition or urinary bladder contraction, and this reflux phenomenon can be increased or exacerbated by treatment-induced obstructions. The retrograde nephropathy in male

rats correlated with increased urea and creatinine in plasma and with urinary changes (red/brown discolored urine, increased volume, decreased pH, presence of blood and WBCs and RBCs in sediment) (Cohen 2002; Tannehill-Gregg 2009). No kidney findings were observed in dogs.

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

For tenofovir disoproxil, renal tubular epithelial karyomegaly was observed in rats, dogs, and monkeys (Memorandum 2001). In dogs, the species most sensitive to tenofovir disoproxil-related effects on the kidney, additional microscopic alterations following chronic administration of tenofovir disoproxil (10 mg/kg/day for 42 weeks) included individual tubular cell necrosis, tubular dilatation, tubular degeneration/regeneration, pigment accumulation, and interstitial nephritis. This was associated with biochemical changes such as slight elevation in serum creatinine, glucosuria, proteinuria, and increased urine volume. The incidence and severity of nephrotoxicity was dose-related. Effects were reversible following cessation of treatment. In Rhesus monkeys, biochemical and/or histopathologic evidence of nephrotoxicity was observed at high doses. In rats, slight elevations in serum creatinine were observed without any histopathology correlation.

For TAF, minimal renal cortical tubular karyomegaly and/or basophilia was seen in rats and dogs. In addition, minimal renal cortical tubular degeneration/regeneration were reported in dogs. No renal findings were reported in monkeys (EMA Vemlidy 2016).

Based on the available toxicology data, there are no specific concerns about additive or synergistic toxicities in the kidney when JNJ-6379 or JNJ-3989 are combined with ETV, tenofovir disoproxil or TAF. In addition, no clinically relevant DDIs are expected when JNJ-6379 or JNJ-3989 are combined with ETV, or tenofovir disoproxil, or TAF.

2.2.2.3. Combination of JNJ-3989 or JNJ-6379 With PegIFN-α2a

2.2.2.3.1. Combination of JNJ-6379 With PegIFN-α2a

As there is no appropriate species for studying the combination of JNJ-6379 with PegIFN-α2a, an in vitro study on human bone marrow derived erythroid and myeloid progenitors using colony forming assays was conducted. JNJ-6379 (5-100 µM) and PegIFN-α2a (Pegasys®, 0.00005-0.1 µM) were tested in combination in order to evaluate their potential additive or synergistic effects (study TOX14629).

The half maximal inhibitory concentration (IC_{50}) values of the combination treatment were markedly lower compared to JNJ-6379 alone for all tested concentrations but similar to the values with PegIFN-α2a alone. When the higher concentrations of PegIFN-α2a were tested in

combination with JNJ-6379, the reduction in colonies was mainly due to the strong toxicity of PegIFN-α2a at these concentrations.

Comparing the predicted (adding the percent of reduction of JNJ-6379 and PegIFN-α2a alone) and the actual percent reduction in colonies relative to the solvent control, it became clear that there were only minimal differences, pointing more to an additive effect and not a synergistic effect when JNJ-6379 and PegIFN-α2a were combined.

2.2.2.3.2. Combination of JNJ-3989 with PegIFN-α2a

The objective of study TOX14273 was to determine the potential additive or synergistic effects when combining JNJ-3989 (60 or 180 mg/kg, once monthly) with PegIFN-α2a (Pegasys® 0.015 mg/kg twice weekly) given subcutaneously for 3 months to the Cynomolgus monkey (study TOX14273).

There were no JNJ-3989 related mortalities. JNJ-3989 (alone or combined with PegIFN-α2a) was well tolerated and did not induce relevant effects on clinical signs, body weight, food consumption, ophthalmoscopic examination, electrocardiology evaluation, coagulation, clinical chemistry or urinalysis parameters, cytokines IP-10 and IFNα, as well as organ weight and macroscopic examination.

JNJ-3989 induced minimal to mild hematological changes starting at 60 mg/kg. These clinical pathology changes were limited to transient, non-dose-related increases in neutrophils and total white blood cells in males and females administered 180 mg/kg JNJ-3989 alone or in combination ≥60/0.015 mg/kg JNJ-3989/PegIFN-α2a on Day 30 only. In addition, comparable transient increases in neutrophils and total white blood cells were also observed in both males and females administered 0.015 mg/kg PegIFN-α2a alone.

PegIFN-α2a induced increases in IFNα and IP-10 after the first injection. Levels were at baseline values prior to dosing on Day 30 and no increases were observed after dosing as well as after dosing on Day 90. Combination of JNJ-3989 at 60 or 180 mg/kg with PegIFN-α2a did not induce any further effects than the increases observed with PegIFN-α2a given alone.

JNJ-3989 induced microscopic findings in the lymph nodes and liver. In the mesenteric, axillary, popliteal and/or other lymph nodes, minimal to mild vacuolation of macrophages were observed in both sexes administered ≥60 mg/kg/0.015 mg/kg JNJ-3989/PegIFN-α2a or 180 mg/kg JNJ-3989 alone. In the liver, minimal hypertrophy of Kupffer cells was observed in 1 female administered 180 mg/kg/0.015 mg/kg JNJ-3989/PegIFN-α2a and 2 females administered 180 mg/kg JNJ-3989 alone. The microscopic changes were comparable between the animals administered with JNJ-3989 alone or in combination with PegIFN-α2a indicating an absence of additive or synergistic effect.

In conclusion, the intermittent subcutaneous administration of JNJ-3989 given alone or combined with PegIFN-α2a for 3 months was well tolerated in Cynomolgus monkeys at levels of 60 and 180 mg/kg. Treatment only induced transient hematological changes and microscopic findings in liver and lymph nodes, all considered as non-adverse. The administration of JNJ-3989 in

combination with PegIFN-α2a did not amplify any toxicological effect. Based on these results, there are no additive or synergistic effects on the toxicological profile and no DDI when the test item is combined with the reference item. The NOAEL of the test item was considered to be CCI mg/kg per administration, whether given alone or in combination with the reference item.

2.2.3. Clinical Studies

2.2.3.1. JNJ-3989 and JNJ-6379

JNJ-3989

At the time of protocol writing, JNJ-3989 is being evaluated in 5 clinical studies. One Phase 1 study (Study 73763989HPB1001) in healthy adult Japanese participants is completed. One Phase 1/2a study (Study AROHBV1001) with a single ascending dose part in healthy adult participants and a multiple ascending dose part in adult participants with CHB is completed with final analysis and report writing ongoing. One Phase 1 study (Study 73763989HPB1002) in adult participants with or without hepatic impairment, and 2 Phase 2 studies (Study 73763989HPB2001 [REEF-1] and Study 73763989PAHPB2002 [REEF-2]) in adult CHB participants are ongoing. In total, 58 healthy, 435 CHB participants, and 6 participants with moderately impaired hepatic function have been dosed in the aforementioned studies.

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 incidences and resolved while on study treatment.

Efficacy was assessed using snapshot data through 26 March 2020. Antiviral activity data were available for 56 CHB participants who received 3 subcutaneous injections of 25 to 400 mg JNJ-3989 every 4 weeks (Q4W). The antiviral activity data showed that administration of JNJ-3989 at doses of 25 to 400 mg resulted, on average, in pronounced HBsAg decline which was generally sustained at least until Day 168 (ie, 16 weeks after last dose) across all doses. No apparent dose response was observed at doses between 100 and 400 mg JNJ-3989; a numerically smaller mean decline was observed at the lower doses of 25 and 50 mg, mainly apparent after end of JNJ-3989 dosing. Treatment status (ie, virologically suppressed or not treated) did not seem to affect HBsAg changes. Other measurable serological and virological markers (HBV DNA, HBV RNA, HBeAg, hepatitis B core-related antigen [HBcrAg]) also showed responses to JNJ-3989, indicating that JNJ-3989 shows target activity on all detectable viral products.

JNJ-6379

At the time of protocol writing, 148 healthy and 242 CHB-infected participants have been dosed with JNJ-6379 in 7 completed Phase 1 studies (56136379HPB1001, 56136379HPB1002,

56136379HPB1003, 56136379HPB1004, 56136379HPB1005, 56136379HPB1007, and 56136379HPB1008), 1 completed Phase 2 study (56136379HPB2001, also referred to as JADE; final analysis and report writing are currently ongoing), and 1 ongoing Phase 1 study (56136379HPB1006).

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 pharmacokinetic (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 $AUC_{0\text{-}24h}$ 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 drug exposure levels using a novel tablet formulation, containing hydroxypropylmethylcellulose E5-based spray-dried powder, were similar to exposure levels observed in Study 56136379HPB1001 using the original formulation, both in fed conditions. The relative bioavailability of new 25-mg oral tablets of JNJ-6379 administered as a 150-mg dose under fasting and fed conditions, and of new 100-mg oral tablets of JNJ-6379 administered as a 300-mg dose under fasting conditions, was assessed in healthy adult participants. Assuming proportionality, based on the geometric mean ratios between the 3x 100-mg dose, fasting (test) and the 6x 25-mg dose, fasting (reference) of the dose-normalized PK parameters, C_{max} was 21.56% lower for the 100-mg tablet strength compared to the 25-mg tablet strength, and $AUC_{0\text{-}last}$ and AUC_{∞} were similar. The median time to reach C_{max} (t_{max}) was around 1.75 hours when 150 mg JNJ-6379 was dosed as 6x 25-mg oral tablets, and around 3.00 hours when 300 mg JNJ-6379 was dosed as 3x 100-mg oral tablets.

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

parameter values are comparable to the PK parameters obtained after administration of JNJ-6379 formulated as hydroxypropylmethylcellulose E5-based spray-dried powder tablet.

Multiple-dose Studies in Healthy Participants

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

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

Multiple-dose Studies in Chronic HBV-infected Participants

In Sessions 8, 9, 10, 11, and A of Study 56136379HPB1001, treatment-naïve chronic HBV-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

Oral contraceptives: When administered simultaneously with 3 mg drospirenone/0.02 mg ethinylestradiol in Study 56136379HPB1004, JNJ-6379 increases the extent of exposure and decreases the CL/F of ethinylestradiol while the peak plasma concentration decreased. In contrast, JNJ-6379 has no clear effect on the extent of exposure and CL/F of drospirenone, a cytochrome P450 (CYP)3A4-sensitive progestin: peak plasma concentration decreased while no change in exposure and apparent clearance was observed. Consequently, oral contraceptives are still

considered to be effective when administered simultaneously with JNJ-6379. However, as a precaution to avoid high exposure to ethinylestradiol, ethinylestradiol-containing contraceptives are only allowed if the ethinylestradiol content is ≤20 µg.

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

Itraconazole: In Study 56136379HPB1008, coadministration of a single 250-mg dose of JNJ-6379 with multiple-dose itraconazole 200 mg QD, a strong inhibitor of CYP3A, CYP2C19, P-gp, and BCRP, showed a 1.38-fold increase in the $AUC_{0\text{-}408h}$ of JNJ-6379 compared to when JNJ-6379 was given alone. Oral administration of JNJ-6379 as a single dose and in combination with itraconazole under fed conditions was generally safe and well tolerated in this study.

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 (unblinded Week 24 data) are available from the Phase 2a JADE study. In this study, 232 chronic HBV-infected participants were randomized to receive JNJ-6379 QD (75 or 250 mg) or placebo in combination with an NA (tenofovir disoproxil/ETV) or JNJ-6379 (75 or 250 mg) alone. Of these, 172 participants were enrolled in the combination treatment arms: 88 chronic HBV-infected participants not treated at screening and 84 virologically suppressed chronic HBV-infected participants. Of the 88 participants not treated at screening, 33 received 75 mg QD JNJ-6379 in addition to an NA, 33 received 250 mg QD JNJ-6379 in addition to an NA, and 22 received placebo in addition to an NA. Of the 84 virologically suppressed participants, 33 received 75 mg QD JNJ-6379 in addition to an NA, 30 received 250 mg QD JNJ-6379 in addition to an NA, and 21 received placebo in addition to an NA.

In currently not treated HBeAg-positive participants (mean baseline HBV DNA levels 7.65 to 8.24 $\log_{10}$ IU/mL), there were pronounced declines in mean (standard error [SE]) HBV DNA from baseline of 5.53 (0.23) and 5.88 (0.34) $\log_{10}$ IU/mL for JNJ-6379 75 mg and 250 mg + NA, respectively, and 5.21 (0.42) $\log_{10}$ IU/mL for placebo + NA. In currently not treated HBeAg-negative participants (mean baseline HBV DNA levels 4.89 to 5.40 $\log_{10}$ IU/mL), interpretation of mean (SE) HBV DNA decline was confounded since many participants had HBV DNA < lower limit of quantification (LLOQ) from Week 4 onwards.

In currently not treated participants, JNJ-6379 75 mg and 250 mg + NA showed a clear mean (SE) HBV RNA decline from baseline (2.82 [0.25] and 3.13 [0.35] $\log_{10}$ copies/mL, respectively) compared with placebo + NA (1.43 [0.32] $\log_{10}$ copies/mL), thereby differentiating JNJ-6379 from

NAs. HBV RNA was target not detected (TND) at Week 24 in 16/27 (59%), 19/25 (76%) and 9/20 (45%) participants, respectively.

The 24-week interim efficacy data in virologically suppressed participants showed that most participants had HBV DNA levels below the limit of quantification at baseline. All virologically suppressed participants on JNJ-6379 + NA who had detectable HBV RNA at baseline achieved HBV RNA TND at Week 24 (13/13 participants on 75 mg JNJ-6379 and 8/8 participants on 250 mg JNJ-6379) vs 1/7 (14%) participants on placebo + NA.

In currently not treated HBeAg-positive participants, JNJ-6379 75 mg and 250 mg + NA resulted in a mean (SE) HBsAg decline of 0.13 (0.10) and 0.40 (0.15) $\log_{10}$ IU/mL, respectively, compared with 0.22 (0.11) for placebo + NA at Week 24. Participants with HBsAg declines also had HBeAg declines and frequently had early on-treatment isolated ALT flares. In both JNJ-6379 + NA arms:

- Maximal individual HBsAg and HBeAg reductions were 1.28 and 1.8 $\log_{10}$ IU/mL, respectively, at Week 24;
- The proportion of currently not treated HBeAg-positive participants with >0.3 $\log_{10}$ IU/mL reductions from baseline in:
  - HBsAg was 8/23 (35%) vs 1/8 (13%) for placebo + NA;
  - HBeAg was 19/23 (83%) vs 4/8 (50%) for placebo + NA;
- The proportion of virologically suppressed HBeAg-positive participants with >0.3 $\log_{10}$ IU/mL reductions in HBeAg was 7/19 (37%) vs 1/5 (20%) for placebo + NA.

No cases of virologic breakthrough were observed in any of the arms combining JNJ-6379/placebo with NA treatment. Confirmed viral breakthrough (defined as confirmed on-treatment HBV DNA increase by >1 $\log_{10}$ IU/mL from nadir) occurred in 5/28 participants on JNJ-6379 75 mg monotherapy. All 5 participants with virologic breakthrough had an emerging core amino acid mutation T33N (JNJ-6379 fold change of 85), 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. A futility rule was implemented in the 250-mg JNJ-6379 monotherapy arm (if ≥1 participant in the 250-mg monotherapy arm experienced virologic breakthrough during the first 24 weeks of treatment, NA treatment was to 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 with non-response (<1 $\log_{10}$ IU/mL decline from baseline at Week 4) had subsequent virologic breakthrough. This participant (genotype E) carried I105T baseline polymorphism (fold change of 2.7) and had no emerging mutations at HBV core protein positions of interest. The participant discontinued JNJ-6379 treatment and started NA treatment at the withdrawal visit, due to meeting non-response criteria. NA treatment was 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 the Week 24 interim analysis (IA) conducted for the Phase 2a JADE study, which was mentioned above. There were no deaths or SAEs considered at least possibly related to the study intervention. Most AEs were grade 1 or 2 in severity. The majority of reported AEs were considered unrelated to JNJ-6379 by the investigator. Adverse events leading to treatment discontinuation were reported in 1 participant on placebo + NA (abdominal discomfort/gastrointestinal upset) and 1 participant on JNJ-6379 75 mg + NA (streptococcal toxic shock syndrome, acute cardiac failure, myocarditis and muscle necrosis). Most frequent grade 3 or 4 AEs were gastrointestinal disorders (colitis and dyspepsia in the placebo + NA arm) and investigations (ALT and ALT elevations in the JNJ-6379 75 mg + NA and JNJ-6379 250 mg + NA arms).

Increased cholesterol is considered a laboratory abnormality of interest for JNJ-6379, based on safety review from nonclinical and clinical studies. 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 Phase 1/2a AROHBV1001 study (Cohort 12). Twelve adult chronic HBV mono-infected participants have received 3 subcutaneous 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 IA cut-off date of 29 October 2019, no deaths, SAEs, or treatment-emergent adverse events (TEAEs) leading to study drug 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 drug 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).

Since the initial protocol writing, interim results of the REEF-1 and REEF-2 studies had become available. In the primary REEF-1 analysis (Week 48, end of treatment) the mean reduction of HBsAg levels in the triple arm (JNJ-6379+JNJ-3989 100mg+NA) appeared to be less than in the dual arm (JNJ-3989 100mg+NA). More recent interim results of the REEF-2 study (Week 48, end of treatment) confirmed this observation when the effect of JNJ-6379+JNJ-3989 200mg+NA on mean HBsAg level reduction in REEF-2 study is compared to JNJ-3989 200mg+NA in the REEF-1 study. To match with the REEF-2 population, this cross-study comparison focused on the REEF-1 subpopulation of HBeAg negative, virologically suppressed participants with chronic hepatitis B. PK-PD modelling analyses accounting for variability in baseline characteristics further support this observation. Therefore, a negative effect of JNJ-6379 on the HBsAg lowering effect of JNJ-3989+NA is suspected.

2.2.3.2. 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.

There is no common target organ between JNJ-6379 or JNJ-3989 and ETV (Memorandum 2005).

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

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

The single common toxicity target organ between JNJ-6379, JNJ-3989, and tenofovir disoproxil or TAF is the kidney (see Section 2.2.2.2, Combination of JNJ-3989 or JNJ-6379 With Entecavir, Tenofovir Disoproxil, or Tenofovir Alafenamide).

Clinical data on dual combination treatment of JNJ-6379 and NA are available from the ongoing Phase 2a 56136379HPB2001 study (IB JNJ-6379 2021). In participants treated with tenofovir disoproxil, C_{trough} concentrations of tenofovir at Week 12 were higher in participants receiving tenofovir disoproxil in combination with JNJ-6379 than in participants receiving tenofovir disoproxil as monotherapy (94.2 [30.0] and 115 [66.0] ng/mL for 75- and 250-mg JNJ-6379, respectively in combination with tenofovir disoproxil, vs 66.8 [37.0] ng/mL as tenofovir disoproxil monotherapy).

Clinical data of triple combination treatment of JNJ-3989, JNJ-6379, and NA are available from the Phase 1/2a AROHBV1001 study (see Section 2.2.3.1, JNJ-3989 and JNJ-6379). Dosing JNJ-6379 with NA for 12 weeks did not show any clinically relevant changes in kidney parameters/glomerular function.

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

Overall Assessment of the Combination Therapy

Based on the points listed below, no clinically relevant DDIs and no specific concerns about additive or synergistic toxicities in the kidney are expected when JNJ-6379 or JNJ-3989 are combined with ETV, or tenofovir disoproxil, or TAF:

- Available toxicology data, described in Section 2.2.2.2, Combination of JNJ-3989 or JNJ-6379 With Entecavir, Tenofovir Disoproxil, or Tenofovir Alafenamide.
- In vitro drug transporters.
- Metabolic interaction data.
- Absence of relevant DDIs in the combination toxicity studies up to 3 months with JNJ-6379 and JNJ-3989.
- Absence of synergistic or additive histology findings in the kidney observed in the combination toxicity studies up to 3 months with JNJ-6379 and JNJ-3989.
- Available clinical data with JNJ-6379 (JADE study [56136379HPB2001]) up to 24 weeks treatment on the absence of changes in kidney parameters/glomerular function.
- Available clinical data of triple combination treatment of JNJ-3989, JNJ-6379, and NA described in Section 2.2.3.1, JNJ-3989 and JNJ-6379.

In addition, pancytopenia in 1 rat and a mild platelet decrease were seen in the combination groups in the 3-month combination toxicity study (preliminary data, Section 2.2.2.1, JNJ-3989 and JNJ-6379). No significant abnormalities of hematologic parameters have been observed in clinical studies to date. The sponsor is implementing additional monitoring of significant on-treatment hematologic changes in clinical studies with dosing longer than 4 weeks (see Section 8.3.6.6, Hematologic Abnormalities). For further information, refer to the latest version of the IBs for JNJ-3989 and JNJ-6379 (IB JNJ-3989 2020; IB JNJ-6379 2021).

2.2.3.3. Combination of JNJ-3989 and JNJ-6379 with PegIFN-α2a

PegIFN-α2a is a covalent conjugate of recombinant alfa-2a interferon that is indicated for the treatment of CHB in adult and pediatric patients at least 3 years of age. In addition, PegIFN-α2a in combination with other medicinal products is indicated for the treatment of chronic hepatitis C virus (HCV)-infection in adult and pediatric patients at least 5 years of age and not treated before. The most common adverse reactions (≥10% of participants) are anorexia, anxiety, headache, concentration impairment, dyspnea, cough, alopecia, dermatitis, pruritis, dry skin, myalgia, arthralgia, asthenia, pyrexia, and fatigue. For further information regarding PegIFN-α2a, refer to the currently approved prescribing information.

Treatment with PegIFN-α2a has been associated with decreases in platelet count (common adverse reaction). In the Phase 1/2a AROHBV1001 study (see Section 2.2.3.1, JNJ-3989 and JNJ-6379), no effect on platelet count has been observed in the triple combination treatment cohort 12 (JNJ-3989, JNJ-6379, and NA). Of the 84 adult chronic HBV-infected participants that received 3 subcutaneous injections of JNJ-3989, 6 participants developed grade 1 platelet reduction with no general trend towards a continuous decline. For JNJ-6379, no effect on platelet count has been observed in ongoing Phase 2a 56136379HPB2001 study (JADE) for the 189 adult chronic HBV-infected participants that were dosed with JNJ-6379.

Based on pre-clinical data, a potential common toxicity target organ between JNJ-6379, JNJ-3989, and PegIFN-α2a is the bone marrow (see Section 2.2.2, Nonclinical Studies). Bone marrow suppression is a known side effect of PegIFN-α2a (rare).

No PK interaction is expected between JNJ-3989 or JNJ-6379 and PegIFN-α2a based on the known pharmacologic profile of the compounds (IB JNJ-3989 2020; IB JNJ-6379 2021; Yeh 2019).

Since initial protocol writing, 2 clinical studies using the combination of JNJ-3989 and PegIFN-α2a are ongoing: REEF-IT and PENGUIN. Nonclinical studies to investigate the effect on platelet count decreases were completed and results are summarized in Section 2.2.2.3, Combination of JNJ-3989 or JNJ-6379 With PegIFN-α2a. Up to 48-week hematology data from the ongoing Phase 2 clinical study REEF-1 are available and overall around 5% of the participants experienced AEs or laboratory abnormalities related to hematologic abnormalities, the majority of mild to moderate severity. The hematologic abnormalities resolved on continued JNJ-3989+NA treatment.

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 (IB JNJ-3989 2020; IB JNJ-6379 2021).

For the benefit-risk evaluation of ETV, tenofovir disoproxil, TAF, and PegIFN-α2a, refer to the respective prescribing information and Summary of Product Characteristics.

JNJ-6379 was initially part of the study intervention but has been removed as study intervention with the implementation of an urgent safety measure, as described in Protocol Amendment 3. Emerging data from the REEF-1 and REEF-2 studies resulted in an unfavorable benefit-risk balance of JNJ-6379 in combination with JNJ-3989+NA, compared to JNJ-3989+NA alone. Therefore, the Sponsor decided to discontinue treatment with JNJ-6379 in all ongoing clinical studies effective immediately and as an urgent safety measure. Participants who were on treatment with JNJ-6379 were contacted and requested to stop taking JNJ-6379, while continuing treatment with NA, JNJ-3989 and PegIFN-α2a. For newly enrolled participants, JNJ-6379 was taken out of the treatment regimen. For completeness, the benefit-risk assessment for JNJ-6379 is still included in this section.

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, NAs, and PegIFN-α2a may be useful for the development of a novel therapeutic approach for chronic HBV infection.

The combination of JNJ-6379 and JNJ-3989 on a background of NAs would target different stages of the viral life cycle. While NA treatment reduces HBV DNA to levels close to or below the LLOQ of the HBV DNA assay, HBV replication is not completely inhibited, resulting in replenishment of the cccDNA pool. The addition of JNJ-6379, which targets the HBV capsid assembly ("primary" mode of action [MoA]) and the de novo cccDNA formation ("secondary" MoA), is expected to block HBV replication more profoundly by inhibiting formation of HBV RNA and DNA containing particles, and to inhibit de novo cccDNA formation, ultimately leading to reduction in cccDNA levels/transcriptional activity and HBsAg seroclearance ("intensified viral suppression"). The addition of JNJ-3989 is expected to intensify viral suppression 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 (Fang 2015; Li 2018; Wang 2013). By acting on both viral replication and by reducing barriers to the host immune-responses, higher functional cure rates may be achieved.

The addition of short-term PegIFN-α2a (12 weeks) to the regimen may lead to further improvement of the immune response (such as reactivation of NK-cells) and ultimately could lead to immune control of HBV (ie, functional cure). In addition, PegIFN-α2a has shown to have direct antiviral effects on HBV which could also contribute to the efficacy of the regimen. By adding short-term PegIFN-α2a to the regimen, 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.

Side effect profile of PegIFN-α2a is well established and includes, but is not limited to, neuropsychiatric, autoimmune, ischemic, ophthalmologic, hematological, and infectious disorders. In many, but not all cases, these disorders resolve after stopping PegIFN-α2a therapy. For a full list of known risks for PegIFN-α2a, refer to the respective prescribing information and Summary of Product Characteristics.

2.3.2.2. Potential Risks

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

Patients with positive HBV DNA and positive HBsAg can always experience increases in liver transaminases which may indicate immune activation and may result in the reduction of viral parameters such as HBV DNA and/or HBsAg/HBeAg. 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, Background, for details on the safety results in the studies conducted to date.

2.3.2.2.1. Potential Risks for JNJ-3989

Reproductive Risks and Pregnancy

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

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

Potential Genotoxicity

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

Other Potential Toxicity/Events of Special Interest

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

Viral Resistance

Treatment with JNJ-3989 may lead to viral resistance, but resistance to JNJ-3989 is not anticipated to impact treatment with other 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

Since the initial protocol writing, interim results of the REEF-1 and REEF-2 studies had become available. The data suggested that JNJ-6379 has a negative impact on the HBsAg lowering effect of JNJ-3989+NA (see Section 2.2.3.1). In addition, there were new insights in the adverse renal profile of JNJ-6379, resulting from increase in biomarkers of proximal renal tubular injury observed in REEF-2. Taken together, it was concluded that JNJ-6379 had an unfavorable benefit-risk balance in combination with JNJ-3989+NA, compared to JNJ-3989+NA alone. Therefore, the

Sponsor decided to discontinue treatment with JNJ-6379 in all ongoing clinical studies effective immediately. For completeness, the potential risks for JNJ-6379 are still described in this section.

Reproductive Risks and Pregnancy

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

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

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

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

Potential Genotoxicity

JNJ-6379 was not genotoxic in the in vitro and in vivo tests.

JNJ-6379 did not affect male or female fertility. Carcinogenicity studies are not yet conducted.

Other Potential Toxicity/Events of Special Interest

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

Viral Resistance

Treatment with JNJ-6379 may lead to emergence of viral variants with reduced susceptibility or resistance to JNJ-6379. Based on nonclinical data, these variants remain susceptible to tenofovir disoproxil 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 2.2.3.1, JNJ-3989 and JNJ-6379, for the results of the IA).

Drug-drug Interactions

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

2.3.2.2.3. Potential Risks for Entecavir, Tenofovir Disoproxil, Tenofovir Alafenamide, and PegIFN-α2a

For the general potential risks of ETV, tenofovir disoproxil, TAF, and PegIFN-α2a, refer to the respective prescribing information and Summary of Product Characteristics.

Risks specific for this study design are listed below:

- PegIFN-α2a might increase the immunogenicity of JNJ-3989.
- Combination of PegIFN-α2a with JNJ-3989 and JNJ-6379 might increase the risk of hematologic abnormalities and/or of bone marrow suppression.
- JNJ-6379 might increase tenofovir plasma concentrations.

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 Phase 1/2a Study AROHBV1001 (see Section 2.2.3, Clinical Studies). All but one AE were mild or moderate in severity. All ISRs, identified as adverse drug reactions for JNJ-3989, were mild in intensity.
- No clinically significant safety concerns had been raised for JNJ-6379 at the time of initial protocol writing, based on the safety information from studies in healthy adult participants and adult participants with chronic HBV infection. Most observed AEs at that time were mild in severity and considered not related to JNJ-6379 by the investigator (see Section 2.2.3, Clinical Studies). At the time of Protocol Amendment 3 writing, it was concluded that JNJ-6379 has an unfavorable benefit-risk balance in combination with JNJ-3989+NA, compared to JNJ-3989+NA alone (see Section 2.3.2.2.2). Therefore, the Sponsor decided to discontinue treatment with JNJ-6379 in all ongoing clinical studies effective immediately, as a measure to minimize risk to participants of this and other study.
- Events of Special Interest are significant AEs that are judged to be of special interest because of clinical importance, known class effects or based on nonclinical signals. Events of Special Interest that will be carefully monitored during the study include ISRs, ALT/AST elevations, renal complications, hematologic abnormalities, and events related to cholesterol increase (see Section 8.3.6, Adverse Events of Special Interest, and Section 8.2.4, Clinical Safety Laboratory Assessments). In addition, the following toxicities will also be carefully monitored: rash and acute systemic allergic reactions (Section 8.3.6, Adverse Events of Special Interest).
- Continued careful assessment of the safety, efficacy, and PK during treatment is included in this study.
- To minimize potential risk and stress to participants, the following measures are in place:
  - Utilization of selection criteria which exclude participants who may potentially be at higher risk of an AE (see Section 5, Study Population).

- Utilization of withdrawal criteria (see Section 7, Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal). If a participant drops out due to withdrawal of consent, he/she retains the option to participate in the safety follow-up procedures.
- At regular time points throughout the study (see Schedule of Activities), blood samples for biochemistry, blood coagulation, and hematology and urine samples for urinalysis, urine chemistry, and renal biomarkers will be collected. Vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature), height (only at screening), body weight, and electrocardiograms (ECGs) will be recorded throughout the study. Physical examinations will be performed and AEs will be assessed (see Section 8.2, Safety Assessments). Events of Special Interest will be closely monitored (Section 8.3.6, Adverse Events of Special Interest).

- Based on pre-clinical and clinical data available today, the combination of JNJ-3989, NA (ETV, tenofovir disoproxil, or TAF), and PegIFN-α2a is considered safe. Data from nonclinical combination toxicity studies (Section 2.2.2.3, Combination of JNJ-3989 or JNJ-6379 With PegIFN-α2a) confirmed that combination of PegIFN-α2a with JNJ-3989 did not induce any synergistic or additive effect in monkeys up to 3 months of treatment and combination of PegIFN-α2a with JNJ-6379 induces minimal additive effect in in vitro study. Forty-eight (48)-week hematology data of ongoing Phase 2 clinical study REEF-1 (Section 2.2.3.3, Combination of JNJ-3989 and PegIFN-α2a) has been reviewed and no safety concern has been identified.
- An internal Data Review Committee (DRC) will be established for continuous monitoring of SAEs, AEs leading to discontinuation, and ALT flares to ensure the continuing safety of the participants enrolled in the current study (see Section 9.6, Data Review Committee). In addition, an Independent Flare Expert Panel (IFLEP) will be appointed to characterize and adjudicate each ALT flare (see Section 9.7, Independent Flare Expert Panel).
- After stopping treatment with JNJ-3989, JNJ-6379, PegIFN-α2a, and NA, if NA completion criteria are met at Week 24 (EOSI), participants will be monitored closely during the FU Period, with frequent follow-up visits and pre-defined NA re-treatment criteria in case of flares (Section 6.7.1, NA Re-treatment Criteria and Monitoring After Stopping of NA).
- The post-treatment monitoring and NA re-treatment criteria were further updated based on findings from a case of post-treatment HBV reactivation with subacute hepatic failure and assessment of additional REEF-2 study data (Section 6.7.1, NA Re-treatment Criteria and Monitoring After Stopping of NA)
- JNJ-3989 will be administered using a proper subcutaneous technique to decrease the risk of ISRs. ISRs will be managed as outlined in Section 8.3.6, Adverse Events of Special Interest.
- Any clinically significant abnormalities persisting at the end of the study/early discontinuation will be followed up by the investigator until resolution (return to baseline) or until stabilization (to be agreed upon with the sponsor).

3. OBJECTIVES AND ENDPOINTS

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

Objectives	Endpoints
Primary	
• To evaluate the efficacy in terms of HBsAg levels of the study intervention (ie, JNJ-3989 + JNJ-6379[d] + NA and PegIFN-α2a).	• Proportion of participants with a reduction of at least 2 $\log_{10}$ IU/mL in HBsAg levels from baseline to Week 24 (end of study intervention [EOSI]).
Secondary	
• To evaluate the safety and tolerability of the study intervention.	• Safety and tolerability including but not limited to the proportion of participants with (S)AEs and abnormalities in clinical laboratory tests (including hematology, blood biochemistry, blood coagulation, urinalysis, urine chemistry, renal biomarkers), 12-lead ECGs, vital signs, and ophthalmic and physical examinations throughout the study.
• To evaluate the efficacy of the study intervention at the end of the 24-week treatment period.	• Proportion of participants meeting the protocol-defined NA treatment completion criteria at EOSI.
• To evaluate the efficacy of the study intervention as measured by blood markers (such as HBsAg, HBeAg[a], HBV DNA, and ALT) during the study intervention and follow-up (FU) period.	• Proportion of participants with HBeAg[a], HBsAg, HBV DNA, and ALT levels below/above different cut-offs. • Proportion of participants with HBsAg and/or HBeAg[a] seroconversion. • Change from baseline over time in HBsAg, HBeAg[a], and/or HBV DNA. • Time to achieve HBsAg and/or HBeAg[a] seroclearance/seroconversion, and/or HBV DNA <LLOQ.
• To evaluate the frequency of virologic breakthrough[b] during the 24-week treatment period, as well as during the FU period for participants who continue treatment with NA.	• Proportion of participants with virologic breakthrough[b].
• To evaluate the efficacy of the study intervention during the FU period.	• Proportion of participants with HBsAg seroclearance at Week 48 (ie, 24 weeks after completion of all study interventions at Week 24) without re-starting NA treatment. • Proportion of participants with HBV DNA <LLOQ at Week 48 (ie, 24 weeks after completion of all study interventions at Week 24) without re-starting NA treatment. • Frequency of virologic and/or biochemical flares.

Objectives	Endpoints
	• Proportion of participants requiring NA re-treatment.
• To evaluate the PK of JNJ-3989 (JNJ-3924 and JNJ-3976) and optionally of JNJ-6379, NA and PegIFN-α2a.	• PK parameters of JNJ-3989 (JNJ-3924 and JNJ-3976). • Optionally, PK parameters of JNJ-6379, NA and/or PegIFN-α2a compared to historical data.
Exploratory	
• To explore host and viral baseline and on-treatment markers associated with end of treatment and/or off-treatment response.	• Association of baseline characteristics and baseline/on-treatment host and viral blood markers (such as age and HBsAg levels) with selected on or off-treatment efficacy variables.
• To explore changes in the severity of liver disease.	• Changes in fibrosis (according to Fibroscan liver stiffness measurements) at EOSI and the end of the FU period versus baseline.
• To explore efficacy of the study intervention in terms of changes in HBV RNA and HBcrAg levels during the study intervention and FU period.	• Changes from baseline in HBV RNA and HBcrAg levels over time.
• To explore the relationship of PK with selected pharmacodynamic (PD) parameters of efficacy and safety.	• Relationship of various PK parameters with selected efficacy and safety endpoints.
• To explore the effect of PegIFN-α2a coadministration on the PK of JNJ-3989 (JNJ-3924 and JNJ-3976) and JNJ-6379[e], as applicable (PK substudy).	• Effect of PegIFN-α2a coadministration on the PK of JNJ-3989 (JNJ-3924 and JNJ-3976) and JNJ-6379, as applicable.
• To explore the HBV genome sequence during the study intervention and FU period.	• Assessment of intervention-associated mutations over time.
• To explore HBV-specific T-cell responses during the study intervention and FU period.[c]	• Changes from baseline in HBV-specific peripheral blood T-cell responses over time.[c]
• To explore the efficacy of NA re-treatment in participants who meet the criteria for NA re-treatment.	• Proportion of participants who reach HBV DNA <LLOQ after re-start of NA treatment during the FU period.

[a] In HBeAg-positive participants only.
[b] For the definition of virologic breakthrough, refer to Section 10.1, Appendix 1: Abbreviations and Definitions of Terms.
[c] Peripheral blood mononuclear cell (PBMC) samples for immune analyses will be collected at selected sites only.
[d] As of Protocol Amendment 3, JNJ-6379 has been removed as study intervention and the study will continue with JNJ-3989, NA and PegIFN-α2a only. Participants had to stop JNJ-6379 treatment immediately.
[e] Not all participants completed treatment with JNJ-6379, as JNJ-6379 has been removed as study intervention with the implementation of Protocol Amendment 3.

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

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

HYPOTHESIS

As this is an exploratory single-arm study, no formal statistical hypothesis has been formulated.

4. STUDY DESIGN

4.1. Overall Design

This ISA describes a Phase 2a study of the combination regimen of JNJ-3989 with NA and PegIFN-α2a. Prior to Protocol Amendment 3, the study intervention also included JNJ-6379. This ISA is a companion document to the Master Protocol PLATFORMPAHPB2001, which describes the common design elements of the Platform study in participants with CHB. This ISA describes specific and/or additional protocol elements applicable to this open-label, single-arm, multicenter, interventional study to evaluate the efficacy, safety, tolerability, and PK of the combination of JNJ-3989, NAs, and PegIFN-α2a in approximately 50 patients with CHB.

Note that as of Protocol Amendment 3, JNJ-6379 has been removed as study intervention and the study will continue with JNJ-3989, NA and PegIFN-α2a only. Participants had to stop JNJ-6379 treatment immediately.

Approximately 50 virologically suppressed CHB-infected participants, 18-65 years (inclusive) of age, will be enrolled in this study. Approximately 40% HBeAg-positive participants will be enrolled.

This open-label study will be conducted in 4 periods:

- Screening Period (4 weeks [if necessary, can be extended to a maximum of 8 weeks decided on a case-by-case basis and in agreement with the sponsor]).
- Treatment Period 1 (12 weeks) consisting of combination treatment with JNJ-3989 + NA.
- Treatment Period 2 (12 weeks) adding PegIFN-α2a to the combination treatment regimen of Treatment Period 1.
- Follow-up (FU) Period (48 weeks).

The total duration of individual participation will be up to 76 weeks (including 4 weeks of screening).

Enrolled participants will start Treatment Period 1 with the following combination treatment regimen for a duration of 12 weeks:

200 mg JNJ-3989 (subcutaneous injection Q4W) +

NA (tablets QD): tenofovir disoproxil (245 mg), or TAF (25 mg), or ETV (0.5 mg).At Week 12, participants who still meet the eligibility criteria for PegIFN-α2a (see Section 5.2, Exclusion Criteria) will start Treatment Period 2 for a duration of 12 weeks:

200 mg JNJ-3989 (subcutaneous injection Q4W) +

NA (tablets QD): tenofovir disoproxil (245 mg), or TAF (25 mg), or ETV (0.5 mg) +

180 µg PegIFN-α2a (subcutaneous injection once weekly).Participants no longer meeting the PegIFN-α2a eligibility criteria at Week 12 will continue with the Period 1 treatment until Week 24.

At Week 24, all participants will stop treatment with JNJ-3989 + PegIFN-α2a and start the FU Period. If the protocol-defined NA treatment completion criteria (HBsAg <10 IU/mL, and HBeAg-negative, and HBV DNA <LLOQ, and ALT <3x ULN) have been met at Week 24, NA will be stopped at the next scheduled visit (ie, FU Week 2), otherwise NA treatment will continue during the complete FU Period. Participants who meet the protocol-defined NA treatment completion criteria will be monitored closely during the 48-week FU Period and should re-start NA treatment immediately if NA re-treatment criteria are met (see Section 6.7.1, NA Re-treatment Criteria and Monitoring After Stopping of NA, for more details).

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

Participants may optionally participate in a PK substudy. Participants in the PK substudy will have intensive blood sampling for PK of JNJ-3989, and optionally for PK of NA and PegIFN-α2a, over 24 hours at Week 4 (or 8) during Treatment Period 1 and at Week 20 (or 16) during Treatment Period 2.

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

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

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

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

A population PK analysis may be performed based on the available data for JNJ-3989 (ie, JNJ-3976 and JNJ-3924), 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 (see Section 8.5, Pharmacokinetics). To assess the effect of PegIFN-α2a on JNJ-6379 (as applicable) and JNJ-3989, the PK parameters of JNJ-6379 (as applicable), JNJ-3976, and JNJ-3924 coadministered with PegIFN-α2a at Week 20 (or 16) will be compared to those of JNJ-6379 (as applicable), JNJ-3976 and JNJ-3924 at Week 4 (or 8) as reference.

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

A pharmacogenomic blood sample and samples for epigenetic testing will be collected from participants who consent separately to this component of the study (see Section 8.8, Host Genetics).

Participants will be considered to have completed the study if they have completed all the assessments of the end of study (EOS) visit (ie, FU Week 48).

If a participant prematurely discontinues the investigational intervention (before Week 24/EOSI), the participant will have an early withdrawal visit and will enter the 48-week FU Period as per the Schedule of Activities, unless the participant withdraws consent.

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

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

An internal DRC will be commissioned for monitoring safety of participants enrolled in this study (Section 9.6, Data Review Committee). In addition, an IFLEP will be appointed (Section 9.7, Independent Flare Expert Panel).

The Coronavirus Disease 2019 (COVID-19) pandemic or similar pandemics may impact the conduct of this clinical study, therefore additional guidance is provided in Section 10.10, Appendix 10: Study Conduct During a Natural Disaster.

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

4.2. Scientific Rationale for Study Design

Addition of PegIFN-α2a to Treatment Regimen

The combination of the treatment regimen of JNJ-3989 + NA with PegIFN-α2a is based on 2 different properties of IFN-α: a direct antiviral effect and an immune boosting effect. The direct antiviral activity against HBV replication, and in some cases HBsAg production, was demonstrated for PegIFN-α2a (Belloni 2012). In addition, IFN-α is expected to act as immune booster with potential to reactivate NK-cells (Gill 2016). Addition of short-term PegIFN-α2a (12 weeks) to the treatment regimen is expected to enhance antiviral activity of JNJ-3989 + NA and may lead to a shorter overall treatment duration (ie, 24 weeks) needed to achieve functional cure.

Study Design Change – Protocol Amendment 3

Based on emerging data from the REEF-1 (73763989HPB2001) and REEF-2 (73763989PAHPB2002) studies, the study design has been adapted in Protocol Amendment 3.

In summary, the data from the REEF-1 and REEF-2 studies suggested that JNJ-6379 has a negative impact on the HBsAg lowering effect of JNJ-3989+NA (see details in Section 2.2.3.1) and that JNJ-6379 in combination with TDF may further contribute to renal tubulo-toxicity (see details in Section 2.3.2.2.2). Together, this led to a conclusion of an unfavorable benefit-risk balance of JNJ-6379 in combination with JNJ-3989+NA, compared to JNJ-3989+NA alone. Therefore, the Sponsor decided to discontinue treatment with JNJ-6379 in all ongoing clinical studies effective immediately and as an urgent safety measure. Participants currently on treatment with JNJ-6379 were contacted and requested to stop taking JNJ-6379, while continuing treatment with NA, JNJ-3989, and PegIFN-α2a. For newly enrolled participants, JNJ-6379 was taken out of the treatment regimen.

Furthermore, the sponsor decided to make additional changes to the study design because of a severe clinical ALT flare that was reported following discontinuation of NA treatment in a participant who was randomized to the control arm (placebo + placebo + NA) in the REEF-2 study. Discontinuation of NA treatment was following the protocol-defined criteria and in line with recent EASL treatment guidelines (EASL 2017). Flares following NA discontinuation are not unexpected, but the rapid evolution and clinical deterioration seen in this participant who had no history or evidence of liver cirrhosis was unforseeable. Therefore, to protect the safety of participants, the protocol was amended: more frequent monitoring of participants who discontinued NA treatment during follow-up was included and the NA re-treatment criteria for all participants who discontinued NA treatment were revised.

Criteria for Completion of NA Treatment

At the end of Treatment Period 2 (Week 24/EOSI), all participants will enter the FU Period and stop treatment with JNJ-3989 and PegIFN-α2a. If the protocol-defined NA treatment completion criteria (described in Section 6.6, Study Intervention Completion at Week 24) have been met at Week 24, NA will also be stopped at the next scheduled visit (ie, at FU Week 2), otherwise NA treatment will continue during the complete FU duration. The NA 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 stop all study intervention. Across a range of studies, HBsAg levels below 100 IU/mL are consistently associated with favorable off-treatment response (Jeng 2018; Papatheodoridis 2018). The stringent HBsAg cut-off of 10 IU/mL for NA treatment completion was chosen to account for the direct effect of JNJ-3989 on HBsAg levels.

After stopping all study interventions, participants will be monitored closely during the 48-week FU Period and should re-start NA treatment in accordance with the NA re-treatment criteria (see Section 6.7.1, NA Re-treatment Criteria and Monitoring After Stopping of NA, for more details).

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

To ensure safety of patients during the FU Period, an ALT flare management plan is in place, including weekly visits for patients with ALT/AST ≥3xULN and ≥3x nadir (ie, lowest value during study participation) until stabilization.

Increases in ALT and HBV DNA are frequently seen in patients after discontinuation of NA treatment. These ALT elevations may be reflecting an activation of the host cellular immune response and can as such lead to functional cure. Cases of fulminant HBV reactivation with fatal outcome were described after cessation of NA treatment, but the vast majority of such cases were described in patients with decompensated liver disease at the time of NA discontinuation. These patients are not eligible to participate in the study. Still, a vigilant follow-up of patients during this phase of the study is critical to ensure patient safety. Signs of decreased liver function, or an HBV DNA value of >100,000 IU/mL (irrespective of confirmation and/or ALT increase), will trigger immediate re-initiation of NA treatment based on protocol-defined NA re-treatment criteria (see Section 6.7.1, NA Re-treatment Criteria and Monitoring After Stopping of NA).

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

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

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

NA re-treatment criteria during follow-up are presented graphically in Section 10.12 Appendix 12: NA Re-treatment and Monitoring After Stopping of NA.

Host DNA and Exploratory Host Biomarker Collection

Refer to Section 4.2 of the Master Protocol PLATFORMPAHPB2001.

4.2.1. Study-Specific Ethical Design Considerations

Refer to Section 4.2.1 of the Master Protocol PLATFORMPAHPB2001.

The total blood volume to be collected (see Section 8) is considered to be an acceptable amount of blood to be collected over this time period from the population in this study.

4.3. Justification for Dose and Treatment Duration

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) (ie, 200 mg for JNJ-3989). Addition of short-term PegIFN-α2a (12 weeks) to the treatment regimen is expected to enhance antiviral activity of JNJ-3989 + NA and may lead to a shorter overall treatment duration (ie, 24 weeks) needed to achieve functional cure.

Note: JNJ-6379 was initially part of the study intervention, but has been removed as study intervention with the implementation of an urgent safety measure, as described in Protocol Amendment 3.

4.3.1. JNJ-3989

Clinical data on PK and safety of JNJ-3989 are available from the Phase 1/2a AROHBV1001 study with a data cut-off date of 29 October 2019. In addition, snapshot efficacy and PD data are available with a data cut-off date of 26 March 2020. The study has been completed and final analysis and report writing are ongoing. Twenty adult healthy participants have received single subcutaneous 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 subcutaneous 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 subcutaneous injections of 25 to 400 mg JNJ-3989 Q4W (Gane 2019; Yuen 2019; IB JNJ-3989 2020). 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. The HBsAg levels at Day 392 were variable with some patients having HBsAg levels close to baseline levels while a substantial proportion of patients still had HBsAg levels >1 $\log_{10}$ IU/mL lower than the baseline levels. JNJ-3989 showed activity on other viral markers (HBV DNA, HBV RNA, HBeAg and HBcrAg), frequently with sustained reduction at least until Day 362. No apparent dose response was observed

at doses between 100 mg and 400 mg JNJ-3989, a numerically smaller mean decline was observed at the lower doses of 25 mg and 50 mg, mainly apparent after end of JNJ-3989 dosing.

A dose of 200 mg 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.

The Phase 2b study REEF-1 is designed to establish the optimal dose of JNJ-3989. Based on data from the Phase 1/2a study AROHBV1001 with limited treatment duration, 200 mg was selected as the highest dose of JNJ-3989 tested in REEF-1. Until lower doses are proven equivalently effective in REEF-1, additional combination studies with JNJ-3989 and JNJ-6379 are conducted with 200 mg of JNJ-3989.

4.3.2. JNJ-6379

Note: JNJ-6379 was initially part of the study intervention but has been removed as study intervention with the implementation of an urgent safety measure, as described in Protocol Amendment 3.

At the time of initial protocol writing, a dose of 250 mg JNJ-6379 QD was chosen for this study.

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

Interim analysis data are available from the ongoing Phase 2a JADE study in which the 250-mg dose is being tested for 48 weeks. Unblinded Week 24 data from 63 chronic HBV-infected participants who received 250 mg QD JNJ-6379 in addition to an NA showed that there were no deaths or AEs leading to discontinuation. Most AEs were mild or moderate in severity. Grade 3 or 4 AEs were reported in 6 (10%) participants in this treatment arm (most frequently ALT and AST elevations).

4.4. End of Study Definition

End of Study Definition

The EOS is considered as the last visit (FU 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 of the EOS visit (ie, FU 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 Period may be extended up to a maximum of 8 weeks on a case-by-case basis and in agreement with the sponsor. Refer to Section 5.4, Screen Failures, of the Master Protocol PLATFORMPAHPB2001 for conditions under which the repeat of any screening procedures is allowed.

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

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.

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

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

5.1. Inclusion Criteria

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

A01 (adapted from M01)	Male or female participants ≥18 years of age (or older if the legal age of consent in the jurisdiction in which the study is taking place is >18) to ≤65 years of age.
M02	Participants must be medically stable based on physical examination, medical history, vital signs, and 12-lead ECG performed at screening. If there are abnormalities, they must be consistent with the underlying illness in the study population. This determination must be recorded in the participant's source documents and initialed by the investigator.

A03 (adapted from M03a)	Participants must have chronic HBV infection. HBV infection must be 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. If none of the above are available, the following ways of documenting chronicity are acceptable at the time of screening: liver biopsy with changes consistent with chronic HBV, or absence of marker for acute HBV infection such as positive immunoglobulin M (IgM) anti-hepatitis B surface (HBs) and anti-HBc antibodies. Participants should: • be on stable HBV treatment, defined as currently receiving NA treatment for at least 6 months prior to screening and having been on the same NA treatment regimen (at the same dose) as used in this study for at least 3 months at the time of screening, AND • have serum HBV DNA <60 IU/mL on 2 sequential measurements at least 6 months apart (one of which is at screening), AND • have documented ALT values <2.0x ULN on 2 sequential measurements at least 6 months apart (one of which is at screening).
M04	Participants must have a body mass index (BMI; weight in kg divided by the square of height in meters) between 18.0 and 35.0 kg/m^2, extremes included.
A05 (adapted from M05)	Participants must sign a Master ICF (specific for the Master Protocol PLATFORMPAHPB2001) and must sign an ICF specific for this intervention cohort, indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.
M06	Participants must sign a separate ICF if he or she agrees to provide an additional optional DNA sample for research (where local regulations permit). Refusal to give consent for the optional DNA research sample does not exclude a participant from participation in the study. ***Note:*** a mandatory sample for human leukocyte antigen (HLA) haplotyping will be collected from all participants.
A07 (adapted from M07)	Criterion modified per Amendment 3 A07.1 Female participants must be (as defined in Section 10.5 Appendix 5: Contraceptive and Barrier Guidance): a. Not of childbearing potential, OR 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 provided in Section 10.5 Appendix 5: Contraceptive and Barrier Guidance.

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 (no longer applicable as of Protocol Amendment 3, because of the removal of JNJ-6379 as study intervention): Female participants of childbearing potential who are on a stable treatment regimen with hormonal contraceptives (ie, same dose and not starting or stopping hormonal contraceptive use for at least 30 days prior to screening) should continue the same dose regimen until 90 days after the last dose of study intervention. Ethinylestradiol-containing contraceptives are only allowed if the ethinylestradiol content is ≤20 µg. Female participants stable on an ethinylestradiol-containing regimen with a dose >20 µg who switch to an ethinylestradiol-containing regimen with a dose ≤20 µg, should be on that new regimen for at least 1 week before the first dose of study intervention. For female participants of childbearing potential who will start a hormonal contraceptive treatment during the study, ethinylestradiol-containing contraceptives are not allowed.

M08	Female participants of childbearing potential must have a negative highly sensitive serum pregnancy test (β-human chorionic gonadotropin) at screening and a negative urine pregnancy test on Day 1 before the first dose of study intervention.
M09	In the investigator's opinion, the participant is able to understand and comply with protocol requirements, instructions, and study restrictions and is likely to complete the study as planned per ISA (including the procedures outlined in the Master Protocol PLATFORMPAHPB2001).
A10 (adapted from M10)	Male participants must agree to wear a condom when engaging in any activity that allows for passage of ejaculate to another person during the study intervention period and until 90 days after last dose of study intervention.
A11	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.
A12	Male participants must agree not to donate sperm for the purpose of reproduction during the study intervention period and until 90 days after last dose of study intervention.
A13	Criterion modified per Amendment 1:

A13.1 Participants must have serum HBsAg >100 IU/mL at screening, as assessed by quantitative HBsAg assay.

A14 Participants must have:

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

b. If a Fibroscan result is not available: a liver biopsy result classified as Metavir F0-F2 within 1 year prior to screening.

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

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

A15 Participants must separately consent if he or she agrees to participate in the PK substudy. Refusal to give consent does not exclude participation in the main study.

5.2. Exclusion Criteria

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

A01 (adapted from M01) Criterion modified per Amendment 3

A01.1 Participants with evidence of hepatitis A virus infection (hepatitis A antibody IgM), HCV infection (HCV antibody), hepatitis D virus (HDV) infection (HDV antibody), hepatitis E virus (HEV) infection (hepatitis E antibody IgM), or HIV-1 or HIV-2 infection (confirmed by antibodies) at screening.

Note:

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

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

– Participants with a positive HIV-1 or HIV-2 antibody/antigen test at screening should have a confirmatory HIV RNA test, to rule out false positive results. They can be enrolled if they have a negative HIV RNA test at screening. Participants with evidence of HIV-1 or HIV-2 infection who are on antiretroviral treatment are excluded.

A02 (adapted from M02) Participants with evidence of hepatic decompensation at any time point prior to or at the time of screening:

a. Total bilirubin >1.5x ULN[b], OR
b. Direct bilirubin >1.2x ULN[b], OR
c. Prothrombin time >1.3x ULN (unless caused by anticoagulation therapy or vitamin K deficiency)[b], OR
d. Serum albumin <3.2 g/dL[b].

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

M04 Participants with evidence of liver disease of non-HBV etiology. This includes but is not limited to hepatitis infections mentioned in exclusion criterion A01, drug- or alcohol-related liver disease, autoimmune hepatitis, hemochromatosis, Wilson's disease, α-1 antitrypsin deficiency, primary biliary cholangitis, primary sclerosing cholangitis, Gilbert's syndrome (mild cases are allowed) or any other non-HBV liver disease considered clinically significant by the investigator.

A05 (adapted from M05) Participants with signs of hepatocellular carcinoma (HCC) or clinically relevant renal abnormalities on an abdominal ultrasound performed within 3 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 has been ruled out by a more specific imaging procedure (contrast-enhanced ultrasound, CT or MRI).

A06 (adapted from M06) Criterion modified per Amendment 3

A06.1 Participants with one or more of the following laboratory abnormalities at screening as defined by the Division of Acquired Immunodeficiency Syndrome (DAIDS) Toxicity Grading Scale (see Section 10.9, Appendix 9: DAIDS Table):

[a] Negative HEV RNA may also be acceptable to rule out active HEV infection depending on local standard practices.

[b] Unless explained by a clinical setting that is not hepatic decompensation.

a. Estimated glomerular filtration rate (eGFR) <80 mL/min/1.73 m^2 at screening, calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula;

b. Pancreatic lipase elevation ≥grade 3;

c. Pancreatic amylase elevation ≥grade 3;

d. Hemoglobin ≤10.9 g/dL (males), ≤10.4 g/dL (females);

e. Platelet count ≤lower limit of normal (LLN);

f. Alpha-fetoprotein (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 (also see exclusion criterion A02).

M07 Participants with hemoglobin A1c >8% at screening.

M08 Participants with a history of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy, which are considered cured with minimal risk of recurrence).

M09 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.

M10 Participants with a history of or current cardiac arrhythmias (eg, extrasystole, tachycardia at rest), history of risk factors for Torsade de Pointes syndrome (eg, hypokalemia, family history of long QT Syndrome) or history or other clinical evidence of significant or unstable cardiac disease (eg, angina, congestive heart failure, myocardial infarction, diastolic dysfunction, significant arrhythmia and/or coronary heart disease), moderate to severe valvular disease, or uncontrolled hypertension at screening.

M11 Participants with any current or previous illness for which, in the opinion of the investigator and/or sponsor, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments. This may include but is not limited to significant vascular, pulmonary (eg, chronic obstructive pulmonary disease), gastrointestinal (eg, significant diarrhea, gastric stasis, or constipation that in the investigator's opinion could influence drug absorption or bioavailability), endocrine (eg, thyroid disease), neurologic, hematologic, rheumatologic,

	psychiatric, neoplastic, or metabolic disturbances. Any condition possibly affecting drug absorption (eg, gastrectomy or other significant gastrointestinal tract surgery, such as gastroenterostomy, small bowel resection, or active enterostomy) will also lead to exclusion.
M12	Participants who have received an organ transplant (except for skin, hair, or cornea transplants).
M13	Participants with any history of or current clinically significant skin disease requiring regular or periodic treatment.
M14	Participants with clinically relevant alcohol or drug abuse within 12 months of screening.
M15	Participants with history of clinically relevant drug rash.
A16 (adapted from M16)	Participants who have taken any disallowed therapies as noted in Section 6.5, Concomitant Therapy, before screening or baseline.
M17	Participants having used any invasive investigational medical device within 3 months, or having received an investigational intervention or a biological product, immunoglobulin or other blood product not intended for the treatment of HBV within 6 months or 5 half-lives (whichever is longer), before the planned first dose of study intervention, or is currently enrolled in an interventional clinical study with an investigational product.
A18 (adapted from M18)	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.
A19 (adapted from M19)	Male participants who plan to father a child while enrolled in this study or within 90 days after the last dose of study intervention.
M20	Participants who had major surgery (eg, requiring general anesthesia), excluding diagnostic surgery, within 12 weeks before screening; or will not have fully recovered from surgery; or 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.

M21	Participant is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.
M22	Vulnerable participants (eg, incarcerated individuals, individuals under a legal protection measure).
A23	Criterion modified per Amendment 3 A23.1 Participants with known allergies, hypersensitivity, or intolerance to JNJ-3989 or its excipients (refer to the IB [IB JNJ-3989 2020]) and NA and PegIFN-α2a or their excipients (refer to the respective prescribing information).
A24	Participants with prior IFN use.
A25	A25.1 Criterion modified per Amendment 1 Criterion modified per Amendment 3 A25.2 Participants who meet any of the additional exclusion criteria for PegIFN-α2a as described in the prescribing information (refer to Pegasys SmPC or Pegasys USPI for a complete list) per the investigator's discretion. Key exclusion criteria for PegIFN-α2a include: 1. Patients with signs or symptoms compatible with autoimmune disorders. 2. Participants with bone marrow suppression. 3. Patients with hypoglycaemia, hyperglycaemia, and/or diabetes mellitus, who cannot be effectively controlled by medication. 4. Participants with pre-existing ophthalmologic disorders. 5. Participants with one or more of the following laboratory abnormalities: – Absolute neutrophil count <1,500 cells/mm^3 (<1,000 cells/mm^3 for black or African American participants). – Serum creatinine >1.5x ULN. – Inadequately controlled thyroid function (thyroid stimulating hormone [TSH] and thyroxine [T4]). – CD4+ cell count <200 cells/mm^3. 6. Participants with a history of a severe psychiatric disorder, including severe depression, suicidal ideation and attempted suicide, or a current depression or other psychiatric disorder that is not adequately controlled on a stable medication regimen. ***Note:*** Contraindications to the use of PegIFN-α2a need to be checked at screening and again prior to the start of Treatment Period 2.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. The required source documentation to support meeting the enrollment criteria are noted in Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

5.3. Lifestyle Considerations

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

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

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

5.4. Screen Failures

Refer to Section 5.4 of the Master Protocol PLATFORMPAHPB2001 for handling of screen failures and use of participant identification, enrollment, and screening logs.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Intervention(s) Administered

Description of Interventions

Intervention Name	JNJ-3989	JNJ-6379***	PegIFN-α2a	Tenofovir disoproxil	Tenofovir alafenamide (TAF)*	Entecavir (ETV) monohydrate
Type	Drug	Drug	Drug	Drug	Drug	Drug
Dose Formulation	Solution for injection	Tablets	Solution for injection	Film-coated tablets	Film-coated tablets	Film-coated tablets
Unit Dose Strength(s)	200 mg/mL	25 and 100 mg	180 µg/0.5 mL	245 mg	25 mg	0.5 mg
Dosage Level(s)	200 mg once every 4 weeks (Q4W)	250 mg once daily (QD)	180 µg once weekly (QW)	245 mg QD	25 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)
Route of Administration	Subcutaneous injection (in the abdomen)	Oral	Subcutaneous injection (in the thigh or abdomen)	Oral	Oral	Oral
Use	Investigational intervention	Investigational intervention	Investigational intervention	Background intervention	Background intervention	Background intervention
Investigational Medicinal Product (IMP)	Yes	Yes	Yes	Yes	Yes	Yes
Non-investigational Medicinal Product/ Auxiliary Medicinal Product (NIMP/AxMP)	No	No	No	No	No	No

Intervention Name	JNJ-3989	JNJ-6379***	PegIFN-α2a	Tenofovir disoproxil	Tenofovir alafenamide (TAF)*	Entecavir (ETV) monohydrate
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	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.	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	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 the prescribing information	Per the prescribing information	Per the prescribing information	Per the prescribing information

Q4W: once every 4 weeks; QD: once daily; QW: once weekly.

* In countries where TAF is available, it will be one of the NA treatment options.
** 2 tablets of 0.5 mg.
*** Participants enrolled before Protocol Amendment 3 was in effect, may have received JNJ-6379 as part of their study intervention. As of Protocol Amendment 3: Study intervention includes JNJ-3989, NA and PegIFN-α2a

Physical Description of Study Interventions

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

JNJ-3989 will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients (IB JNJ-3989 2020).

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. Refer to the prescribing information for a list of excipients.

PegIFN-α2a formulated as solution for subcutaneous injection in a prefilled syringe with 180 µg/0.5 mL of PegIFN-α2a, will be provided by the sponsor. Refer to the prescribing information for a list of excipients.

Packaging and Labeling

All study interventions will be packaged with each unit labeled with a unique medication ID number. Packaging and labeling of JNJ-3989, the NAs, and PegIFN-α2a will be done in an open-label way. Commercial supplies of NAs and PegIFN-α2a will be sourced and a clinical study label will be applied. Study intervention labels will contain information to meet the applicable regulatory requirements.

NA and PegIFN-α2a treatment may 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 subcutaneously in the abdomen at the study site.

NA and PegIFN-α2a treatment will be provided by the sponsor. Investigators should follow guidance detailed in the respective prescribing information, including special warnings and precaution for use.

In between study visits, participants will take their NA at home and they will bring their NA with them to each study visit. Study site personnel will instruct participants on how to take their NA at home. At study visits, NA should be taken on site to allow biochemistry and renal biomarker samples to be taken in fasted conditions.

During the study, participants will continue the same NA treatment (ETV, tenofovir disoproxil, or TAF) they were receiving at the 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. 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 after consultation with the sponsor.

For PegIFN-α2a, weekly administration should preferably be done on the same day of the week in the evening by self-injection.[a] Study site personnel will instruct participants on how to self-administer, where applicable, their PegIFN-α2a injections at home. Used PegIFN-α2a syringes should be separated from the needle via the sharps container and then placed into their original box and returned to the site at the next study visit, if allowed per local guidelines and regulations. The used needles in the sharps container will be returned to the study site after completion of Treatment Period 2 or disposed of following local standard procedures. If desired, participants can also choose to have the weekly administration of PegIFN-α2a performed at the study site irrespective of the time of day.

JNJ-3989 and PegIFN-α2a should be injected subcutaneously and the approximate location should be recorded. If both are injected in the abdomen, different areas of the abdomen should be used.

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

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

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

Study site personnel will instruct participants on how to store 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 NA and PegIFN-α2a (if self-administered) to the participant, and the return of NA and PegIFN-α2a (if self-administered) 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 study intervention. The JNJ-3989 and PegIFN-α2a injections administered to the participant at the study

[a] For participants in Japan, weekly administration of PegIFN-α2a must be performed at the study site by the investigator or his/her designee.

site 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.

Participants who stopped JNJ-6379 per Protocol Amendment 3, must return their JNJ-6379 supply at the next scheduled visit. The return of JNJ-6379 from the participant must be documented on the intervention accountability form.

Study intervention must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention, and study intervention returned by the participant, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study intervention, or used returned study intervention for destruction, will be documented on the intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the intervention return form.

Potentially hazardous materials containing hazardous liquids, such as used ampules, needles, and vials, should be disposed of immediately in a safe manner and therefore will not be retained for intervention accountability purposes. Details on handling of used PegIFN-α2a syringes are described in Section 6.1, Study Intervention(s) Administered.

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 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

As this is a single-arm study, randomization procedures are not applicable.

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 subcutaneous injection by qualified study site personnel to assure compliance with study requirements.

The participants will be requested to bring unused 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.

- 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 prescribing information.
- If an injection of PegIFN-α2a is missed, the participant should follow the guidelines in the prescribing information.

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.

Participants who are administering PegIFN-α2a by self-injection[a] will be requested to complete a self-injection tracker. The completed self-injection trackers are reviewed by the site staff and discussed with the participants for compliance monitoring and counseling. Completed self-injection trackers will be returned to the site staff who will transcribe the data into the CRF.

6.5. Concomitant Therapy

Note: With the removal of JNJ-6379 as study intervention in Protocol Amendment 3, JNJ-6379-specific disallowed medications and concomitant medications to be used with caution are no longer applicable and have been removed.

An overviews of ISA-specific disallowed medication is provided in Table 3.

Local guidelines on the use of live vaccines in participants receiving PegIFN-α2a should be followed, including for the second dose of Sputnik V (which contains rAd5, with a theoretical risk

[a] Not applicable for participants in Japan, where weekly administration of PegIFN-α2a must be performed at the study site by the investigator or his/her designee.

of replication competence). Sputnik Light, which is the first dose of Sputnik V (with rAd26) is not considered a live vaccine. See below for further guidance on the use of COVID-19 vaccines.

Note that locally approved COVID-19 vaccines (including those that received emergency use authorization or conditional marketing authorization) are allowed throughout the study. For participants receiving PegIFN-α2a the following recommendations should be applied to accommodate COVID-19 vaccination during Treatment Period 2:

- COVID-19 vaccine and PegIFN-α2a should not be administered on the same day.
- If required, PegIFN-α2a injection can be delayed with 2 days. The next PegIFN-α2a injection should be performed at the scheduled time.
- If required, skipping a PegIFN-α2a injection may be considered after consultation with the Sponsor.
- Vaccination with Sputnik V should take above mentioned consideration about live vaccines into account.

All COVID-19 vaccination-related data (eg, COVID-19 vaccination, AEs, AE management) should be appropriately captured in the CRF and source documents. Refer to the COVID-19 vaccine and/or PegIFN-α2a prescribing information for more details.

For general concomitant therapy considerations, refer to Section 6.5 of the Master Protocol PLATFORMPAHPB2001.

Table 3: Disallowed Medication
Disallowed at any time prior to screening until end of follow-up:
• Any CAM, oligonucleotide-based treatment (eg, siRNA, nucleic acid polymers, and antisense oligonucleotides), and IFN, other than the study intervention taken in the context of this study. ***Note:*** Prior hepatic treatment with herbal or nutritional products is also allowed but should be stopped at screening.
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). ***Note:*** Approved COVID-19 vaccines or COVID-19 vaccines with conditional marketing authorization, emergency use authorization or special approval for emergency are allowed.
Disallowed from 6 months prior to baseline until end of follow-up:
• Any systemically (eg, intravenously, intramuscularly, orally, subcutaneously) administered medication that directly or indirectly interferes with immune responses (eg, cyclosporine, interleukins, systemic corticosteroids exceeding 5 mg of prednisolone equivalent/day).
Disallowed from screening until end of follow-up:
• 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 between screening and baseline. • 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.

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

The prescribing information for ETV, tenofovir disoproxil, TAF, and PegIFN-α2a should be consulted for any additional prohibited medication. In case of flu-like symptoms after administration of PegIFN-α2a, paracetamol up to a maximum of 2 g per 24 hours and a maximum of 6 g per week is allowed.

Medications requiring subcutaneous injection (other than JNJ-3989 and PegIFN-α2a; eg, insulin) should be administered away from the JNJ-3989 and PegIFN-α2a injection sites.

6.6. Study Intervention Completion at Week 24

With the implementation of Protocol Amendment 3, all participants had to stop JNJ-6379 treatment immediately.

Participants will stop treatment with JNJ-3989 and PegIFN-α2a at Week 24 (EOSI). If all of the following NA treatment completion criteria are met at Week 24, treatment with NA will also be stopped at the next scheduled visit (ie, FU Week 2):

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

Note: In case of ALT elevation ≥3x ULN at Week 24, 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 FU Week 2, 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 24 should continue NA treatment during the 48-week FU Period.

If a participant prematurely discontinues investigational intervention before Week 24, 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. Dose Modification

Dose modifications of JNJ-3989 and NA (increase or decrease of dose level) are not allowed during the study.

For PegIFN-α2a, dose adjustment guidelines are applicable for participants who develop laboratory abnormalities during PegIFN-α2a treatment, as recommended in the locally approved prescribing information for PegIFN-α2a and upon investigator's assessment.

In exceptional circumstances (ie, laboratory abnormalities during PegIFN-α2a treatment) the use of a local laboratory may be considered in parallel to the central laboratory testing, at the study investigator's discretion, to obtain rapid results to ensure patient safety. If applicable, a copy of the local laboratory report should be reviewed by the investigator and filed with the source documents, along with reference ranges.

For participants who prematurely discontinue PegIFN-α2a, treatment with PegIFN-α2a may be restarted according to the recommendations from the locally approved prescribing information for PegIFN-α2a.

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

Participants who meet the protocol-defined NA treatment completion criteria outlined in Section 6.6, Study Intervention Completion at Week 24, will be monitored closely during the FU Period.

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

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

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

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

- With confirmed* post-treatment increases in HBV DNA >20,000 IU/mL.

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

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

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

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

Management of intervention-emergent ALT/AST elevations is discussed in Section 8.3.6.4, Intervention-emergent ALT/AST Elevations.

NA re-treatment criteria during follow-up are presented graphically in Section 10.12 Appendix 12: NA Re-treatment and Monitoring After Stopping of NA.

6.8. Continued Access to Study Intervention After the End of the Study

Refer to Section 6.7 of the Master Protocol PLATFORMPAHPB2001.

The investigator should consider to re-start NA treatment per local standard of care at the EOS visit (Follow-up Week 48) for participants who met the NA treatment completion criteria at Week 24, who did not re-start NA treatment during the follow-up phase, and who did not achieve and maintain HBsAg seroclearance. NA will not be provided by the sponsor after the final study visit.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

If a participant discontinues study intervention for any reason before Week 24/EOSI, the participant will have an early withdrawal visit and will enter follow-up unless he/she withdraws consent. If the reason for withdrawal from the study is withdrawal of consent, then the participant will be offered an optional safety follow-up visit. Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant.

7.1. Discontinuation of Study Intervention

With the implementation of Protocol Amendment 3, all participants had to stop JNJ-6379 treatment immediately.

Treatment with JNJ-3989 (and PegIFN-α2a during Treatment Period 2) must be discontinued before Week24/EOSI if any of the discontinuation criteria listed below are met. Criteria specific for this ISA are highlighted (colored fill). For the few criteria from the Master Protocol that are specified or more restricted in this ISA, the changes compared to the Master Protocol are also highlighted (colored fill). If JNJ-3989 is discontinued, PegIFN-α2a (only applicable in Treatment Period 2) should also be discontinued. NA treatment may be continued or, in consultation with the sponsor, discontinued based on investigator judgement.

The discontinuation criteria are:

- The participant withdraws consent to receive study intervention.
- The investigator believes that for safety or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue JNJ-3989 (and PegIFN-α2a, if applicable).
- The participant becomes pregnant.
- The participant has a ≥grade 3 rash (see Section 10.6, Appendix 6: Rash Management) or allergic reaction (see Section 8.3.6.3, Acute Systemic Allergic Reactions).
- The participant has signs of hepatic decompensation (ie, clinical evidence of ascites, bleeding varices, or hepatic encephalopathy) or an increase in direct bilirubin >1.5x ULN in combination with INR ≥1.5x ULN or albumin <3.0 g/dL, treatment with JNJ-3989 should be discontinued and alternative treatment options (outside the study) should be considered in discussion with the sponsor.
- The participant has a confirmed ≥grade 3 eGFR abnormality, considered at least possibly related to JNJ-3989 (or PegIFN-α2a, if applicable) that persists despite change of tenofovir disoproxil to ETV or TAF (if the patient was receiving tenofovir disoproxil). Change of NA treatment should be considered according to the prescribing information (see Section 8.3.6.5, Renal Complications).
- The participant has a QTcF prolongation (defined as a QTcF value of >500 ms, or an increase from baseline of >60 ms) at any given time point.
- The participant requires ≥7 days of treatment with any of the disallowed medications listed in Section 6.5, Concomitant Therapy, 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 8.3.6.4, Intervention emergent ALT/AST Elevations, and Schedule of Activities).
- The participant has ALT/AST elevations, as described in Section 8.3.6.4, Intervention-emergent ALT/AST Elevations.

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

In addition, PegIFN-α2a must immediately be discontinued for any of the following reasons:

- Participant has platelet count <25,000 cells/mm^3.
- Participant has ANC <500 cells/mm^3.

Note: PegIFN-α2a treatment can be restarted when ANC values return to more than 1,000 cells/mm^3 (see details in Section 6.7, Dose Modification)

- Participant develops evidence of hepatic decompensation during treatment, or ALT increase clinically significant or accompanied by direct bilirubin increase.
- Participant develops thyroid disorders or diabetes during treatment and cannot be controlled with medication.
- Participant develops new or worsening ophthalmologic disorders.
- Participant develops any deterioration of cardiovascular status.
- Participant develops serious, acute hypersensitivity reaction (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis).
- Participant develops serious infection (bacterial, viral, fungal) and sepsis.
- Participant develops persistent or unexplained pulmonary infiltrates or pulmonary function impairment.
- Participant with onset or worsening of psoriatic lesion.
- Participant develops moderate or severe depression, or other psychiatric symptoms (for mild depression, treatment discontinuation may be considered).

Note: Participants who develop a neuropsychiatric AE during PegIFN-α2a treatment, will be monitored closely until the neuropsychiatric AE resolves, with frequent (at least weekly) follow-up phone calls.

- Participant develops colitis symptoms (such as but not limited to abdominal pain, bloody diarrhea, and fever).
- Participant develops symptoms or signs suggestive of pancreatitis.

7.2. Participant Discontinuation/Withdrawal From the Study

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

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

Refer to Section 7.2.1 of the Master Protocol PLATFORMPAHPB2001.

7.3. Lost to Follow-up

Refer to Section 7.3 of the Master Protocol PLATFORMPAHPB2001.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

Refer to Section 8 of the Master Protocol PLATFORMPAHPB2001.

The total blood volume to be collected from each participant during planned assessments for the entire study will be approximately 945 mL.[a] In addition, PBMC samples (at selected sites only; approximately 450 mL), optional exploratory host genotyping and epigenetic research samples (approximately 20 mL) and optional intensive PK samples (approximately 200 mL) may be collected.

Note: The total blood volume to be collected from each participant may vary, depending on several factors (eg, unscheduled re-tests, unscheduled sampling for safety management, re-sampling, individual variations, follow-up visits that are not mandatory for participants who continue NA treatment or have restarted NA treatment during the follow-up period).

Sample Collection and Handling

Refer to Section 8 of the Master Protocol PLATFORMPAHPB2001.

Study-Specific Materials

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

- Prescribing Information for ETV, tenofovir disoproxil, TAF, and PegIFN-α2a.
- Contact information page(s).

8.1. Efficacy Assessments

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

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

HBV DNA and HBV RNA will be assessed at central laboratories using validated assays for the quantification of HBV DNA and HBV RNA. Samples for the determination of HBV DNA will be

[a] For participants in Japan only, the total blood volume to be collected during planned assessments for the entire study will be approximately 985 mL due to additional hematology assessments.

processed in real-time. Samples for the determination of HBV RNA can be analyzed in batch and at the sponsor's request.

HBV 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 JNJ-3989 (and PegIFN-α2a in Treatment Period 2) are discontinued in participants with confirmed virologic breakthrough (see Section 7.1, Discontinuation of Study Intervention).
- To assess if the protocol-defined NA treatment completion criteria are met (see Section 6.6, Study Intervention Completion at Week 24).
- To assess whether re-start of NA treatment during follow-up is needed (see Section 6.7.1, NA Re-treatment Criteria and Monitoring After Stopping of NA).

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

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

8.1.1. Sequencing

Viral genome sequence analysis will be performed to evaluate mutations associated with the study intervention.

Sequencing of the HBV genome will be performed to monitor HBV variants present at the time points indicated in the Schedule of Activities. The sequencing of samples may be triggered by the sponsor virologist based on changes in HBV DNA levels observed in each individual participant and the limits of the sequencing assay.

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

8.2. Safety Assessments

Safety and tolerability (AEs, clinical safety laboratory assessments, ECGs, vital signs and physical examinations) will be evaluated as described in Section 8.2 and Section 8.3 of the Master Protocol PLATFORMPAHPB2001 and at predefined time points as specified in the Schedule of Activities. In addition, ophthalmic examinations will be performed at the time points specified in the Schedule of Activities.

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

8.2.1. Physical Examinations

Refer to Section 8.2.1 of the Master Protocol PLATFORMPAHPB2001.

8.2.2. Vital Signs

Refer to Section 8.2.2 of the Master Protocol PLATFORMPAHPB2001.

Clinically relevant abnormalities in vital signs are defined in Section 10.8, Appendix 8: Cardiovascular Safety – Abnormalities.

8.2.3. Electrocardiograms

Refer to Section 8.2.3 of the Master Protocol PLATFORMPAHPB2001.

Clinically relevant abnormalities in ECG are defined in Section 10.8, Appendix 8: Cardiovascular Safety – Abnormalities.

8.2.4. Clinical Safety Laboratory Assessments

Refer to Section 8.2.4 of the Master Protocol PLATFORMPAHPB2001.

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

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

8.2.5. Ophthalmic Examinations

Ophthalmic examinations (including fundoscopy) will be performed at the time points specified in the Schedule of Activities. Any participant experiencing a decrease or loss of vision at any time point during study participation, must have a prompt ophthalmic examination. Medical records of the examination should be collected and assessed by the investigator.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

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

For further details on AEs and SAEs (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to Attachment 4 of the Master Protocol PLATFORMPAHPB2001.

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

Refer to Section 8.3.1 of the Master Protocol PLATFORMPAHPB2001.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Refer to Section 8.3.2 of the Master Protocol PLATFORMPAHPB2001.

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

Refer to Section 8.3.3 of the Master Protocol PLATFORMPAHPB2001.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

Refer to Section 8.3.4 of the Master Protocol PLATFORMPAHPB2001.

8.3.5. Pregnancy

Refer to Section 8.3.5 of the Master Protocol PLATFORMPAHPB2001.

8.3.6. Adverse Events of Special Interest

Events of Special Interest are significant AEs that are judged to be of special interest because of clinical importance, known class effects or based on nonclinical signals. Events of Special Interest that will be carefully monitored during the study include ISRs, ALT/AST elevations, renal complications, hematologic abnormalities, and events related to cholesterol increase (Section 8.2.4, Clinical Safety Laboratory Assessments). In addition, the following toxicities will also be carefully monitored: rash and acute systemic allergic reactions.

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

Note: renal complications and cholesterol increase are AESIs specific for JNJ-6379, which was part of the study intervention prior to Protocol Amendment 3 and has been removed with the implementation of Protocol Amendment 3. Because most participants who were enrolled before Protocol Amendment 3 was in effect, also received JNJ-6379 as part of their study intervention, the AESIs have not been revised with the removal of JNJ-6379.

8.3.6.1. Rash

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

All rash events should be captured in the AE section of the CRF. 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 5 in Section 10.6, Appendix 6: 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, JNJ-3989 (and PegIFN-α2a in Treatment Period 2) needs to be permanently discontinued. NAs 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.

8.3.6.2. 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) will need to be recorded in the special events section of the CRF.

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

8.3.6.3. Acute Systemic Allergic Reactions

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

Participants may continue the intake of study interventions.

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

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

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

Participants may continue the intake of study interventions.

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

Participants should be advised to contact the investigator immediately if there is any worsening of the acute systemic allergic reaction, in which case the participant will permanently discontinue the intake of JNJ-3989 (and PegIFN-α2a in Treatment Period 2). 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 PegIFN-α2a in Treatment Period 2). Rechallenge is not allowed. The participant's NA treatment may be discontinued based on investigator judgement in consultation with the sponsor.

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

8.3.6.4. 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 10.7, Appendix 7: Intervention-emergent ALT/AST Elevations, and is described below.

Any intervention-emergent elevation of ALT and/or AST ≥3x ULN and ≥3x nadir (ie, lowest value during study participation) should trigger an assessment of confounding factors (alcohol intake, change in concomitant medication, and comorbidities) and should trigger a confirmatory study visit to repeat laboratory testing of AFP, ALT, AST, ALP, bilirubin (total and direct), INR, albumin, and HBV DNA. Additional tests should be considered based on clinical judgement (refer to Section 10.7, Appendix 7: Intervention-emergent ALT/AST Elevations). This confirmatory visit should be scheduled as soon as possible 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, JNJ-3989 (and PegIFN-α2a in Treatment Period 2) should be discontinued. In both cases, NA treatment should be continued. The participant will be monitored (laboratory testing of AFP, ALT, AST, ALP, bilirubin [total and direct], INR, albumin, and HBV DNA) on a weekly basis or more frequently until ALT and/or AST levels have returned to <5x ULN and HBV DNA is <20,000 IU/mL.

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

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

the participant should discontinue JNJ-3989 (and PegIFN-α2a in Treatment Period 2) and should be monitored on a weekly basis or more frequently, or as per good clinical practice, until ALT and

AST levels have returned to <5x ULN, HBV DNA is <20,000 IU/mL and, if present, liver-related symptoms have improved. NA treatment should be continued. Additional tests can be considered based on clinical judgement (refer to Section 10.7, Appendix 7: Intervention-emergent ALT/AST Elevations).

PegIFN-α2a may need to be discontinued in clinically significant cases of ALT increase or in combined increase of ALT and direct bilirubin. Refer to the prescribing information for PegIFN-α2a (Pegasys SmPC or Pegasys USPI).

The NA re-treatment criteria during follow-up are presented in Section 6.7.1, NA Re-treatment Criteria and Monitoring After Stopping of NA.

8.3.6.5. 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 will change their NA from tenofovir disoproxil to ETV or TAF (if the patient was receiving tenofovir disoproxil). If the abnormality persists despite change of NA or if the patient is not receiving tenofovir disoproxil, he or she will permanently discontinue the intake of JNJ-3989 (and PegIFN-α2a in Treatment Period 2) if considered at least possibly related to JNJ-3989 (or PegIFN-α2a in Treatment Period 2) and should be followed appropriately until resolution of the AE or toxicity. Rechallenge is not allowed. Change of NA treatment should be considered according to the prescribing information.

For all participants having received at least one dose of JNJ-6379, renal safety monitoring will be continued.

8.3.6.6. Hematologic Abnormalities

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

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

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

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

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

In case of confirmed grade 3 or grade 4 hematologic abnormalities, discontinuation of investigational study treatment (JNJ-3989 [and PegIFN-α2a in Treatment Period 2]) should be considered. In case of discontinuation, NA treatment should be continued.

8.4. Treatment of Overdose

For this study, any dose of JNJ-3989 greater than the protocol-specified dose (refer to Section 6.1, Study Intervention(s) Administered) will be considered an overdose; any dose of NA (ETV, tenofovir disoproxil, or TAF) and PegIFN-α2a greater than the prescribed dose will be considered an overdose. The sponsor does not recommend specific treatment for an overdose.

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

- Contact the Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- 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.

8.5. Pharmacokinetics

Plasma or serum samples, as applicable, will be used to evaluate the PK of the study intervention. Samples collected for PK may additionally be used to evaluate safety or efficacy aspects.

8.5.1. Evaluations

Venous blood samples will be collected for measurement of plasma or serum (as applicable) concentrations of JNJ-3989 (ie, JNJ-3976 and JNJ-3924) and, optionally, NA and/or PegIFN-α2a, at time points specified in the Schedule of Activities. Bioanalysis of NA and/or PegIFN-α2a is

optional at the discretion of the sponsor. Bioanalysis of JNJ-6379 may also be done on samples collected from participants who received JNJ-6379 prior to Protocol Amendment 3.

All participants will have sparse PK sampling during the treatment periods. Participants who consent to participate in the intensive PK substudy (optional) will also undergo intensive PK sampling at time points specified in the Schedule of Activities.

8.5.2. Analytical Procedures

Pharmacokinetics

At the sponsor's discretion, a selection of samples may be analyzed to determine concentrations of JNJ-3989 (ie, JNJ-3976 and JNJ-3924) and, optionally, JNJ-6379, NA and/or PegIFN-α2a using a validated, specific, and sensitive liquid chromatography-mass spectrometry method or liquid chromatography fluorescence method, as applicable, by or under the supervision of the sponsor.

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

8.5.3. Pharmacokinetic Parameters and Evaluations

Parameters

Concentration-time data for JNJ-3989 (ie, JNJ-3976 and JNJ-3924) and optionally JNJ-6379, NA and/or PegIFN-α2a will be analyzed via noncompartmental methods for all participants who underwent intensive PK sampling. The PK parameters will be C_{max}, plasma concentration 24 hours after administration (C_{24h}), and AUC_{24h}. Additional PK parameters may be calculated if applicable. To assess the effect of PegIFN-α2a on JNJ-3989, the PK parameters of JNJ-3976 and JNJ-3924 coadministered with PegIFN-α2a at Week 20 (or 16) will be compared to those of JNJ-3976 and JNJ-3924 at Week 4 (or 8) as reference (time points as specified in the Schedule of Activities).

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

8.6. Pharmacokinetic/Pharmacodynamic Evaluations

Relationships of individual PK parameters for JNJ-3976 and JNJ-3924, and optionally JNJ-6379, NA and/or PegIFN-α2a, with selected efficacy and/or safety endpoints may be evaluated, if applicable.

8.7. Immune Assessments

At selected sites, PBMC samples for immune analyses will be collected during study intervention and follow-up and will be analyzed centrally for HBV-specific responses by enzyme-linked immunospot (ELISpot) and/or intracellular cytokine staining (ICS) after stimulation with HBV-specific antigens. ELISpot detects T-cells that secrete gamma interferon (IFN-γ) in response

to a specific antigenic stimulation, whereas ICS determines the frequency of CD4+ and CD8+ T-cells secreting cytokines such as IFN-γ, interleukin (IL)-2 and tumor necrosis factor (TNF)-α in response to a specific antigenic stimulation.

Additional experiments may be performed to further phenotypically and functionally characterize PBMCs using proliferation or cytotoxic assays or other methods such as cytometry by time of flight to evaluate innate and adaptive immune responses. Leftover PBMC samples may be used at the sponsor's discretion for additional exploratory research (eg, assessment of other immune cells such as NK-cells, myeloid-derived suppressor cells [MDSCs], dendritic cells [DCs], and B-cells) related to HBV infection or study intervention (safety/efficacy).

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

8.8. Host Genetics

A mandatory sample for HLA haplotyping will be collected from all participants.

An optional pharmacogenomic (host DNA) blood sample may be collected (preferably at baseline) to allow for host pharmacogenomic research, where local regulations permit. In addition, host DNA blood samples to allow for epigenetic analyses will be collected. These samples could for example be used to assess changes in frequencies of immune cells such as MDSCs. Complete host genomic testing may be done to search for links of specific genes to (HBV-related) liver disease or to the PK, PD, efficacy, safety, or tolerability of the study intervention. These samples will only be collected from participants who consent separately to this component of the study. Further, a participant may withdraw such consent at any time without affecting their participation in other aspects of the study, or their future participation in the Platform study (see Section 7.2.1 of the Master Protocol PLATFORMPAHPB2001).

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

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

8.9. Exploratory Host Biomarkers

The study includes collection of blood samples for exploratory analysis of host blood biomarkers at the host RNA, protein, and cell level. Sampling will be performed at the time points indicated in the Schedule of Activities. Leftovers of other samples might also be used for exploratory research of host and viral markers.

The analyses may include gene expression and cytokine analyses assessing markers such as interferon-stimulated genes (ISGs), IFN-α, and interferon γ-induced protein 10 (IP-10).

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

Blood samples will be taken at the time points indicated in the Schedule of Activities which can be used to explore immunogenicity of JNJ-3989 and optionally PegIFN-α2a. The emergence of antidrug antibodies to JNJ-3989 and optionally to PegIFN-α2a might be analyzed using assays such as an enzyme-linked immunosorbent assay or functional assays.

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

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

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

As this is an exploratory single-arm study, no formal statistical hypothesis has been formulated.

9.2. Sample Size Determination

No formal sample size calculation was performed, as this is a single-arm study for exploratory and proof of concept (PoC) purposes. However, with a sample size of 50 participants having data for the primary efficacy endpoint at Week 24, if at least 25 (50%) participants are responders, it can be concluded with 90% confidence that the true response rate is at least 0.38, with a confidence interval (CI) width of 0.248 (90% CI: 0.376-0.624). With a sample size of 20 participants (for one of the IAs), the precision of the estimate of the primary efficacy endpoint decreases, as the two-sided 90% CI width increases. For the same assumed proportion of responders of 50% (10 out of 20 participants), the 90% CI width becomes 0.396. Table 4 shows the 90% CI and the corresponding width for proportion of responders of 0.30, 0.50, 0.70, and 0.90.

Table 4: Sample Size Determination

	N=20		N=50	
Proportion of responders	**90% CI***	**Width of CI**	**90% CI***	**Width of CI**
0.30	0.140-0.508	0.368	0.195-0.424	0.229
0.50	0.302-0.698	0.396	0.376-0.624	0.248
0.70	0.492-0.860	0.368	0.576-0.805	0.229
0.90	0.717-0.982	0.265	0.801-0.960	0.159

CI: confidence interval.
* Clopper-Pearson exact method is used.

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Screened	All participants who signed the ICF for the Master Protocol and an ICF specific for this ISA.
Enrolled	All participants who were enrolled in this ISA.
Intent-to-treat (ITT)	All participants who were enrolled and who received at least 1 dose of study intervention within this ISA.
IFN-ITT	All participants who were enrolled and who received at least 1 dose of PegIFN-α2a within this ISA.

9.4. Statistical Analyses

The SAP 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.

9.4.1. General Considerations

Refer to Section 9.4.1 of the Master Protocol PLATFORMPAHPB2001.

9.4.2. Efficacy Analyses

The primary efficacy analysis will be performed when all participants have completed Week 24 (EOSI) or discontinued earlier. The final analysis will be performed when all participants have completed the last study visit (FU Week 48) or discontinued earlier.

To evaluate the efficacy, the primary analysis set will be the ITT population (defined in Section 9.3, Populations for Analysis Sets). Selected efficacy analyses will be repeated for the IFN-ITT analysis set and described in the SAP.

All efficacy summaries will be presented with descriptive statistics and 90% CIs. If the endpoint is continuous, the descriptive statistics will include the number of participants, mean, standard deviation (SD), median, and range. If the endpoint is binary or categorical, the frequency distribution with the number and percentage of participants in each category will be calculated. For time-to-event variables, a summary table including number of participants included in the analysis, number of participants censored, 25^{th} and 75^{th} percentiles and median time-to-event will be shown. Graphic displays will also be used to summarize the data.

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

Additional analyses of efficacy to generate new hypotheses and guide the design of new studies may be performed on the primary efficacy endpoint and/or selected secondary endpoints using, for example, the Bayesian methodology or other methodologies to leverage the Platform Study framework. Such analyses may incorporate external data and/or data from other ISAs which are currently in the platform study or may enter in the future. Details on these analyses will be provided in a separate document (SAP or Modeling and Simulation Report, as applicable).

9.4.2.1. Primary Efficacy Endpoint

The primary endpoint is the proportion of participants with a reduction of at least 2 $\log_{10}$ IU/mL in HBsAg levels from baseline to Week 24. Participants who do not have HBsAg data in the analysis window of Week 24 will be defined as non-responders.

The primary efficacy endpoint will be summarized with the point estimate paired with its 90% CI using the Clopper-Pearson exact method. The same method will apply in a secondary analysis of the primary endpoint to the IFN-ITT analysis set comprising the ITT participants who have received at least 1 dose of PegIFN-α2a (see Section 9.3, Populations for Analysis Sets).

9.4.2.2. Secondary Efficacy Endpoints

Descriptive statistics and 90% CIs will be used to summarize all efficacy endpoints.

Specific key selected endpoints may be analyzed using suitable categorical data approaches (eg, Clopper-Pearson interval or logistic regression for proportions or other categorical type of endpoint), longitudinal repeated measures models (eg, for continuous types of variables), or survival analysis based on the Kaplan-Meier estimates (for time-to-event variables), as appropriate.

9.4.2.3. Resistance Analyses

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

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

9.4.3. Safety Analyses

Safety analyses are specified in Section 9.4.3 of the Master protocol PLATFORMPAHPB2001.

Safety will be evaluated by means of descriptive summaries of (S)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 period. Results will be presented in tabular format and/or graphically over time, as appropriate.

9.4.4. Other Analyses

Pharmacokinetic Analyses

Descriptive statistics (n, mean, SD, coefficient of variation [CV], geometric mean, median, minimum, and maximum) will be calculated for the plasma concentrations of JNJ-3989 (JNJ-3976, and JNJ-3924) and, optionally, of NA, PegIFN-α2a and/or JNJ-6379, and for the derived plasma PK parameters for noncompartmental PK analyses.

For each participant with intensive PK sampling, plasma concentration-time data of JNJ-3976 and JNJ-3924, and, optionally, of NA, PegIFN-α2a and/or JNJ-6379, will be graphically presented. Similarly, graphs of the mean plasma concentration-time profiles and overlay graphs with combined individual plasma concentration-time profiles will be produced. Plasma PK parameters in participants undergoing intensive PK sampling will be calculated via noncompartmental methods for JNJ-3976 and JNJ-3924, and, optionally, NA, PegIFN-α2a and/or JNJ-6379. The PK parameters will be C_{max}, C_{24h}, and AUC_{24h}; other PK parameters may also be calculated. The PK parameters will be subjected to an exploratory graphical analysis, including various transformations, to get a general overview.

To assess the effect of PegIFN-α2a on JNJ-6379 (as applicable) and JNJ-3989, the PK parameters of JNJ-6379 (as applicable) and JNJ-3989 coadministered with PegIFN-α2a at Week 20 (or 16) will be compared to those of JNJ-6379 (as applicable) and JNJ-3989 at Week 4 (or 8) as reference. The primary PK parameters are C_{max} and AUC_{24h} on the logarithmic scale. A mixed effects model will be fitted to log-transformed PK parameters with treatment period as a fixed effect and participant as a random effect.

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

Population PK analysis of plasma concentration-time data of JNJ-3976 and JNJ-3924 may be performed using non-linear 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. If a population PK analysis is conducted, the results will be presented either in the clinical study report or in a separate report.

Pharmacokinetic/Pharmacodynamic Analyses

Relationships of PK parameters for JNJ-3976 and JNJ-3924, and, optionally, of NA, PegIFN-α2a and/or JNJ-6379 with selected efficacy and/or 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 may be investigated. Other biomarkers may be explored at the sponsor's discretion. If conducted, the results will be presented in a separate report.

Immune Analyses

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

or CD8+ T-cells expressing at least 1 of the cytokines amongst IL-2, TNF-α or IFN-γ for 1 of the HBV antigens as defined by ELISpot and/or ICS, respectively, will be determined. Other immune cells, such as NK-cells, MDSCs, DCs, and B-cells, may be evaluated/explored.

Pharmacogenomic Analyses

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

Host Biomarker Analyses

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

9.5. Interim Analyses

Interim analyses (IAs) will be conducted to assess safety and efficacy to support the sponsor's interactions with health authorities, as well as to inform internal decisions about additional studies and/or investigation of other treatment combinations. The IAs are planned when:

- Approximately 20 participants have completed Week 24 (EOSI) or discontinued earlier
- All participants have completed Week 36 (FU Week 12) or discontinued earlier
- All participants have completed Week 48 (FU Week 24) or discontinued earlier.

An optional IA may be conducted when all participants have completed Week 60 (FU Week 36) or discontinued earlier.

The study is open-label, and the sponsor will conduct the pre-planned IAs. Hence, the study team and the DRC will have access to the IA results, while the investigators and participants will not.

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

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

9.6. Data Review Committee

The internal DRC established for the Platform study will review interim data and formulate recommendations to protect the safety and well-being of the participants. Description of the DRC is provided in Section 9.6 of the Master Protocol PLATFORMPAHPB2001. The possible recommendations and role of the DRC will be further detailed in the DRC charter for this ISA.

9.7. Independent Flare Expert Panel

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

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

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

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Definitions of Terms

Abbreviations

AE	adverse event
AFP	alpha-fetoprotein
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC_{∞}	area under the plasma concentration-time curve to last sampling point from time zero extrapolated to infinity
AUC_{τ}	area under the plasma concentration-time curve over the dosing interval (τ)
$AUC_{0\text{-last}}$	area under the plasma concentration-time curve from administration to last quantifiable sampling point
$AUC_{0\text{-xh}}$	area under the plasma concentration-time curve from administration to x hours
BMI	body mass index
bpm	beats per minute
C_{24h}	plasma concentration 24 hours after administration
CAM(-N)	(Class N) capsid assembly modulator
cccDNA	covalently closed circular deoxyribonucleic acid
CHB	chronic hepatitis B
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	total apparent oral clearance
C_{max}	maximum plasma concentration
CRF	case report form
CT	computed tomography
CV	coefficient of variation
CYP	cytochrome P450
DAIDS	Division of Acquired Immunodeficiency Syndrome
DC	dendritic cell
DDI	drug-drug interaction
DNA	deoxyribonucleic acid
DRC	Data Review Committee
EC_{90}	90% effective concentration
ECG	electrocardiogram
EFD	embryofetal development
eGFR	estimated glomerular filtration rate
ELISpot	enzyme-linked immunospot
EOS	end of study
EOSI	end of study intervention
ETV	entecavir
FOIA	Freedom of Information Act
FU	follow-up
GLDH	glutamate dehydrogenase
HBc	hepatitis B core protein
HBcrAg	hepatitis B core-related antigen
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBs	hepatitis B surface protein
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 1/2)
HLA	human leukocyte antigen
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICS	intracellular cytokine staining
IFLEP	Independent Flare Expert Panel
IFN(-α/γ)	(alpha/gamma) interferon
IgG	immunoglobulin G
IgM	immunoglobulin M
IL	interleukin
INR	International Normalized Ratio
ISA	intervention-specific appendix
ISR	injection site reaction
ITT	intent-to-treat
LLN	lower limit of normal
LLOQ	lower limit of quantification
MDSC	myeloid-derived suppressor cell
MoA	mode of action
MRI	magnetic resonance imaging
NA	nucleos(t)ide analog
NK	natural killer
NOAEL	no observed adverse effect level
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PegIFN-α2a	pegylated interferon alpha-2a
pgRNA	pre-genomic ribonucleic acid
PK	pharmacokinetic(s)
PoC	proof of concept
Q4W	every 4 weeks
QD	once daily
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RBC	red blood cell
rcDNA	relaxed circular deoxyribonucleic acid
RNAi	ribonucleic acid interference
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SDM	site-directed mutant
SE	standard error
siRNA	small interfering ribonucleic acid
$t_{1/2term}$	terminal half-life
T4	thyroxine
TAF	tenofovir alafenamide
TEAE	treatment-emergent adverse event
t_{max}	time to reach C_{max}
TND	target not detected
TNF	tumor necrosis factor
TSH	thyroid stimulating hormone
WBC	white blood cell

Definitions of Terms

ALT/AST nadir	Lowest ALT/AST value during study participation
End of study intervention (EOSI)	Time of the last administration of study intervention
HBsAg 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
IC_{50}	half maximal inhibitory concentration
Study intervention	As of Protocol Amendment 3: JNJ-73763989 (JNJ-3989), NA (either ETV, tenofovir disoproxil, or TAF), and PegIFN-α2a (in Treatment Period 2)
Virologic breakthrough	Confirmed on-treatment HBV DNA increase by >1 $\log_{10}$ IU/mL from nadir or confirmed on-treatment HBV DNA level >200 IU/mL in participants who had HBV DNA level <LLOQ of the HBV DNA assay

10.2. Appendix 2: Clinical Laboratory Tests

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

Below is the list of protocol-required safety laboratory assessments that will be evaluated in this study. The additional assessments specific for this ISA are highlighted (colored fill).

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
Red blood cell count
Hemoglobin
Hematocrit</td><td><u>RBC Indices:</u>
MCV
MCH
% Reticulocytes</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>Clinical Chemistry</td><td colspan="2">Sodium
Potassium
Chloride
Bicarbonate
Blood urea nitrogen (BUN)
Creatinine
Glucose
Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Gamma-glutamyltransferase (GGT)
α_1-acid glycoprotein
Calculated creatinine clearance (by CKD-EPI formula)
Fibrinogen (on blood)
eGFR calculation based on Cystatin C</td><td>Total, direct, indirect bilirubin
Alkaline phosphatase
Creatine phosphokinase (CPK)
Lactic acid dehydrogenase (LDH)
Uric acid
Calcium
Phosphate
Albumin
Total protein
Total cholesterol
High-density lipoprotein cholesterol
Low-density lipoprotein cholesterol
Triglycerides
Magnesium
Lipase
Amylase (reflex testing of pancreatic amylase should be done in case of amylase or lipase increase from screening onwards)</td></tr>
</table>

Laboratory Assessments	Parameters	
Routine Urinalysis	Dipstick Specific gravity pH Glucose Protein Blood Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase	Sediment (if dipstick result is abnormal) Red blood cells White blood cells Epithelial cells Crystals Casts Bacteria
	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).	
Urine Chemistry (quantitative measurement)	Creatinine Sodium Phosphate	Glucose Protein Albumin
Renal Biomarkers	Retinol binding protein[a] Beta-2-microglobulin[a] ***Note:*** Other biomarkers might be measured.	

Other Tests	• At screening, a follicle-stimulating hormone (FSH) test will be performed for postmenopausal women (see Section 10.5, Appendix 5).
	• At screening, a HIV-1 and -2 test, and hepatitis A, C, D, and E tests will be performed.
	• At screening, hemoglobin A1c will be measured.
	• At screening and time points as indicated in the Schedule of Activities, alpha-fetoprotein will be measured.
	• At screening and time points as indicated in the Schedule of Activities, tests for coagulation parameters will be performed. The international normalized ratio (INR) will be calculated by the central laboratory.
	• At screening serum pregnancy testing will be done for women of childbearing potential only.
	• At baseline (Day 1) and time points as indicated in the Schedule of Activities, a urine pregnancy test will be performed for women of childbearing potential only.
	• Testing for HBsAg, HBeAg, and anti-HBs, anti-HBc and anti-HBe antibodies at the time points indicated in the Schedule of Activities.
	• Thyroid function tests (TSH and T4) will be performed at screening and time points indicated in the Schedule of Activities.
	• Optional tests in response to ALT flare (refer to Section 10.7, Appendix 7):
	  ○ Testing for HIV-1 and -2, and hepatitis A, C, and E
	  ○ Testing for CMV, HSV, EBV infection
	  ○ Ig-Electrophoresis	

[a] Retinol binding protein and beta-2-microglobulin need to be assessed based on the same urine sample.

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

10.3.1. Regulatory and Ethical Considerations

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

10.3.2. Financial Disclosure

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

10.3.3. Informed Consent Process

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

10.3.4. Data Protection

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

10.3.5. Long-Term Retention of Samples for Additional Future Research

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

10.3.6. Committees Structure

Data Review Committee

The internal DRC established for the Platform study will review interim data and formulate recommendations to protect the safety and well-being of the participants. Description of the DRC is provided in Section 9.6 of the Master Protocol PLATFORMPAHPB2001. The possible recommendations and role of the DRC will be further detailed in the DRC charter for this ISA.

Independent Flare Expert Panel

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

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

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

10.3.7. Publication Policy/Dissemination of Clinical Study Data

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

10.3.8. Data Quality Assurance

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

10.3.9. Case Report Form Completion

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

10.3.10. Source Documents

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

10.3.11. Monitoring

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

10.3.12. On-Site Audits

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

10.3.13. Record Retention

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

10.3.14. Study and Site Start and Closure

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

10.4. Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. Adverse Event Definitions and Classifications

Refer to Attachment 4 of the Master Protocol PLATFORMPAHPB2001.

10.4.2. Attribution Definitions

Refer to Attachment 4 of the Master Protocol PLATFORMPAHPB2001.

10.4.3. Severity Criteria

Refer to Attachment 4 of the Master Protocol PLATFORMPAHPB2001.

10.4.4. Special Reporting Situations

Refer to Attachment 4 of the Master Protocol PLATFORMPAHPB2001.

10.4.5. Procedures

Refer to Attachment 4 of the Master Protocol PLATFORMPAHPB2001.

10.4.6. Product Quality Complaint Handling

Refer to Attachment 4 of the Master Protocol PLATFORMPAHPB2001.

10.4.7. Contacting Sponsor Regarding Safety, Including Product Quality

Refer to Attachment 4 of the Master Protocol PLATFORMPAHPB2001.

10.5. Appendix 5: Contraceptive and Barrier Guidance

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

Definitions

Woman of Childbearing Potential (WOCBP)

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

Woman Not of Childbearing Potential

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

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

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

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

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Tubal closure (eg, bilateral tubal occlusion, bilateral tubal ligation)

• Azoospermic partner *(vasectomized or due to medical cause)* *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

10.6. Appendix 6: Rash Management

Table 5: Management of Rash Events by Severity Grade

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

Table 5: Management of Rash Events by Severity Grade

	Definition	Study Intervention Action	Activities by Day[a]	Referral to Dermatologist and Dermatology Activities
			higher grade, safety laboratory assessments of the higher grade should be followed. Digital pictures[c] of skin lesions may be taken at the investigator's discretion.	
Grade 3 rash[b]	Vesiculation, moist desquamation, or ulceration OR Any cutaneous event with 1 of the following: - Elevations in AST/ALT >2×baseline value - Fever >38°C or 100°F - Eosinophils >1.00×10^3/μL - Serum sickness-like reaction	Must permanently discontinue JNJ-3989 and PegIFN-α2a; no rechallenge allowed NA treatment may be discontinued based on investigator judgement in consultation with the sponsor	Day 0: required on-site visit. Safety laboratory assessments required to be performed. Digital pictures[c] of skin lesions may be taken at the investigator's discretion (recommended). Determine if participant was adhering to the recommended sun-protective measures. If appropriate, provide sun protection counseling. Day 1: required on-site visit. Safety laboratory assessments required to be performed. Digital pictures[c] of skin lesions may be taken at the investigator's discretion (recommended). Further visit(s): appropriate follow-up required until resolution of rash or until clinical stability is reached. Safety laboratory assessments and photography (digital pictures[c] of skin lesions) are recommended to be performed until the rash severity resolves to grade 2 or grade 1.	Required[d] Biopsy not required, but may be performed at the dermatologist's discretion.

Table 5: Management of Rash Events by Severity Grade

	Definition	Study Intervention Action	Activities by Day[a]	Referral to Dermatologist and Dermatology Activities
Grade 4 rash	Exfoliative dermatitis OR Mucous membrane involvement in at least 2 distinct sites OR Erythema multiforme major OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis OR Necrosis requiring surgery	Must permanently discontinue JNJ-3989 and PegIFN-α2a; no rechallenge allowed NA treatment may be discontinued based on investigator judgement in consultation with the sponsor	Day 0: required on-site visit. Safety laboratory assessments required to be performed. Digital pictures[c] of skin lesions may be taken at the investigator's discretion (recommended). Determine if participant was adhering to the recommended sun-protective measures. If appropriate, provide sun protection counseling. Day 1: required on-site visit. Safety laboratory assessments required to be performed. Digital pictures[c] of skin lesions may be taken at the investigator's discretion (recommended). Further visit(s): appropriate follow-up required until resolution of rash or until clinical stability is reached. Safety laboratory assessments and photography (digital pictures[c] of skin lesions) are recommended to be performed until the rash severity resolves to grade 2 or grade 1.	Required[d] Biopsy required and to be performed as soon as possible after the onset of the rash.

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

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

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

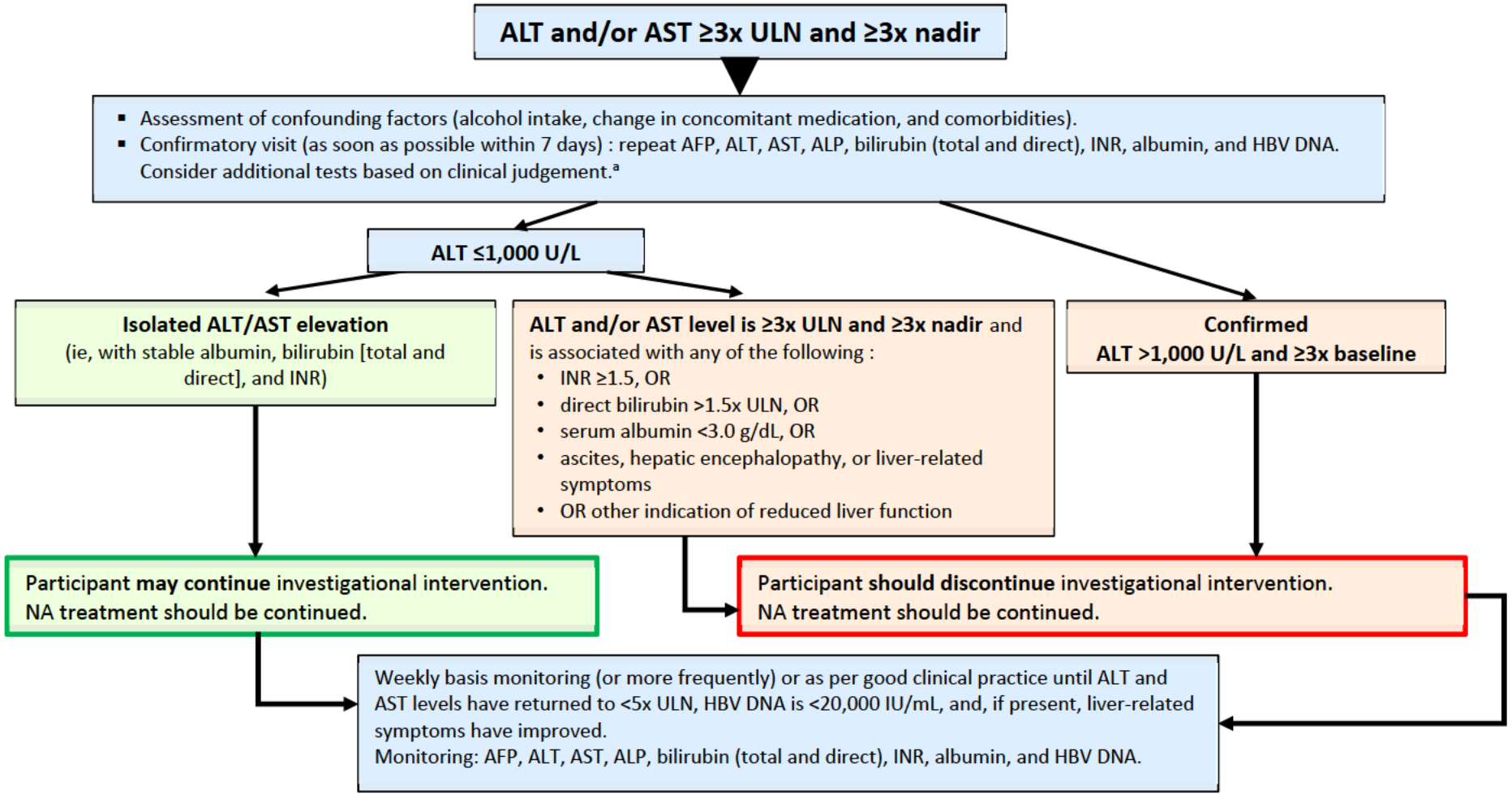
[c] Digital pictures to be taken at the clinical site upon consent of the participant.

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

Notes:

- *Local laboratory assessments are to be used for rash management. The values of the local laboratory assessments need to be transcribed in the CRF by the study site personnel.*
- *A copy of the dermatologist's report, biopsy, and/or digital pictures if performed, should be made anonymous and provided to the sponsor.*

10.7. Appendix 7: Intervention-emergent ALT/AST Elevations



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

- Hepatitis A, Delta, C, E: IgM anti-HAV; delta IgM, IgG and PCR, HCV RNA, IgM and IgG anti-HEV, HEV RNA
- CMV, HSV, EBV infection: IgM and IgG anti-CMV, IgM and IgG anti-HSV; IgM and IgG anti-EBV, PCR
- HIV
- Ig-Electrophoresis

10.8. Appendix 8: Cardiovascular Safety – Abnormalities

ECG

All important abnormalities from the ECG readings will be listed.

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

ECG: electrocardiogram; NAP = not applicable
For absolute QTc parameters the categories are defined based on the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E14 Guidance[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.

10.9. Appendix 9: DAIDS Table

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

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

General Instructions

Grading Adult and Pediatric Adverse Events

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

Determining Severity Grade for Parameters Between Grades

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

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

Definitions

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

Estimating Severity Grade for Parameters not Identified in the Grading Table

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

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

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

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

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

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

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

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

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

IV: intravenous; NAP: not applicable

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

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

NAP: not applicable

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

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

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

IV: intravenous; NAP: not applicable

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

IV: intravenous; NAP: not applicable

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

BMD: bone mineral density; NAP: not applicable

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

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

CNS: central nervous system; NAP: not applicable

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

NAP: not applicable

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

ID: identity, NAP: not applicable
[g] A pregnancy loss occurring at <20 weeks gestational age.

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

NAP: not applicable

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

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

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

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

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

IV: intravenous; NAP: not applicable

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

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

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

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

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

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

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

NAP: not applicable

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

NAP: not applicable

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

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

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

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

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

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

LABORATORY VALUES				
CHEMISTRIES				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Calcium, High (mg/dL; *mmol/L*)				
aged ≥7 days	10.6 to <11.5 *2.65 to <2.88*	11.5 to <12.5 *2.88 to <3.13*	12.5 to <13.5 *3.13 to <3.38*	≥13.5 *≥3.38*
aged <7 days	11.5 to <12.4 *2.88 to <3.10*	12.4 to <12.9 *3.10 to <3.23*	12.9 to <13.5 *3.23 to <3.38*	≥13.5 *≥3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	>ULN to <6.0 *>ULN to <1.5*	6.0 to <6.4 *1.5 to <1.6*	6.4 to <7.2 *1.6 to <1.8*	≥7.2 *≥1.8*
Calcium, Low (mg/dL; *mmol/L*)				
aged ≥7 days	7.8 to <8.4 *1.95 to <2.10*	7.0 to <7.8 *1.75 to <1.95*	6.1 to <7.0 *1.53 to <1.75*	<6.1 *<1.53*
aged <7 days	6.5 to <7.5 *1.63 to <1.88*	6.0 to <6.5 *1.50 to <1.63*	5.50 to <6.0 *1.38 to <1.50*	<5.50 *<1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	<LLN to 4.0 *<LLN to 1.0*	3.6 to <4.0 *0.9 to <1.0*	3.2 to <3.6 *0.8 to <0.9*	<3.2 *<0.8*
Cardiac Troponin I, High	NAP	NAP	NAP	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to <6×ULN	6 to <10×ULN	10 to <20×ULN	≥20×ULN
Creatinine, High *Report only 1*[p]	1.1 to 1.3×ULN	>1.3 to 1.8×ULN OR Increase to 1.3 to <1.5×participant's baseline	>1.8 to <3.5×ULN OR Increase to 1.5 to <2.0×participant's baseline	≥3.5×ULN OR Increase of ≥2.0×participant's baseline
Creatinine Clearance[q] **or eGFR, Low** *Report only 1*[p]	NAP	<90 to 60 ml/min or ml/min/1.73 m^2 OR 10% to <30% decrease from participant's baseline	<60 to 30 ml/min or ml/min/1.73 m^2 OR 30% to <50% decrease from participant's baseline	<30 ml/min or ml/min/1.73 m^2 OR ≥50% decrease from participant's baseline or dialysis needed
Glucose (mg/dL; *mmol/L*)				
Fasting, High	110 to <125 *6.11 to <6.95*	125 to <250 *6.95 to <13.89*	250 to <500 *13.89 to <27.75*	≥500 *≥27.75*
Nonfasting, High	116 to <160 *6.44 to <8.89*	160 to <250 *8.89 to <13.89*	250 to <500 *13.89 to <27.75*	≥500 *≥27.75*
Glucose, Low (mg/dL; *mmol/L*)				
aged ≥1 month	55 to 64 *3.05 to <3.55*	40 to <55 *2.22 to <3.05*	30 to <40 *1.67 to <2.22*	<30 *<1.67*
aged <1 month	50 to 54 *2.78 to <3.00*	40 to <50 *2.22 to <2.78*	30 to <40 *1.67 to <2.22*	<30 *<1.67*
Lactate, High	ULN to <2.0×ULN without acidosis	≥2.0×ULN without acidosis	Increased lactate with pH <7.3 without life-threatening consequences	Increased lactate with pH <7.3 with life-threatening consequences

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

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

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

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

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

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

LABORATORY VALUES				
HEMATOLOGY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Absolute $CD4^+$ Count, Low (cells/mm^3; *cells/L*) *aged >5 years (not HIV-infected)*	300 to <400 *0.300×10^9 to <0.400×10^9*[s]	200 to <300 *0.200×10^9 to <0.300×10^9*[s]	100 to <200 *0.100×10^9 to <0.200×10^9*[s]	<100 *<0.100×10^9*[s]
Absolute Lymphocyte Count, Low (cells/mm^3; *cells/L*) *aged >5 years (not HIV-infected)*	600 to <650 *0.600×10^9 to <0.650×10^9*	500 to <600 *0.500×10^9 to <0.600×10^9*	350 to <500 *0.350×10^9 to <0.500×10^9*	<350 *<0.350×10^9*
Absolute Neutrophil Count, Low (cells/mm^3; *cells/L*) *aged >7 days*	800 to 1,000 *0.800×10^9 to 1.000×10^9*	600 to 799 *0.600×10^9 to 0.799×10^9*	400 to 599 *0.400×10^9 to 0.599×10^9*	<400 *<0.400×10^9*
aged 2 to 7 days	1,250 to 1,500 *1.250×10^9 to 1.500×10^9*	1,000 to 1,249 *1.000×10^9 to 1.249×10^9*	750 to 999 *0.750×10^9 to 0.999×10^9*	<750 *<0.750×10^9*
aged ≤1 day	4,000 to 5,000 *4.000×10^9 to 5.000×10^9*	3,000 to 3,999 *3.000×10^9 to 3.999×10^9*	1,500 to 2,999 *1.500×10^9 to 2.999×10^9*	<1,500 *<1.500×10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to <200 *1.00 to <2.00* OR 0.75 to <1.00×LLN	75 to <100 *0.75 to <1.00* OR ≥0.50 to <0.75×LLN	50 to <75 *0.50 to <0.75* OR 0.25 to <0.50×LLN	<50 *<0.50* OR <0.25×LLN OR Associated with gross bleeding
Hemoglobin[t], Low (g/dL; *mmol/L*)[u] *aged ≥13 years (male only)*	10.0 to 10.9 *6.19 to 6.76*	9.0 to <10.0 *5.57 to <6.19*	7.0 to <9.0 *4.34 to <5.57*	<7.0 *<4.34*
aged ≥13 years (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to <9.5 *5.25 to <5.88*	6.5 to <8.5 *4.03 to <5.25*	<6.5 *<4.03*
aged 57 days to <13 years (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to <9.5 *5.25 to <5.88*	6.5 to <8.5 *4.03 to <5.25*	<6.5 *<4.03*
aged 36 to 56 days (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to <8.5 *4.32 to <5.26*	6.0 to <7.0 *3.72 to <4.32*	<6.0 *<3.72*
aged 22 to 35 days (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to <9.5 *4.94 to <5.88*	6.7 to <8.0 *4.15 to <4.94*	<6.7 *<4.15*
aged 8 to ≤21 days (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to <11.0 *5.57 to <6.81*	8.0 to <9.0 *4.96 to <5.57*	<8.0 *<4.96*
aged ≤7 days (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to <13.0 *6.19 to <8.05*	9.0 to <10.0 *5.59 to <6.19*	<9.0 *<5.59*

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

[s] Revised by the sponsor.

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

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

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

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

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

NAP: not applicable; RBC: red blood cell

10.10. Appendix 10: Study Conduct During a Natural Disaster

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the CRF.

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL

The following emergency provisions are meant to ensure participant safety on study while site capabilities are compromised by COVID-19-related restrictions. Remote medical consultation and alternatives to study intervention dispensing, administration, and clinical laboratory assessments may allow continued study participation for participants in this trial. Before implementing any of these emergency provisions, the sponsor should be consulted to perform a benefit-risk analysis and to ensure the measures are executed and documented correctly.

As restrictions are lifted and the acute phase of the COVID-19 pandemic resolves, sites should revert to original protocol conduct as soon as feasible and in accordance with any country-specific regulatory requirements.

Screening and Randomization:

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

Dispensing/Administration of Study Intervention:

- For participants able to visit the study site, but who request to reduce visit frequency, or for whom limited access to the site is expected, an additional supply of oral study intervention, as well as PegIFN-α2a where allowed per local regulations[a], can be provided.
- For participants unable to visit the study site, direct-to-patient (DTP) shipment or handover to a caregiver or delegate of oral study intervention may be implemented, where allowed per local regulations and if requested by the treating study physician. Where DTP shipments or handover to delegates are deemed necessary, the process must be coordinated between the site and sponsor staff following standard DTP procedures for arranging shipment and adhering to associated approvals and documentation requirements.
- JNJ-3989 should always be administered by a nurse at the study site or, if site visits are not possible, at the participant's home. Refer to Section 6.4, Study Intervention Compliance, in case a scheduled administration of study intervention (JNJ-3989, NA, or PegIFN-α2a) is missed.

Continuation of Study Intervention:

- Any issue with continuation and/or provision of study intervention should be discussed with the sponsor and should be well documented.
- Study intervention should be continued if, in the assessment of the investigator, it does not result in risk to the participant. If at any time the participant's safety is considered at risk due

[a] Providing additional PegIFN-α2a to study participants is not applicable for sites in Japan, where weekly administration of PegIFN-α2a must be performed at the study site by the investigator or his/her designee.

to study intervention, study intervention will be temporarily or permanently discontinued, while every effort should be made to maintain follow-up on study. The benefit of continuing study intervention should be assessed by the investigator for each individual participant, considering the potential impact of reduced direct clinical supervision on participant safety.

- If a participant develops a SARS-CoV-2 infection, the investigator should contact the sponsor to discuss plans for study intervention and follow-up. A decision to continue study intervention should be made by the investigator depending on symptoms and concomitant medication(s) used for the treatment of COVID-19. Study intervention must be discontinued if prohibited medication is used.
- When a participant, for whom study intervention has been interrupted, recovers from suspected or confirmed SARS-CoV-2 infection or related disease and all adverse events (AEs) related to SARS-CoV-2 infection improve to grade ≤1, the investigator should discuss with the sponsor about resuming study intervention.

COVID-19 vaccination during the study:

Local guidelines on the use of live vaccines in participants receiving PegIFN-α2a should be followed, including for the second dose of Sputnik V (which contains rAd5, with a theoretical risk of replication competence). Sputnik Light, which is the first dose of Sputnik V (with rAd26) is not considered a live vaccine. See below for further guidance on the use of COVID-19 vaccines.

Locally approved COVID-19 vaccines (including those that received emergency use authorization or conditional marketing authorization) are allowed throughout the study. For participants receiving PegIFN-α2a the following recommendations should be applied to accommodate COVID-19 vaccination during Treatment Period 2:

- COVID-19 vaccine and PegIFN-α2a should not be administered on the same day.
- If required, PegIFN-α2a injection can be delayed with 2 days. The next PegIFN-α2a injection should be performed at the scheduled time.
- If required, skipping a PegIFN-α2a injection may be considered after consultation with the Sponsor.
- Vaccination with Sputnik V should take above mentioned consideration about live vaccines into account.

All COVID-19 vaccination-related data (eg, COVID-19 vaccination, AEs, AE management) should be appropriately captured in the CRF and source documents. Refer to the COVID-19 vaccine and/or PegIFN-α2a prescribing information for more details.

Study Visits and Assessments:

- If possible, central laboratory testing as outlined in the Schedule of Activities is to be continued. If central laboratory tests cannot be performed, the use of a local laboratory is

allowed for study evaluations. A copy of the local laboratory report should be reviewed by the investigator and filed with the source documents, along with reference ranges.

- To safely maintain participants on study intervention while site capabilities are compromised by COVID-19-related restrictions, study visits may be performed by a nurse (who received study-specific training) at the patient's home (home health nurse) until such time that on-site visits can be resumed. The following activities may be completed as required per the Schedule of Activities and as feasible:
  - Sampling, processing and shipping of laboratory samples (as described above).
  - Checking study compliance: medication diary (if available), intake of oral study intervention, storage of oral study intervention.
  - Performing electrocardiograms (ECGs).
  - If JNJ-3989 is administered at the patient's home, it will need to be done by a nurse (who received study-specific training).
  - Delivering oral study interventions, as well as PegIFN-α2a where allowed per local regulations.[a]
- Any data related to AEs, concomitant medication, vital signs, and ECGs will be reviewed and assessed by the investigator.
- In addition, participants may have tele-health visits conducted by qualified site personnel via phone or video conversation as per local regulation. Assessments may include review of AEs (including injection site reactions), concomitant medications, and study intervention accountability. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.
- Procedures and timings should follow the Schedule of Activities as closely as possible. Standard AE/serious adverse event (SAE) reporting requirements apply.
- Ultrasound (and Fibroscan where applicable) should be done as close as possible to the time points specified in the Schedule of Activities. However, if this is not possible due to COVID-19-related restrictions, the imaging test should be performed as soon as possible.

Informed Consent:

- Consenting and re-consenting of participants (including also remote consenting by phone or video consultation) will be performed as applicable for the measures taken and according to local guidance for informed consent applicable during the COVID-19 pandemic. The process is to be documented in the source documents.

Source Data Verification/Monitoring:

- In case on-site monitoring visits are not possible, the site monitor may contact the investigator to arrange monitoring activities remotely (in accordance with site and local requirements).

[a] Delivering PegIFN-α2a is not applicable for sites in Japan, where weekly administration of PegIFN-α2a must be performed at the study site by the investigator or his/her designee.

Additional on-site monitoring visits may be needed in the future to catch up on source data verification.

Site Audits:

- During the COVID-19 pandemic and at the impacted sites, study site Good Clinical Practice (GCP) audits with direct impact/engagement from the investigator and study site personnel would not be conducted in order to comply with national, local, and/or organizational social distancing restrictions. Additional quality assurance activities such as remote audits or focused review of study-related documents may take place with limited impact/engagement if possible.

10.11. Appendix 11: Protocol Amendment History

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

Amendment 3 (04 October 2021)

Overall Rationale for the Amendment:

The primary reason for this amendment is to remove JNJ-56136379 as study intervention, to add a new nucleos(t)ide analog (NA) re-treatment criterion for participants who discontinued NA treatment during follow-up, and to include more frequent monitoring for participants who discontinued NA treatment during follow-up.

Based on emerging data from recent interim analyses of the REEF-1 (73763989HPB2001) and REEF-2 (73763989PAHPB2002) studies, the benefit-risk profile of JNJ-6379 in combination with JNJ-3989+NA is unfavorable compared to JNJ-3989+NA.

In the primary REEF-1 analysis (Week 48, end of treatment) the mean reduction of hepatitis B surface antigen (HBsAg) levels in the triple arm (JNJ-6379+JNJ-3989 100mg+NA) appeared to be less than in the dual arm (JNJ-3989 100mg+NA). More recent interim results of the REEF-2 study (Week 48, end of treatment) confirmed this observation when the effect of JNJ-6379+JNJ-3989 200mg+NA on mean HBsAg level reduction in the REEF-2 study is compared to JNJ-3989 200mg+NA in the REEF-1 study. To match with the REEF-2 population, this cross-study comparison focused on the REEF-1 subpopulation of hepatitis B e antigen (HBeAg) negative, virologically suppressed participants with chronic hepatitis B. Pharmacokinetic-pharmacodynamic modelling analyses accounting for variability in baseline characteristics further support this observation. Therefore, a negative impact of JNJ-6379 on the HBsAg lowering effect of JNJ-3989+NA is suspected.

From a safety perspective, transient reductions of estimated glomerular filtration rate based on creatinine (eGFRcr) in JNJ-6379 containing treatment arms with fast recovery after end of treatment had been described in the Jade study (56136379HPB2001) and confirmed in the REEF-1 study. In absence of a pattern of increased biomarkers of proximal tubulo-toxicity (the beta-2microglobulin/creatinine and the retinol binding protein/creatinine ratios), the eGFRcr reduction during treatment was interpreted as transporter inhibition at the level of creatinine excretion from the proximal tubule rather than renal toxicity.

Recent data from REEF-2 confirm the transient pattern of eGFRcr declines but, in addition, show an increase of the beta-2microglobulin/creatinine and the retinol binding protein/creatinine ratios in some participants when tenofovir disoproxil fumarate (TDF) treatment was continued and combined with JNJ-6379+JNJ-3989. These new data are suggesting that JNJ-6379 in combination with TDF may contribute to renal tubulo-toxicity. There was no apparent increase in the beta-2-microglobulin/creatinine or retinol binding protein/creatinine ratios in participants receiving entecavir (ETV; active or control arm), nor in participants receiving TDF+placebo.

The negative impact of JNJ-6379, when combined with JNJ-3989+NA, on HBsAg reduction taken together with the adverse renal profile leads to conclusion of an unfavorable benefit-risk balance of JNJ-6379 in combination with JNJ-3989+NA, compared to JNJ-3989+NA alone. Therefore, the Sponsor has decided to discontinue treatment with JNJ-6379 in all ongoing clinical studies effective immediately. Participants currently on treatment with JNJ-6379 will be contacted and requested to stop taking JNJ-6379, while continuing treatment with NA, JNJ-3989 and pegylated interferon alpha-2a (PegIFN-α2a; as applicable). For newly enrolled participants, JNJ-6379 will no longer be included in the treatment regimen.

In addition, a new NA re-treatment criterion and more frequent monitoring for participants who discontinued NA treatment during follow-up were included. The reason for these changes is a severe

clinical alanine aminotransferase (ALT) flare that was reported following discontinuation of NA treatment in a virologically suppressed HBeAg negative participant on long-term TDF treatment who was randomized to the control arm (placebo + placebo + NA) in the REEF-2 study. The participant presented with hepatitis B virus (HBV) DNA levels that increased rapidly, before any relevant changes in liver markers were noted. Discontinuation of NA treatment was following the protocol-defined criteria and was in line with recent European Association for the Study of the Liver (EASL) treatment guidelines (EASL 2017). Flares following NA discontinuation are not unexpected, but the rapid evolution and clinical deterioration seen in this participant who was anti-HBe antibody positive at screening and had no history or evidence of liver cirrhosis was unforseeable. Therefore, to protect safety of participants, the protocol was amended as detailed below.

Furthermore, the PegIFN-α2a eligibility criteria, the PegIFN-α2a discontinuation criteria, and the monitoring of neuropsychiatric adverse events during PegIFN-α2a treatment were amended to be consistent with the PegIFN-α2a prescribing information.

Other clarifications and corrections were also made as detailed below.

Description of Change	**Brief Rationale**	**Section number and Name**
JNJ-6379 has been removed as study intervention. Participants enrolled before Protocol Amendment 3 had to stop JNJ-6379 treatment immediately. They will continue with JNJ-3989+NA treatment up to the end of Treatment Period 1 (12 weeks) and will then enter Treatment Period 2 (12 weeks) during which they will have PegIFN-α2a added to their treatment regimen. Throughout the protocol, elements specific for JNJ-6379 have been modified.	Based on emerging data from recent interim analyses of the REEF-1 and REEF-2 studies, showing that the benefit-risk profile of JNJ-6379 in combination with JNJ-3989+NA is unfavorable compared to JNJ-3989+NA.	1.1 Synopsis 1.2 Schema 1.3 Schedule of Activities 2 INTRODUCTION 2.1 Study Rationale 2.2 Background 2.2.3.1 JNJ-3989 and JNJ 6379 2.3 Benefit-Risk Assessment 2.3.2.2.2 Potential Risks for JNJ-6379 2.3.3 Benefit-Risk Assessment for Study Participation 3 OBJECTIVES AND ENDPOINTS 4.1 Overall Design 4.2 Scientific Rationale for Study Design 4.3 Justification for Dose and Treatment Duration 4.3.2 JNJ-6379 5.2 Exclusion Criteria 6.1 Study Intervention(s) Administered 6.2 Preparation/Handling/Storage/Accountability 6.4 Study Intervention Compliance 6.5 Concomitant Therapy 6.6 Study Intervention Completion at Week 24 7.1 Discontinuation of Study Intervention 8.1 Efficacy Assessments 8.3.6 Adverse Events of Special Interest 8.3.6.1 Rash 8.3.6.3 Acute Systemic Allergic Reactions 8.3.6.4 Intervention emergent ALT/AST Elevations 8.3.6.5 Renal Complications 8.3.6.6 Hematologic Abnormalities 8.4 Treatment of Overdose 8.5 Pharmacokinetics

Description of Change	Brief Rationale	Section number and Name
		8.6 Pharmacokinetic/Pharmacodynamic Evaluations 9.4.4 Other Analyses 10.1 Appendix 1: Abbreviations and Definitions of Terms 10.6 Appendix 6: Rash Management 10.7 Appendix 7: Intervention-emergent ALT/AST Elevations 10.10 Appendix 10: Study Conduct During a Natural Disaster
A new NA re-treatment criterion was added for participants who discontinued NA treatment during follow-up.	To ensure that participants with significant HBV DNA increases during treatment free follow-up are monitored at least weekly and/or immediately re-start NA treatment irrespective of ALT levels.	1.1 Synopsis 1.3 Schedule of Activities 4.2 Scientific Rationale for Study Design 6.7.1 NA Re-treatment Criteria During Follow-up 6.8 Continued Access to Study Intervention After the End of the Study 8.3.6.4 Intervention emergent ALT/AST Elevations 10.12 Appendix 12: NA Re-treatment During Follow-up
Participants who discontinue NA treatment during follow-up, will be monitored more frequently, with a study visit at least once every 4 weeks. The visit frequency for participants who continue NA treatment or have restarted NA treatment during the follow-up period and for whom the HBV DNA and ALT values are stable remains at least once every 12 weeks. For participants with increased follow-up, the total blood volume to be collected during the study will increase.	To further protect the safety of participants.	1.1 Synopsis 1.3 Schedule of Activities 4.2 Scientific Rationale for Study Design 6.7.1 NA Re-treatment Criteria During Follow-up 8 STUDY ASSESSMENTS AND PROCEDURES REFERENCES
The PegIFN-α2a discontinuation criteria were updated to clarify that participants with moderate or severe depression or other psychiatric symptoms should immediately discontinue PegIFN-α2a treatment. In addition, participants will be closely monitored for neuropsychiatric adverse events during the PegIFN-α2a treatment period. Participants who develop a neuropsychiatric adverse event during PegIFN-α2a treatment will be monitored closely until the	Upon Health Authority request and to be consistent with the PegIFN-α2a prescribing information.	1.3 Schedule of Activities 5.2 Exclusion Criteria 7.1 Discontinuation of Study Intervention

Description of Change	Brief Rationale	Section number and Name
neuropsychiatric adverse event resolves, by frequent (at least weekly) follow-up phone calls. Furthermore, exclusion criterion A25 was amended to exclude participants with a history of a severe psychiatric disorder.		
The contraceptive guidance from the Master Protocol was replaced by ISA-specific contraceptive guidance, which includes the following updates versus the Master Protocol version: the list of examples which are not allowed as sole method of contraception during the study and the footnote concerning possible interaction between hormonal contraception and the study intervention have been removed. Additional clarifications were also made.	Upon Health Authority request and to align with the latest version of the sponsor's protocol template.	1.3 Schedule of Activities 5.1 Inclusion Criteria 10.5 Appendix 5: Contraceptive and Barrier Guidance
It was clarified that NA will not be dispensed at the end of study visit, and that NA will not be administered during an early withdrawal visit.	Correction.	1.3 Schedule of Activities
Recommendations regarding the use of live vaccines during the study were added.	Clarification regarding the use of live vaccines during the study.	6.5 Concomitant Therapy 10.10 Appendix 10: Study Conduct During a Natural Disaster
It was clarified that venous blood samples will be collected for measurement of JNJ-3989, NA, and PegIFN-α2a. Bioanalysis of JNJ-6379 may also be done on samples collected from participants who received JNJ-6379 prior to Protocol Amendment 3.	Clarification.	1.1 Synopsis 1.3 Schedule of Activities 3 OBJECTIVES AND ENDPOINTS 8.5.1 Evaluations
Exclusion criterion A01 was adapted to clarify that participants with a positive HIV-1 or HIV-2 antibody/antigen test at screening should have a confirmatory HIV RNA test, to rule out false positive results. They can be enrolled if they have a negative HIV RNA test at screening. It was also clarified that participants with	Clarification upon Health Authority request.	5.2 Exclusion Criteria

Description of Change	Brief Rationale	Section number and Name
evidence of HIV-1 or HIV-2 infection who are on antiretroviral treatment are excluded.		
Text was added on dose modifications for PegIFN-α2a.	For completeness.	6.7 Dose Modification 7.1 Discontinuation of Study Intervention
The footnote for Japan only in the Schedule of Activities (SOA) was adapted to clarify that weekly visits are to be scheduled up to Week 23 for assessments of safety, concomitant therapy, and adverse events.	Correction.	1.3 Schedule of Activities
It was clarified that a copy of the dermatologist's report, biopsy, and/or digital pictures if performed for rash management, should be made anonymous and provided to the sponsor.	Clarification	10.6 Appendix 6: Rash Management
Text was updated with 48-week hematology data from study REEF-1.	Update based on the availability of new data.	2.2.3.3 Combination of JNJ-3989 and JNJ-6379 with PegIFN-α2a 2.3.3 Benefit-Risk Assessment for Study Participation
Minor errors were corrected, and minor clarifications were made.	Correction and clarification.	Throughout the protocol.

Amendment 2 (07 May 2021)

Overall Rationale for the Amendment: The primary reason for this amendment is to add guidance on the concomitant use of COVID-19 vaccines and PegIFN-α2a.

Description of Change	Brief Rationale	Section number and Name
Guidance was added on the concomitant use of COVID-19 vaccines and PegIFN-α2a	Due to overlapping safety profiles of PegIFN-α2a and COVID-19 vaccines	6.5 Concomitant Therapy 10.10 Appendix 10: Study Conduct During a Natural Disaster
Language on urine pregnancy testing for at-home use was updated	To provide additional guidance on urine pregnancy testing at home	1.3 Schedule of Activities
Minor formatting change was made	Minor error was noted	5.2 Exclusion Criteria

Amendment 1 (10 March 2021)

Overall Rationale for the Amendment: The primary reason for this amendment is to increase the sample size from 20 to approximately 50 participants. In addition, other changes and minor clarifications and corrections were made as detailed below.

Description of Change	Brief Rationale	Section Number and Name
The overall sample size was increased from 20 to approximately 50 participants. Update of the sample size determination and interim analyses (IAs) sections, respectively.	This change will allow to increase the value of data collected from this study to support strategic and informed decision-making for the upcoming JNJ-3989 Phase 3 program. To align the sample size justification to the increased size of approximately 50. To adjust the timing of the planned IAs to the larger sample size.	1.1 Synopsis 4.1 Overall Design 9.4.2 Efficacy Analyses 9.2 Sample Size Determination 9.5 Interim Analyses
Exclusion criterion A25 was updated to include a separate, lower absolute neutrophil count (ANC) cut off for black or African American participants.	The black or African American population generally has lower ANC values compared with other populations.	5.2 Exclusion Criteria
If JNJ-6379 is discontinued, participants may continue JNJ-3989 (and PegIFN-α2a if applicable) after a consultation with the sponsor.	Assessing a continued treatment with JNJ-3989 and NA (and PegIFN-α2a if applicable) is of value even if JNJ-6379 needs to be discontinued.	1.3 Schedule of Activities 7.1 Discontinuation of Study Intervention
Anticoagulants were moved from the list of disallowed medications to the list of concomitant medications to be used with caution.	Preclinical and clinical data for JNJ-3989 and JNJ-6379 do not show evidence of coagulopathy.	6.5 Concomitant Therapy
Nonclinical data on the combination of JNJ-3989 or JNJ-6379 with PegIFN-α2a were added.	These data confirm that: • Combination of PegIFN-α2a with JNJ-3989 did not induce any synergistic or additive effect in monkeys up to 3 months of treatment. • Combination of PegIFN-α2a with JNJ-6379 induces minimal additive effect in *in vitro* study.	2.2.2.3 Combination of JNJ-3989 or JNJ-6379 With PegIFN-α2a 2.2.2.3.1 Combination of JNJ-6379 With PegIFN-α2a 2.2.2.3.2 Combination of JNJ-3989 with PegIFN-α2a 2.3.3 Benefit-Risk Assessment for Study Participation
Additional renal monitoring by eGFR calculation based on Cystatin C was added to the blood chemistry panel. PK information on the combination of tenofovir disoproxil with JNJ-6379 was added.	To assess whether eGFR based on creatinine vs Cystatin C differs in participants receiving JNJ-6379. Clinical data suggest increased tenofovir disoproxil plasma concentrations when given in combination with JNJ-6379.	10.2 Appendix 2: Clinical Laboratory Tests 2.2.3.2 Combination of JNJ-3989 and JNJ-6379 with Entecavir, Tenofovir Disoproxil, or Tenofovir Alafenamide 2.3.2.2.3 Potential Risks for Entecavir, Tenofovir Disoproxil, Tenofovir Alafenamide, and PegIFN-α2a
The footnote for Japan only in the Schedule of Activities (SOA) was adapted to clarify that in case of twice weekly scheduled visits, the same visit window should be applied for both visits.	Clarification	1.3 Schedule of Activities

Description of Change	Brief Rationale	Section Number and Name
A footnote was added to exclusion criteria A02 (a, b, c and d) to clarify that bilirubin, prothrombin time and serum albumin above or below the cut off are exclusionary unless they can be explained by anything other than hepatic decompensation.	Clarification	5.2 Exclusion Criteria
A footnote was added to exclusion criterion A01 to allow for the use of HEV RNA results to rule out active HEV infection.	Clarification	5.2 Exclusion Criteria
A footnote was added to the disallowed medication table, allowing the use of approved or conditionally authorized COVID-19 vaccines, as an exception.	Clarification	6.5 Concomitant Therapy
Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted	Throughout the protocol

10.12. Appendix 12: NA Re-treatment and Monitoring After Stopping of NA

Participants who meet the NA treatment completion critera will be monitored for NA re-treatment during the follow-up phase

Frequency of monitoring:

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

Re-start of NA treatment:

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

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

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

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INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: [electronic signature appended at the end of the protocol] Date: _____
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	01-Dec-2021 22:20:38 (GMT)	Document Approval