Janssen Research & Development *

Clinical Protocol

Protocol Title

A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Study with Deferred Active Treatment to Investigate the Efficacy, Safety, and Pharmacokinetics of JNJ-73763989 + Nucleos(t)ide Analog in Participants Co-infected with Hepatitis B and Hepatitis D Virus

REEF-D

Protocol 73763989HPB2004; Phase 2
Version: Amendment 5

JNJ-73763989

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Studies conducted at sites in the United States (US) will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

Studies conducted at sites in the European Economic Area (EEA) will be conducted under Regulation [EU] No 536/2014.

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 5	27 March 2024
Amendment 4	7 April 2023
Amendment 3	6 December 2021
Amendment 2	17 June 2021
Amendment 1	6 August 2020
Original Protocol	18 May 2020

Amendment 5 (27 March 2024)

Overall Rationale for the Amendment:

As described in Amendment 4 dated 7 April 2023, due to the strategic decision taken by the sponsor to discontinue further investment in its hepatitis B and D discovery and development programs, enrollment of new participants into the REEF-D study was not re-opened and the study was modified to continue with the enrolled participants as planned.

The overall reason for the present amendment is to facilitate an early completion of the REEF-D study by reducing the study duration for participants in Part 2 while ensuring that all participants have the possibility to receive at least 48 weeks of JNJ-73763989 (JNJ-3989) treatment and adequate follow-up. At the time of the present protocol amendment, all participants in Part 1 and Part 2 are beyond the double-blind phase. All 22 participants in Part 1 have completed the investigational study treatment. This amendment will not affect the participants in the follow-up phase in Part 1 and will only affect the participants in Part 2. In Part 2, participants either have completed the study (n 11), entered the open-label phase following the 52 weeks of double-blind treatment (n 17), or are in the follow-up phase (n 2). Once the present amendment will be approved and in effect at a given study site, the next planned visit for participants in the open-label phase, but not earlier than Week 96 (Arm 1) and Week 100 (Arm 2), will be the end of treatment (EOT) visit. At this EOT visit, JNJ-3989 will not be administered and participants will continue treatment with NA until the last study visit in the follow-up phase. All participants in Part 2 will follow a reduced follow-up phase of at least 24 weeks when the present amendment becomes effective. The decision to reduce the study duration of Part 2 is due to the sponsor's strategic decision to discontinue the development of JNJ-3989 in chronic hepatitis D disease and is not triggered by any safety findings.

The changes made to the clinical protocol 73763989HPB2004 as part of Protocol Amendment 5 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.11, Appendix 11: Protocol Amendment History.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis	Updated to reflect all the pertinent changes as described in rows below.	Refer to overall rationale for the amendment and rationale for each section below.
1.3 Schedule of Activities	Added modified SoA of open-label study intervention phase (Week 52-EOT) for conducting Part 2 of the study after Protocol Amendment 5 is in effect. Added SoA of reduced follow-up phase (at least 24 weeks) for participants in Part 2 at the time this amendment becomes effective.	Refer to the overall rationale for the amendment.
1.2 Schema 4.1 Overall Design 4.4 End of Study 9 Statistical Considerations	Updated study schema to align with the following modifications in Part 2 of the study: **T**reatment with JNJ-3989 will be stopped at the next planned visit (ie, EOT) but not earlier than Week 96 (Arm 1) and Week 100 (Arm 2) when Protocol Amendment 5 is in effect. **F**ollow-up will be reduced to 24 weeks for all Part 2 participants who have not reached FU Week 24 (including those in the open-label phase) when the amendment is in effect. Participants who have reached FU Week 24 or later will receive the EOS assessments at the next planned visit. Accordingly, the definition of EOS and study completion is updated for Part 2.	Refer to the overall rationale for the amendment. The open-label phase in Part 2 was modified in a way that at least 96 weeks of treatment with JNJ-3989 in Arm 1 and 48 weeks of treatment with JNJ-3989 in Arm 2 will be ensured in the study intervention phase.
2.3.3 Benefit-risk Assessments for Study Participation 4.1 Overall Design 6.3 Measures to Minimize Bias: Randomization and Blinding 6.7 Concomitant Therapy 8 Study Assessments and Procedures	The time frame for open-label treatment with JNJ-3989, NA treatment, monitoring for transaminase flares and for HBV/HDV recurrence as well as recording of concomitant therapy was updated in accordance with the overall rationale for the study amendment which now includes different intervention and follow-up periods across the study parts.	Refer to the overall rationale for the amendment.
2.3.3 Benefit-risk Assessments for Study Participation 4.1 Overall Design 4.2 Scientific Rationale for Study Design 6.4 Study Intervention Compliance 6.5 Re-treatment with NA during the Follow-up Phase	The stopping criteria for NA treatment during the follow-up phase were removed for Part 2.	Due to the reduced treatment duration in Part 2 per protocol amendment, the criteria for discontinuation of NA treatment will not be applicable. Treatment with NA will be continued until the end of the study visit.

Section number and Name	Description of Change	Brief Rationale
3 Objectives and Endpoints	Evaluation of PK of JNJ-3989 and the corresponding endpoint were removed from the 'Other Secondary Objectives and Endpoints'.	Sparse PK samples will be analyzed for plasma concentrations. Population PK will not be conducted due to the strategic decision taken by the sponsor to discontinue further investment in hepatitis.
9.5.2 Interim Analyses of Study Part 2	The IA of Part 2 and any potential IAs that may be performed in the open-label phase were removed.	Additional IAs will no longer be necessary as the study duration for Part 2 will be reduced and no further interactions with health authorities are planned.
9.5.4 Internal Data Review Committee 10.3.6 Committees Structure	The following was added: A DRC will be established for continuous monitoring of SAEs, AEs leading to discontinuation, and ALT flares **when all participants have completed double-blind phase and IDMC has completed its review**.	The transition of the safety monitoring responsibilities from IDMC to DRC after the completion of the double-blind phase was further clarified.
Throughout the protocol	Changes to align with the sponsor's current protocol template wording.	Update to the most recent template.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Study with Deferred Active Treatment to Investigate the Efficacy, Safety, and Pharmacokinetics of JNJ-73763989 + Nucleos(t)ide Analog in Participants Co-infected with Hepatitis B and Hepatitis D Virus.

JNJ-73763989 (JNJ-3989) is a 2:1 molar mixture of 2 synthetic, double-stranded, N-acetylgalactosamine (GalNac) conjugated RNAi triggers (JNJ-73763976 and JNJ-73763924, 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 hepatitis B virus (HBV) transcripts derived from covalently closed circular DNA (cccDNA) and integrated viral DNA. This is made possible by the fact that all HBV transcripts expressed from cccDNA, including the RNA transcript (pre-genomic ribonucleic acid [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-73763924) 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-73763976), which targets the HBsAg encoding region, was designed to knock down expression of hepatitis B surface antigen (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. Since HBsAg is required for replication of hepatitis D virus (HDV), by allowing HDV to infect new cells, reducing HBsAg levels is anticipated to lead to inhibition of HDV replication.

Study intervention refers to JNJ-3989 or placebo and nucleos(t)ide analog (NA).

BENEFIT-RISK ASSESSMENT

Overall, JNJ-3989 administration was generally safe and well tolerated in the completed and ongoing studies, all of which except REEF-D are in CHB patients or healthy participants.

Alanine aminotransferase (ALT) elevations are considered an important potential risk for JNJ-3989. During Part 1 of this study, in HBV/HDV co-infected participants, a higher frequency of ALT elevations was observed when receiving JNJ-3989 compared to placebo. This led to introduction of risk mitigation measures, including stricter eligibility criteria (exclusion of participants with cirrhosis as well as participants with high HDV RNA and in Part 2), more conservative criteria for JNJ-3989 discontinuation, and more frequent monitoring.

Optional biopsy procedures will be performed during this study for research purposes, only in participants who consented separately to this procedure. Risks and complications of these procedures may include pain and discomfort, bleeding at the biopsy site, and infection and internal bleeding and/or puncture of other internal organs (gall bladder, lung, intestine, or kidney) which can lead to serious complications (uncommon – 1 in 1,000 to 1 in 100) including the need for emergency surgery, blood transfusion, or removal of organs. Deaths directly related to liver biopsy occur rarely (approximately 1 in every 10,000 biopsies).

The clinical benefit of JNJ-3989 remains to be established. Potential benefits include reduction of HBsAg levels directly via JNJ-3989, leading to a reduced number of HDV particles and less de novo infections, and inhibition of HDV replication and improved clinical outcomes. Treatment with JNJ-3989 in combination with NAs might lead to HBsAg seroclearance which could result in complete elimination of HDV (ie, cure). The combination of JNJ-3989 and NAs is also expected to intensify suppression of HBV replication compared to NA alone, by further downregulating the levels of the HBV proteins and pgRNA, which may allow a restoration of the host immune response and sustained HBsAg seroclearance (ie, functional cure for HBV).

Based on the available data and proposed safety measures, the overall risk/benefit assessment for JNJ-3989 clinical studies is considered favorable. 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).

OBJECTIVES AND ENDPOINTS

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

Objectives	Endpoints
Primary	
To evaluate on-treatment efficacy against HDV of JNJ-3989 + NA regimen compared to NA alone.	• Proportion of participants with HDV RNA ≥2 $\log_{10}$ IU/mL decline from baseline or HDV RNA target not detected (TND) in combination with normal ALT at Week 48.
Key Secondary	
To evaluate on-treatment efficacy of the JNJ-3989 + NA regimen in suppressing HDV replication as measured by HDV RNA.	• Proportion of participants with HDV RNA ≥2 $\log_{10}$ IU/mL decline from baseline or HDV RNA TND at Week 48.
To evaluate efficacy of the JNJ-3989 + NA regimen on liver inflammation during study intervention phase.	• Proportion of participants with normal ALT at Week 48.
To evaluate the efficacy of the JNJ-3989 + NA regimen in terms of HBsAg response.	• Proportion of participants with HBsAg seroclearance at Week 48.
To evaluate the efficacy of the JNJ-3989 + NA regimen on liver fibrosis.	• Proportion of participants with ≥2 kPa reduction from baseline in liver stiffness measurement (LSM) assessed by vibration-controlled transient elastography (VCTE) (FibroScan) at Week 48.
Other Secondary	
To evaluate the efficacy of the JNJ-3989 + NA regimen during study intervention phase and follow-up phase.	• Proportion of participants with HDV RNA ≥2 $\log_{10}$ IU/mL decline from baseline or HDV RNA TND in combination with normal ALT. • Proportion of participants with HDV RNA ≥2 $\log_{10}$ IU/mL decline from baseline in combination with normal ALT. • Proportion of participants with HDV RNA TND in combination with normal ALT. • Proportion of participants with HDV RNA ≥2 $\log_{10}$ IU/mL decline from baseline or HDV RNA TND. • Proportion of participants with HDV RNA ≥2 $\log_{10}$ IU/mL decline from baseline.

Objectives	Endpoints
	• Proportion of participants with HDV RNA TND. • Proportion of participants with normal ALT. • Time to reach HDV RNA ≥2 $\log_{10}$ IU/mL decline or HDV RNA TND. • Changes from baseline in HDV RNA. • Changes from baseline in ALT.
To evaluate the safety and tolerability of the study intervention throughout the study.	• Proportion of participants with incidences of (serious) adverse events (AEs) and abnormalities in clinical laboratory tests (including hematology, blood biochemistry, blood coagulation, urinalysis, urine chemistry, and renal biomarkers), 12-lead electrocardiograms (ECGs), vital signs, and physical examination.
To evaluate the efficacy of the JNJ-3989 + NA regimen as measured by HBV blood markers (such as HBsAg, HBeAg*, HBV DNA) during study intervention and follow-up.	• Proportion of participants with HBsAg seroclearance and/or seroconversion. • Change from baseline over time in HBsAg, HBeAg*, HBV DNA. • Proportion of participants with HBsAg, HBeAg*, and/or HBV DNA levels or changes from baseline below/above different cut-offs. • Time to reach efficacy thresholds such as HBsAg <1 IU/mL.
To evaluate the frequency of HBV virologic breakthrough throughout the study.	• Proportion of participants with HBV DNA virologic breakthrough.
To evaluate changes in liver fibrosis during study intervention and follow-up.	• Proportion of participants with ≥2 kPa reduction from baseline in LSM assessed by VCTE (FibroScan). • Change from baseline in LSM over time assessed by VCTE (FibroScan).
To evaluate the anti-HDV efficacy during the follow-up phase.	• Proportions of participants with sustained HDV response off-treatment post end of JNJ-3989 treatment. • Proportions of participants with HDV relapse post end of JNJ-3989 treatment.
To evaluate the anti-HBV efficacy during the follow-up phase.	• Proportions of participants with sustained HBV response off-treatment post end of JNJ-3989 treatment.

Objectives	Endpoints
	• Proportions of participants with HBV flare (virologic, biochemical, and clinical) post end of treatment.

* in HBeAg-positive participants only

Hypothesis

The original protocol had as primary hypothesis that the combination regimen of JNJ-3989 + NA is more efficacious than NA treatment alone in reducing HDV replication and improving the associated liver inflammation, as measured by the primary efficacy endpoint, the proportion of participants with HDV RNA decline ≥2 $\log_{10}$ IU/mL from baseline or HDV RNA TND in combination with normal ALT at Week 48. Due to the decision to stop enrollment at 30 participants in Part 2 of the study, the statistical analyses will be descriptive.

OVERALL DESIGN

This is a 2-part, Phase 2, randomized, double-blind, placebo-controlled, parallel, multicenter, interventional study with deferred active treatment to investigate the efficacy, safety, and PK of JNJ-3989 + nucleos(t)ide analog (NA) in participants co-infected with HBV and HDV.

The study consists of 2 parts:

- Part 1 will evaluate the safety, tolerability and antiviral activity of JNJ-3989 + NA in a small number of participants (N=20), prior to enrolling a larger number of participants in Part 2. The primary aim of Part 1 is to assess if the antiviral activity criteria to start Part 2 are met.
- Part 2 (N=30) will evaluate the safety and efficacy of the JNJ-3989 + NA regimen in the treatment of HBV/HDV co-infection.

Note that Part 2 of the study will only be initiated once the antiviral activity criteria in Part 1 have been met, and if the results of Part 1 IA1 (when all participants of Part 1 have completed at least Week 16 or discontinued earlier) support initiation of Part 2. The antiviral activity criteria are defined in the statistical analysis plan (SAP). Participants in Part 1 may not participate in Part 2.

Before Protocol Amendment 5, Part 1 and Part 2 include 3 identical phases:

- a 4-week screening phase (may be extended up to a maximum of 8 weeks[a]),
- a 144-week study intervention phase (Arm 1) and 148-week study intervention phase (Arm 2). The first 52 weeks of the intervention phase are double-blind followed by 92 and 96 weeks of open-label treatment for participants in Arms 1 and 2, respectively.
- a 48-week follow-up phase.

[a] If necessary (eg, for operational reasons), the screening phase may be extended up to a maximum of 8 weeks on a case-by-case basis and in agreement with the sponsor. Depending on the duration of the screening phase, selected screening assessments may have to be repeated prior to enrollment.

Per Protocol Amendment 5, Part 2 will include modified phases after screening:

- a 4-week screening phase (may be extended up to a maximum of 8 weeks[a]),
- for both Arm 1 and Arm 2, the double-blind 52 weeks of intervention will be followed by an open-label phase of at least 48 weeks of JNJ-3989 for all participants, including for those participants who were randomized to placebo in the intervention phase. Arm 1 will have a total minimum of 96-week intervention and Arm 2 a total minimum of 100-week intervention.
- a reduced follow-up phase (at least 24 weeks):
  - for participants who have reached FU Week 24 or later when Protocol Amendment 5 is in effect, the EOS assessments will be scheduled at the next planned visit; *OR*
  - for participants who have not reached FU Week 24 (including participants in the open-label phase) when Protocol Amendment 5 is in effect, they will enter a 24-week follow-up phase.

The duration of individual study participation will be between 196 and 204 weeks for Part 1 and between 124 and 204 weeks for Part 2.

Before Protocol Amendment 5, at Week 144 (Arm 1) and Week 148 (Arm 2), treatment with JNJ-3989 will be stopped in both parts. After Protocol Amendment 5 is in effect, treatment with JNJ-3989 will be stopped in Part 2 at the next planned visit (ie, end of treatment [EOT]) but not earlier than Week 96 (Arm 1) and Week 100 (Arm 2).

Participants who complete treatment with JNJ-3989 at the end of the open-label phase[b] in Part 1 and Part 2 will be closely monitored for transaminase flares and for HBV/HDV recurrence during the follow-up phase.

Before Protocol Amendment 5, for non-cirrhotic patients, NA treatment should be continued until the last study visit (including the visit in the follow-up phase) unless confirmed HBsAg seroclearance, ALT <3x upper limit of normal (ULN), and HBV DNA < lower limit of quantitation (LLOQ) is observed, in which case NA treatment may be discontinued upon discussion with the sponsor. For cirrhotic patients, NA treatment should be continued during the entire follow-up phase according to treatment guidelines.

Amongst the non-cirrhotic participants who stop treatment with NA, NA treatment will be restarted if any of the following criteria are met:

- If there are signs of decreasing liver function based on laboratory findings (INR or direct bilirubin) or clinical assessment (follow guidance on study intervention discontinuation in case of an increase in direct bilirubin >1.5x ULN in combination with INR ≥1.5x ULN or serum albumin <3.0 g/dL),
- HBeAg seroreversion among participants who had previously experienced HBeAg loss,
- Post-treatment values of HBV DNA >2,000 IU/mL and ALT >5x ULN.
- Post-treatment values of HBV DNA >20,000 IU/mL.

Earlier restarting of NA treatment is at the investigator's discretion, even if the above criteria are not met yet.

[a] If necessary (eg, for operational reasons), the screening phase may be extended up to a maximum of 8 weeks on a case-by-case basis and in agreement with the sponsor. Depending on the duration of the screening phase, selected screening assessments may have to be repeated prior to enrollment.

[b] At Week 144 (Arms 1) or Week 148 (Arms 2) in Part 1 and Part 2 before Protocol Amendment 5; at Week 96 or later (Arm 1) or Week 100 or later (Arm 2) in Part 2 after Protocol Amendment 5.

Per Protocol Amendment 5, NA treatment will be continued in all participants in Part 2 until the last study visit (including visit in the follow-up phase).

Part 1

Approximately 20 participants co-infected with HBV and HDV will be randomized in a 4:1 ratio to Arms 1 or 2.

- Arm 1: 100 mg JNJ-3989 (subcutaneous [SC] injection every 4 weeks [Q4W]) + NA once daily (qd) for 144 weeks (n=16; immediate active treatment arm);
- Arm 2: placebo for JNJ-3989 (SC injection Q4W) + NA qd for 52 weeks, followed by 100 mg JNJ-3989 (SC injection Q4W) + NA qd for 96 weeks (n=4; deferred active treatment arm).

NA=nucleos(t)ide analog=entecavir monohydrate (ETV), tenofovir disoproxil, or tenofovir alafenamide (TAF). NA treatment is continued or started from Day 1 in both arms.

Part 2

Part 2 of the study will be initiated since the antiviral activity criteria in Part 1 have been met, and the results of Part 1 IA1 (when all participants of Part 1 have completed at least Week 16 or discontinued earlier) support initiation of Part 2. Cirrhotic participants will be excluded from participation in Part 2 of the study.

Approximately 30 participants co-infected with HBV and HDV will be randomized in a 4:1 ratio to Arms 1 or 2.

- Arm 1: 100 mg JNJ-3989 (SC injection Q4W) + NA qd for at least 96 weeks (approximately, n=24; immediate active treatment arm);
- Arm 2: placebo for JNJ-3989 (SC injection Q4W) + NA qd for 52 weeks, followed by 100 mg JNJ-3989 (SC injection Q4W) + NA qd for at least 48 weeks (approximately, n=6; deferred active treatment arm).

NA= ETV, tenofovir disoproxil, or TAF. NA treatment is continued or started from Day 1 in both arms.

Study Details

This study consists of 2 parts. Part 1 (N=20) aims to observe antiviral anti-HDV activity in a limited number of participants treated with the active regimen (ie, proof of concept) and to exclude futility before enrolling a larger number of participants to be exposed to the 144-week treatment regimen of JNJ-3989 + NA. Part 1 IA1 will be conducted after all participants of Part 1 have completed at least Week 16 (or discontinued earlier), to enable the Sponsor Committee to decide on the initiation of Part 2. A second IA of Part 1 (Part 1 IA2) will be conducted after all participants of Part 1 have completed at least Week 48 (or discontinued earlier), to confirm the preliminary benefit-risk ratio of the investigational regimen with longer term data on participants of Part 1.

Part 2 (N=30) will generate additional data. The randomization ratio will be fixed to 4:1 (active:control).

The conclusions of the study will be described separately on data from Part 1, Part 2, and pooled from Part 1 and Part 2 together (if applicable).

Randomization will be stratified by:

- presence of compensated cirrhosis at screening (yes or no) (Part 1 only),
- HDV RNA testing laboratory location (China versus outside of China), and
- HBeAg status at screening (positive versus negative).

Before Protocol Amendment 5, participants in Part 1 and Part 2 will be considered to have completed the study if they have completed the end of study (EOS) assessments at Week 48 week of the follow-up phase (ie, EOS visit at FU Week 48). After Protocol Amendment 5, the participants in Part 2 will be considered to have completed the study if they have completed the EOS assessments assigned per Protocol Amendment 5:

- Participants who have not reached FU Week 24 (including participants in the open-label phase) when Protocol Amendment 5 is in effect will enter the 24-week follow-up phase (ie, EOS visit at FU Week 24).
- Participants who have reached FU Week 24 or later when Protocol Amendment 5 is in effect will receive the EOS assessments at the next planned visit (ie, EOS visit at FU Week 30 or later).

NUMBER OF PARTICIPANTS

In total for Part 1 and Part 2, 50 participants were planned to be enrolled in this study, specifically with a target of 20 participants in Part 1 and 30 participants in Part 2. The minimum number of participants to be enrolled will be 20 if futility is observed and Part 2 is not initiated.

Eligible participants will be aged ≥18 to 65 years and co-infected with HBV and HDV. Patients with HBV/HDV co-infection will be eligible regardless of HBeAg status and treatment history. Patients with compensated cirrhosis are allowed to be enrolled in Part 1 and patients with cirrhosis will be excluded from Part 2 of this study.

Description of Interventions

Intervention Name	JNJ-3989	Placebo for JNJ-3989	ETV monohydrate	Tenofovir disoproxil	TAF[a]
Type	Drug	Drug	Drug	Drug	Drug
Dose Formulation	Solution for injection	Solution for injection	Film-coated tablets	Film-coated tablets	Film-coated tablets
Unit Dose Strength(s)	200 mg/mL	0.9% saline	0.5 mg	245 mg	25 mg
Dosage Regimen	100 mg Q4W	Q4W	0.5 mg qd Lamivudine-refractory participants: 1 mg[b] qd (but should preferably be treated with tenofovir disoproxil or TAF instead)	245 mg qd	25 mg qd
Route of Administration	Subcutaneous injection (in the abdomen)	Subcutaneous injection (in the abdomen)	Oral	Oral	Oral
Use	Investigational intervention	Investigational intervention	Background intervention	Background intervention	Background intervention
IMP and NIMP	IMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Each unit will be labeled with unique medication ID number	Each unit will be labeled with unique medication ID number	Commercial supplies will be sourced and a clinical study label applied	Commercial supplies will be sourced and a clinical study label applied	Commercial supplies will be sourced and a clinical study label applied
			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

ETV: entecavir; ID: identification; IMP: Investigational Medicinal Product; JNJ 3989: JNJ 73763989; NA: nucleos(t)ide analog; NIMP: Non investigational Medicinal Product; Q4W: once every 4 weeks; qd: once daily; TAF: tenofovir alafenamide

[a] In countries where TAF is commercially available, it will be one of the NA treatment options.

[b] 2 tablets of 0.5 mg

EFFICACY EVALUATIONS

HDV RNA will be quantified at central testing laboratory locations (China versus outside of China) using a validated commercially available in vitro nucleic acid amplification tests for the quantification of HDV RNA. Samples may be processed in real-time or could be analyzed in batch.

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

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

Liver stiffness measurement by VCTE (FibroScan) will be performed to determine changes in the liver fibrosis.

Samples may be used by the sponsor for additional exploratory assessments analyzing the serologic and virologic characteristics of HBV or HDV infection (including semi-quantitative anti-HDV IgM antibodies) and efficacy or safety of the study intervention.

Sequencing

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

Core Liver Biopsy and Fine Needle Aspirate Biopsy (Optional with Separate Consent, Part 2 only)

If participants agree to undergo an optional liver biopsy, percutaneous core liver biopsies and/or fine needle aspirate biopsies (FNABs) will be performed preferentially at Week 0 and Week 24. Percutaneous core liver biopsies will be prioritized over FNAB if only one sample can be collected.

SAFETY EVALUATIONS

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

Any clinically relevant changes occurring during the study must be recorded in the AE section of the case report form.

Adverse events of special interest in line with the known pharmacological profile of the study intervention (and the drug classes) evaluated in this study are implemented.

Any intervention-emergent elevation of ALT and/or AST ≥3x ULN and ≥2x 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 as specified below. Repeat laboratory values should include AFP, ALT, AST, ALP, bilirubin (total and direct), INR, albumin, HBV DNA, and HDV RNA. Additional tests should be considered based on clinical judgement. The confirmatory visit should be scheduled preferably within 3 days of the receipt of the initial ALT/AST results.

Weekly basis monitoring (or more frequently as long as values increase) until ALT/AST levels have returned to <3x ULN or <2x nadir, and if present, liver-related symptoms have improved. With ALT and/or AST values ≥3x ULN and ≥2x nadir, visit intervals may be extended to 14 days if values have been stable or decreasing on three consecutive visits. The participant will be monitored (laboratory testing of ALT, AST, ALP, bilirubin [total and direct], INR, albumin, HBV DNA, and HDV RNA) on a weekly basis or more frequently until ALT and/or AST levels have returned to 50% of the maximal value.

Note: In case of urgency, local laboratory assessments could be considered. In case of IWRS participant unblinding and if the investigator requires to be unblinded in case of an emergent safety event (ie, study intervention discontinuation due to ALT flares) to allow further treatment of the participant, a sponsor request can be made to have the investigator and sponsor unblinded to all HDV RNA and HBsAg data from the double-blind phase. Off-treatment local HDV RNA test can be done to exclude/assess for HDV driven flare).

Management of intervention-emergent ALT and/or AST elevations:

JNJ-3989 treatment should be stopped, and NA treatment needs to be continued in the following situations:

- Participants with liver cirrhosis:
  - Confirmed ALT/AST elevation >5x ULN and ≥2x nadir
  - ALT/AST elevation ≥3xULN and ≥2x nadir for >4 weeks.
  - If the ALT and/or AST level is ≥3x ULN and ≥2x 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.
- Participants without liver cirrhosis:
  - Confirmed ALT/AST elevation >10x ULN and ≥2x nadir
  - First on-treatment ALT/AST elevation 3 to 5x ULN for >12 weeks
  - Second or following on-treatment ALT/AST elevation 3 to 5x ULN for >4 weeks
  - ALT/AST elevation >5 to 10x ULN for >4 weeks

- If the ALT and/or AST level is ≥3x ULN and ≥2x 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.

From Week 52 onwards, results of HBsAg and HDV RNA assessment will be reported to the investigators.

Management of flares observed in the follow-up phase after end of treatment:

In case of ALT flares that are observed during the follow-up phase, repeat laboratory values should include AFP, ALT, AST, ALP, bilirubin (total and direct), INR, albumin, HBV DNA, and HDV RNA. The participant should be monitored on a weekly basis (or more frequently as long as values increase) until ALT and/or AST levels have returned to <3x ULN or <2x nadir. With ALT and/or AST values ≥3x ULN and ≥2x nadir, visit intervals may be extended to 14 days if values have been stable or decreasing on three consecutive visits. For guidance on re-treatment with NA during the follow-up phase, refer to the re-treatment criteria mentioned under Overall Design.

PHARMACOKINETIC EVALUATIONS

Sparse PK samples for JNJ-3989 will be collected and plasma concentration-time data for JNJ-3989 (JNJ-73763924 and JNJ-73763976) will be analyzed. Data from this study may be combined with data from a selection of Phase 1 and 2 studies via population PK modeling.

PHARMACOKINETICS/PHARMACODYNAMICS

Relationships of individual PK parameters for JNJ-3989 (JNJ-73763924 and JNJ-73763976) with selected efficacy and/or with selected safety endpoints may be evaluated, if applicable.

IMMUNE EVALUATIONS

At selected sites, peripheral blood mononuclear cell (PBMC) samples for immune analyses will be collected during study intervention and may 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 HBV-specific T-cells that secrete gamma interferon (IFN-γ) in response to a specific antigenic stimulation, whereas ICS determines the frequency of CD4+ and CD8+ HBV T-cells secreting cytokines such as IFN-γ, interleukin (IL)-2 and tumor necrosis factor (TNF)-α in response to a specific antigenic stimulation.

PBMC samples may also be analyzed for HDV-specific responses using ELISpot and ICS after stimulation with HDV-specific antigens.

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

Additional PBMC samples may be taken until Week 48 in case of ALT flares, upon discussion with the sponsor, which may require an unscheduled visit.

HOST GENETICS

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

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

HOST BIOMARKERS

The study includes collection of blood samples for exploratory analysis of host blood biomarkers (eg, cytokines) at the host RNA, protein, and cell level. Exploratory serology samples may be used for this host serum protein testing.

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

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

LIVER BIOPSY

Part 2 of the study includes the option to perform liver biopsies in participants who consented separately to this procedure (only in sites and in selected countries where this is feasible, and after all relevant approvals are in place and operational set-up is completed). Samples may be used to assess HDV and HBV markers in the liver such as, but not limited to, HDAg and HDV RNA, HBsAg, pgRNA, total intracellular HBV RNA and DNA, and HBcAg. Changes in the quantity and potentially changes in the spatial distribution of these markers under JNJ-3989 treatment will be assessed.

Intrahepatic immune status at baseline and in response to treatment may be assessed. Both innate and adaptive immune compartment may be characterized, by measuring the relative number of specific cells and the expression of functional markers in each cell population using various single cell approaches, such as single cell transcriptomics in FNABs and Immunofluorescence staining, and transcriptomics and proteomics profiling in core needle biopsies. Depending on the latest platform developments (spatial transcriptomics, in situ sequencing approaches etc.) methods for immune cells characterization might be adjusted.

Remaining samples may be used for research on viral and host biomarkers and immune markers at the viral and/or host RNA/DNA, protein, and cell level.

Samples can only be used for research related to JNJ-3989, chronic HBV or HDV infection, or chronic HBV or HDV infection related disease or may be used to develop tests/assays related to JNJ-3989, NA, or chronic HBV or HDV infection. These latter exploratory analyses will be performed at the sponsor's discretion and will always be under the sponsor's supervision.

MEDICAL RESOURCE UTILIZATION

Medical resource utilization data, associated with medical encounters, will be collected in the case report form (CRF) by the investigator and study-site personnel for all participants throughout the study.

Protocol-mandated procedures, tests, and encounters are excluded. The data collected may be used to conduct exploratory economic analyses and will include:

- Number and type of medical visits (eg, in/out hospital, ER visit).
- Number (proportion) of participants requiring hospitalization and duration of hospitalization (total days length of stay, including duration by wards; eg, ICU).
- Number and character of diagnostic and therapeutic tests and procedures (inpatient and outpatient).

STATISTICAL METHODS

The primary analysis in this study will be performed when all participants in the study (both parts if Part 2 has started) have reached Week 48 or have discontinued earlier.

The final analysis will be performed when all participants in the study (both parts if Part 2 of the study has started) have reached the final study visit in the follow-up phase, or have discontinued earlier.

Statistical Hypothesis

The original protocol had as primary hypothesis of this study that the combination regimen of JNJ-3989 + NA has superior efficacy compared to NA treatment alone in reducing HDV replication and improving the associated liver inflammation, as measured by the primary efficacy endpoint at Week 48 (the proportion of participants with HDV RNA decline ≥2 $\log_{10}$ IU/mL from baseline or HDV RNA TND in combination with normal ALT at Week 48). Due to the decision to stop enrollment at 30 participants in Part 2 of the study (see details in section below), the statistical analyses will be descriptive.

Sample Size Determination

The sample size in Part 1 (N=20) is primarily driven by the objectives of Part 1 to provide sufficient evidence of safety and early antiviral activity of JNJ-3989 and to exclude futility of the regimen in a small number of HBV/HDV co-infected participants before initiating the larger Part 2 of the study. No formal statistical power calculations were conducted for Part 1.

A total sample size of 130 participants for Part 2 in the original protocol would yield a statistical power >90% to detect a between-arm difference of ≥26% in the primary efficacy endpoint at Week 48, at a 1-sided Type 1 error rate of 0.025, based on the test for the between-arm difference with normal approximation. Per Protocol Amendment 4, the sample size in Part 2 was reduced to 30 participants.

In the original protocol, sample size re-estimation was planned at the single IA during Part 2 to allow for an increase to a maximum of 170 participants in Part 2 for the conditional power at the end of the study to be at least 80% in case the assumed 0.04 response rate for placebo was too conservative. Due to reduction in sample size per Protocol Amendment 4, the single IA with sample size re-estimation was removed.

In the original protocol, the number of participants included in this study was planned to be a minimum of approximately N=20 (if Part 2 is not initiated) or between a minimum of N=165 and a maximum of N=190 if Part 2 is initiated. Per Protocol Amendment 4, the planned number of participants included in the study will be N=20 in Part 1 and N=30 in Part 2.

Efficacy Analyses

To evaluate the efficacy, the primary analysis set will be the Intent-to-treat (ITT) population, ie, all participants who were randomly assigned to an intervention arm and who received at least 1 dose of study intervention. Participants will be analyzed according to the study intervention they were randomly assigned to.

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

Primary Estimand

The main analysis of the primary endpoint will be addressed by using the following estimand attributes:

1. **Study Intervention:**
   - Arm 1: JNJ-3989+NA
   - Arm 2: Placebo+ NA
2. **Study population:** Participants 18 to 65 years of age, inclusive, with HBV/HDV co-infection.
3. **Variable:** Response status defined as having HDV RNA decline ≥2 $\log_{10}$ IU/mL from baseline or HDV RNA TND in combination with normal ALT at Week 48.
4. **Intercurrent events (ICEs)**:
   a. Treatment discontinuation prior to Week 48: if the participant discontinued treatment prior to Week 48 then the participant will be considered as non-responder (composite strategy).
   b. Selected major protocol deviations (identified as ICEs): participants who experienced major protocol deviations considered ICE and who have missing ALT and/or HDV RNA data for the primary endpoint at Week 48 will be considered as non-responders (composite strategy).
   c. Deaths prior to Week 48 are handled in a composite strategy as participants who die prior to Week 48 will be considered as non-responders.
5. **Population level summary:** Difference in proportion of responders between the 2 intervention arms (Arm 1-Arm 2).

Note: The SAP will list the major protocol deviations used for the purpose of efficacy analyses and flag those that are to be considered ICEs.

Assumptions:

- Missing Data for HDV RNA and ALT are Missing At Random (MAR)
- The treatment effect is homogeneous across strata.

Data Included

All available data from randomized participants that have received at least one dose is included (ITT analysis set in Part 2), after taking into account all the ICEs and applying the ICE strategies.

Missing Data Handling Rules

Participants who withdraw from the study prior to Week 48 will be considered as non-responders.

If a participant remains in the study after early discontinuing treatment or after experiencing a major protocol deviation (defined for the purpose of efficacy analyses and is an intercurrent event) and has missing Week 48 value for HDV RNA and/or ALT, then the imputation to non-response will be applied. If the value for the primary endpoint at Week 48 is available, then such data will be used to determine their response status.

For the participants still in the study at Week 48 or for participants that have neither discontinued treatment early nor experienced any major protocol violations (defined for the purpose of efficacy analyses and is an intercurrent event), and, either HDV RNA or ALT values are missing at Week 48, the primary method to handle missing data will be the Multiple Imputation (MI) approach, applied in a joint multivariate fashion

to leverage the correlation between HDV RNA and ALT values over time. More details regarding the multiple imputation multivariate model will be included in the SAP.

To challenge and assess the impact of the MAR assumption in presence of intercurrent events, different approaches to handle missing data will be used as sensitivity analyses of the main estimator. One approach is the tipping point analysis based on the Missing Not At Random (MNAR) assumption. As a supplementary estimator, the analysis where all participants with missing HDV RNA and ALT values in the analysis window of Week 48 in each arm are imputed as non-responders will be conducted, to provide a comprehensive overview of the robustness for the assumption of MAR and the type of missing data.

Main Estimator

The proportion of responders will be compared between the 2 arms using, if possible, the stratum-adjusted Mantel-Haenszel test on the difference of proportions, with the following stratification factors: presence of compensated cirrhosis at screening (yes or no) (Part 1 only), HDV RNA testing laboratory location (China versus outside of China), and HBeAg status at screening (positive versus negative).

Key Secondary Endpoints

The key secondary endpoints at Week 48 are defined as follows:

1. Proportion of participants with HDV RNA ≥2 $\log_{10}$ IU/mL decline from baseline or HDV RNA TND at Week 48.
2. Proportion of participants with normal ALT levels at Week 48.
3. Proportion of participants with HBsAg seroclearance at Week 48.
4. Proportion of participants with ≥2 kPa reduction from baseline in LSM assessed by VCTE (FibroScan) at Week 48.

The 4 key secondary endpoints are binary and will be analyzed using, if possible, the stratum-adjusted Mantel-Haenszel test similarly to the primary efficacy endpoint with corresponding 95% CIs on the difference of proportions.

Other Secondary and Exploratory Endpoints

Descriptive statistics will be used for all efficacy endpoints which will be summarized by intervention arm over time and by study phase, using the whole study data as well as by stage. Specific endpoints may be analyzed using suitable categorical data approaches (eg, Mantel-Haenszel test, logistic regression for proportions or other categorical type of endpoint), longitudinal repeated measures or ANCOVA models (eg, for continuous types of variables), or survival analysis based on the Kaplan-Meier estimates (for time-to-event variables), as appropriate.

The statistical inference to compare the efficacy between Arm 1 and Arm 2 as measured by the other secondary endpoints at Week 48 will utilize the weighted inverse normal combination method as described for the primary efficacy endpoint. No further adjustment for multiplicity will be made and no imputation rule will be used in case of missing data.

Subgroup analyses will be conducted to evaluate the potential association between treatment outcome and selected demographic and baseline characteristics (including but not limited to age, presence of compensated cirrhosis at screening, HDV genotype, baseline values for HDV RNA, ALT, and HBsAg, etc.). Multivariate model analyses with exploration of interaction terms might also be performed. The primary and key secondary efficacy endpoints, respectively, will be analyzed by means of a logistic regression model. Exploratory descriptive summaries will be displayed by subgroups with corresponding 95% CIs without multiplicity adjustment. Forest plots will be used for the graphical displays. Subgroup

analyses, as exploratory, might be conducted both on Part 2 data only, and the 2 parts combined to leverage the total sample size of the whole study (Part 1 and Part 2).

Graphic data displays will also be used to summarize the efficacy data by intervention arm and over time. In addition, the potential association between HBsAg and HDV RNA will be explored graphically over time.

Resistance Analyses

The results of HBV and potentially HDV viral sequencing will be evaluated by the sponsor virologist. Relevant changes of amino acid and/or nucleic acid variations (eg, substitutions) in the HBV and/or HDV genomes will be tabulated and described. Additional exploratory characterization of the HBV and/or HDV viral sequence and phenotype may be performed and reported separately.

Safety Analyses

The Safety Analysis Set will be used for all safety analyses based on pooled data from Part 1 and Part 2 of the study. In addition, part of the safety analysis may be reported by study part. Relevant analysis by study part will be indicated in the SAP.

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

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 (ie, JNJ-73763924 and JNJ-73763976).

Population PK analysis of concentration-time data of JNJ-73763976, and JNJ-73763924 may be performed using non-linear mixed effects modeling. Data may be combined with selected Phase 1 and/or 2 studies to support a relevant structural model. For operational reasons, a snapshot date for PK samples to be analyzed will be defined, if required. Samples collected before this date will be analyzed for JNJ-73763976 and JNJ-73763924 and may be included in the population PK analysis. Samples collected after the snapshot date will be analyzed at a later date, and may be included in a population PK re-analysis when they become available after database lock. Available participant characteristics (eg, demographics, laboratory variables, genotypes) will be included in the model as necessary.

Pharmacokinetic/Pharmacodynamic Analyses

Relationships of PK parameters for JNJ-3989 (JNJ-73763976 and JNJ-73763924), with selected efficacy and safety endpoints may be evaluated and graphically displayed, if applicable.

Immune Analyses

Descriptive statistics (n, mean, SD, CV, geometric mean, median, minimum, and maximum) may 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 HDV and HBV antigen) as defined by ELISpot and/or ICS, respectively. Changes from baseline (if present) may also be tabulated for PBMCs during study intervention. The proportion (%) of patients with positive responses based on the magnitude of the IFN- γ T-cell response or the percentage of CD4+ or CD8+ T-cells expressing one of the cytokines

(eg, IL-2, TNF- α or IFN-γ) for at least 1 of the HDV and HBV antigens as defined by ELISpot and/or ICS, respectively, may be determined.

Pharmacogenomic Analyses

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

Host Biomarker Analyses

Statistical approaches to explore correlations between clinical outcome and blood and liver biomarkers vary and depend on the different data types of the applied technology platforms, as well as on the extent of observed 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 CSR or a separate report.

Interim Analyses

Interim Analyses of Study Part 1

During the double-blind phase of Part 1, 2 IAs will be conducted by the sponsor. Part 1 IA1 will be conducted after all participants of Part 1 have completed at least Week 16 (or discontinued earlier) to allow a comprehensive review of ALT elevations observed during treatment. The sponsor will become unblinded to Part 1 efficacy and safety data for this IA, to inform the decision of the Sponsor Committee for the initiation of Part 2 in conjunction with the IDMC recommendations. Part 1 IA2 will be conducted after all participants of Part 1 have completed at least Week 48 visit (or discontinued earlier).

From the moment of data unblinding for Part 1 IA1 onwards, the sponsor will remain unblinded to Part 1 data. The investigators, participants, site personnel, and operational sponsor team members involved with the sites will remain blinded. For safety-related decisions, HDV RNA and HBsAg data may be discussed with investigators on a case-by-case basis.

Interim Analysis of Study Part 2

The original protocol included an IA of Part 2 when all participants had reached Week 148, (EOT or discontinued earlier). This IA of Part 2 was to be conducted to assess safety and evaluate the time course of different disease markers and to support the sponsor's interactions with health authorities. Due to the decision to reduce the study duration of Part 2 and since interactions with health authorities are no longer planned, the IA of Part 2 was removed per Protocol Amendment 5.

Independent Data Monitoring Committee

An IDMC will be established for continuous monitoring of SAEs, AEs leading to discontinuation, and ALT flares. In addition, the IDMC will review unblinded efficacy parameters measured by HBV/HDV disease blood markers (eg, HDV RNA, HBV DNA, HBeAg, HBsAg) during the double-blind phase. During the open-label phase, all data will be unblinded. When all participants are in the open-label phase or discontinued earlier, the IDMC responsibilities will be covered by the internal Data Review Committee (DRC) (see section below).

The IDMC members will be appointed before the start of the study to review unblinded interim data for both safety and efficacy and formulate recommendation(s) to the sponsor Committee, who will make the final decision(s). Possible recommendations of the IDMC include, but are not limited to, continuing the study unchanged, stopping the study for safety concerns, or for futility or make a study amendment.

The IDMC will consist of at least one medical expert in the relevant therapeutic area and at least 1 statistician. The IDMC role and responsibilities, communication flow with other stakeholders, and procedures will be documented in the IDMC charter.

Internal Data Review Committee

A DRC will be established for continuous monitoring of SAEs, AEs leading to discontinuation, and ALT flares when all participants have completed double-blind phase and IDMC has completed its review. This committee will consist of at least one medical expert in the relevant therapeutic area (hepatology) and at least one statistician; committee membership responsibilities, authorities, and procedures will be documented in the DRC charter. The committee will meet periodically to review data of the efficacy parameters measured by different HBV and HDV disease blood markers (eg, HDV RNA, HBV DNA, HBeAg, HBsAg, etc).

The DRC members will be appointed to review the interim data for both safety and efficacy and formulate recommendation(s) to the Sponsor Committee (see section below), who will make the final decision(s). Details on the roles and responsibilities of the DRC and Sponsor Committee, as well as the flows of communication, will be documented in the DRC charter.

Sponsor Committee

The Sponsor Committee includes representatives from the sponsor's clinical, biostatistics, Global Medical Safety, and virology departments who are not involved in the study conduct.

The Sponsor Committee will review selected efficacy and safety parameters to assess the predefined antiviral activity criteria and decide to start Part 2 based on the results of the Part 1 IA1 (when all participants of Part 1 have completed at least Week 16 or discontinued earlier).

After Part 2 has commenced, all sponsor personnel, including the Sponsor Committee, will remain blinded to subsequent IDMC data reviews during the double-blind phase. During the open-label phase, all data will be unblinded. The efficacy monitoring will be conducted by the IDMC to protect the well-being of the participants against unexpected absence of further HBV RNA decline and/or HDV RNA frequent rebound contrary to the initial antiviral activity criteria.

The criteria to trigger the start of Part 2 and to exclude futility will be defined in terms of the antiviral activity as measured by a predefined threshold of HDV RNA and HBsAg reduction from baseline and will be paired with an assessment of the benefit-risk ratio based on the Part 1 IA1 data.

Independent Flare Expert Panel

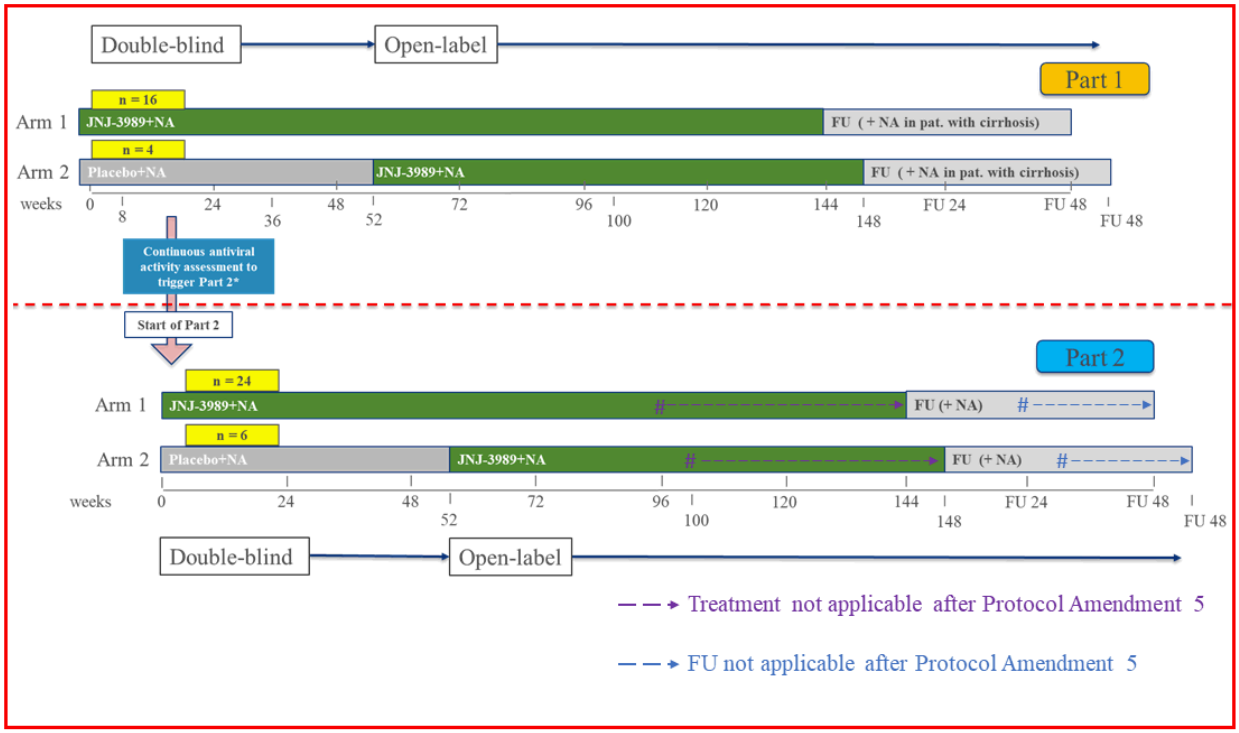
An IFLEP will be appointed. The IFLEP is composed of 3 independent medical experts with experience and expertise in HBV/HDV. The responsibilities of the IFLEP include: conduct regular review of all relevant and available individual participant blinded study data related to ALT flares; determine and adjudicate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

In order to allow for an unbiased assessment, members of the committee will not serve as study investigators or as members of the IDMC and will remain blinded to the treatment assigned to each participant up to the time of Part 1 IA1, when the IFLEP will become unblinded to the Part 1 data. In Part 2, the IFLEP will also be blinded to the treatment assigned to each participant up to unblinding of the Part 2 clinical data.

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

1.2. Schema

Figure 1: Schematic Overview of the Study



FU: follow-up; JNJ-3989: JNJ-73763989; n: number of participants; NA: nucleos(t)ide analog
* The antiviral activity assessments monitored in Part 1 of the study are described in Section 8.1.1.
# indicates the end of the intervention phase with JNJ-3989 treatment up until minimum Week 96 (Arm 1) and minimum Week 100 (Arm 2) in Part 2 per Protocol Amendment 5. Participants who stop treatment with JNJ-3989 after Protocol Amendment 5 will enter a 24-week FU phase.

1.3. Schedule of Activities

1.3.1. Schedule of Activities – Screening and Double-blind Study Intervention Phase (First 48 Weeks)

The Schedule of Activities (SoA) from screening to double-blind study intervention phase is the same for both Part 1 and Part 2 of the study, except for the liver biopsy samples which are scheduled only in Part 2 of the study.

Assessments from Week 52 until end of treatment (EOT) are described in Section 1.3.2, Schedule of Activities Open-label Study Intervention Phase (Weeks 52 EOT).

Study Phase	Screening	Double-Blind Study Intervention													
Week (W)	W 4 to 0[b]	W0[c]	W2	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48/ WD[a]
Study Day (Window)	28	1	15 +/ 2d	29 +/ 2d	57 +/ 2d	85 +/ 2d	113 +/ 3d	141 +/ 3d	169 +/ 3d	197 +/ 3d	225 +/ 3d	253 +/ 3d	281 +/ 3d	309 +/ 3d	337 +/ 3d
Screening/Administrative															
ICF[d]	X														
ICF for optional liver biopsy[nn]	(X)														
Inclusion/exclusion criteria[e]	X														
Prestudy therapy (including prior anti HBV/HDV therapy)	X														
Medical/surgical history and demographics[f]	X														
Preplanned surgery/procedure(s)	X														
FibroScan or liver biopsy[g]	X														
HLA testing[kk]		X													
Abdominal ultrasound[h]	X														
Serum IgM anti HBc antibody test	X														
Serum anti HDV antibody test[oo]	X														
Testing for hepatitis A, B, C, and E virus, HIV 1 and 2	X														
AFP	X														
Hemoglobin A1c test	X														
FSH test (postmenopausal women only)[k]	X														
Serum pregnancy test (women of childbearing potential only)	X														

Study Phase	Screening	Double-Blind Study Intervention													
Week (W)	W 4 to 0[b]	W0[c]	W2	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48/ WD[a]
Study Day (Window)	28	1	15 +/ 2d	29 +/ 2d	57 +/ 2d	85 +/ 2d	113 +/ 3d	141 +/ 3d	169 +/ 3d	197 +/ 3d	225 +/ 3d	253 +/ 3d	281 +/ 3d	309 +/ 3d	337 +/ 3d
Study Intervention Administration															
Randomization		X													
Administer JNJ 3989 (or placebo)		X		X	X	X	X	X	X	X	X	X	X	X	X
Dispense NA		X		X	X	X	X	X	X	X	X	X	X	X	X
Intake of NA[l]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
NA accountability			X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Evaluations															
Complete physical examination[m]	X								X						X
Symptom directed physical examination[o]		X	X	X	X	X	X	X		X	X	X	X	X	
Liver ultrasound[n]		X							X						X
Vital signs[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Triplicate 12 lead ECG[q]	X	X		X		X			X			X			X
Injection site reactions[r]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests															
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry (including liver function tests)[s,t,u]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood coagulation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis and urine chemistry[v]	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test (women of childbearing potential only)		X		X	X	X	X	X	X	X	X	X	X	X	X
Renal biomarkers[w]		X				X			X			X			X
Efficacy Evaluations															
FibroScan[y]		(X)[x]													(X)[x,z]
HBV and HDV Virology															
HBV genotype[i]		X													
HDV genotype[j]		X													
Blood sampling for HDV RNA[aa]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sampling for HBV DNA	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Blood sampling for HBV RNA[bb]		X				X			X			X			X
Sampling for viral genome sequencing[cc]	X	X				X			X						X

Study Phase	Screening	Double-Blind Study Intervention													
Week (W)	W 4 to 0[b]	W0[c]	W2	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48/ WD[a]
Study Day (Window)	28	1	15 +/ 2d	29 +/ 2d	57 +/ 2d	85 +/ 2d	113 +/ 3d	141 +/ 3d	169 +/ 3d	197 +/ 3d	225 +/ 3d	253 +/ 3d	281 +/ 3d	309 +/ 3d	337 +/ 3d
HBV and HDV Serology															
Blood sampling for:															
Anti HBs (quantitative) and anti HBe		X							X						X
HBsAg HBeAg (qualitative)	X														
HBeAg (qualitative)	X								X						X
HBsAg (quantitative)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBeAg[dd] (quantitative)		X				X			X			X			X
HBcrAg[bb]		X				X			X			X			X
Exploratory serology[ee]	X	X				X			X			X			X
Pharmacokinetics															
Blood sampling for sparse PK of JNJ 3989 [ff]		X		X		X			X						X
Liver Biopsy (optional)[ll]															
Percutaneous core liver biopsy sample		X[mm]							X[mm]						
FNAB		X[mm]							X[mm]						
Exploratory Biomarkers															
Antidrug antibodies (to JNJ 3989)[gg]		X							X						X
Immune Monitoring															
Immune cells (PBMCs) (selected sites only)[hh]		X													X
Pharmacogenomics (DNA)															
Exploratory host DNA genotyping (optional)[ii]		X													
Medical resource utilization[ij]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ongoing Participant Review															
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

General Note: The ECGs should preferably be completed before any tests, procedures or other consultations for that visit to prevent influencing the participant's perceptions.

AFP: alpha-fetoprotein; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CRF: case report form; CT: computed tomography; D/d: Day/days; DBP: diastolic blood pressure; DNA: deoxyribonucleic acid; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; FSH: follicle-stimulating hormone; HBc: hepatitis B core protein; HBe(Ag): hepatitis B e (antigen); HBcrAg: hepatitis B core-related antigen; HBs(Ag): hepatitis B surface (antigen); HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HDV: hepatitis D virus; HIV-1 (-2): human immunodeficiency virus type 1 (type 2); ICF: informed consent form; IgG: immunoglobulin G; IgM: immunoglobulin M; IWRS: interactive web response system;

JNJ-3989: JNJ-73763989; MRI: magnetic resonance imaging; NA: nucleos(t)ide analog; PBMC: peripheral blood mononuclear cells; PK: pharmacokinetic; RNA: ribonucleic acid; SBP: systolic blood pressure; ULN: upper limit of normal; W: Week; WD: withdrawal.

a. Participants who discontinue JNJ-3989/placebo early will have an early WD visit, that should be scheduled as soon as possible, and will enter follow-up (as specified in Section 1.3.3) unless they withdraw consent. In case these participants continue in the follow-up phase, the follow-up visits can be scheduled based on WD visit date. Participants who withdraw consent will be offered an optional safety follow-up visit 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.
b. If necessary (eg, for operational reasons), the screening phase may be extended up to a maximum of 8 weeks on a case-by-case basis and in agreement with the sponsor. Depending on the duration of the screening phase, selected screening assessments may have to be repeated prior to enrollment.
c. Day 1 samples are to be collected before the first dose of study intervention.
d. The ICF must be signed before the first study-related activity. Participants must sign a separate ICF if they agree to provide an optional DNA sample for pharmacogenomic 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.
e. Minimum criteria for the availability of documentation supporting the eligibility criteria are described in the Source Documents section of Section 10.3, Appendix 3: Regulatory, Ethical, and Study Oversight Considerations. Clinical status will be checked at screening and again before first dose of study intervention. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records that becomes available during the screening phase) 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.
f. Medical history also includes mode of HBV and HDV transmission and stage of liver fibrosis. Historical HDV RNA, anti-HDV antibodies, and HBV DNA to be reported in the CRF. HBsAg, HBeAg and ALT data, if available, to be recorded in source documents, but not in the CRF.
g. 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). If FibroScan is not available, acoustic radiation force impulse (ARFI) may be used if standard practice at the site or if otherwise validated and agreed with the sponsor (refer to Section 5.1, Inclusion Criteria for more information).
h. Participants must have absence of signs of HCC or clinically relevant renal abnormalities on an abdominal ultrasound performed within 6 months prior to screening or at the time of screening. In case MRI monitoring is used per patient's standard of care, these MRI results may also be used. In case of suspicious findings on conventional ultrasound the participant may still be eligible if HCC or clinically relevant renal abnormalities has been ruled out by a more specific imaging procedure (contrast enhanced ultrasound, CT or MRI).
i. HBV genotype will be determined at baseline using standard genotyping assay if HBV DNA levels are sufficiently high. For participants with low HBV DNA levels, available historical data on previous HBV genotype assessment will be collected in the CRF. Exploratory genotyping assays might be performed.
j. HDV genotype may be determined by sequencing. For participants with low HDV RNA levels, available historical data on previous HDV genotype assessment will be collected in the CRF. Exploratory genotyping assays might be performed.
k. 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.
l. In between study visits, participants will take NA at home and they will bring their NA with them to each study visit.
m. Complete physical examination, including height (at screening only), skin examination, and other body systems.
n. A liver ultrasound is performed every 24 weeks from Day 1 for HCC screening in all participants. The liver ultrasound does not need to be repeated at baseline if it was done 3 months prior to screening or at time of screening. If a liver ultrasound is required at baseline, it can be performed between the Day 1 and the Week 2 visit (visit days included). For any subsequent liver ultrasound, a window of 1 week is allowed before or after the scheduled visit. In case MRI monitoring is used per patient's standard of care, these MRI results may also be used.
o. Symptom-directed physical examination.

p. Vital signs include supine SBP, DBP, pulse rate, body weight, and body temperature.
q. All ECGs will be read centrally. Only on Day 1, the ECG will also be read locally prior to dosing to assess eligibility.
r. All injection site reactions (ISRs; including ISRs below grade 1) will need to be recorded in the special events section of the CRF (see Section 8.3.6.2).
s. Biochemistry samples must be taken after fasting for at least 10 hours for measurement of phosphate, calcium, creatinine, and lipids.
t. Creatinine clearance (eGFR calculated by the CKD-EPI formula) will be assessed.
u. Intervention-emergent ALT/AST elevations (ie, ALT and/or AST ≥3x ULN and ≥2x nadir [ie, lowest value during study participation]), should trigger an assessment of confounding factors (alcohol intake, change in concomitant medication, and comorbidities) and a confirmatory visit, to be scheduled preferably within 3 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, HBV DNA, and HDV RNA. Note that in case of urgency, local laboratory assessments could be considered (except for HDV RNA and HBsAg to protect the blind). Off-treatment local HDV RNA test can be done to exclude/assess for HDV driven flare. Additional tests should be considered based on clinical judgement. For more details and further management guidance refer to Section 8.3.6.1, Intervention-emergent ALT/AST Elevations and Section 10.6, Appendix 6: Intervention-emergent ALT/AST Elevations.
v. Urine chemistry sample (quantitative measurement): creatinine, sodium, phosphate, glucose, protein, and albumin.
Urinalysis by dipstick: specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic analysis if needed. In case of a positive dipstick result, a urine sample will be set aside for additional examination of the positive parameter at the central laboratory (eg, quantification as applicable).
w. Urine sample for selected renal biomarkers including retinol binding protein and beta-2-microglobulin.
x. A FibroScan assessment will only be done at baseline if it was not done at screening.
y. Only applicable to participants who are enrolled at a site with access to a FibroScan device.
z. At Week 52, participants of Arm 2 will switch to JNJ-3989 + NA, therefore, the FibroScan assessment at Week 48 is the baseline assessment for these participants.
aa. For sites in the US, HDV RNA tests used to determine the participant's eligibility should be performed by a local laboratory.
bb. HBcrAg and HBV RNA samples may be batched and only selected samples may be tested at the sponsor's discretion. Samples can be used for assessment of other serologic/virologic markers of HBV and HDV.
cc. Sequencing at baseline (Day 1 predose) may be performed by default if HBV DNA levels and HDV RNA levels are within the ranges required for the sequencing assay; other samples may be sequenced upon the sponsor virologist's request. Samples might be used for exploratory analyses related to HBV/HDV or study intervention.
dd. Quantitative HBeAg assessment will be performed throughout the study in participants who are HBeAg-positive at screening. In participants who are HBeAg-negative at screening, quantitative HBeAg testing should only be performed starting from the first qualitative HBeAg test result being positive.
ee. Exploratory serology samples may be analyzed at the sponsor's discretion. Samples may be used to assess virologic or serologic markers of HBV/HDV including semi-quantitative anti-HDV IgM antibodies. These samples may also be used for host serum protein testing (eg, cytokines).
ff. All participants will have sparse PK sampling. For all samples, the time of the preceding 2 intakes of NA and the time of PK sampling should be recorded.
One sample at any time between 2 and 8 hours after JNJ-3989 dosing with collection of the time interval between last administration and blood draw. Before leaving the study site, the participant's well-being should be confirmed. In the event of special circumstances (eg, COVID-19 pandemic), the sample may be taken between 15 minutes to less than 2 hours postdose but the sponsor should approve first.
gg. Antidrug antibodies samples should be collected prior to JNJ-3989 administration.
hh. PBMC samples will be collected at selected sites only and as operationally feasible. Additional PBMC samples may be taken until Week 48 in case of ALT flares, upon discussion with the sponsor, which may require an unscheduled visit.
ii. The pharmacogenomic (host DNA) sample is optional and will only be collected from participants who consent separately to this component of the study. The pharmacogenomic (host DNA) sample should preferably be collected at baseline.

jj. The medical resource utilization data will include: (1) number and type of medical visits, (2) number (proportion) of participants requiring hospitalization and duration of hospitalization, and (3) number and character of diagnostic and therapeutic tests and procedures (inpatient and outpatient). For more details, refer to Section 8.9.

kk. The sample for HLA haplotyping should preferably be collected during the Day 1 visit, but may occur at any other study visit during the double-blind study intervention phase.

ll. The preferable time points for collections are indicated but for post-baseline samples might be adapted at investigator's discretion and in consultation with the sponsor. Percutaneous core liver biopsy sample will be prioritized over FNAB if only one sample can be collected.

mm. Following local standard practice the biopsy location will be identified with ultrasound (which will also be used to rule out contraindicating conditions for a biopsy) and after application of local anesthesia the FNAB samples and core liver biopsy samples will be collected. Prior to any on-treatment biopsy, a recent (≤1 week) coagulation and hematology panel are required (pre-biopsy visit). Prior to the baseline or off-treatment biopsies, blood coagulation and platelets will be assessed according to local practice. On-treatment (pre)biopsy can only occur during a regularly scheduled visit. It should be noted that antiplatelet aggregating agents should be paused at least 9 days prior to liver biopsy procedures or according to local standard practice.

nn. If participants agree to undergo an optional liver biopsy, they must provide a separate consent at screening or at any time prior to the optional liver biopsy and additional exclusion criteria apply (Section 5.2, Exclusion Criteria). Refusal to give consent for these optional liver biopsy samples does not exclude a participant from participation in the study. Liver biopsies will be collected only in sites and in selected countries where this is feasible, and after all relevant approvals are in place and operational set-up is completed.

oo. Total anti-HDV antibodies and anti-HDV IgM antibodies may be assessed (qualitative and semi-quantitative).

1.3.2. Schedule of Activities – Open-label Study Intervention Phase (Weeks 52 – EOT)

1.3.2.1. Schedule of Activities – Open-label Study Intervention Phase (Before Protocol Amendment 5)

Before Protocol Amendment 5, the SoA is the same for both Part 1 and Part 2 of the study. However, the SoA is different for Arm 1 (A1) and Arm 2 (A2) as highlighted in the table.

Before Protocol Amendment 5, after completing the open-label phase (ie, after the Week 144 [Arms 1] and 148 [Arms 2] visits) or after early discontinuation visit, participants will enter the 48-week follow-up phase (see Section 1.3.3.1).

Refer to Section 1.3.2.2 for Part 2's Open-label Study Intervention Phase per Protocol Amendment 5.

Study Phase		Open-label Study Intervention (Before Protocol Amendment 5; Part 1 and Part 2)																									
Week (W)	Arm	W52	W54	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	W96	W100	W104	W108	W112	W116	W120	W124	W128	W132	W136	W140	W144	EOT[b]/ WD[a]
Study Day (Window)		365 +/-3d	379 +/-3d (Arm 2 only)	393 +/-7d	421 +/-7d	449 +/-7d	477 +/-7d	505 +/-7d	533 +/-7d	561 +/-7d	589 +/-7d	617 +/-7d	645 +/- 7d	673 +/- 7d	701 +/-7d	729 +/-7d	757 +/-7d	785 +/-7d	813 +/-7d	841 +/-7d	869 +/-7d	897 +/-7d	925 +/-7d	953 +/-7d	981 +/-7d	1,009 +/-7d (Arm 2 only)	1,009 (Arm 1) or 1,037 (Arm 2) +/-7d
Study Intervention Administration																											
Administer JNJ 3989	A1	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
	A2	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense NA	A1	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		(X)[d]
	A2	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)[d]
Intake of NA[c]	A1	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		(X)[d]
	A2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)[d]
NA accountability	A1	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
	A2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Evaluations																											
Complete physical examination[f]	A1&A2																										X
Symptom directed physical examination[g]	A1	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
	A2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Liver ultrasound[e]	A1							X						X						X							X
	A2								X						X						X						X

Study Phase	Open-label Study Intervention (Before Protocol Amendment 5; Part 1 and Part 2)																										
Week (W)	Arm	W52	W54	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	W96	W100	W104	W108	W112	W116	W120	W124	W128	W132	W136	W140	W144	EOT[b]/ WD[a]
Study Day (Window)		365 +/-3d	379 +/-3d (Arm 2 only)	393 +/-7d	421 +/-7d	449 +/-7d	477 +/-7d	505 +/-7d	533 +/-7d	561 +/-7d	589 +/-7d	617 +/-7d	645 +/- 7d	673 +/- 7d	701 +/-7d	729 +/-7d	757 +/-7d	785 +/-7d	813 +/-7d	841 +/-7d	869 +/-7d	897 +/-7d	925 +/-7d	953 +/-7d	981 +/-7d	1,009 +/-7d (Arm 2 only)	1,009 (Arm 1) or 1,037 (Arm 2) +/-7d
Vital signs[h]	A1	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
	A2	X	X	X	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[i]	A1				X			X			X			X			X			X			X				X
	A2	X		X		X			X			X			X			X			X			X			X
Injection site reactions[j]	A1	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
	A2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests																											
Hematology	A1	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
	A2	X	X	X	X	X	X	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)[k,l,m]	A1	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
	A2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood coagulation	A1	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
	A2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis and urine chemistry[o]	A1				X			X			X			X			X			X			X				X
	A2	X		X	X	X	X	X	X	X	X	X	X	X	X			X			X			X				X
Urine pregnancy test (women of childbearing potential only)	A1	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
	A2	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Evaluations																											
FibroScan	A1&A2																										(X)[n]
HBV and HDV Virology																											
Blood sampling for HDV RNA	A1	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
	A2	X	X	X	X	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 DNA	A1	X		X		X		X		X		X		X		X		X		X		X		X			X
	A2	X		X		X		X		X		X		X		X		X		X		X		X		X	X
Blood sampling for HBV RNA[p]	A1							X						X						X							X
	A2	X							X						X						X						X

Study Phase	Open-label Study Intervention (Before Protocol Amendment 5; Part 1 and Part 2)																										
Week (W)	Arm	W52	W54	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	W96	W100	W104	W108	W112	W116	W120	W124	W128	W132	W136	W140	W144	EOT[b]/ WD[a]
Study Day (Window)		365 +/-3d	379 +/-3d (Arm 2 only)	393 +/-7d	421 +/-7d	449 +/-7d	477 +/-7d	505 +/-7d	533 +/-7d	561 +/-7d	589 +/-7d	617 +/-7d	645 +/- 7d	673 +/- 7d	701 +/-7d	729 +/-7d	757 +/-7d	785 +/-7d	813 +/-7d	841 +/-7d	869 +/-7d	897 +/-7d	925 +/-7d	953 +/-7d	981 +/-7d	1,009 +/-7d (Arm 2 only)	1,009 (Arm 1) or 1,037 (Arm 2) +/-7d
Sampling for viral genome sequencing[q]	A1							X						X						X							X
	A2	X							X						X						X						X
HBV and HDV Serology																											
Blood sampling for:																											
Anti HBs (quantitative) and anti HBe	A1							X						X						X							X
	A2	X							X						X						X						X
HBsAg (qualitative)	A1																										X
	A2																										X
HBeAg (qualitative)	A1							X						X													X
	A2								X						X												X
HBsAg (quantitative)	A1	X		X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X			X
	A2	X		X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X	X
HBeAg[r] (quantitative)	A1							X						X													X
	A2	X				X			X						X												X
HBcrAg[p]	A1							X						X													X
	A2					X			X						X												X
Exploratory serology[s]	A1							X						X													X
	A2	X				X			X						X												X
Pharmacokinetics																											
Blood sampling for sparse PK of JNJ 3989[t]	A1							X						X						X							
	A2	X		X		X			X						X						X						
Exploratory Biomarkers																											
Antidrug antibodies (to JNJ 3989)[v]	A1							X						X						X							X
	A2	X							X						X						X						X
Medical resource utilization[u]	A1	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
	A2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ongoing Participant Review																											
Concomitant therapy	A1	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
	A2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Phase	Open-label Study Intervention (Before Protocol Amendment 5; Part 1 and Part 2)																										
Week (W)	Arm	W52	W54	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	W96	W100	W104	W108	W112	W116	W120	W124	W128	W132	W136	W140	W144	EOT[b]/ WD[a]
Study Day (Window)		365 +/-3d	379 +/-3d (Arm 2 only)	393 +/-7d	421 +/-7d	449 +/-7d	477 +/-7d	505 +/-7d	533 +/-7d	561 +/-7d	589 +/-7d	617 +/-7d	645 +/- 7d	673 +/- 7d	701 +/-7d	729 +/-7d	757 +/-7d	785 +/-7d	813 +/-7d	841 +/-7d	869 +/-7d	897 +/-7d	925 +/-7d	953 +/-7d	981 +/-7d	1,009 +/-7d (Arm 2 only)	1,009 (Arm 1) or 1,037 (Arm 2) +/-7d
Adverse events	A1	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
	A2	X	X	X	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 preferably be completed before any tests, procedures or other consultations for that visit to prevent influencing the participant's perceptions.

A1: Arm 1; A2: Arm 2; AFP: alpha-fetoprotein; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CRF: case report form; CT: computed tomography; D/d: Day/days; DBP: diastolic blood pressure; DNA: deoxyribonucleic acid; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; EOT: end of treatment; FSH: follicle-stimulating hormone; HBc: hepatitis B core protein; HBe(Ag): hepatitis B e (antigen); HBcrAg: hepatitis B core-related antigen; HBs(Ag): hepatitis B surface (antigen); HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HDV: hepatitis D virus; HIV-1 (-2): human immunodeficiency virus type 1 (type 2); ICF: informed consent form; IgM: immunoglobulin M; IWRS: interactive web response system; JNJ-3989: JNJ-73763989; MRI: magnetic resonance imaging; NA: nucleos(t)ide analog; PK: pharmacokinetic; RNA: ribonucleic acid; SBP: systolic blood pressure; ULN: upper limit of normal; W: Week; WD: withdrawal.

a. Participants who discontinue JNJ-3989 early will have an early WD visit, that should be scheduled as soon as possible, and will enter follow-up (Section 1.3.3) unless they withdraw consent. In case these participants continue in the follow-up phase, the follow-up visits can be scheduled based on WD visit date. Participants who withdraw consent will be offered an optional safety follow-up visit 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.
b. The end of treatment (EOT) visit will be performed at Week 144 and Week 148 for participants of Arms 1 and Arms 2, respectively.
c. In between study visits, participants will take NA at home and they will bring their NA with them to each study visit.
d. NA treatment will continue for all study participants until the last study visit (FU W48). Only for non-cirrhotic participants, NA treatment can be discontinued during the follow-up phase in case of a confirmed HBsAg seroclearance, ALT <3x ULN, and HBV DNA <LLOQ. Amongst the non-cirrhotic participants who discontinue treatment with NA, NA treatment will be restarted if any of the criteria listed in Section 6.5 are met.
e. A liver ultrasound is performed approximately every 24 weeks from start of open-label phase for HCC screening in all participants. A window of 1 week is allowed before or after the scheduled visit. In case MRI monitoring is used per patient's standard of care, these MRI results may also be used.
f. Complete physical examination, including height (at screening only), skin examination, and other body systems.
g. Symptom-directed physical examination.
h. Vital signs include supine SBP, DBP, pulse rate, body weight, and body temperature.
i. All ECGs will be read centrally.
j. All injection site reactions (ISRs; including ISRs below grade 1) will need to be recorded in the special events section of the CRF.
k. Biochemistry samples must be taken after fasting for at least 10 hours for measurement of phosphate, calcium, creatinine, and lipids.
l. Creatinine clearance (eGFR calculated by the CKD-EPI formula) will be assessed.

m. Intervention-emergent ALT/AST elevations (ie, ALT and/or AST ≥3x ULN and ≥2x nadir [ie, lowest value during study participation]), should trigger an assessment of confounding factors (alcohol intake, change in concomitant medication, and comorbidities) and a confirmatory visit, to be scheduled preferably within 3 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, HBV DNA, and HDV RNA. Note that in case of urgency, local laboratory assessments could be considered. (except for HDV RNA and HBsAg to protect the blind) Off-treatment local HDV RNA test can be done to exclude/assess for HDV driven flare. Additional tests should be considered based on clinical judgement. For more details and further management guidance refer to Section 8.3.6.1, Intervention-emergent ALT/AST Elevations and Section 10.6, Appendix 6: Intervention-emergent ALT/AST Elevations.
n. Only applicable to participants who are enrolled at a site with an access to a FibroScan device.
o. Urine chemistry sample (quantitative measurement): creatinine, sodium, phosphate, glucose, protein, and albumin.
Urinalysis by dipstick: specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic analysis if needed. In case of a positive dipstick result, a urine sample will be set aside for additional examination of the positive parameter at the central laboratory (eg, quantification as applicable).
p. HBcrAg and HBV RNA samples may be batched and only selected samples may be tested at the sponsor's discretion. Samples can be used for assessment of other serologic/virologic markers of HBV and HDV.
q. Samples may be sequenced upon on the sponsor virologist's request. Samples might be used for exploratory analyses related to HBV/HDV or study intervention.
r. Quantitative HBeAg assessment will be performed throughout the study in participants who are HBeAg-positive at screening. In participants who are HBeAg-negative at screening, quantitative HBeAg testing should only be performed starting from the first qualitative HBeAg test result being positive.
s. Exploratory serology samples may be analyzed at the sponsor's discretion. Samples may be used to assess virologic or serologic markers of HBV/HDV including semi-quantitative anti-HDV IgM antibodies. These samples may also be used for host serum protein testing (eg, cytokines).
t. All participants will have sparse PK sampling. For all samples, the time of the preceding 2 intakes of NA and the time of PK sampling should be recorded.
One sample at any time between 2 and 8 hours after JNJ-3989 dosing with collection of the time interval between last administration and blood draw. Before leaving the study site, the participant's well-being should be confirmed. In the event of special circumstances (eg, COVID-19 pandemic), the sample may be taken between 15 minutes to less than 2 hours postdose but the sponsor should approve first.
u. The medical resource utilization data will include: (1) number and type of medical visits, (2) number (proportion) of participants requiring hospitalization and duration of hospitalization, and (3) number and character of diagnostic and therapeutic tests and procedures (inpatient and outpatient). For more details, refer to Section 8.9.
v. Antidrug antibodies samples should be collected prior to JNJ-3989 administration.

1.3.2.2. Schedule of Activities – Open-label Study Intervention Phase (per Protocol Amendment 5)

Per Protocol Amendment 5, participants in Part 2 will follow a modified open-label intervention phase. The SoA difference between Arm 1 (A1) and Arm 2 (A2) is highlighted in the table in dark grey shading. Study procedures that will not be applicable per Protocol Amendment 5 are indicated in the table in yellow shading.

Participants who stop treatment with JNJ-3989 after Protocol Amendment 5 will enter a 24-week follow-up phase (see Section 1.3.3.2) after the EOT (or early discontinuation) visit.

Study Phase		Open-label Study Intervention (Per Protocol Amendment 5; Part 2)																									
Week (W)	Arm	W52	W54	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	W96	W100[u]	W104[u]	W108[u]	W112[u]	W116[u]	W120[u]	W124[u]	W128[u]	W132[u]	W136[u]	W140[u]	W144[u]	EOT[b]/ WD[a]
Study Day (Window)		365 +/-3d	379 +/-3d (Arm 2 only)	393 +/-7d	421 +/-7d	449 +/-7d	477 +/-7d	505 +/-7d	533 +/-7d	561 +/-7d	589 +/-7d	617 +/-7d	645 +/- 7d	673 +/- 7d	701 +/-7d	729 +/-7d	757 +/-7d	785 +/-7d	813 +/-7d	841 +/-7d	869 +/-7d	897 +/-7d	925 +/-7d	953 +/-7d	981 +/-7d	1,009 +/-7d (Arm 2 only)	Min 673 (Arm 1) or min 701 (Arm 2) +/-7d
Study Intervention Administration																											
Administer JNJ 3989	A1	X		X	X	X	X	X	X	X	X	X	X	X[u]	X	X	X	X	X	X	X	X	X	X	X		
	A2	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense NA	A1	X		X	X	X	X	X	X	X	X	X	X	X[u]	X	X	X	X	X	X	X	X	X	X	X		(X)[d]
	A2	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)[d]
Intake of NA[c]	A1	X		X	X	X	X	X	X	X	X	X	X	X[u]	X	X	X	X	X	X	X	X	X	X	X		(X)[d]
	A2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)[d]
NA accountability	A1	X		X	X	X	X	X	X	X	X	X	X	X[u]	X	X	X	X	X	X	X	X	X	X	X		X
	A2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Evaluations																											
Complete physical examination[f]	A1&A2																										X
Symptom directed physical examination[g]	A1	X		X	X	X	X	X	X	X	X	X	X	X[u]	X	X	X	X	X	X	X	X	X	X	X		
	A2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Liver ultrasound[e]	A1							X						X[u]						X							X
	A2								X						X						X						X

Study Phase	Open-label Study Intervention (Per Protocol Amendment 5; Part 2)																									
Week (W)	Arm	W52	W54	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	W96	W100[u]	W104[u]	W108[u]	W112[u]	W116[u]	W120[u]	W124[u]	W128[u]	W132[u]	W136[u]	W140[u]	W144[u]	EOT[b]/ WD[a]
Study Day (Window)		365 +/-3d	379 +/-3d (Arm 2 only)	393 +/-7d	421 +/-7d	449 +/-7d	477 +/-7d	505 +/-7d	533 +/-7d	561 +/-7d	589 +/-7d	617 +/-7d	645 +/- 7d	673 +/- 7d	701 +/-7d	729 +/-7d	757 +/-7d	785 +/-7d	813 +/-7d	841 +/-7d	869 +/-7d	897 +/-7d	925 +/-7d	953 +/-7d	981 +/-7d	1,009 +/-7d (Arm 2 only)	Min 673 (Arm 1) or min 701 (Arm 2) +/-7d
Vital signs[h]	A1	X		X	X	X	X	X	X	X	X	X	X	X[u]	X	X	X	X	X	X	X	X	X	X	X		X
	A2	X	X	X	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[i]	A1				X			X			X			X[u]			X			X			X				X
	A2	X		X		X			X			X			X			X			X			X			X
Injection site reactions[j]	A1	X		X	X	X	X	X	X	X	X	X	X	X[u]	X	X	X	X	X	X	X	X	X	X	X		X
	A2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests																											
Hematology	A1	X		X	X	X	X	X	X	X	X	X	X	X[u]	X	X	X	X	X	X	X	X	X	X	X		X
	A2	X	X	X	X	X	X	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)[k,l,m]	A1	X		X	X	X	X	X	X	X	X	X	X	X[u]	X	X	X	X	X	X	X	X	X	X	X		X
	A2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood coagulation	A1	X		X	X	X	X	X	X	X	X	X	X	X[u]	X	X	X	X	X	X	X	X	X	X	X		X
	A2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis and urine chemistry[o]	A1				X			X			X			X[u]			X			X			X				X
	A2	X		X	X	X	X	X	X	X	X	X	X	X	X			X			X			X				X
Urine pregnancy test (women of childbearing potential only)	A1	X		X	X	X	X	X	X	X	X	X	X	X[u]	X	X	X	X	X	X	X	X	X	X	X		X
	A2	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Evaluations																											
FibroScan	A1&A2																										(X)[n]
HBV and HDV Virology																											
Blood sampling for HDV RNA	A1	X		X	X	X	X	X	X	X	X	X	X	X[u]	X	X	X	X	X	X	X	X	X	X	X		X
	A2	X	X	X	X	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 DNA	A1	X		X		X		X		X		X		X[u]		X		X		X		X		X			X
	A2	X		X		X		X		X		X		X		X		X		X		X		X		X	X

Study Phase	Open-label Study Intervention (Per Protocol Amendment 5; Part 2)																										
Week (W)	Arm	W52	W54	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	W96	W100[u]	W104[u]	W108[u]	W112[u]	W116[u]	W120[u]	W124[u]	W128[u]	W132[u]	W136[u]	W140[u]	W144[u]	EOT[b]/ WD[a]
Study Day (Window)		365 +/-3d	379 +/-3d (Arm 2 only)	393 +/-7d	421 +/-7d	449 +/-7d	477 +/-7d	505 +/-7d	533 +/-7d	561 +/-7d	589 +/-7d	617 +/-7d	645 +/- 7d	673 +/- 7d	701 +/-7d	729 +/-7d	757 +/-7d	785 +/-7d	813 +/-7d	841 +/-7d	869 +/-7d	897 +/-7d	925 +/-7d	953 +/-7d	981 +/-7d	1,009 +/-7d (Arm 2 only)	Min 673 (Arm 1) or min 701 (Arm 2) +/-7d
Blood sampling for HBV RNA[p]	A1							X						X[u]						X							X
	A2	X							X						X						X						X
Sampling for viral genome sequencing[q]	A1													X[u]													X
	A2	X													X												X
HBV and HDV Serology																											
Blood sampling for:																											
Anti HBs (quantitative) and anti HBe	A1							X						X[u]						X							X
	A2	X							X						X						X						X
HBsAg (qualitative)	A1																										X
	A2																										X
HBeAg (qualitative)	A1													X[u]													X
	A2														X												X
HBsAg (quantitative)	A1	X		X	X	X	X	X	X	X	X	X	X	X[u]		X		X		X		X		X			X
	A2	X		X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X	X
HBeAg[r] (quantitative)	A1							X						X[u]													X
	A2	X				X			X						X												X
HBcrAg[p]	A1							X						X[u]													X
	A2					X			X						X												X
Exploratory serology[s]	A1																										
	A2	X																									
Medical resource utilization[t]	A1	X		X	X	X	X	X	X	X	X	X	X	X[u]	X	X	X	X	X	X	X	X	X	X	X		X
	A2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Phase	Open-label Study Intervention (Per Protocol Amendment 5; Part 2)																										
Week (W)	Arm	W52	W54	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	W96	W100[u]	W104[u]	W108[u]	W112[u]	W116[u]	W120[u]	W124[u]	W128[u]	W132[u]	W136[u]	W140[u]	W144[u]	EOT[b]/ WD[a]
Study Day (Window)		365 +/-3d	379 +/-3d (Arm 2 only)	393 +/-7d	421 +/-7d	449 +/-7d	477 +/-7d	505 +/-7d	533 +/-7d	561 +/-7d	589 +/-7d	617 +/-7d	645 +/- 7d	673 +/- 7d	701 +/-7d	729 +/-7d	757 +/-7d	785 +/-7d	813 +/-7d	841 +/-7d	869 +/-7d	897 +/-7d	925 +/-7d	953 +/-7d	981 +/-7d	1,009 +/-7d (Arm 2 only)	Min 673 (Arm 1) or min 701 (Arm 2) +/-7d
Ongoing Participant Review																											
Concomitant therapy	A1	X		X	X	X	X	X	X	X	X	X	X	X[u]	X	X	X	X	X	X	X	X	X	X	X		X
	A2	X	X	X	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	A1	X		X	X	X	X	X	X	X	X	X	X	X[u]	X	X	X	X	X	X	X	X	X	X	X		X
	A2	X	X	X	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 preferably be completed before any tests, procedures or other consultations for that visit to prevent influencing the participant's perceptions.

A1: Arm 1; A2: Arm 2; AFP: alpha-fetoprotein; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CRF: case report form; CT: computed tomography; D/d: Day/days; DBP: diastolic blood pressure; DNA: deoxyribonucleic acid; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; EOT: end of treatment; FSH: follicle-stimulating hormone; HBc: hepatitis B core protein; HBe(Ag): hepatitis B e (antigen); HBcrAg: hepatitis B core-related antigen; HBs(Ag): hepatitis B surface (antigen); HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HDV: hepatitis D virus; HIV-1 (-2): human immunodeficiency virus type 1 (type 2); ICF: informed consent form; IgM: immunoglobulin M; IWRS: interactive web response system; JNJ-3989: JNJ-73763989; MRI: magnetic resonance imaging; NA: nucleos(t)ide analog; PK: pharmacokinetic; RNA: ribonucleic acid; SBP: systolic blood pressure; ULN: upper limit of normal; W: Week; WD: withdrawal.

a. Participants who discontinue JNJ-3989 early will have an early WD visit, that should be scheduled as soon as possible, and will enter follow-up (Section 1.3.3.2) unless they withdraw consent. In case these participants continue in the follow-up phase, the follow-up visits can be scheduled based on WD visit date. Participants who withdraw consent will be offered an optional safety follow-up visit 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.
b. The end of treatment (EOT) visit will be performed at Week 96 and Week 100 in Arm 1 and Arm 2, respectively. If at the timepoint that Amendment 5 is in effect a participant is at >Week 96 (Arm 1) or >Week 100 (Arm 2) in the open label phase, the EOT visit should be scheduled at the next planned visit (ie, 4 weeks after the last JNJ-3989 administration).
c. In between study visits, participants will take NA at home and they will bring their NA with them to each study visit.
d. NA treatment will continue for all study participants until the last study visit (FU W24).
e. A liver ultrasound is performed approximately every 24 weeks from start of open-label phase for HCC screening in all participants. A window of 1 week is allowed before or after the scheduled visit. In case MRI monitoring is used per patient's standard of care, these MRI results may also be used.
f. Complete physical examination, including height (at screening only), skin examination, and other body systems.
g. Symptom-directed physical examination.

h. Vital signs include supine SBP, DBP, pulse rate, body weight, and body temperature.
i. All ECGs will be read centrally.
j. All injection site reactions (ISRs; including ISRs below grade 1) will need to be recorded in the special events section of the CRF.
k. Biochemistry samples must be taken after fasting for at least 10 hours for measurement of phosphate, calcium, creatinine, and lipids.
l. Creatinine clearance (eGFR calculated by the CKD-EPI formula) will be assessed.
m. Intervention-emergent ALT/AST elevations (ie, ALT and/or AST ≥3x ULN and ≥2x nadir [ie, lowest value during study participation]), should trigger an assessment of confounding factors (alcohol intake, change in concomitant medication, and comorbidities) and a confirmatory visit, to be scheduled preferably within 3 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, HBV DNA, and HDV RNA. Note that in case of urgency, local laboratory assessments could be considered. (except for HDV RNA and HBsAg to protect the blind) Off-treatment local HDV RNA test can be done to exclude/assess for HDV driven flare. Additional tests should be considered based on clinical judgement. For more details and further management guidance refer to Section 8.3.6.1, Intervention-emergent ALT/AST Elevations and Section 10.6, Appendix 6: Intervention-emergent ALT/AST Elevations.
n. Only applicable to participants who are enrolled at a site with an access to a FibroScan device.
o. Urine chemistry sample (quantitative measurement): creatinine, sodium, phosphate, glucose, protein, and albumin.
Urinalysis by dipstick: specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic analysis if needed. In case of a positive dipstick result, a urine sample will be set aside for additional examination of the positive parameter at the central laboratory (eg, quantification as applicable).
p. HBcrAg and HBV RNA samples may be batched and only selected samples may be tested at the sponsor's discretion. Samples can be used for assessment of other serologic/virologic markers of HBV and HDV.
q. Samples may be sequenced upon on the sponsor virologist's request. Samples might be used for exploratory analyses related to HBV/HDV or study intervention.
r. Quantitative HBeAg assessment will be performed throughout the study in participants who are HBeAg-positive at screening. In participants who are HBeAg-negative at screening, quantitative HBeAg testing should only be performed starting from the first qualitative HBeAg test result being positive.
s. Exploratory serology samples may be analyzed at the sponsor's discretion. Samples may be used to assess virologic or serologic markers of HBV/HDV including semi-quantitative anti-HDV IgM antibodies. These samples may also be used for host serum protein testing (eg, cytokines).
t. The medical resource utilization data will include: (1) number and type of medical visits, (2) number (proportion) of participants requiring hospitalization and duration of hospitalization, and (3) number and character of diagnostic and therapeutic tests and procedures (inpatient and outpatient). For more details, refer to Section 8.9, Medical Resource Utilization.
u. Procedures not applicable per Protocol Amendment 5.

1.3.3. Schedule of Activities – Follow-up Phase

1.3.3.1. Schedule of Activities – 48-Week Follow-up Phase (Before Protocol Amendment 5)

Before Protocol Amendment 5, after completion of the open-label study intervention phase (or early discontinuation), all participants in Part 1 and Part 2 will enter the 48-week follow-up phase (unless they withdraw consent).

All participants in Part 2 when Protocol Amendment 5 is in effect will receive reduced follow-up schedules as specified in Section 1.3.3.2 (unless they withdraw consent).

Study Phase	Follow-up[a,b] (Before Protocol Amendment 5; Part 1 and Part 2)											
Follow up (FU) Week (W)	FU W2	FU W4	FU W6	FU W8	FU W12	FU W16	FU W20	FU W24	FU W30	FU W36	FU W42	FU W48 EOS/WD[b]
FU Study Day (Window)	15 +/ 4d	29 +/ 4d	43 +/ 7d	57 +/ 7d	85 +/ 7d	113 +/ 7d	141 +/ 7d	169 +/ 7d	211 +/ 7d	253 +/ 7d	295 +/ 7d	337 +/ 7d
Study Intervention Administration												
Dispense NA[c]		X		X	X	X	X	X	X	X	X	
Intake of NA[c]	X	X	X	X	X	X	X	X	X	X	X	X
NA accountability[c]		X		X	X	X	X	X	X	X	X	X
Safety Evaluations												
Symptom directed physical examination[d]	X	X	X	X	X	X	X	X	X	X	X	X
Liver ultrasound[e]								X				X
Vital signs[f]	X	X		X		X		X	X		X	X
Triplicate 12 lead ECG[g]		X										
Clinical Laboratory Tests												
Hematology	X	X		X		X		X		X		X
Blood chemistry (including liver function tests)[h,i,j]	X	X	X[k]	X[k]	X	X[k]	X[k]	X	X[k]	X	X	X
Blood coagulation	X	X		X		X		X		X		X
Urinalysis and urine chemistry[l]		X										
Urine pregnancy test (women of childbearing potential only)		X		X	X	X	X	X[m]	X[m]	X[m]	X[m]	X
Efficacy Evaluations												
FibroScan								(X)[n]				(X)[n]
HBV and HDV Virology												
Blood sampling for HDV RNA	X	X	X	X	X	X	X	X	X	X	X	X
Blood sampling for HBV DNA	X[o]	X	X[o]	X	X	X	X[o]	X	X[o]	X	X[o]	X
Blood sampling for HBV RNA[p]					X			X				X
Sampling for viral genome sequencing[q]								X				X

Study Phase	Follow-up[a,b] (Before Protocol Amendment 5; Part 1 and Part 2)											
Follow up (FU) Week (W)	FU W2	FU W4	FU W6	FU W8	FU W12	FU W16	FU W20	FU W24	FU W30	FU W36	FU W42	FU W48 EOS/WD[b]
FU Study Day (Window)	15 +/ 4d	29 +/ 4d	43 +/ 7d	57 +/ 7d	85 +/ 7d	113 +/ 7d	141 +/ 7d	169 +/ 7d	211 +/ 7d	253 +/ 7d	295 +/ 7d	337 +/ 7d
HBV and HDV Serology												
Blood sampling for:												
Anti HBs (quantitative) and anti HBe					X			X		X		X
HBeAg (qualitative)								X				X
HBsAg (quantitative)		X		X	X	X	X	X	X	X	X	X
HBeAg (quantitative)[t]								X				X
HBcrAg[p]					X			X		X		X
Exploratory serology[r]		X			X			X				X
Exploratory Biomarkers												
Antidrug antibodies (to JNJ 3989)								X				X
Medical resource utilization[s]	X	X	X	X	X	X	X	X	X	X	X	X
Ongoing Participant Review												
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X

General Note: The ECGs should preferably be completed before any tests, procedures or other consultations for that visit to prevent influencing the participant's perceptions.

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; D/d: Day/days; DBP: diastolic blood pressure; DNA: deoxyribonucleic acid; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; EOS: end of study; Ext FU: extended follow-up; FU: follow-up; HBcrAg: hepatitis B core-related antigen; HBe(Ag): hepatitis B e (antigen); HBs(Ag): hepatitis B surface (antigen); HBV: hepatitis B virus; HDV: hepatitis D virus; JNJ-3989: JNJ-73763989; NA: nucleos(t)ide analog; RNA: ribonucleic acid; SBP: systolic blood pressure; ULN: upper limit of normal; W: Week; WD: withdrawal.

a. All follow-up study visits are to be scheduled relative to the last dose of JNJ-3989 or to the last originally planned JNJ-3989 treatment visit in case of early treatment discontinuation. An unscheduled visit can be performed upon the investigator's discretion, in case of HBV DNA elevations, ALT elevations, other signs of worsening of liver disease, or for any other reason during follow-up. Participants who discontinue JNJ-3989 early will have an early WD visit, that should be scheduled as soon as possible. Other visits during the follow-up phase can be scheduled based on WD visit date.

b. Participants who withdraw consent during follow-up will be offered an optional safety follow-up visit on the day of consent withdrawal. For the optional safety follow-up visit, assessments are at the investigator's discretion and could be similar to the early WD visit.

c. NA treatment will continue for all study participants until the last study visit (FU W48). Only for non-cirrhotic participants, NA treatment can be discontinued in case of a confirmed HBsAg seroclearance, ALT <3x ULN, and HBV DNA <LLOQ. In that case, follow-up visits need to be scheduled every 6 weeks. Amongst the non-cirrhotic participants who discontinue treatment with NA, NA treatment will be restarted if any of the criteria listed in Section 6.5 are met. Criteria for re-treatment with NA are described in Section 6.5, Re-treatment With NA During the Follow-up Phase.

d. Symptom-directed physical examination.

e. A liver ultrasound is performed every 24 weeks from start of FU for HCC screening in all participants. A window of 1 week is allowed before or after the scheduled visit. In case MRI monitoring is used per patient's standard of care, these MRI results may also be used.
f. Vital signs include supine SBP, DBP, pulse rate, body weight, and body temperature.
g. All ECGs will be read centrally.
h. Biochemistry samples must be taken after fasting for at least 10 hours for measurement of phosphate, calcium, creatinine, and lipids.
i. Creatinine clearance (eGFR calculated by the CKD-EPI formula) will be assessed.
j. ALT/AST elevations (ie, ALT and/or AST ≥3x ULN and ≥2x nadir [ie, lowest value during study participation]), should trigger an assessment of confounding factors (alcohol intake, change in concomitant medication, and comorbidities) and a confirmatory visit, to be scheduled preferably within 3 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, HBV DNA, and HDV RNA. Note that in case of urgency, local laboratory assessments could be considered (except for HDV RNA and HBsAg to protect the blind). Off-treatment local HDV RNA test can be done to exclude/assess for HDV driven flare. Additional tests should be considered based on clinical judgement. For more details and further management guidance refer to Section 8.3.6.1, Intervention-emergent ALT/AST Elevations and Section 10.6, Appendix 6: Intervention-emergent ALT/AST Elevations.
k. Liver function tests only.
l. Urine chemistry sample (quantitative measurement): creatinine, sodium, phosphate, glucose, protein, and albumin.
Urinalysis by dipstick: specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic analysis if needed. In case of a positive dipstick result, a urine sample will be set aside for additional examination of the positive parameter at the central laboratory (eg, quantification as applicable).
m. Urine pregnancy tests for at-home use will be provided to the participants from Follow-up Week 24 onwards as urine pregnancy test should be done at least every 4 weeks. Results will be reported at the next visit. If urine pregnancy test is positive, the investigator needs to be informed immediately by the participant.
n. Only applicable to participants who are enrolled at a site with an access to a FibroScan device.
o. Only applicable to participants who stopped NA treatment.
p. HBcrAg and HBV RNA samples may be batched and only selected samples may be tested at the sponsor's discretion. Samples can be used for assessment of other serologic/virologic markers of HBV.
q. Samples may be sequenced upon on the sponsor virologist's request. Samples might be used for exploratory analyses related to HBV/HDV or study intervention.
r. Exploratory serology samples may be analyzed at the sponsor's discretion. Samples may be used to assess virologic or serologic markers of HBV/HDV including semi-quantitative anti-HDV IgM antibodies. These samples may also be used for host serum protein testing (eg, cytokines).
s. The medical resource utilization data will include: (1) number and type of medical visits, (2) number (proportion) of participants requiring hospitalization and duration of hospitalization, and (3) number and character of diagnostic and therapeutic tests and procedures (inpatient and outpatient). For more details, refer to Section 8.9.
t. Quantitative HBeAg assessment will be performed throughout the study in participants who are HBeAg-positive at screening. In participants who are HBeAg-negative at screening, quantitative HBeAg testing should only be performed starting from the first qualitative HBeAg test result being positive.

1.3.3.2. Schedule of Activities – Reduced Follow-up Phase (per Protocol Amendment 5)

All participants in Part 2 who have not reached FU Week 24 (including those in the open-label phase) when Protocol Amendment 5 is in effect will follow a 24-week follow-up phase with the EOS visit scheduled at FU Week 24 (unless they withdraw consent). Participants in Part 2 who have reached FU Week 24 or later when Protocol Amendment 5 is in effect will receive the EOS visit at the next planned visit (unless they withdraw consent). Study procedures that will not be applicable per Protocol Amendment 5 are indicated in the table in yellow shading.

Participants in Part 1 will not be affected by Protocol Amendment 5 and will continue with the 48-week follow-up schedule (Refer to Section 1.3.3.1).

Study Phase	Follow-up[a,b] (Per Protocol Amendment 5; Part 2)											
Follow up (FU) Week (W)	FU W2[t]	FU W4	FU W6[t]	FU W8	FU W12	FU W16	FU W20	FU W24[u]	FU W30[u]	FU W36[u]	FU W42[u]	EOS[c]/WD[b]
FU Study Day (Window)	15 +/ 4d	29 +/ 4d	43 +/ 7d	57 +/ 7d	85 +/ 7d	113 +/ 7d	141 +/ 7d	169 +/ 7d	211 +/ 7d	253 +/ 7d	295 +/ 7d	Min 169 +/ 7d
Study Intervention Administration												
Dispense NA[d]		X		X	X	X	X	X	X	X	X	
Intake of NA[d]	X	X	X	X	X	X	X	X	X	X	X	X
NA accountability[d]		X		X	X	X	X	X	X	X	X	X
Safety Evaluations												
Symptom directed physical examination[e]	X	X	X	X	X	X	X	X	X	X	X	X
Liver ultrasound[f]								X				X
Vital signs[g]	X	X		X		X		X	X		X	X
Triplicate 12 lead ECG[h]		X										
Clinical Laboratory Tests												
Hematology	X	X		X		X		X		X		X
Blood chemistry (including liver function tests)[i,j,k]	X	X	X[l]	X[l]	X	X[l]	X[l]	X	X[l]	X	X	X
Blood coagulation	X	X		X		X		X		X		X
Urinalysis and urine chemistry[m]		X										
Urine pregnancy test (women of childbearing potential only)		X		X	X	X	X	X[n]	X[n]	X[n]	X[n]	X
Efficacy Evaluations												
FibroScan								(X)[o]				(X)[o]
HBV and HDV Virology												
Blood sampling for HDV RNA		X		X	X	X	X	X	X	X	X	X
Blood sampling for HBV DNA		X		X	X	X		X		X		X
Blood sampling for HBV RNA[p]								X				X

Study Phase	Follow-up[a,b] (Per Protocol Amendment 5; Part 2)											
Follow up (FU) Week (W)	FU W2[t]	FU W4	FU W6[t]	FU W8	FU W12	FU W16	FU W20	FU W24[u]	FU W30[u]	FU W36[u]	FU W42[u]	EOS[c]/WD[b]
FU Study Day (Window)	15 +/ 4d	29 +/ 4d	43 +/ 7d	57 +/ 7d	85 +/ 7d	113 +/ 7d	141 +/ 7d	169 +/ 7d	211 +/ 7d	253 +/ 7d	295 +/ 7d	Min 169 +/ 7d
Sampling for viral genome sequencing[q]								X				X
HBV and HDV Serology												
Blood sampling for:												
Anti HBs (quantitative) and anti HBe												X
HBeAg (qualitative)												X
HBsAg(quantitative)		X			X			X		X		X
HBeAg (quantitative)[s]								X				X
HBcrAg[p]								X				X
Medical resource utilization[r]	X	X	X	X	X	X	X	X	X	X	X	X
Ongoing Participant Review												
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X

General Note: The ECGs should preferably be completed before any tests, procedures or other consultations for that visit to prevent influencing the participant's perceptions.

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; D/d: Day/days; DBP: diastolic blood pressure; DNA: deoxyribonucleic acid; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; EOS: end of study; Ext FU: extended follow-up; FU: follow-up; HBcrAg: hepatitis B core-related antigen; HBe(Ag): hepatitis B e (antigen); HBs(Ag): hepatitis B surface (antigen); HBV: hepatitis B virus; HDV: hepatitis D virus; JNJ-3989: JNJ-73763989; NA: nucleos(t)ide analog; RNA: ribonucleic acid; SBP: systolic blood pressure; ULN: upper limit of normal; W: Week; WD: withdrawal.

a. All follow-up study visits are to be scheduled relative to the last dose of JNJ-3989 or to the last originally planned JNJ-3989 treatment visit in case of early treatment discontinuation. An unscheduled visit can be performed upon the investigator's discretion, in case of HBV DNA elevations, ALT elevations, other signs of worsening of liver disease, or for any other reason during follow-up. Participants who discontinue JNJ-3989 early will have an early WD visit, that should be scheduled as soon as possible. Other visits during the follow-up phase can be scheduled based on WD visit date.
b. Participants who withdraw consent during follow-up will be offered an optional safety follow-up visit on the day of consent withdrawal. For the optional safety follow-up visit, assessments are at the investigator's discretion and could be similar to the early WD visit.
c. The end-of-study visit will be performed at FU W24 for participants who have not reached FU W24 (including those in the open-label phase) when Protocol Amendment 5 is in effect. For participants who have reached FU Week 24 or later when Protocol Amendment 5 is in effect, the EOS visit will be performed at the next planned visit.
d. NA treatment will continue for all study participants until the last study visit (FU W24 or later).
e. Symptom-directed physical examination.

f. For participants who have not reached FU W24 (including those in the open-label phase) when Protocol Amendment 5 is in effect, liver ultrasound is performed at the EOS visit (ie, FU W24) for HCC screening. A window of 1 week is allowed before or after the scheduled visit. In case MRI monitoring is used per patient's standard of care, this MRI result may also be used.
g. Vital signs include supine SBP, DBP, pulse rate, body weight, and body temperature.
h. All ECGs will be read centrally.
i. Biochemistry samples must be taken after fasting for at least 10 hours for measurement of phosphate, calcium, creatinine, and lipids.
j. Creatinine clearance (eGFR calculated by the CKD-EPI formula) will be assessed.
k. ALT/AST elevations (ie, ALT and/or AST ≥3x ULN and ≥2x nadir [ie, lowest value during study participation]), should trigger an assessment of confounding factors (alcohol intake, change in concomitant medication, and comorbidities) and a confirmatory visit, to be scheduled preferably within 3 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, HBV DNA, and HDV RNA. Note that in case of urgency, local laboratory assessments could be considered (except for HDV RNA and HBsAg to protect the blind). Off-treatment local HDV RNA test can be done to exclude/assess for HDV driven flare. Additional tests should be considered based on clinical judgement. For more details and further management guidance refer to Section 8.3.6.1, Intervention-emergent ALT/AST Elevations and Section 10.6, Appendix 6: Intervention-emergent ALT/AST Elevations.
l. Liver function tests only.
m. Urine chemistry sample (quantitative measurement): creatinine, sodium, phosphate, glucose, protein, and albumin.
Urinalysis by dipstick: specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic analysis if needed. In case of a positive dipstick result, a urine sample will be set aside for additional examination of the positive parameter at the central laboratory (eg, quantification as applicable).
n. Urine pregnancy tests for at-home use will be provided to the participants from Follow-up Week 24 onwards as urine pregnancy test should be done at least every 4 weeks. Results will be reported at the next visit. If urine pregnancy test is positive, the investigator needs to be informed immediately by the participant. The procedures will not be applicable per Protocol Amendment 5.
o. Only applicable to participants who are enrolled at a site with an access to a FibroScan device.
p. HBcrAg and HBV RNA samples may be batched and only selected samples may be tested at the sponsor's discretion. Samples can be used for assessment of other serologic/virologic markers of HBV.
q. Samples may be sequenced upon on the sponsor virologist's request. Samples might be used for exploratory analyses related to HBV/HDV or study intervention.
r. The medical resource utilization data will include: (1) number and type of medical visits, (2) number (proportion) of participants requiring hospitalization and duration of hospitalization, and (3) number and character of diagnostic and therapeutic tests and procedures (inpatient and outpatient). For more details, refer to Section 8.9, Medical Resource Utilization.
s. Quantitative HBeAg assessment will be performed throughout the study in participants who are HBeAg-positive at screening. In participants who are HBeAg-negative at screening, quantitative HBeAg testing should only be performed starting from the first qualitative HBeAg test result being positive.
t. To be performed only in case of early discontinuation.
u. Procedures not applicable per Protocol Amendment 5.

2. INTRODUCTION

HBV/HDV Co-infection

Hepatitis B virus (HBV) is a small deoxyribonucleic acid (DNA) virus that specifically infects the human liver. It consists of a nucleocapsid in which the viral DNA is packed by the hepatitis B core protein (HBc) surrounded by a membranous envelope containing hepatitis B surface antigen (HBsAg). The acute phase of the infection (typically less than 6 months) is either followed by an immune controlled state (spontaneous cure from the infection) or progression to chronic hepatitis B (CHB) (persistence of the virus over more than 6 months). Chronic HBV infection may lead to serious illnesses such as liver cirrhosis and decompensation, and hepatocellular carcinoma (HCC), often with fatal outcome.[26]

Hepatitis D virus (HDV) is a small single-stranded ribonucleic acid (RNA) virus. HDV requires HBsAg to form infectious viral particles and therefore can only occur as a co-infection or super-infection in HBsAg-positive CHB patients. Chronic HDV infection is considered the most severe form of chronic viral hepatitis. Chronic HDV infection is life-threatening and debilitating in the long-term as it can lead to cirrhosis, liver failure, and HCC.[7] HDV infection is associated with more rapid progression of liver disease as well as increased frequency of HCC.[25] The mechanism in which HDV causes more severe hepatitis and a faster progression of fibrosis than with HBV alone remains unclear.[27]

At least 13% of people with chronic HBV infection are co-infected with HDV, resulting in a total of 48-60 million people infected with HDV worldwide.[17] However, prevalence might be underestimated due to limited testing and unreliable tests in older studies. A recent meta-analysis reported a worldwide HBV/HDV co-infection prevalence of 62-72 million.[5] Areas of high HDV prevalence include Eastern and Mediterranean Europe, the Middle East, Central and North Asia, the Amazon basin, and parts of Africa.[5] In the EU, HDV infection affected approximately 4 in 10,000 people in 2015. This was equivalent to approximately 205,000 people and is within the limits to qualify for orphan disease in the EU, which is set at 5 people in 10,000.[19] HDV prevalence is thought to be relatively low in the United states (US) overall, but may be increased in certain subpopulations, such as injecting drug users and people born or having lived in countries where the disease is endemic. Population-based data from the UN Population Division World Population Prospects 2019 and the WHO Global Hepatitis Report 2017 estimated that the anti-HDV antibody prevalence among US born adults in the US is 0.04% and the prevalence of HBsAg 0.7%.[21] Based on the low prevalence in the US with <200,000 persons affected,[18] hepatitis D is considered an orphan disease. Therefore, drug products in development for the treatment of HDV infection may be eligible for an orphan drug designation.[10]

Two types of HDV infection are defined according to the WHO: acute hepatitis due to co-infection and superinfection.[27]

- Acute hepatitis: simultaneous infection with HBV and HDV can lead to a mild-to-severe or even fulminant hepatitis, but recovery is usually complete and development of chronic hepatitis D (CHD) is rare (less than 5% of acute hepatitis).
- Superinfection: HDV can infect a person already chronically infected with HBV. The superinfection of HDV on chronic HBV accelerates progression to a more severe disease in 70% 90% of patients (all ages). HDV superinfection accelerates progression to cirrhosis almost a decade earlier than HBV mono-infected persons, although HDV suppresses HBV replication.

At present there are no drugs approved for the treatment of chronic HDV infection. Pegylated interferon-alpha (PegIFN-α) is used in chronic HDV infection but is associated with significant toxicity and tolerability is poor in patients with decompensated cirrhosis. Treatment with PegIFN-α results in "sustained" virologic response rates (defined as undetectable HDV RNA levels 6 months after treatment) of 25%-30%.[8,25] However, late virologic relapses after achieving "sustained" virologic response are common following treatment with PegIFN-α, and it is not known if HDV sustained clearance can be achieved in the setting of persistent HBsAg positivity.[13] Although currently available HBV therapies are effective in suppressing HBV replication, the rate of HBsAg reduction and/or loss remains low.[22] In the absence of HBsAg loss, HDV infection may persist. Therefore, therapies directly targeting HBsAg are expected to be of clinical benefit for hepatitis D treatment as well.[23]

Suppression of HDV replication in combination with normal alanine aminotransferase (ALT) levels are the primary goals of HDV treatment since this has been shown to lead to improved clinical outcome.[3] Consistent with this, the recent US Food and Drug Administration (FDA)'s draft guidance on the treatment of chronic HDV infection recommends the following as surrogate endpoint and primary endpoint for pivotal studies: a decline in virologic replication (eg, serum HDV RNA target not detected [TND] and/or HDV RNA decline of >2 $\log_{10}$ IU/mL from baseline) and an improvement in associated liver inflammation as evidenced by biochemical response (eg, normal ALT).[24]

For the most comprehensive nonclinical and clinical information regarding JNJ-73763989 (JNJ-3989), refer to the latest version of the Investigator's Brochure (IB) for JNJ-3989.

The term "study intervention" throughout the protocol, refers to JNJ-3989 or placebo, and nucleos(t)ide analog (NA).

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

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

2.1. Study Rationale

Infection with HDV leads to a chronic liver disease for which no effective treatment is approved. HDV infection only occurs in the context of co-infection with HBV as it requires the presence of HBsAg for HDV to form infectious viral particles.

There is a high unmet medical need for patients co-infected with HBV and HDV since co-infection is associated with earlier development of liver cirrhosis, increased risk for development of HCC and increased liver-related and overall mortality compared to HBV mono-infected. At present there are no drugs approved for the treatment of chronic HDV infection. The currently available therapeutic options for HDV infection are suboptimal and untreated patients have a rapid progression of disease.

JNJ-3989 is a small interfering RNA (siRNA) specifically engineered to silence all HBV viral products including HBsAg derived from HBV covalently closed circular DNA (cccDNA) and from HBV genes integrated in the host genome. In the Phase 1/2a Study AROHBV1001 with HBV mono-infected patients, administration of JNJ-3989 has been associated with a significant decline in HBsAg with 3 monthly doses. Ongoing studies are evaluating longer administration of JNJ-3989 in combination with NA with or without JNJ-56136379 (an orally administered capsid assembly modulator).

Reduction of HBsAg levels directly via JNJ-3989 is expected to lead to a reduced number of infectious HDV particles and less de novo infections ultimately leading to inhibition of HDV RNA replication. Suppressing HDV RNA replication, the primary treatment goal in this study, is associated with the normalization of liver enzymes and histological improvement of liver disease which is expected to improve clinical outcomes.

2.2. Background

2.2.1. Primary Pharmacology

JNJ-3989 is a 2:1 molar mixture of 2 synthetic, double-stranded, N-acetylgalactosamine (GalNac) conjugated RNAi triggers (JNJ-73763976 and JNJ-73763924, 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 (pre-genomic ribonucleic acid [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-73763924) 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-73763976), 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.

Since HBsAg is required for replication of HDV, by allowing HDV to infect new cells, reducing HBsAg levels is anticipated to lead to inhibition of HDV replication.

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.

2.2.2. Nonclinical Studies

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 (SC) 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 SC injection at 30 up to 300 mg/kg. In the 24- or 37-week studies, JNJ-3989 was administered once weekly for the first month, followed by once monthly thereafter at 30 up to 180 mg/kg. JNJ-3989 was well tolerated in these studies.

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

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

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

A second 24-week study in rats identified adverse findings: foci of cellular alteration in liver; likely rat-specific; poorly differentiated injection site sarcoma, possibly spontaneous and/or associated with repeated injections at the same location. These are not expected to translate to humans. The animal-to-human exposure ratios are shown in Table 1.

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 SC injection site. Findings included Kupffer cell basophilia/hypertrophy in the liver, vacuolated macrophages in the lymph nodes, and macrophage infiltrates in the injection site. Partial reversibility was observed for these findings. This likely represented the distribution, accumulation, and clearance of JNJ-3989 and was considered not to be adverse due to the low severity and/or nature of the findings. These are commonly described findings for N-acetylgalactosamine-conjugated RNAi.[16] A non-adverse minimally increased ALP activity was observed at 180 mg/kg without a microscopic correlate. The NOAEL in the monkey was considered to be the highest dose tested, ie, CCI mg/kg in the 37-week study.

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

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

The pre- and postnatal development study in rats showed no effects on pre- and postnatal development, including no effects on sexual maturation, neurobehavioral assessments, or reproductive performance of the F1 offspring at doses up to 120 mg/kg/administration. There was negligible placental and/or lactational transfer.

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 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 NOAELs from the 24-week studies in rat and the 37-week study in monkey, respectively, and human exposures after a dose of 200 mg JNJ-3989 every 4 weeks (Q4W) in chronic HVB-infected participants (73763989HPB2001) (Table 1), refer to the latest IB[15] for the most comprehensive results.

For rats, when combining the findings of the two 24-week studies, the most conservative NOAEL over both studies is retained for calculations. This resulted in an NOAEL in male rats of C mg/kg, based on adverse findings at CCI mg/kg in the second 24-week study and a clean C mg/kg dose in the first 24-week study, and an NOAEL in female rats of C mg/kg, based on adverse findings at C mg/kg in the second 24-week study, and a clean C mg/kg dose in the first 24-week study.

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

		Sex	NOAEL (mg/kg)	C_{max} (ng/mL)	AUC_{0-24h} (ng·h/mL)	Ratio Total Concentration C_{max} A/H Ratio	Ratio Total Concentration AUC A/H Ratio
JNJ-73763976	Human exposure[a]	1.031	CCI	-		-	
	24-week rat[c]	M		23,500	199,000	22.8	12.0
		F		12,200	31,400	11.8	1.9
	37-week monkey[c]	M		73,200	1,230,000	71.0	74.2
		F		65,800	988,000	63.8	59.6
JNJ-73763924	Human exposure[a]	212		-		-	
	24-week rat[b]	M		14,400	124,000	67.9	39.3
		F		7,780	20,600	36.7	6.5
	37-week monkey[c]	M		21,600	383,000	101.9	121.3
		F		23,000	392,000	108.5	124.1

[a] Q4W (Week 4, 8, 12 and 16) dose of 200 mg of JNJ 73763989 in chronic HBV infected participants (Study 73763989HPB2001).
[b] Once weekly dosing for 5 weeks, followed by once monthly dosing up to a total of 24 weeks.
[c] Once weekly dosing for 5 weeks, followed by once monthly dosing, up to a total of 37 weeks.
AUC_{0-24h} area under the plasma concentration time curve from administration to 24 h; A/H ratio animal/human ratio;
F female; M male; Q4W every 4 weeks; NOAEL: no observed adverse effect level; C_{max}: maximum plasma concentration.

2.2.3. Clinical Studies

At the time of data cut-off for IB Edition 7 (15 February 2023)[15], JNJ-3989 was being evaluated in several clinical studies. Four Phase 1 studies were completed in different study populations: healthy adult Japanese participants (Study 73763989HPB1001), adult participants with or without hepatic impairment (Study 73763989HPB1002), healthy adult Chinese participants (Study 73763989HPB1004), and healthy adult participants (PK and relative bioavailability, Study 73763989HPB1005). One Phase 1/2a study (Study AROHBV1001) in healthy adult participants and in participants with CHB was also completed. Two Phase 2 studies were completed in participants with CHB (Study 73763989HPB2001 [REEF-1] and Study 73763989PAHPB2002 [REEF-2]). In total, 107 healthy, 546 CHB participants, and 8 participants with moderately impaired hepatic function have been dosed with JNJ-3989 in the completed Studies AROHBV1001, 73763989HPB1001, 73763989HPB1002, 73763989HPB1004, 73763989HPB1005, 73763989HPB2001, and 73763989PAHPB2002.

At the time of data cut-off for IB Edition 7, clinical activities were ongoing in 3 Phase 1/1b studies: PK in participants with or without renal impairment (Study 73763989HPB1003), safety and tolerability of different formulations in healthy participants (Study 73763989HPB1008), and efficacy in participants with CHB (OSPREY) (Study 73763989PAHPB1006). Four Phase 2 studies were ongoing in adult CHB participants: INSIGHT (Study 73763989HPB2003), REEF-IT (Study 73763989PAHPB2005), PENGUIN (Study 73763989PAHPB2006), and OCTOPUS-1 (Study 73763989PAHPB2008). One Phase 2 study was ongoing in CHB/CHD co-infected participants: REEF-D (Study 73763989HPB2004).

JNJ-3989 was generally safe and well tolerated with no deaths. The majority of serious adverse events (SAEs) were considered not related to the study intervention. Adverse events (AEs) leading

to study intervention discontinuation were infrequent. Most AEs and laboratory abnormalities were distributed across all dose levels and also occurred on placebo treatment.

At the time of initial protocol writing, efficacy was assessed using snapshot data through 26 March 2020. Antiviral activity data were available for 56 CHB participants who received 3 SC injections of 25 to 400 mg JNJ-3989 every 4 weeks. The antiviral activity data showed that administration of JNJ-3989 at doses of 25 to 400 mg resulted, on average, in pronounced HBsAg decline which was generally sustained at least until Day 168 (ie, 16 weeks after last dose) across all doses. No apparent dose response was observed at doses between 100 and 400 mg JNJ-3989; a 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. Refer to the latest IB[15] for the most recent efficacy data.

Part 1 REEF-D Study Data (Study 73763989HPB2004)

Of the 22 participants with CHD enrolled into Part 1 of the REEF-D study, 17 were randomized to treatment with JNJ-3989 100 mg + NA and 5 were randomized to placebo + NA. The predefined antiviral activity criteria to start Part 2 of the study (at least 8 JNJ-3989 treated participants with ≥0.5 log reduction from baseline in HBsAg and HDV RNA and 4 of those with ≥1 log reduction in HDV RNA) were met.

The second interim analysis (IA) was performed when all Part 1 participants (N 22) had reached Week 48 or later, or discontinued earlier.

REEF-D Safety Data at Week 48 for Part 1

At Week 48, 6/17 (35.3%) participants in the JNJ-3989 + NA arm were reported with a Grade ≥3 AE.

Adverse events were considered related to JNJ-3989 by the investigator in 11/17 (64.7%) participants who received JNJ-3989 + NA treatment.

Among the adverse events of special interest (AESIs) defined in the study protocol, ALT/AST elevations were reported in 13/17 (76.5%) participants in the JNJ-3989 + NA arm and no participants in the placebo + NA arm. For 2 of these 13 participants, the ALT elevation criteria according to the protocol were not met nor the discontinuation criteria for JNJ-3989. One additional participant met the ALT elevation criteria and discontinued JNJ-3989, but the event was not reported as an AE.

During follow-up, 4/11 (36.4%) participants in the JNJ-3989 + NA arm reported treatment-emergent AEs, which were AESIs (ie, ALT/AST elevations).

No deaths were reported. Two (11.8%) participants in the JNJ-3989+NA arm experienced 3 SAEs: ALT increased and AST increased in 1 (5.9%) participant, and transaminases increased in 1 (5.9%) participant, which lead to withdrawal from study drug.

Twelve of 22 (54.5%) participants enrolled in Part 1 experienced ALT elevations on treatment up to the 48-week timepoint; all 12 were treated with JNJ-73763989 + NA. These ALT elevations were Grade 3 in 5 participants and Grade 4 in 7 participants. The mean (SD) change from baseline was 5.6 (80.05) U/L. The majority of these ALT elevations had a peak of ALT between 120 and 650 U/L. A single case marked a peak of 1,162 U/L, which showed levels below 1,000 U/L on confirmatory tests. None of the participants with ALT elevations showed signs of decreased hepatic function, but 1 participant showed clinical symptoms of epigastric pain, nausea and vomiting for 4 days during the peak of ALT elevation. Management of these acute elevations was following protocol-defined criteria. Some of the cases showed a prolonged pattern of ALT elevation for which no management criteria were provided in the protocol at the time of the event.

No clinically significant safety ECG or vital sign findings were observed.

REEF-D Efficacy Data at Week 48 for Part 1

In all JNJ-3989-treated participants, treatment with JNJ-3989 led to reductions in HBsAg, and subsequently, HDV RNA.

At Week 48, 4/17 (23.5%) participants in the JNJ-73763989 + NA and none in the NA arm achieved the primary composite endpoint of HDV RNA decline from baseline of ≥2 log10 IU/mL (or undetectable) and normal ALT. Among the 5 participants without ALT elevations in the JNJ-73763989+NA arm, 4/5 (80.0%) participants achieved the primary composite endpoint, of which 2/5 (40.0%) participants had HDV RNA <LLOQ.

2.3. Benefit-risk Assessment

More detailed information about the known and expected benefits and risks of JNJ-3989 can be found in the IB.[15]

2.3.1. Risks for Study Participation

2.3.1.1. Known Risks

Overall, JNJ-3989 administration was generally safe and well tolerated in the completed and ongoing studies, all of which (except REEF-D) are in CHB patients or healthy participants.

2.3.1.2. Potential Risks

All therapies have the potential to cause adverse experiences.

Patients with positive HDV RNA, 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 HDV RNA, HBV DNA, and/or HBsAg.

ALT elevations are considered an important potential risk for JNJ-3989. Two distinct patterns of ALT elevations have been observed in participants receiving JNJ-3989: a rapidly rising and resolving ALT elevation or a more sustained pattern of ALT elevation. During Parts 1 and 2 of this study, the latter has been observed in HBV/HDV co-infected participants, when receiving JNJ-3989 compared to placebo. In Part 2 of this study, the risk of confirmed ALT elevations was higher in participants with HBsAg levels >10,000 IU/mL at screening or baseline. A causal relationship between JNJ-3989 and ALT elevations is suspected. However, the mechanism for this type of confirmed ALT elevations seen with JNJ-3989 in treatment of patients with HBV/HDV co-infection is not yet understood.

The participants who are randomized to the deferred active treatment arm, could also be at increased risk for liver disease progression during the 52 weeks of placebo + NA treatment.

Participants who are HBV DNA suppressed are at risk for hepatitis B reactivation if NA treatment is discontinued. Reactivation of hepatitis B is defined by a sudden increase in HBV-DNA replication in participants with previously inactive CHB (resolved HBV infection or virologically suppressed). Although HBV reactivation can occur spontaneously, it can be triggered by immunosuppressive therapy (for autoimmune diseases or in the transplant setting), diseases associated with an immunocompromised state (cancer, human immunodeficiency virus infection), or the withdrawal of antiviral drugs.

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 cytochrome P450 (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. Hematologic abnormalities and injection site reactions (ISRs) are AESIs for JNJ-3989 and are routinely monitored in clinical trials. Other toxicities that are also monitored in this study as AESIs include renal complications and events related to cholesterol increase.

Viral Resistance

Treatment with JNJ-3989 may lead to viral resistance. This viral resistance is not expected to impact the treatment with other siRNAs. Using JNJ-3989 in combination with ETV, tenofovir alafenamide (TAF), or tenofovir disoproxil is expected to minimize the risk of emerging resistant viral variants.

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

2.3.1.3. Risks Due to Study Procedures

Potential Risks and Inconvenience Associated with the Optional Liver Biopsy Procedures

Percutaneous core liver biopsies and fine needle aspiration biopsies (FNABs) will be performed during this study for research purposes only in participants who consented separately to this procedure. Liver biopsies will be collected only in sites and in selected countries where this is feasible, and after all relevant approvals are in place and operational set-up is completed.

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

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

2.3.2. Benefits for Study Participation

2.3.2.1. Known Benefits

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

2.3.2.2. Potential Benefits

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

Reduction of HBsAg levels directly via JNJ-3989 is expected to result in a reduced number of infectious HDV particles and less de novo infections ultimately leading to inhibition of HDV replication. Treatment with JNJ-3989 in combination with NAs might lead to HBsAg seroclearance which could result in complete elimination of HDV (ie, cure). Reduced and complete inhibition of HDV replication, is associated with the normalization of liver enzymes and histological improvement of liver disease which is expected to improve clinical outcomes.

In addition, the combination of JNJ-3989 and NAs is expected to intensify suppression of HBV replication compared to NA alone, by further downregulating the levels of the HBV proteins and pgRNA, the precursor of viral relaxed circular DNA. The inhibition of HBV proteins, including HBsAg, may allow a restoration of the host immune response and could lead to sustained HBsAg seroclearance (ie, functional cure for HBV).

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 clinical studies is considered favorable for the following reasons:

- Overall, JNJ-3989 administration was safe and well tolerated in completed and ongoing studies, all of which (except REEF-D) are in CHB patients or healthy participants.

- Events of Special Interest are significant AEs that are judged to be of special interest because of clinical importance, known class effects or based on nonclinical signals. Events of Special Interest that will be carefully monitored during the study include ISRs, ALT/AST elevations, renal complications, hematologic abnormalities, and events related to cholesterol increase (Section 8.3.6, Adverse Events of Special Interest and Section 8.2.4, Clinical Safety Laboratory Assessments). In addition, the following toxicities will also be carefully monitored: rash and acute systemic allergic reactions (Section 8.3.6, Adverse Events of Special Interest).

- Continued careful assessment of the safety, efficacy, and PK during treatment is included in this study.

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

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

        - Participants with liver cirrhosis are not eligible for Part 2 of the study.

        - Additional criteria based on HBsAg and HDV RNA levels will be used for Part 2 to reduce the risk of ALT/AST elevations on-treatment.

    - 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.

    - Restriction of placebo + NA treatment to 52 weeks.

    - Inclusion of treatment discontinuation criteria for signs of hepatic decompensation (see Section 7.1).

- Individuals showing signs of decreasing liver function during study conduct will discontinue treatment with JNJ-3989/placebo and alternative treatment options outside the study will be considered in discussion with the sponsor.

- 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, body weight, and body temperature), height (only at screening), and electrocardiograms (ECGs) will be recorded throughout the study. Physical examinations will be performed and AEs will be assessed (see Section 8.2, Safety Assessments). Events of Special Interest will be closely monitored (Section 8.3.6, Adverse Events of Special Interest).

- An Independent Data Monitoring Committee (IDMC) will be established for continuous monitoring of SAEs, AEs leading to discontinuation, and ALT flares to ensure the continuing safety of the participants enrolled in the current study (see Section 9.5.3, Independent Data Monitoring Committee). When all participants are in the open-label phase or discontinued earlier, the IDMC responsibilities will be covered by the internal Data Review Committee (DRC) (see Section 9.5.4, Internal Data Review Committee). In addition, an Independent Flare Expert Panel (IFLEP) will be appointed to characterize and adjudicate each ALT flare (see Section 9.5.6, Independent Flare Expert Panel).

- All participants will continue NA treatment until the last study visit (including the visit in follow-up phase for Part 1 and Part 2). NA will be provided as study medication until the end of the study. Before Protocol Amendment 5, in case of confirmed HBsAg seroclearance, ALT <3x ULN, and HBV DNA < lower limit of quantitation (LLOQ) in non-cirrhotic participants, NA treatment may be discontinued upon discussion with the sponsor. NA treatment should be restarted as specified in Section 6.5, Re-treatment With NA During the Follow-up Phase. Per Protocol Amendment 5, NA treatment will be continued in all participants in Part 2 until the last study visit.

- JNJ-3989 will be administered using a proper SC technique to decrease the risk of ISRs. ISRs will be managed as outlined in Section 8.3.6, Adverse Events of Special Interest.

- Following local standard practice, the biopsy location will be identified with ultrasound (which will also be used to rule out contraindicating conditions for a biopsy). Prior to any on-treatment biopsy, a recent (≤1 week) coagulation and hematology panel are required (pre-biopsy visit) to ensure normal platelet count and normal coagulation parameters. Prior to the baseline or off-treatment biopsies, blood coagulation and platelet count will be assessed according to local practice. Site selection will be based on their experience in the performance of core liver biopsies and FNABs.

- Unblinding of the Part 2 double-blind phase laboratory data for HDV RNA and HBsAg data (Day 1 to Week 48 visit) per investigator's request at any time prior to Week 48 visit to the investigator, in case this is required for medical/clinical patient management.

- Unblinding of the double-blind phase in Part 2 for treatment allocation and all laboratory data including HDV RNA and HBsAg data (Day 1 to Week 48 visit) when a participant has completed the Week 48 visit or discontinued earlier, to the investigator, site personnel, sponsor, and participants.

- In Part 2, participants with HBsAg values >10,000 IU/mL at screening or baseline, who were assigned to Arm 1 (placebo), will not roll-over to the open-label phase and will enter the follow-up phase (see Section 7.1).

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

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate on-treatment efficacy against HDV of JNJ-3989 + NA regimen compared to NA alone.	• Proportion of participants with HDV RNA ≥2 $\log_{10}$ IU/mL decline from baseline or HDV RNA TND in combination with normal ALT at Week 48.
Key Secondary	
To evaluate on-treatment efficacy of the JNJ-3989 + NA regimen in suppressing HDV replication as measured by HDV RNA.	• Proportion of participants with HDV RNA ≥2 $\log_{10}$ IU/mL decline from baseline or HDV RNA TND at Week 48.
To evaluate efficacy of the JNJ-3989 + NA regimen on liver inflammation during study intervention phase.	• Proportion of participants with normal ALT at Week 48.
To evaluate the efficacy of the JNJ-3989 + NA regimen in terms of HBsAg response.	• Proportion of participants with HBsAg seroclearance at Week 48.
To evaluate the efficacy of the JNJ-3989 + NA regimen on liver fibrosis.	• Proportion of participants with ≥2 kPa reduction from baseline in liver stiffness measurement (LSM) assessed by vibration-controlled transient elastography (VCTE) (FibroScan) at Week 48.
Other Secondary	
To evaluate the efficacy of the JNJ-3989 + NA regimen during study intervention phase and follow-up phase.	• Proportion of participants with HDV RNA ≥2 $\log_{10}$ IU/mL decline from baseline or HDV RNA TND in combination with normal ALT.

Objectives	Endpoints
	• Proportion of participants with HDV RNA ≥2 $\log_{10}$ IU/mL decline from baseline in combination with normal ALT. • Proportion of participants with HDV RNA TND in combination with normal ALT. • Proportion of participants with HDV RNA ≥2 $\log_{10}$ IU/mL decline from baseline or HDV RNA TND. • Proportion of participants with HDV RNA ≥2 $\log_{10}$ IU/mL decline from baseline. • Proportion of participants with HDV RNA TND. • Proportion of participants with normal ALT. • Time to reach HDV RNA ≥2 $\log_{10}$ IU/mL decline or HDV RNA TND. • Changes from baseline in HDV RNA. • Changes from baseline in ALT.
To evaluate the safety and tolerability of the study intervention throughout the study.	• Proportion of participants with incidences of (S)AEs and abnormalities in clinical laboratory tests (including hematology, blood biochemistry, blood coagulation, urinalysis, urine chemistry, and renal biomarkers), 12-lead ECGs, vital signs, and physical examination.
To evaluate the efficacy of the JNJ-3989 + NA regimen as measured by HBV blood markers (such as HBsAg, HBeAg*, HBV DNA) during study intervention and follow-up.	• Proportion of participants with HBsAg seroclearance and/or seroconversion. • Change from baseline over time in HBsAg, HBeAg*, HBV DNA. • Proportion of participants with HBsAg, HBeAg*, and/or HBV DNA levels or changes from baseline below/above different cut-offs. • Time to reach efficacy thresholds such as HBsAg <1 IU/mL.
To evaluate the frequency of HBV virologic breakthrough throughout the study.	• Proportion of participants with HBV DNA virologic breakthrough.
To evaluate changes in liver fibrosis during study intervention and follow-up.	• Proportion of participants with ≥2 kPa reduction from baseline in LSM assessed by VCTE (FibroScan). • Change from baseline in LSM over time assessed by VCTE (FibroScan).
To evaluate the anti-HDV efficacy during the follow-up phase.	• Proportions of participants with sustained HDV response off-treatment post end of JNJ-3989 treatment.

Objectives	Endpoints
	• Proportions of participants with HDV relapse post end of JNJ-3989 treatment.
To evaluate the anti-HBV efficacy during the follow-up phase.	• Proportions of participants with sustained HBV response off-treatment post end of JNJ-3989 treatment. • Proportions of participants with HBV flare (virologic, biochemical, and clinical) post end of treatment.
Exploratory	
To explore the relationship between PK parameters (JNJ-3989) and selected pharmacodynamic (PD) parameters of efficacy and/or safety, as applicable.	• Relationship between various PK parameters (JNJ-3989) and selected efficacy and/or safety endpoints, as applicable.
To explore the relationship between HBsAg and HDV RNA.	• Correlation between HBsAg decline and HDV RNA levels/changes.
To explore the impact of the viral and host baseline characteristics on safety and efficacy.	• Correlation of viral and host baseline characteristics (such as HBV/HDV genotype, baseline HBV DNA levels, baseline HDV RNA levels, age, sex, body mass index [BMI]) with selected efficacy and safety variables.
To explore the effect of any baseline variation in the HBV and HDV (if feasible) genome on efficacy.	• Correlation of HBV and HDV genome sequence with selected efficacy parameters.
To explore changes in the HBV and HDV (if feasible) genome sequence during study intervention and follow-up.	• Emergence of intervention-associated mutations.
To explore efficacy as measured by HBV RNA and HBcrAg during study intervention and follow-up.	• Changes from baseline in HBV RNA and HBcrAg levels. • Time to reach undetectability of HBV RNA and HBcrAg.
To explore HBV-specific T-cell responses during study intervention. **	• Changes from baseline in peripheral blood T-cell responses.
To explore medical resource utilization (MRU) to manage participants during study intervention and follow-up.	• Number and type of medical visits. • Number (proportion) of participants requiring hospitalization and duration of hospitalization (total days length of stay, including duration by wards; eg, ICU). • Number and character of diagnostic and therapeutic tests and procedures.

Objectives	Endpoints
To explore liver viral responses during study intervention.***	• Changes from baseline in intrahepatic viral parameters (such as HDV RNA, HDAg, cccDNA, pgRNA, intrahepatic RNA, or HBsAg in terms of copy number, or number of positive cells). • Changes from baseline in intrahepatic cccDNA. • levels and transcriptional activity (pgRNA/cccDNA ratio).
To explore liver immune responses during study intervention.***	• Changes between baseline and on-treatment liver biopsy in intrahepatic immune response (eg, CD45+ T-cells, CD4+ T-cells, CD8+ T-cells, Natural Killer cells, and dendritic cells) in terms of proportion of cells, cell types, and spatial redistribution
To explore the relationship of intrahepatic markers with blood markers (immune and viral).	• Association between levels and changes in intrahepatic and blood markers.

* in HBeAg-positive participants only
** Peripheral blood mononuclear cell (PBMC) samples for immune analyses will be collected at selected sites only and as operationally feasible
*** If sufficient number of participants contribute to the liver biopsy collection

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

HYPOTHESIS

The original protocol had as primary hypothesis that the combination regimen of JNJ-3989 + NA is more efficacious than NA treatment alone in reducing HDV replication and improving the associated liver inflammation, as measured by the primary efficacy endpoint, the proportion of participants with HDV RNA decline ≥2 $\log_{10}$ IU/mL from baseline or HDV RNA TND in combination with normal ALT at Week 48. Due to the decision to stop enrollment at 30 participants in Part 2 of the study, the statistical analyses will be descriptive.

4. STUDY DESIGN

4.1. Overall Design

This is a 2-part, Phase 2, randomized, double-blind, placebo-controlled, parallel, multicenter, interventional study with deferred active treatment to investigate the efficacy, safety, and PK of JNJ-3989 + NA in participants co-infected with HBV and HDV.

The study consists of 2 parts:

- Part 1 will evaluate the safety, tolerability and antiviral activity of JNJ-3989 + NA in a small number of participants (N 20), prior to enrolling a larger number of participants in Part 2. The primary aim of Part 1 is to assess if the antiviral activity criteria to start Part 2 are met.
- Part 2 (N 30) will evaluate the safety and efficacy of the JNJ-3989 + NA regimen in the treatment of HBV/HDV co-infection.

  Note that Part 2 of the study will only be initiated once the antiviral activity criteria in Part 1 have been met, and if the results of Part 1 IA1 (when all participants of Part 1 have completed at least Week 16 or discontinued earlier) support initiation of Part 2 (see Section 9.5). The antiviral activity criteria are defined in the statistical analysis plan (SAP). Participants in Part 1 may not participate in Part 2.

In total for Part 1 and Part 2, 50 participants were planned to be enrolled, specifically with a target of 20 participants in Part 1 and 30 participants in Part 2. The minimum number of participants to be enrolled will be 20 if futility is observed and Part 2 is not initiated.

The conclusions of the study will be described separately on data from Part 1, Part 2, and pooled from Part 1 and Part 2 together (if applicable).

An IDMC will be established for continuous monitoring of SAEs, AEs leading to discontinuation, and ALT flares. In addition, the IDMC will support the Sponsor Committee in assessing whether there is early evidence supporting antiviral activity criteria of JNJ-3989 + NA in reducing HDV replication measured by HDV RNA reduction. Before Part 1 IA1, the Sponsor Committee, who is not directly involved in the study conduct, will be involved in the unblinded review of selected efficacy and safety parameters to decide when to trigger the start of Part 2. At the time of the Part 1 IA1 (when all participants of Part 1 have completed at least Week 16 or discontinued earlier), the sponsor, including the Sponsor Committee, will become unblinded to the Part 1 data. Once Part 2 has commenced, all sponsor personnel, including the Sponsor Committee, will remain blinded to subsequent IDMC data review during the double-blind phase. During the open-label phase, all data will be unblinded. When all participants are in the open-label phase or discontinued earlier, the IDMC responsibilities will be covered by the DRC (see Sections 9.5.4 and 10.3.6).

Before Protocol Amendment 5, Part 1 and Part 2 include 3 identical phases:

- a 4-week screening phase (may be extended up to a maximum of 8 weeks[a]),
- a 144-week study intervention phase (Arm 1) and 148-week study intervention phase (Arm 2). The first 52 weeks of the intervention phase are double-blind followed by 92 and 96 weeks of open-label treatment for participants in Arms 1 and 2, respectively.
- a 48-week follow-up phase.

Per Protocol Amendment 5, Part 2 will include modified phases after screening:

- a 4-week screening phase (may be extended up to a maximum of 8 weeks[a]),
- for both Arm 1 and Arm 2, the double-blind 52 weeks of intervention will be followed by an open-label phase of at least 48 weeks of JNJ-3989 for all participants, including for those participants who were randomized to placebo in the intervention phase. Arm 1 will have a total minimum of 96-week intervention and Arm 2 a total minimum of 100-week intervention.
- a reduced follow-up phase (at least 24 weeks):
  - for participants who have reached FU Week 24 or later when Protocol Amendment 5 is in effect, the EOS assessments will be scheduled at the next planned visit; *OR*
  - for participants who have not reached FU Week 24 (including participants in the open-label phase) when Protocol Amendment 5 is in effect, they will enter a 24-week follow-up phase.

The duration of individual study participation will be between 196 and 204 weeks for Part 1 and between 124 and 204 weeks for Part 2.

Before Protocol Amendment 5, at Week 144 (Arm 1) and Week 148 (Arm 2), treatment with JNJ-3989 will be stopped in both parts. After Protocol Amendment 5 is in effect, treatment with JNJ-3989 will be stopped in Part 2 at the next planned visit (ie, EOT), but not earlier than Week 96 (Arm 1) and Week 100 (Arm 2).

Participants who complete treatment with JNJ-3989 at the end of the open-label phase[b] in Part 1 and Part 2 will be closely monitored for transaminase flares and for HBV/HDV recurrence during the follow-up phase.

Before Protocol Amendment 5, for non-cirrhotic patients, NA treatment should be continued until the last study visit (including the visit at the follow-up phase) unless confirmed HBsAg seroclearance, ALT <3x ULN, and HBV DNA <LLOQ is observed, in which case NA treatment

[a] If necessary (eg, for operational reasons), the screening phase may be extended up to a maximum of 8 weeks on a case-by-case basis and in agreement with the sponsor. Depending on the duration of the screening phase, selected screening assessments may have to be repeated prior to enrollment.

[b] At Week 144 (Arms 1) or Week 148 (Arms 2) in Part 1 and Part 2 before Protocol Amendment 5; at Week 96 or later (Arm 1) or Week 100 or later (Arm 2) in Part 2 after Protocol Amendment 5.

may be discontinued upon discussion with the sponsor. For cirrhotic patients, NA treatment should be continued during the entire follow-up phase according to treatment guidelines. In the event of signs of decreasing liver function, HBeAg seroconversion among participants who had previously experienced HBeAg loss, post-treatment increases in HBV DNA >2,000 IU/mL and ALT >5x ULN, or post-treatment increases in HBV DNA >20,000 IU/mL, NA treatment will be restarted for the non-cirrhotic participants who stopped NA treatment after confirmed HBsAg seroclearance, ALT <3x ULN, and HBV DNA <LLOQ (see Section 6.5, Re-treatment With NA During the Follow-up Phase).

Per Protocol Amendment 5, NA treatment will be continued in all participants in Part 2 until the last study visit (including visit in the follow-up phase).

Part 1

Approximately 20 participants co-infected with HBV and HDV will be randomized in a 4:1 ratio to Arms 1 or 2.

- Arm 1: 100 mg JNJ-3989 (SC injection Q4W) + NA once daily (qd) for 144 weeks (n 16; immediate active treatment arm);
- Arm 2: placebo for JNJ-3989 (SC injection Q4W) + NA qd for 52 weeks, followed by 100 mg JNJ-3989 (SC injection Q4W) + NA qd for 96 weeks (n 4; deferred active treatment arm).

NA nucleos(t)ide analog ETV, tenofovir disoproxil, or TAF. NA treatment is continued or started from Day 1 in both arms.

Part 2

Part 2 of the study will be initiated since the antiviral activity criteria in Part 1 have been met, and the results of Part 1 IA1 (when all participants of Part 1 have completed at least Week 16 or discontinued earlier) support initiation of Part 2. Cirrhotic participants will be excluded from participation in Part 2 of the study.

Approximately 30 participants co-infected with HBV and HDV will be randomized in a 4:1 ratio to Arms 1 or 2.

- Arm 1: 100 mg JNJ-3989 (SC injection Q4W) + NA qd for at least 96 weeks (approximately, n 24; immediate active treatment arm);
- Arm 2: placebo for JNJ-3989 (SC injection Q4W) + NA qd for 52 weeks, followed by 100 mg JNJ-3989 (SC injection Q4W) + NA qd for at least 48 weeks (approximately, n 6; deferred active treatment arm).

NA ETV, tenofovir disoproxil, or TAF. NA treatment is continued or started from Day 1 in both arms.

Study Details

In total across both Part 1 and Part 2, a target of approximately 50 participants, aged ≥18 to 65 years, co-infected with HDV and HBV will be enrolled in this study. If Part 2 is not initiated, the number of participants will be approximately 20.

Patients with HBV/HDV co-infection will be eligible regardless of HBeAg status and treatment history. Patients with compensated cirrhosis are only allowed to be enrolled in Part 1 of this study. Cirrhotic patients will be excluded from participation in Part 2 of the study.

Randomization will be stratified by:

- presence of compensated cirrhosis at screening (yes or no) (Part 1 only),
- HDV RNA testing laboratory location (China versus outside of China) (Note: All sites in China will utilize the laboratory testing in China and all sites in other countries will utilize the laboratory outside of China), and
- HBeAg status at screening (positive versus negative).

In those countries/sites where HDV testing is not part of standard of care, possible study candidates can be prescreened for HDV testing (HDV RNA and/or anti-HDV antibody) after signing a prescreening informed consent form (ICF). Results will be reviewed by the investigator to confirm if they could qualify for study participation.

Participants will be considered to have completed the study if they have completed the assessments of the end of study (EOS) visit as defined in Section 4.4.

Following assessments will be included in both parts of the study: blood sampling: efficacy (eg, HDV RNA, HBsAg, HBeAg, HBV DNA), safety (eg, AEs, laboratory abnormalities, ECGs), PK, PK/PD, viral genome sequencing/genotyping, immune analyses, HLA haplotyping, exploratory biomarker, and pharmacogenomic analyses (see Section 8).

A pharmacogenomic blood sample will be collected from participants who consent separately to this component of the study (see Section 8.7, Host Genetics).

Medical resource utilization will be assessed (see Section 8.9).

Clinical outcomes such as death, cirrhosis decompensation, or liver transplantation will be captured.

The primary analysis of this study will be performed when all participants in the study (both parts if Part 2 has started) have reached Week 48 or have discontinued earlier.

The investigators, participants, and all site personnel will remain blinded to study intervention allocation until a participant has completed the Week 48 visit or has discontinued earlier. When a participant has completed the Week 48 visit or discontinued earlier, the investigator, site personnel, sponsor, and participant will be unblinded for treatment allocation and all laboratory data, including HDV RNA and HBsAg data. After Week 48, it will be communicated to the investigators whether the participant was allocated to either the immediate active treatment (Arms 1) or the deferred active treatment (Arms 2) to allow that the participant follows the correct visit schedule during the open-label phase (see Section 1.3.2, Schedule of Activities Open-label Study Intervention Phase (Weeks 52 EOT)).

In case of premature discontinuation of JNJ-3989/placebo before the end of the study intervention phase (ie, Week 144 [Arms 1] or Week 148 [Arms 2] in both parts before Amendment 5 and Week 96 or later [Arm 1] or Week 100 or later [Arm 2] in Part 2 after Amendment 5), participants will have an early withdrawal visit and will enter the follow-up phase as specified in Section 1.3.3, unless they withdraw consent.

In addition to the IDMC and internal DRC, an IFLEP will be appointed (see Sections 9.5.6 and 10.3.6).

In case a participant withdraws consent before completing the study, the reason (if known) should be documented. Participants who withdraw consent will be offered an optional safety follow-up visit 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 withdrawal visit.

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.

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

4.2. Scientific Rationale for Study Design

Study Population

Patients with HBV/HDV co-infection will be eligible regardless of HBeAg status and treatment history.

Patients with compensated cirrhosis will only be enrolled in Part 1 of this study. Patients with cirrhosis will be excluded from Part 2 of the study.

Blinding

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

Randomization and Stratification

Randomization will be performed using a 4:1 ratio (immediate active treatment, ie, Arm 1: deferred active treatment, ie, Arm 2), regardless of the study part, to minimize bias in the assignment of participants to intervention arms, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment arms, and to enhance the validity of statistical comparisons across intervention arms.

The randomization ratio was determined to balance statistical efficiency considerations with high unmet medical needs, patients' perspectives, acceleration of the decision making based on an early signal of antiviral activity to expand enrollment to a larger sample, and clinical and operational feasibility considerations related to an orphan disease.

Randomization will be stratified by the presence of compensated cirrhosis at screening (yes or no, Part 1 only), HDV RNA testing laboratory location (China versus outside of China), and HBeAg status at screening (positive versus negative) in order to provide an evenly balanced representation across the 2 arms.

Deferred Active Arms

To characterize efficacy and safety of the investigational treatment regimen, the study includes a double-blind comparison of JNJ-3989 versus placebo on the background of NA treatment. Participants on placebo will be switched to active JNJ-3989 treatment at Week 52. Participants in both intervention arms will continue with JNJ-3989 + NA until Week 144 (Arm 1) and Week 148 (Arm 2) for Part 1 and until at least Week 96 (Arm 1) and Week 100 (Arm 2) for Part 2 in an open-label fashion. The deferred active treatment design allows all participants in the study to receive the JNJ-3989 + NA regimen while allowing for a valid comparison with placebo + NA and a rigorous quantitative assessment of the treatment effect.

NA Treatment

All participants will receive NA treatment (ie, ETV, tenofovir disoproxil, or TAF) during the entire treatment period to maximize the resistance barrier of the regimen and to ensure complete HBV suppression since reduction in HDV replication can be associated with increased HBV replication. Before Protocol Amendment 5, for non-cirrhotic patients, NA treatment should be continued until the last study visit (including the visit in the follow-up phase) unless confirmed HBsAg seroclearance, ALT <3x ULN, and HBV DNA <LLOQ is observed in which case NA treatment may be discontinued upon discussion with the sponsor. For cirrhotic patients, NA treatment should be continued during the entire follow-up phase according to treatment guidelines. Per Protocol Amendment 5, NA treatment will be continued in all participants in Part 2 until the last study visit.

Providing the NA already in the deferred active arm from Day 1 onwards increases the validity and robustness of the comparisons and ensures that NA will be given to all patients who have an indication for NA treatment (ie, patients with cirrhosis and/or patients with detectable HBV DNA). This approach is consistent with other HDV studies.

Host DNA and Biomarker Collection

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

Biomarker samples will be collected to allow evaluation of the mechanism of action of JNJ-3989 + NA or help to explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to a treatment. The goal of the biomarker analyses is to evaluate the safety, efficacy, and PK of study intervention and HBV infection or to develop assays for study intervention or HBV/HDV infection.

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

Liver Biopsy

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

Both core liver biopsies and FNABs will be optionally collected at selected sites for high dimensional profiling of the liver tissue. The core biopsies will allow characterization of the infected hepatocytes compartment and phenotyping of the major immune cell populations (proportion of cells and spatial distribution). The liver tissue may be used to assess HDV and HBV markers in the liver such as, but not limited to HDAg and HDV RNA, HBsAg, pgRNA, total intracellular HBV RNA and DNA, and HBcAg. Changes in the quantity and potentially changes in the spatial distribution of these markers under JNJ-3989 treatment will be assessed. Viral genome (RNA or DNA) sequencing of the samples as well as assessment of HBV viral transcripts and HBV DNA integrants in the host genome may be performed. This will also allow to compare viral parameters assessed in the liver with viral parameters in the blood compartment.

FNABs may be profiled by single-cell transcriptomics approaches to better understand the innate and adaptive immune cells composition and functional status[11] (very few hepatocytes are expected to be collected with fine needle aspirates). Hepatitis B virus-specific T-cells will be one of the main targeted cell populations, detected and sorted by multimers binding assays. Downstream transcriptomic profiling of collected HBV specific T-cells may be performed by T-cell receptor sequencing and RNA sequencing.

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

4.2.1. Study-specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled. Written consent may be obtained through various sources (eg, paper or electronic such as eConsent, eSignature, or digital signature) as determined by regulations as well as study and/or participant preferences.

At the time of protocol writing, there is no approved treatment for HBV/HDV co-infection. Therapies that efficiently decrease HBsAg levels in patients with HBV/HDV co-infection, eg, JNJ-3989, are expected to lead to suppression or inhibition of the HDV replication (as measured by reduction of HDV RNA in blood). Complete suppression (ie, seroclearance) of HBsAg is expected to lead to a sustained control of the HDV infection, either in response to chronic suppression by continued treatment or by achieving HBV functional cure after completion of therapy.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study (less than standard blood donation based upon recommendations of the World Health Organization [WHO], ie, 450 mL ± 10% for participants weighing at least 50 kg over a period of 12 weeks for male participants and 16 weeks for female participants) (Section 8.1)[2].

4.3. Justification for Dose

100 mg Q4W JNJ-3989 will be administered SC. Treatment with JNJ-3989 (given as 3 SC injections Q4W) has shown substantial reduction in HBsAg in the Phase 1/2a first in-human Study AROHBV1001. No difference in tolerability and safety was noted between the different JNJ-3989 doses in the AROHBV1001 study. No apparent dose response in terms of HBsAg decline was observed at doses between 100 and 400 mg JNJ-3989, suggesting that maximal HBsAg reduction in this short-term study is reached with those doses. A slightly reduced mean decline in HBsAg was observed at the lower doses of 25 mg and 50 mg. Given the absence of a dose response from 100 to 400 mg in the AROHBV1001 study and the extended treatment period of 144 weeks in a population including participants with compensated cirrhosis, the 100 mg dose has been selected for this study.

4.4. End of Study Definition

End of Study Definition

The end of study (EOS) is considered as the last visit (in the follow-up phase 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.

Participant Study Completion Definition

Part 1

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

Part 2

Before Protocol Amendment 5, a participant will be considered to have completed the study if he or she has completed EOS assessments at Week 48 of the follow-up phase (ie, EOS visit at FU Week 48).

After Protocol Amendment 5, a participant will be considered to have completed the study if he or she has completed the EOS assessments assigned per Protocol Amendment 5:

- Participants who have not reached FU Week 24 (including those in the open-label phase) when Protocol Amendment 5 is in effect will enter the 24-week follow-up phase with EOS visit scheduled at FU Week 24.
- Participants who have reached FU Week 24 or later when Protocol Amendment 5 is in effect will receive the EOS assessments scheduled at the next planned visit (ie, EOS visit at FU Week 30 or later).

5. STUDY POPULATION

Screening for eligible participants will be performed within 4 weeks before administration of the study intervention. If necessary, eg, for operational reasons, the screening phase may be extended up to a maximum of 8 weeks on a case-by-case basis and in agreement with the sponsor. Depending on the duration of the screening phase, selected screening assessments may have to be repeated prior to enrollment.

In those countries/sites where HDV testing is not part of standard of care, possible study candidates can be prescreened for HDV testing (HDV RNA and/or anti-HDV antibody) after signing a prescreening ICF. Results will be reviewed by the investigator to confirm if they could qualify for study participation.

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

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

5.1. Inclusion Criteria

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

1. male or female (according to their reproductive organs and functions assigned by chromosomal complement).

2. Criterion modified per Amendment 1

   2.1. 18 (or the legal age of consent in the jurisdiction in which the study is taking place, provided that the legal age of consent is ≥18 years) to 65 years of age, inclusive.

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

4. must have:

   - chronic hepatitis B infection either HBeAg positive or HBeAg negative and either receiving NA treatment or no NA treatment. Chronic HBV infection documented by serum HBsAg positivity at screening. In addition, chronicity must be documented by serum HBsAg positivity at least 6 months prior to screening or alternative markers of chronicity (HBeAg positivity or HBV DNA positivity at least 6 months prior to screening)
   - chronic HDV infection documented by positive HDV antibodies or HDV RNA at screening. In addition, chronicity must be documented by positive HDV antibodies or HDV RNA at least 3 months prior to screening.

5. Criterion modified per Amendment 3

   5.1

   a) For Part 1: must have HDV RNA values at screening ≥1,000 IU/mL.
   b) For Part 2: must have HDV RNA values at screening ≥500 IU/mL, and must have HBsAg values at screening ≤10,000 IU/mL.

      Note: if HBsAg values are >10,000 IU/mL, the participant can only be enrolled in case HDV RNA values at screening are ≤100,000 IU/mL.

6. Criterion modified per Amendment 1

   6.1. must have ALT levels >ULN and <10x ULN at screening.

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

8. Criterion modified per Amendment 1

   8.1 Criterion modified per Amendment 3

   8.2 Criterion modified per Amendment 4

   8.3. must have presence or absence of compensated cirrhosis (Part 1) based on:

   a. No cirrhosis: LSM <12.5 kPa by VCTE (FibroScan) within 6 months prior to screening or at the time of screening or liver biopsy within 1 year prior to screening, OR

   b. Cirrhosis: LSM ≥12.5 kPa by VCTE (FibroScan) within 6 months prior to screening or at the time of screening or liver biopsy within 1 year prior to screening; and a Child-Pugh score A at screening.

   Must have absence of cirrhosis (Part 2) based on:

   c. LSM <12.5 kPa by VCTE (FibroScan) or histologic exclusion of cirrhosis (core liver biopsy) within 6 months prior to screening or at the time of screening. In case of discordant results, the biopsy readout will be taken for assessment of eligibility.

   Note: If FibroScan is not available, acoustic radiation force impulse (ARFI) may be used at screening if standard practice at the site or if otherwise validated and agreed with the sponsor.

   Note: Conventional imaging procedures (eg, conventional liver ultrasound, computed tomography [CT] or magnetic resonance imaging [MRI]) and serum marker panels are not acceptable for exclusion of cirrhosis.

9. must sign an ICF indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

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

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

12. a woman must be (as defined in Section 10.8, Appendix 8, Contraceptive and Barrier Guidance)

    a. Not of childbearing potential

    b. Of childbearing potential and practicing a highly effective, preferably user independent method of contraception (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 the end of relevant systemic exposure.

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

13. a woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of 90 days after the last dose of study intervention.

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

15. a male participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum 90 days after receiving the last dose of study intervention.

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

17 Criterion added per Amendment 3

must provide separate consent if he or she agrees to provide an optional liver biopsy sample (only in sites and in selected countries where this is feasible, and after all relevant approvals are in place and operational set-up is completed) in Part 2 of the study. Refusal to give consent for the optional liver biopsy sample does not exclude a participant from participation in the study.

5.2. Exclusion Criteria

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

1. Criterion modified per Amendment 3

   1.1 Participants with evidence of hepatitis A virus infection (hepatitis A antibody immunoglobulin M [IgM]), hepatitis C virus (HCV) infection (HCV antibody), or hepatitis E virus (HEV) infection (hepatitis E antibody IgM), or human immunodeficiency virus type 1 (HIV-1) or HIV type 2 (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 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.
   - 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.

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

   a. Total bilirubin >1.7x ULN,

   b. Direct bilirubin >1.4x ULN,

   c. Prothrombin time >1.3x ULN,

   d. Serum albumin <3.2 g/dL.

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

   Note: Participants with uncomplicated splenomegaly may be enrolled after consultation with the sponsor.

4. Criterion modified per Amendment 3

   4.1 Child-Pugh score B or C at screening (Part 1) and liver cirrhosis at screening (Part 2).

5. evidence of liver disease of non-HDV or non-HBV etiology. This includes but is not limited to hepatitis virus infections mentioned in exclusion criterion 1, drug- or

alcohol-related liver disease, autoimmune hepatitis, hemochromatosis, Wilson's disease, α-1 antitrypsin deficiency, primary biliary cholangitis, primary sclerosing cholangitis, Gilbert's syndrome (mild cases are allowed, see exclusion criterion 2a), or any other non-HBV/HDV or non-viral liver disease considered clinically significant by the investigator.

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

7. Criterion modified per Amendment 3

7.1 Criterion modified per Amendment 4

7.2 One or more of the following laboratory abnormalities at screening as defined by the Division of Acquired Immunodeficiency Syndrome (DAIDS) Toxicity Grading Scale:

a. Estimated glomerular filtration rate (eGFR) ≥grade 3 (ie, <60 mL/min/1.73 m^2) at screening, calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula,
b. Total amylase ≥grade 3,
c. Lipase elevation ≥grade 3,
d. Hemoglobin ≤10.9 g/dL (males), ≤10.4 g/dL (females),
e. Platelet count ≤100,000/μL (Part 1),

   Platelet count ≤140,000/μL (Part 2)
f. Alpha-fetoprotein (AFP) >100 ng/mL,
g. Any other laboratory abnormality considered to be clinically significant by the investigator.

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

8. hemoglobin A1c >8% at screening.

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

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

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

12. 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.

13. any history of or current clinically significant skin disease requiring regular or periodic treatment.

14. history of clinically relevant drug rash.

15. known allergies, hypersensitivity, or intolerance to JNJ-3989 or its excipients (refer to the IB).[15]

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

17. taken any disallowed therapies as noted in Section 6.7, Concomitant Therapy before the planned first dose of study intervention.

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

19. received anti-HDV treatment (investigational or approved) and/or anti-HBV treatment (investigational or approved IFN treatment) within 6 months before the planned first dose of study intervention.

20. female participants who are pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study or within 90 days after the last dose of study intervention.

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

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

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

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

24. 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.

25. vulnerable participants (eg, incarcerated individuals, individuals under a legal protection measure).

26. alcohol or drug abuse within 12 months of screening, judged by the investigator to likely interfere with clinical assessments.

Additional exclusion criteria for optional liver biopsy:

27 Criterion added per Amendment 3

Participants with presence of coagulopathy or bleeding disorder as indicated by

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

b. Partial thromboplastin time >1.1x ULN;

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

28 Criterion added per Amendment 3

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

29 Criterion added per Amendment 3

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

30 Criterion added per Amendment 3

Participants with history of amyloidosis.

31 Criterion added per Amendment 3

Participant refusal to accept blood transfusions.

32 Criterion added per Amendment 3

Participants who use anticoagulants or antiplatelet aggregating agents that cannot be paused prior to the liver biopsy procedures (as described in Section 6.7, Concomitant Therapy).

NOTE: Investigators must 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 must be excluded from participation in the study. Section 5.4, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

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

1. Refer to Section 6.7, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

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

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study site contact for completeness. When available, the investigator may generate screening and enrollment logs directly from an interactive web response system (IWRS).

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

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

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Interventions Administered

Description of Interventions

Intervention Name	JNJ-3989	Placebo for JNJ-3989	ETV monohydrate	Tenofovir disoproxil	TAF[a]
Type	Drug	Drug	Drug	Drug	Drug
Dose Formulation	Solution for injection	Solution for injection	Film-coated tablets	Film-coated tablets	Film-coated tablets
Unit Dose Strength(s)	200 mg/mL	0.9% saline	0.5 mg	245 mg	25 mg
Dosage Regimen	100 mg Q4W	Q4W	0.5 mg qd Lamivudine-refractory participants: 1 mg[b] qd (but should preferably be treated with tenofovir disoproxil or TAF instead)	245 mg qd	25 mg qd
Route of Administration	Subcutaneous injection (in the abdomen)	Subcutaneous injection (in the abdomen)	Oral	Oral	Oral
Use	Investigational intervention	Investigational intervention	Background intervention	Background intervention	Background intervention
IMP and NIMP	IMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Each unit will be labeled with unique medication ID number	Each unit will be labeled with unique medication ID number	Commercial supplies will be sourced and a clinical study label applied	Commercial supplies will be sourced and a clinical study label applied	Commercial supplies will be sourced and a clinical study label applied
			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

ETV: entecavir; ID: identification; IMP: Investigational Medicinal Product; JNJ 3989: JNJ 73763989; NA: nucleos(t)ide analog; NIMP: Non investigational Medicinal Product; Q4W: once every 4 weeks; qd: once daily; TAF: tenofovir alafenamide

[a] In countries where TAF is commercially available, it will be one of the NA treatment options.

[b] 2 tablets of 0.5 mg

Virologically suppressed participants who are already being treated with ETV, tenofovir disoproxil, or TAF at screening, will continue their current NA treatment. Participants who are not receiving any HBV treatment at screening will receive tenofovir disoproxil during the 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 for all participants after consultation with the sponsor.

Study intervention administration must be captured in the source documents and the case report form (CRF). Study-site personnel will instruct participants on how to store study intervention (NA) for at-home use as indicated for this protocol. JNJ-3989 will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.[15]

For a definition of study intervention overdose, refer to Section 6.6, 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.

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

Study intervention must be handled in strict accordance with the protocol and as indicated on 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 such as used ampules, needles, syringes and vials containing hazardous liquids, must be disposed of immediately in a safe manner and therefore will not be retained for intervention accountability purposes.

Study intervention must 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. An intermediate study intervention compliance check is not considered to be a re-dispensing. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study interventions are provided in the Site Investigational Product Procedures Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 intervention arms of each part of the study with ratio 4:1 (JNJ-3989 + NA: placebo + NA) based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor.

The randomization will be balanced by using randomly permuted blocks and will be stratified by the presence of compensated cirrhosis at screening (yes or no, Part 1 only), HDV RNA testing laboratory location (China versus outside of China), and HBeAg status at screening (positive versus negative). The IWRS will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant participant details to uniquely identify the participant.

Blinding

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

The investigators, participants, and all site personnel will remain blinded to study intervention allocation until a participant has completed the Week 48 visit or has discontinued earlier. When a participant has completed the Week 48 visit or discontinued earlier, the investigator, site personnel, sponsor, and participants will be unblinded for treatment allocation and all laboratory data, including HDV RNA and HBsAg data. After Week 48, it will be communicated to the investigators whether the participant was allocated to either the immediate active arm (Arm 1) or the deferred active arm (Arm 2) to allow that the participant follows the correct visit schedule during the open-label phase (see Section 1.3.2, Schedule of Activities Open-label Study Intervention Phase (Weeks 52 EOT)).

As of Week 52 and up and until the end of the study intervention phase, study intervention will be administered in open-label fashion to all participants and efficacy results (eg, HDV RNA and HBsAg data) will be reported to the sites.

The Sponsor Committee will be unblinded to treatment allocation in the initial exploration of the antiviral activity criteria in up to 16 participants randomized in Part 1, based on aggregate interim data of HDV RNA and/or individual HDV RNA profiles and HBsAg data where the individual participant identification will be masked. This is to assess whether the evaluation of antiviral activity on a small number of participants warrants to expand enrollment to the remaining 30 participants (start of Part 2).

At the time of Part 1 IA1 (when all participants of Part 1 have completed at least Week 16 or discontinued earlier), sponsor personnel and members of the IFLEP will become unblinded to the Part 1 data. However, as soon as Part 2 commences, all sponsor personnel, including the Sponsor Committee, and the members of the IFLEP remain blinded to subsequent IDMC data reviews during the double-blind phase. During the open-label phase, all data will be unblinded (see Section 9.5). Study site personnel, investigators, participants, and operational sponsor team members involved with the sites will have no access to any of the evaluations performed by either the sponsor or the IDMC. For safety-related decisions, HDV RNA and HBsAg data may be discussed with investigators on a case-by-case basis.

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

In case of IWRS participant unblinding and if the investigator requires to be unblinded in case of an emergent safety event (ie, study intervention discontinuation due to ALT flares) to allow further treatment of the participant, a sponsor request can be made to have the investigator and sponsor unblinded to all HDV RNA and HBsAg data from the double-blind phase.

During the blinded study treatment phase, HBV/HDV RNA, HBsAg, HBeAg, HBcrAg, anti-HBs, and anti-Hbe antibody tests cannot be done locally.

6.4. Study Intervention Compliance

Preparation of JNJ-3989/placebo, including the necessary blinding, will be performed by an unblinded preparer. JNJ-3989/placebo will be administered as a SC injection by the blinded administrator.

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

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

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

- 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.

  Note: All missed injections and significant delays should be discussed with the sponsor.

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

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

Per Protocol Amendment 5, NA treatment will be continued in all participants in Part 2 until the last study visit.

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

6.5. Re-treatment With NA During the Follow-up Phase

Participants who complete treatment with JNJ-3989 at the end of the open-label phase[a] in Part 1 and Part 2 will be closely monitored for transaminase flares and for HBV/HDV recurrence during the follow-up phase.

Before Protocol Amendment 5, NA treatment should be continued during the entire follow-up phase according to treatment guidelines for cirrhotic patients. For non-cirrhotic patients, NA treatment should be continued until the last study visit (including the visit in the follow-up phase) unless confirmed HBsAg seroclearance, ALT <3x ULN, and HBV DNA <LLOQ is observed, in which case NA treatment may be discontinued upon discussion with the sponsor.

[a] At Week 144 (Arms 1) or Week 148 (Arms 2) in Part 1 and Part 2 before Protocol Amendment 5; at Week 96 or later (Arm 1) or Week 100 or later (Arm 2) in Part 2 after Protocol Amendment 5

Per Protocol Amendment 5, NA treatment will be continued in all participants in Part 2 until the last study visit (including visit in the follow-up visit).

6.5.1. Re-treatment With NA

Amongst the non-cirrhotic participants who stop treatment with NA, NA treatment will be restarted if any of the following criteria are met:

- If there are signs of decreasing liver function based on laboratory findings (INR or direct bilirubin) or clinical assessment.
- HBeAg seroreversion among participants who had previously experienced HBeAg loss.
- Post-treatment values of HBV DNA >2,000 IU/mL and ALT >5x ULN
- Post-treatment values of HBV DNA >20,000 IU/mL.

Earlier restarting of NA treatment is at the investigator's discretion, even if the above criteria are not met yet.

Per Protocol Amendment 5, NA treatment will be continued in all participants in Part 2 until the last study visit (including visit in the follow-up phase).

6.6. Treatment of Overdose

For this study, any dose of JNJ-3989 exceeding the protocol-specified dose with ≥ 25% (refer to Section 6.1) will be considered an overdose. Any dose of NA greater than the prescribed dose (refer to Section 6.1) will be considered an overdose.

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

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities.
- Obtain a plasma sample for PK analysis as soon as possible from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.
- Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

6.7. Concomitant Therapy

Pre-study therapies administered up to 30 days before first dose of study intervention, as well as any prior IFN use, must be recorded at screening. If applicable, the participant's last anti-HBV and/or anti-HDV treatment prior to screening must also be recorded.

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

Note that locally approved COVID-19 vaccines (including those that received emergency use authorization or conditional marketing authorization) are allowed throughout the study.

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 prescribing information for more details.

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

An overview of disallowed medication is provided in Table 2.

Table 2: Disallowed Medication

Disallowed at any time prior to screening until end of follow-up[a]:
• Any oligonucleotide-based treatment (eg, siRNA, nucleic acid polymers, and antisense oligonucleotides), other than the study intervention taken in the context of this study.
Disallowed from 6 months prior to screening until end of follow-up[a]:
• Any anti-HBV/HDV drug (including vaccines, interferons) other than the study intervention taken in the context of this study. **Note:** Study intervention taken in the context of this study (ETV, TD, TAF) is allowed. Prior hepatic treatment with herbal or nutritional products is also allowed but should be stopped at screening. • 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: For investigational COVID-19 vaccines administered within 6 months prior to screening, an exception will be made as long as the vaccine has been approved (or received emergency use authorization or conditional marketing authorization) at the time of screening.
Disallowed from 6 months prior to baseline until end of follow-up[a]:
• 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 1 month prior to screening until end of follow-up[a]:
• Any medication that reduces renal function or competes for active tubular secretion (eg cimetidine, probenecid, quinidine).

Table 2: Disallowed Medication
Disallowed from screening until end of follow-up[a]:
• 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.
[a] Refer to Section 4.1 for the end of follow-up definition before and after Protocol Amendment 5.

Note: The list of disallowed 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.

Note: Anticoagulants are to be used with caution. Aspirin and other antiplatelet aggregating agents are allowed. Further restrictions apply to participants undergoing optional liver biopsy procedures. Antiplatelet aggregating agents should be paused at least 9 days prior to liver biopsy procedures or according to local standard practice.

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

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

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's investigational study intervention (JNJ-3989/placebo) **must** be discontinued if any of the criteria listed below apply. In those cases, NA treatment should be continued.

- The participant withdraws consent to receive study intervention.
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study intervention.
- The participant becomes pregnant.
- The participant has a ≥grade 3 rash (see Section 10.5, Appendix 5, Rash Management) or allergic reaction (see Section 8.3.6.3).
- The participant has signs of hepatic decompensation (ie, clinical evidence of ascites, bleeding varices, or hepatic encephalopathy) or an increase in direct bilirubin >1.5x ULN in combination with INR ≥1.5x ULN or albumin <3.0 g/dL. In this case 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 estimated glomerular filtration rate (eGFR) abnormality and a drop from baseline of >10 mL/min/1.73 m^2, considered at least possibly related to JNJ-3989 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 anytime, according to the prescribing information. (see Section 8.3.6.4).
- The participant has a confirmed QTcF prolongation (defined as a QTcF value of >500 ms, or an increase from baseline of >60 ms) at any given time point.
- The participant requires treatment with any of the disallowed medications listed in Section 6.7 and does not intend to discontinue treatment with the disallowed medication.
- The participant has confirmed HBV virologic breakthrough (ie, confirmed on-treatment HBV DNA increase by >1 log_{10} IU/mL from nadir or confirmed on-treatment HBV DNA level >200 IU/mL in participants who had HBV DNA level <LLOQ of the HBV DNA assay). In case of virologic breakthrough, changing the NA should be considered in consultation with the sponsor. Injection with JNJ-3989 will be stopped if the NA change does not result in a decrease in HBV DNA levels.
- The participant has ALT/AST elevations, as described in Section 8.3.6.1, Intervention-emergent ALT/AST Elevations.
- Per IDMC recommendation, in Part 2, the participants with HBsAg values >10.000 IU/mL at screening or baseline, who were assigned to Arm 1 (placebo), will not roll-over to the open-label phase and will enter the follow-up phase.
- The participant of the placebo group should discontinue study intervention (cannot start JNJ-3989 in the open-label phase in Part 2, Arm 2) if he/she develops cirrhosis at the end of the double-blind phase (based on the Week 48 FibroScan assessment).

If a participant discontinues study intervention for any reason before the end of the double-blind phase, end-of-intervention assessments must be obtained. The participant will enter the follow-up phase and complete the follow-up schedule unless the participant withdraws consent. Participants who withdraw consent will be offered an optional safety follow-up visit (see Section 1.3). Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant.

7.2. Participant Discontinuation/Withdrawal From the Study

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

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

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

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

Withdrawal of Consent

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

7.2.1. Withdrawal From the Use of Research Samples

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

- The collected samples will be retained and used in accordance with the participant's original separate informed consent for optional research samples.
- The participant may withdraw consent for optional research samples and may request destruction of the previously collected samples, in which case the samples will be destroyed and will not be used further. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

Withdrawal from the Optional Research Samples While Remaining in the Main Study

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

Withdrawal from the Use of Samples in Future Research

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

7.3. Lost to Follow-up

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

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

All ECG assessments should preferably be conducted/completed before any tests, procedures, or other consultations for that visit to prevent influencing participant perceptions.

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

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

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

The maximum amount of blood drawn from each participant in this study and during the follow-up phase will not exceed 3,210 mL. Note that with the removal of several sample collections, the amount of blood drawn, and the total blood volume needed will be less.

Note: The total blood volume to be collected from each participant may vary, depending on several factors (eg, treatment arm, unscheduled re-tests, re-sampling, individual and country/territory variations). The maximum amount will only be reached for those participants who participate in the collection of PBMC samples, and DNA sampling and who are treated within the study for the maximal study duration of 148 weeks plus maximum 48 weeks of follow-up. This amount does not include the local laboratory collection of samples required for the optional liver biopsy or any local laboratory safety follow-up as the blood volume taken for these analyses will depend on the local laboratory used.

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

For participants in China, some exploratory assessments may not be collected.

Sample Collection and Handling

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

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

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

Study-specific Materials

The investigator will be provided with the following supplies:

- IB and any addenda for JNJ-3989,
- Prescribing Information for ETV, tenofovir disoproxil, and TAF,
- Pharmacy manual/study site investigational product and procedures manual,
- Laboratory manual,
- IWRS Manual,
- CRF Completion Guidelines,
- Sample ICF,
- Participant diaries.

8.1. Efficacy Assessments

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

HDV RNA will be quantified at central testing laboratory locations (China versus outside of China) using a validated commercially available in vitro nucleic acid amplification tests for the quantification of HDV RNA. Samples may be processed in real-time or could be analyzed in batch.

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

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

HBV DNA results will be provided to the investigator and the sponsor from screening until the end of follow-up.

It is the responsibility of the investigator:

- To monitor HBV DNA results and ensure that investigational intervention is discontinued in participants with virologic breakthrough (see Section 7.1).

For each participant, the post-baseline HDV RNA, HBsAg, HBeAg, HBcrAg, anti-HBs, and anti-Hbe antibody testing results from the Week 52 visit onwards will be provided to the investigator for managing the participant's safety. For Part 1, the sponsor will be unblinded to Part 1 data from the moment of data unblinding for Part 1 IA1 onwards. For Part 2, the sponsor will be blinded until the Week 52 visit. For safety-related decisions, Part 1 HDV RNA and HBsAg data may be discussed with investigators on a case-by-case basis. When a participant has completed the Week 48 visit or discontinued earlier, the investigator, site personnel, sponsor, and participant will be unblinded for treatment allocation and all laboratory data, including HDV RNA and HBsAg data.

Liver stiffness measurements will be performed by VCTE (FibroScan) to determine changes in the liver fibrosis.[1,4]

Samples may be used by the sponsor for additional exploratory assessments analyzing the serologic and virologic characteristics of HBV or HDV infection (including semi-quantitative anti-HDV IgM antibodies) and efficacy or safety of the study intervention. During the blinded study treatment phase, HBV/HDV RNA, HBsAg, HBeAg, HBcrAg, anti-HBs, and anti-HBe antibody tests cannot be done locally.

8.1.1. HBV and HDV Genotyping and Sequencing

HBV genotyping will be performed at baseline using a Line Probe Assay (LiPA assay) and/or sequence-based method. HDV genotyping will be performed at baseline using sequence-based methods.

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

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

Sequence analyses of the HDV genome might be performed.

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

8.1.2. Core Liver Biopsy and Fine Needle Aspirate Biopsy (Optional with Separate Consent, Part 2 Only)

Liver biopsies will be collected only in sites and in selected countries where this is feasible, and after all relevant approvals are in place and operational set-up is completed.

If participants in Part 2 of the study agree to undergo an optional liver biopsy, percutaneous core liver biopsies and FNABs will be performed preferentially at the time points indicated in the Schedule of Activities (Week 0 and Week 24). Percutaneous core liver biopsies will be prioritized over FNAB if only one sample can be collected.

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

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

Intrahepatic viral and host markers may be evaluated over time. Viral markers for HDV and HBV in the liver such as, but not limited to, total intracellular HDV RNA and HDAg, HBV RNA and DNA, HBeAg, HBsAg, and HBcAg. Changes in the quantity and potentially changes in the spatial distribution of these markers under therapy may be assessed. Viral genome(s) or transcript sequencing/analyses as well as assessment of HBV integrants in the host genome may be performed.

Intrahepatic virologic status at baseline and response to treatment will be assessed with a range of methods. HDV RNA may be assessed by RT-PCR based methods. Hepatitis B virus cccDNA levels may be assessed using quantitative polymerase chain reaction (qPCR) methods on a single cell level using laser capture microdissection or bulk analyses. The exact protocol of cccDNA measurement will be determined based on the latest method available considering the performance characteristics and the validation status of the assay. Quantification of intracellular pre-genomic HBV RNA can be used to determine transcriptional activity of HBV cccDNA by assessing the ratio of pgRNA levels over cccDNA levels. Immunostaining approaches (for example for HBsAg, HBcAg, HDAg) and in situ hybridization approach (HBV RNA, HDV RNA) may be applied to evaluate the proportion of positive cells in each sample.

Intrahepatic immune status at baseline and in response to treatment may be assessed. Both innate and adaptive immune compartment will may be characterized, by measuring the relative number of specific cells and the expression of functional markers in each cell population using various single cell approaches, such as single cell transcriptomics in FNABs and immunofluorescence staining, and transcriptomics and proteomics profiling in core needle biopsies. Depending on the latest platform developments (spatial transcriptomics, *in situ* sequencing approaches, etc.) methods for immune cells characterization might be adjusted.

Hepatitis B virus-specific T-cells, although very rare in FNABs, may be characterized and counted by multimers binding assays, staining, and sorting for positive cells. Downstream profiling of collected HBV-specific T-cells may be performed by T-cell receptor sequencing and RNA sequencing. Infiltrating immune cells will be used for the evaluation of innate and adaptive immune responses, which can be compared to responses in PBMCs.

Immune and virologic markers in the liver and/or changes thereof under therapy will be used to assess association with blood markers and/or treatment response and outcome.

Remaining samples may be used for research on viral and host biomarkers and immune markers at the viral and/or host RNA/DNA, protein, and cell level.

Samples can only be used for research related to JNJ-3989, chronic HBV or HDV infection, or chronic HBV or HDV infection related disease or may be used to develop tests/assays related to JNJ-3989, NA, or chronic HBV or HDV infection. These latter exploratory analyses will be performed at the sponsor's discretion and will always be under the sponsor's supervision.

8.2. Safety Assessments

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

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events, Serious Adverse Events, and Other Safety Reporting and Section 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.

The AESIs in line with the known pharmacological profile of the study intervention (and the drug classes) evaluated in this study are implemented (Section 8.3.6).

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

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

8.2.1. Physical Examinations

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

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

8.2.2. Vital Signs

Temperature (tympanic or oral), body weight, pulse rate, and blood pressure will be assessed.

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

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

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

8.2.3. Electrocardiograms

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

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

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

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

All ECGs will be read and interpreted centrally. Preferably, all ECGs will be read and interpreted under supervision of one and the same qualified person. Only on Day 1, the ECG will also be read locally prior to dosing.

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

8.2.4. Clinical Safety Laboratory Assessments

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

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

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

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

8.2.5. Pregnancy Testing

An FSH test (postmenopausal women) will be performed at screening (Appendix 8). Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

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

Timely, accurate, and complete reporting and analysis of safety information, including AE, SAEs, and product quality complaint (PQC), from clinical studies are crucial for the protection of

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

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

In those countries/sites where HDV prescreening is performed, AEs and serious AEs related to this blood collection procedures, as well as death from any cause, will be collected for 30 days after the prescreening procedure.

Note: All reported AEs will be coded according to MedDRA. In addition, the following coding conventions will be applied for the AEs reported by investigators as specified below:

- AEs reporting ALT flare in relation to laboratory test elevation will be coded to the MedDRA PT Alanine aminotransferase increased.
- AEs reporting reactivation of hepatitis B in participants who are HBV DNA suppressed and have, during the off-treatment period, a sudden HBV DNA increase (virologic flare) will be coded to the MedDRA PT Hepatitis B reactivation.
- AEs reporting viral breakthrough in the context of laboratory data will be coded to the MedDRA PT Viral load increased.

For further details on AEs and SAEs (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as PQCs, refer to Section 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.

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

All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until study discontinuation or 30 days after completion of the participant's last study-related procedure, which may include contact for follow-up of safety. The beforementioned AEs must be recorded on specific AE pages of the CRF. During the 30-day period, SAEs, including those spontaneously reported to the investigator, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel immediately, but no later than 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor immediately, but no later than within 24 hours. The initial and follow-up reports of a SAE should be transmitted electronically or by facsimile (fax).

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

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

Solicited Adverse Events

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

Unsolicited Adverse Events

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

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

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

AEs and the special reporting situation of pregnancy will be followed by the investigator as specified in Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

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

8.3.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form.

Any participant who becomes pregnant during the study must discontinue JNJ-3989.

Follow-up information regarding the outcome of the pregnancy for female participants who become pregnant, or where the pregnancy was the result of a male participant and his partner, and any postnatal sequelae in the infant will be required.

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

8.3.6.1. Intervention-emergent ALT/AST Elevations

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

Any intervention-emergent elevation of ALT and/or AST ≥3x ULN and ≥2x 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 as specified below. Repeat laboratory values should include AFP, ALT, AST, ALP, bilirubin (total and direct), INR, albumin, HBV DNA, and HDV RNA. Additional tests should be considered based on clinical judgement (refer to Section 10.6, Appendix 6: Intervention-emergent ALT/AST Elevations). The confirmatory visit should be scheduled preferably within 3 days of the receipt of the initial ALT/AST results.

Weekly basis monitoring (or more frequently as long as values increase) until ALT/AST levels have returned to <3x ULN or <2x nadir, and if present, liver related symptoms have improved. With ALT and/or AST values ≥3x ULN and ≥2x nadir, visit intervals may be extended to 14 days if values have been stable or decreasing on three consecutive visits. The participant will be monitored (laboratory testing of ALT, AST, ALP, bilirubin [total and direct], INR, albumin,

HBV DNA, and HDV RNA) on a weekly basis or more frequently until ALT and/or AST levels have returned to 50% of the maximal value.

Note: In case of urgency, local laboratory assessments could be considered. In case of IWRS participant unblinding and if the investigator requires to be unblinded in case of an emergent safety event (ie, study intervention discontinuation due to ALT flares) to allow further treatment of the participant, a sponsor request can be made to have the investigator and sponsor unblinded to all HDV RNA and HBsAg data from the double-blind phase. Off-treatment local HDV RNA test can be done to exclude/assess for HDV-driven flare.

Management of intervention-emergent ALT and/or AST elevations:

JNJ-3989 treatment should be stopped, and NA treatment needs to be continued in the following situations:

- Participants with liver cirrhosis:
  - Confirmed ALT/AST elevation >5x ULN and ≥2x nadir
  - ALT/AST elevation ≥3xULN and ≥2x nadir for >4 weeks.
  - If the ALT and/or AST level is ≥3x ULN and ≥2x 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.
- Participants without liver cirrhosis:
  - Confirmed ALT/AST elevation >10x ULN and ≥2x nadir
  - First on-treatment ALT/AST elevation 3 to 5x ULN for >12 weeks
  - Second or following on-treatment ALT/AST elevation 3 to 5x ULN for >4 weeks
  - ALT/AST elevation >5 to 10x ULN for >4 weeks
  - If the ALT and/or AST level is ≥3x ULN and ≥2x 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.

From Week 52 onwards, results of HBsAg and HDV RNA assessment will be reported to the investigators.

Management of flares observed in the follow-up phase after EOT:

In case of ALT flares that are observed during the follow-up phase, repeat laboratory values should include AFP, ALT, AST, ALP, bilirubin (total and direct), INR, albumin, HBV DNA, and HDV RNA. The participant should be monitored on a weekly basis (or more frequently as long as values increase) until ALT and/or AST levels have returned to <3x ULN or <2x nadir. With ALT and/or AST values ≥3x ULN and ≥2x nadir, visit intervals may be extended to 14 days if values have been stable or decreasing on three consecutive visits. For guidance on re-treatment with NA during the follow-up phase, refer to Section 6.5, Re-treatment With NA During the Follow-up Phase.

8.3.6.2. Rash

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

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

Monitoring of the evolution of rash events will be performed as described in Table 3 in Section 10.5, Appendix 5: Rash Management.

When safety blood samples are drawn as per the rash management guidelines, these should be processed by the local laboratory. The following parameters will need to be tested: AST, ALT, sedimentation rate, complete blood cell count (including hemoglobin, hematocrit, red blood cell [RBC] count, white blood cell [WBC] count, differential count [neutrophils, lymphocytes, monocytes, eosinophils, and basophils], and platelet count), and creatinine. Relevant laboratory assessment values are to be shared with the sponsor (if applicable and local regulations allow) as per the “Instructions for Investigators for sharing of Digital Pictures and Local lab reports” and should be de-identified.

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

Injection Site Reactions

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

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

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

8.3.6.3. Acute Systemic Allergic Reactions

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

Participants may continue the intake of study interventions.

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

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

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

Participants may continue the intake of study interventions.

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

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

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

8.3.6.4. Renal Complications

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

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

8.3.6.5. Hematologic Abnormalities

As already mentioned in Section 2.1, JNJ-3989 is also being developed in combination with JNJ-6379.

Mild thrombocytopenia was observed in recently conducted nonclinical 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.

Review of laboratory data in the REEF-1 study showed a low number of hematologic laboratory abnormalities and most were of Grade 1 or Grade 2 severity. Low absolute neutrophil count was most frequently reported in the JNJ-3989 (200 mg) + NA arm (Grade 1: 4 [4.3%] participants and Grade 2: 2 [2.1%] participants). Changes in hemoglobin and platelets in the JNJ-3989 + NA +/- JNJ-6379 arms were comparable to the Placebo + NA arm. Few hematologic laboratory abnormalities were also observed in the REEF-2 study (73763989PAHPB2002), which were balanced between the active and placebo arms. In the Phase 1/2a AROHBV1001 study with JNJ-3989, mild transient thrombocytopenia (Grade 1) was observed in 6 out of 84 participants receiving 3 SC injections of JNJ-3989 alone over a period of up to 12 weeks with background of NAs. The transient thrombocytopenia was not considered clinically significant. No thrombocytopenia or pancytopenia was observed in 12 participants when JNJ-3989 and JNJ-6379 were given in combination over a 12-week period.

As these findings were not clearly attributed to JNJ-3989, JNJ-6379, or the combination of the 2 study interventions, measures for close monitoring of hematological changes during the study are in place.

Any relevant abnormalities in hematologic parameters will be carefully monitored as described below:

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

In case any one of the above criteria are met, a confirmatory visit should be scheduled as soon as possible, preferably within 7 days of the receipt of the initial results. Confirmation of the results will trigger weekly or biweekly (every other week) unscheduled visits until improvement or stabilization of the respective parameter(s). Stabilization is defined as no further significant reduction over 2 consecutive visits.

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

8.3.6.6. Complications From Liver Biopsy

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

8.4. Pharmacokinetics

Sparse PK samples for JNJ-3989 will be collected in all participants according to the Schedule of Activities.

Plasma samples will be used to evaluate the PK of JNJ-3989 (JNJ-73763924 and JNJ-73763976). Plasma collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period, or for analysis of plasma concentrations of co-medications.

8.4.1. Evaluations

Venous blood samples will be collected for measurement of plasma concentrations of JNJ-3989 (JNJ-73763924 and JNJ-73763976), at time points specified in the Schedule of Activities.

8.4.2. Analytical Procedures

Pharmacokinetics

At the sponsor's discretion, a selection of plasma samples will be analyzed to determine concentrations of JNJ-3989 (JNJ-73763924 and JNJ-73763976), 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.

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

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

8.4.3. Pharmacokinetic Parameters and Evaluations

Sparse PK samples for JNJ-3989 will be collected and plasma concentration-time data for JNJ-3989 (JNJ-73763924 and JNJ-73763976) will be analyzed. Data from this study may be combined with data from a selection of Phase 1 and 2 studies via population PK modeling. If performed, the population PK analysis will be described in a separate analysis plan and results will be reported separately.

8.5. Pharmacokinetics/Pharmacodynamics

Relationships of individual PK parameters for JNJ-3989 (JNJ-73763924 and JNJ-73763976) with selected efficacy and/or with selected safety endpoints may be evaluated, if applicable.

8.6. Immune Assessments

At selected sites, PBMC samples for immune analyses will be collected during study intervention and may 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 HBV-specific T-cells that secrete gamma interferon (IFN-γ) in response to a specific antigenic stimulation, whereas ICS determines the frequency of CD4+ and CD8+ HBV T-cells secreting cytokines such as IFN-γ, interleukin (IL)-2 and tumor necrosis factor (TNF)-α in response to a specific antigenic stimulation.

PBMC samples may also be analyzed for HDV-specific responses using ELISpot and ICS after stimulation with HDV-specific antigens.

Additional experiments may be performed to further phenotypically and functionally characterize PBMCs using proliferation or cytotoxic assays or other methods such as cytometry by time of flight to evaluate innate and adaptive immune responses. Leftover PBMC samples may be used at

the sponsor's discretion for additional exploratory research related to HBV or HDV infection or study intervention (safety/efficacy).

Additional PBMC samples may be taken until Week 48 in case of ALT flares, upon discussion with the sponsor, which may require an unscheduled visit.

8.7. Host Genetics

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

An optional pharmacogenomic (host DNA) blood sample may be collected (preferably at baseline) to allow for host pharmacogenomic research, where local regulations permit. Complete host genomic testing may be done to search for links of specific genes to (HBV/HDV-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.

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

8.8. Host Biomarkers

The study includes collection of blood samples for exploratory analysis of host blood biomarkers (eg, cytokines) at the host RNA, protein, and cell level. Exploratory serology samples, which will be collected in all participants at the time points indicated in the Schedule of Activities, may be used for this host serum protein testing.

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

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

8.9. Medical Resource Utilization

Medical resource utilization data, associated with medical encounters, will be collected in the CRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded. The data collected may be used to conduct exploratory economic analyses and will include:

- Number and type of medical visits (eg, in/out hospital, ER visit).
- Number (proportion) of participants requiring hospitalization and duration of hospitalization (total days length of stay, including duration by wards; eg, ICU).
- Number and character of diagnostic and therapeutic tests and procedures (inpatient and outpatient).

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 SAP.

The primary analysis in this study will be performed when all participants in the study (both parts if Part 2 has started) have reached Week 48 or have discontinued earlier.

The final analysis will be performed when all participants in the study (both parts if Part 2 of the study has started) have reached the final study visit in the follow-up phase, or have discontinued earlier.

9.1. Statistical Hypotheses

The original protocol had as primary hypothesis of this study that the combination regimen of JNJ-3989 + NA has superior efficacy compared to NA treatment alone in reducing HDV replication and improving the associated liver inflammation, as measured by the primary efficacy endpoint at Week 48 (the proportion of participants with HDV RNA decline ≥2 $\log_{10}$ IU/mL from baseline or HDV RNA TND in combination with normal ALT at Week 48). Due to the decision to stop enrollment at 30 participants in Part 2 of the study (see Section 9.2), the statistical analyses will be descriptive.

9.2. Sample Size Determination

The sample size in Part 1 (N 20) is primarily driven by the objectives of Part 1 to provide sufficient evidence of safety and early antiviral activity of JNJ-3989 and to exclude futility of the regimen in a small number of HBV/HDV co-infected participants before initiating the larger Part 2 of the study. No formal statistical power calculations were conducted for Part 1.

A total sample size of 130 participants for Part 2 in the original protocol would yield a statistical power >90% to detect a between-arm difference of ≥26% in the primary efficacy endpoint at Week 48, at a 1-sided Type 1 error rate of 0.025, based on the test for the between-arm difference

in proportions with the normal approximation. Per Protocol Amendment 4, the sample size in Part 2 was reduced to 30 participants.

In the original protocol, sample size re-estimation was planned at the single IA during Part 2 to allow for an increase to a maximum of 170 participants in Part 2 for the conditional power at the end of the study to be at least 80% in case the assumed 0.04 response rate for placebo was too conservative. Due to reduction in sample size per Protocol Amendment 4, the single IA with sample size re-estimation was removed.

In the original protocol, the number of participants included in this study was planned to be a minimum of approximately N 20 (if Part 2 is not initiated) or between a minimum of N 165 and a maximum of N 190 if Part 2 is initiated. Per Protocol Amendment 4, the planned number of participants included in the study will be N 20 in Part 1 and N 30 in Part 2.

9.3. Participant Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Analysis set	Description
Screened	All participants who signed the ICF.
Randomized	All participants who were randomly assigned to an intervention arm in the study.
Intent-to-treat (ITT)	All participants who were randomly assigned to an intervention arm and who received at least 1 dose of study intervention. Participants will be analyzed according to the study intervention they were randomly assigned to.
Modified intent-to-treat (mITT)	All participants who were randomly assigned to an intervention arm and who received at least 1 dose of study intervention, excluding those participants impacted by the COVID-19 pandemic, defined as those participants who, because of COVID-19 or similar pandemic-related reasons, withdrew prematurely from the study prior to Week 48, or had no efficacy assessment for the primary endpoint. COVID-19 or similar pandemic-related reasons may include for example missed visits due to travel restrictions, shortage of lab kits at the planned visit, missed collection of blood sample at key time points for the primary efficacy endpoint, etc. Participants will be analyzed according to the study intervention they were randomly assigned to.
Safety	All participants who take at least 1 dose of study intervention. Participants will be analyzed according to the study intervention they actually received.

9.4. Statistical Analyses

The SAP will be finalized prior to study start and will include a more technical and detailed description of the statistical analyses described in this section.

9.4.1. General Considerations

The primary analysis set for efficacy will be the ITT set (defined in Section 9.3). All efficacy summaries will be presented with descriptive statistics by intervention arm by study Parts 1 and 2, as well as for the whole study data overall.

If the endpoint is continuous, the descriptive statistics will include the number of participants, mean, standard deviation (SD), median, range and interquartile range. If the endpoint is binary or categorical, the frequency distribution with the number and percentage of participants in each

category will be calculated. For time-to-event variables, a summary table including number of participants included in the analysis, number of participants censored, 25th and 75th percentiles and median time-to-event will be shown by intervention arm. Graphic displays will also be used to summarize the data. Summaries will also be presented by presence of compensated cirrhosis at screening (yes or no).

The baseline measurement is defined as the assessment taken the closest to but before the first administration of study intervention on Day 1.

9.4.2. Primary Endpoint

The primary efficacy endpoint is defined as the proportion of participants with HDV RNA ≥2 $\log_{10}$ IU/mL decline from baseline or HDV RNA TND in combination with normal ALT levels at Week 48.

9.4.2.1. Primary Estimand

The main analysis of the primary endpoint will be addressed by using the following estimand attributes:

1. **Study Intervention:**
   - Arm 1: JNJ-3989 + NA
   - Arm 2: Placebo + NA
2. **Study population:** Participants 18 to 65 years of age, inclusive, with HBV/HDV co-infection
3. **Variable:** Response status defined as having HDV RNA decline ≥2 $\log_{10}$ IU/mL from baseline or HDV RNA TND in combination with normal ALT at Week 48
4. **Intercurrent events (ICEs):**
   a. Treatment discontinuation prior to Week 48: if the participant discontinued treatment prior to Week 48 then the participant will be considered as non-responder (composite strategy).
   b. Selected major protocol deviations (identified as ICEs): participants who experienced major protocol deviations considered ICE and who have missing ALT and/or HDV RNA data for the primary endpoint at Week 48 will be considered as non-responders (composite strategy).
   c. Deaths prior to Week 48 are handled in a composite strategy as participants who die prior to Week 48 will be considered as non-responders.
5. **Population level summary:** Difference in proportion of responders between the 2 intervention arms (Arm 1-Arm 2).

Note: The SAP will list the major protocol deviations used for the purpose of efficacy analyses and flag those that are to be considered ICEs.

Assumptions:

- Missing Data for HDV RNA and ALT are Missing At Random (MAR)
- The treatment effect is homogeneous across strata.

Data Included

All available data from randomized participants that have received at least one dose is included (ITT analysis set in Part 2), after taking into account all the ICEs and applying the ICE strategies.

Missing Data Handling Rules

Participants who withdraw from the study prior to Week 48 will be considered as non-responders.

If a participant remains in the study after early discontinuing treatment or after experiencing a major protocol deviation (defined for the purpose of efficacy analyses and is an intercurrent event) and has missing Week 48 value for HDV RNA and/or ALT, then the imputation to non-response will be applied. If the value for the primary endpoint at Week 48 is available, then such data will be used to determine their response status.

For the participants still in the study at Week 48 or for participants that have neither discontinued treatment early nor experienced any major protocol violations (defined for the purpose of efficacy analyses and is an intercurrent event), and, either HDV RNA or ALT values are missing at Week 48, the primary method to handle missing data will be the Multiple Imputation (MI) approach, applied in a joint multivariate fashion to leverage the correlation between HDV RNA and ALT values over time. More details regarding the multiple imputation multivariate model will be included in the SAP.

To challenge and assess the impact of the MAR assumption in presence of intercurrent events, different approaches to handle missing data will be used as sensitivity analyses of the main estimator. Two sensitivity analyses will be conducted with different rules to handle missing HDV RNA and/or ALT values at Week 48. One sensitivity analysis will be based on the tipping point approach based on the Missing Not At Random (MNAR) assumption, and the other analysis will use a single imputation method. For the latter, the Last Observation Carried Forward (LOCF) in conjunction with the next available observation imputation approach will be used. The non-missing value closest to Week 48 will be selected among the non-missing values for HDV RNA and/or ALT which are no earlier than 12 weeks prior or no later than 4 weeks post Week 48. If both HDV RNA and ALT values are missing at Week 48, the imputed values will be chosen at the same timepoint. If 2 non-missing laboratory values are equidistant, the later observation will be preferred.

As a supplementary estimator, the analysis where all participants with missing HDV RNA and ALT values in the analysis window of Week 48 in each arm are imputed as non-responders will be conducted to provide a comprehensive overview of the robustness for the assumption of MAR and the type of missing data.

The main estimator and statistical model are discussed in the next section. The estimator will be presented for Part 2 data as well as for the whole study data.

9.4.2.2. Analysis of The Main Estimator

The proportion of responders will be compared between the 2 arms using, if possible, the stratum-adjusted Mantel-Haenszel test on the difference of proportions, with the following stratification factors: presence of compensated cirrhosis at screening (yes or no, for Part 1 only), HDV RNA testing laboratory location (China versus outside of China), and HBeAg status at screening (positive versus negative).

9.4.3. Key Secondary Endpoints

The key secondary endpoints at Week 48 are defined as follows:

1. Proportion of participants with HDV RNA ≥2 $\log_{10}$ IU/mL decline from baseline or HDV RNA TND at Week 48.
2. Proportion of participants with normal ALT levels at Week 48.
3. Proportion of participants with HBsAg seroclearance at Week 48.
4. Proportion of participants with ≥2 kPa reduction from baseline in LSM assessed by VCTE (FibroScan) at Week 48.

The 4 key secondary endpoints are binary and will be analyzed using, if possible, the stratum-adjusted Mantel-Haenszel test similarly to the primary efficacy endpoint with corresponding 95% CIs on the difference of proportions between the 2 arms.

The estimand, estimator, and missing data handling rules will be constructed for and applied to each of the key secondary efficacy endpoints in a similar fashion as described earlier for the primary efficacy endpoint. The details are presented in the SAP.

9.4.4. Other Efficacy Endpoints

Descriptive statistics will be used for all efficacy endpoints which will be summarized by intervention arm over time and by study phase, using the whole study data as well as by stage (defined in Section 9.4.2.2). Specific endpoints may be analyzed using suitable categorical data approaches (eg, Mantel-Haenszel test, logistic regression for proportions or other categorical type of endpoint), longitudinal repeated measures or ANCOVA models (eg, for continuous types of variables), or survival analysis based on the Kaplan-Meier estimates (for time-to-event variables), as appropriate.

The statistical inference to compare the efficacy between Arm 1 and Arm 2 as measured by the other secondary endpoints at Week 48 will utilize the weighted inverse normal combination method as described for the primary efficacy endpoint. No further adjustment for multiplicity will be made and no imputation rule will be used in case of missing data. More details are provided in the SAP.

The efficacy of JNJ-3989 +NA during study intervention and follow-up phases will be evaluated in terms of the proportion of participants with

- HDV RNA ≥2 $\log_{10}$ IU/mL decline from baseline or HDV RNA TND in combination with normal ALT,
- HDV RNA ≥2 $\log_{10}$ IU/mL decline from baseline in combination with normal ALT,
- HDV RNA TND in combination with normal ALT,
- HDV RNA ≥2 $\log_{10}$ IU/mL decline from baseline or HDV RNA TND,
- HDV RNA ≥2 $\log_{10}$ IU/mL decline from baseline,
- HDV RNA TND,
- Normal ALT,
- Off-treatment sustained HDV RNA response,
- Off-treatment sustained HDV RNA relapse,

will be tabulated by intervention arm as well as over time. The comparison among the intervention arms for these endpoints at Week 48 will be done using MH chi-square test stratified by the stratification factors and corresponding 95% CIs without adjustment for multiple intervals. The time to reach HDV RNA ≥2 $\log_{10}$ IU/mL decline or HDV RNA TND will be summarized based on Kaplan-Meier estimates in tables and graphs.

In addition, descriptive statistics on values and changes from baseline over time in HDV RNA and ALT will be summarized by intervention arm.

The proportion of participants with HBsAg seroclearance/seroconversion during the study intervention and follow-up phases will also be tabulated by intervention arm, and over time.

The proportion of participants with HBV virologic breakthrough, the proportion of participants with HBV flare (virologic, biochemical, and clinical) post end of treatment, and the proportion of participants with sustained HBV response off-treatment after stopping JNJ-3989 treatment will be tabulated by intervention arm over time.

The change in the liver fibrosis from baseline measured by LSM according to VCTE (FibroScan) at end of JNJ-3989 treatment and during follow-up will be tabulated by intervention arm over time.

In addition, subgroup analyses will be conducted to evaluate the potential association between treatment outcome and selected demographic and baseline characteristics (including but not limited to age, presence of compensated cirrhosis at screening, HDV genotype, baseline values for HDV RNA, ALT, and HBsAg, etc). Multivariate model analyses with exploration of interaction terms might also be performed. The primary and key secondary efficacy endpoints, respectively, will be analyzed by means of a logistic regression model. Exploratory descriptive summaries will be displayed by subgroups with corresponding 95% CIs without multiplicity adjustment. Forest plots will be used for the graphical displays. Subgroup analyses, as exploratory, might be conducted on Part 2 data alone as well as combined data (Part 1 and Part 2) to leverage the total sample size of the entire study.

The HBV blood markers such as HBsAg, HBeAg (for HBeAg-positive participants only), HBV DNA during study intervention and follow-up will also be summarized and plotted in terms of values and changes from baseline over time by intervention arm. The proportion of participants with HBsAg, HBeAg (for HBeAg-positive participants only) and HBV DNA levels as well as changes from baseline below/above different cut-offs will be analyzed as appropriate over time by intervention arm. Time-to-event endpoints, such as time to reach HBsAg <1 IU/mL, will be summarized based on Kaplan-Meier estimates in tables and graphs.

The proportion of participants who reach undetectability of HBV RNA and/or HBcrAg during the study intervention and follow-up phases will also be tabulated by intervention arm. In addition, time to undetectability will be summarized based on Kaplan-Meier estimates in tables and graphs. Descriptive statistics on values and change from baseline in HBV RNA and HBcrAg levels will be summarized by intervention arm.

Graphic data displays will also be used to summarize the efficacy data by intervention arm and over time. In addition, the potential association between HBsAg and HDV RNA will be explored graphically over time.

9.4.5. Resistance Analyses

The results of HBV and potentially HDV viral sequencing will be evaluated by the sponsor virologist. Relevant changes of amino acid and/or nucleic acid variations (eg, substitutions) in the HBV and/or HDV genomes will be tabulated and described. Additional exploratory characterization of the HBV and/or HDV viral sequence and phenotype may be performed and reported separately.

9.4.6. Safety Analyses

The Safety Analysis Set will be used for all safety analyses based on pooled data from Part 1 and Part 2 of the study. In addition, selected safety analyses may be reported by study part. Such descriptive analyses will be indicated in the SAP.

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

Adverse Events

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

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

Clinical Laboratory Tests

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

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

Electrocardiogram

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

The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and corrected QT (QTc) interval corrected for heart rate according to Fridericia's formula (QTcF).[14]

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

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

Vital Signs

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

9.4.7. Other Analyses

9.4.7.1. 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 (ie, JNJ-73763924 and JNJ-73763976).

Population PK analysis of concentration-time data of JNJ-73763976 and JNJ-73763924 may be performed using non-linear mixed effects modeling. Data may be combined with selected Phase 1 and/or 2 studies to support a relevant structural model. For operational reasons, a snapshot date for PK samples to be analyzed will be defined, if required. Samples collected before this date will be analyzed for JNJ-73763976 and JNJ-73763924, and may be included in the population PK analysis. Samples collected after the snapshot date will be analyzed at a later date and may be included in a population PK re-analysis when they become available after database lock. Available participant characteristics (eg, demographics, laboratory variables, genotypes) will be included in the model as necessary. Details will be given in a population PK analysis plan and results of the population PK analysis, if applied, will be presented in a separate report.

9.4.7.2. Pharmacokinetic/Pharmacodynamic Analyses

Relationships of PK parameters for JNJ-3989 (JNJ-73763976 and JNJ-73763924), with selected efficacy and safety endpoints may be evaluated and graphically displayed, if applicable.

Modeling of key PD parameters (eg, HBsAg, HDV RNA) 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.

Details will be described in a population PK/PD analysis plan and results of the PK/PD analysis, if applied, will be presented in a separate report.

9.4.7.3. Immune Analyses

Descriptive statistics (n, mean, SD, CV, geometric mean, median, minimum, and maximum) may 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) may also be tabulated for PBMCs during study intervention. The proportion (%) of patients with positive responses based on the magnitude of the IFN-γ T-cell response or the percentage of CD4+ or CD8+ T-cells expressing one of the cytokines (eg, IL-2, TNF- α or IFN-γ) for at least 1 of the HDV and HBV antigens as defined by ELISpot and/or ICS, respectively, may be determined.

9.4.7.4. Pharmacogenomic Analyses

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

9.4.7.5. Host Biomarkers Analyses

Statistical approaches to explore correlations between clinical outcome and blood and liver biomarkers vary and depend on the different data types of the applied technology platforms, as well as on the extent of observed 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 CSR or a separate report.

9.4.7.6. Medical Resource Utilization

Medical resource utilization data will be descriptively summarized by intervention arm.

9.5. Interim Analyses

9.5.1. Interim Analyses of Study Part 1

During the double-blind phase of Part 1, 2 IAs will be conducted by the sponsor.

Part 1 IA1: One IA will be conducted after all participants of Part 1 have completed at least Week 16 (or discontinued earlier) to allow a comprehensive review of ALT elevations observed during treatment. An in-depth understanding of the kinetics of virological parameters (eg, HDV RNA, HBsAg, HBV DNA, etc) is critical to interpret the observed ALT elevations and their pattern over time, in light of preliminary understanding the benefit-risk ratio of the investigational regimen in HDV-infected participants. The sponsor will become unblinded to Part 1 efficacy and safety data for this IA to inform the decision of the Sponsor Committee for the initiation of Part 2 in conjunction with the IDMC recommendations.

From the moment of data unblinding for Part 1 IA1 onwards, the sponsor will remain unblinded to Part 1 data. The investigators, participants, site personnel, and operational sponsor team members involved with the sites will remain blinded. For safety-related decisions, HDV RNA and HBsAg data may be discussed with investigators on a case-by-case basis.

Part 1 IA2: A second IA will be conducted after all participants of Part 1 have completed at least Week 48 visit (or discontinued earlier).

9.5.2. Interim Analysis of Study Part 2

The original protocol included an IA of Part 2 when all participants had reached Week 148 (EOT or discontinued earlier). This IA of Part 2 was to be conducted to assess safety and evaluate the time course of different disease markers and to support the sponsor's interactions with health authorities. Due to the decision to reduce the study duration of Part 2 and since interactions with health authorities are no longer planned, the IA of Part 2 was removed per Protocol Amendment 5.

9.5.3. Independent Data Monitoring Committee

An IDMC will be established for continuous monitoring of SAEs, AEs leading to discontinuation, and ALT flares. In addition, the IDMC will review unblinded efficacy parameters measured by HBV/HDV disease blood markers (eg, HDV RNA, HBV DNA, HBeAg, HBsAg) during the double-blind phase. During the open-label phase, all data will be unblinded. When all participants are in the open-label phase or discontinued earlier, the IDMC responsibilities will be covered by the internal DRC (see Section 9.5.4).

The IDMC members will be appointed before the start of the study to review unblinded interim data for both safety and efficacy and formulate recommendation(s) to the Sponsor Committee (see Section 9.5.5), who will make the final decision(s). Possible recommendations of the IDMC include, but are not limited to, continuing the study unchanged, stopping the study for safety concerns, or for futility or make a study amendment.

The IDMC will consist of at least one medical expert in the relevant therapeutic area and at least one statistician. The IDMC role and responsibilities, communication flow with other stakeholders, and procedures will be documented in the IDMC charter.

9.5.4. Internal Data Review Committee

A DRC will be established for continuous monitoring of SAEs, AEs leading to discontinuation, and ALT flares when all participants have completed double-blind phase and IDMC has completed its review. This committee will consist of at least one medical expert in the relevant therapeutic area (hepatology) and at least one statistician; committee membership responsibilities, authorities, and procedures will be documented in the DRC charter. The committee will meet periodically to review data of the efficacy parameters measured by different HBV and HDV disease blood markers (eg, HDV RNA, HBV DNA, HBeAg, HBsAg, etc).

The DRC members will be appointed to review the interim data for both safety and efficacy and formulate recommendation(s) to the Sponsor Committee (see Section 9.5.5), who will make the final decision(s). DRC and Sponsor Committee members will not be involved in the study conduct. Details on the roles and responsibilities of the DRC and Sponsor Committee, as well as the flows of communication, will be documented in the DRC charter.

9.5.5. Sponsor Committee

The Sponsor Committee includes representatives from the sponsor's clinical, biostatistics, Global Medical Safety, and virology departments who are not involved in the study conduct.

The Sponsor Committee will review selected efficacy and safety parameters to assess the predefined antiviral activity criteria and decide to start Part 2 based on the results of the Part 1 IA1 (when all participants of Part 1 have completed at least Week 16 or discontinued earlier).

After Part 2 has commenced, all sponsor personnel, including the Sponsor Committee, will remain blinded to subsequent IDMC data reviews during the double-blind phase. During the open-label phase, all data will be unblinded. The efficacy monitoring will be conducted by the IDMC to protect the well-being of the participants against unexpected absence of further HBV RNA decline and/or HDV RNA rebound contrary to the initial antiviral activity criteria.

The criteria to trigger the start of Part 2 and to exclude futility will be defined in terms of the antiviral activity as measured by a predefined threshold of HDV RNA and HBsAg reduction from baseline and will be paired with an assessment of the benefit-risk ratio based on the Part 1 IA1 data. Details will be provided only in the SAP to protect the study integrity and minimize the operational bias.

9.5.6. Independent Flare Expert Panel

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

In order to allow for an unbiased assessment, members of the committee will not serve as study investigators or as members of the IDMC and will remain blinded to the treatment assigned to each participant up to the time of Part 1 IA1, when the IFLEP will become unblinded to the Part 1 data. In Part 2, the IFLEP will also be blinded to the treatment assigned to each participant up to unblinding of the Part 2 clinical data.

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

AE	adverse event
AESI	adverse event of special interest
AFP	alpha-fetoprotein
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
bpm	beats per minute
cccDNA	covalently closed circular deoxyribonucleic acid
CHB	chronic hepatitis B
CHD	chronic hepatitis D
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(s) (paper or electronic as appropriate for this study)
CV	coefficient of variation
CYP	cytochrome P450
DAIDS	Division of Acquired Immunodeficiency Syndrome
DBP	diastolic blood pressure
DNA	deoxyribonucleic acid
DRC	Data Review Committee
ECG	electrocardiogram
eDC	electronic data capture
eGFR	estimated glomerular filtration rate
ELISpot	enzyme-linked immunospot
EOS	end of study
EOT	end of treatment
ETV	entecavir
FDA	Food and Drug Administration
FNAB	fine needle aspirate biopsy
FOIA	Freedom of Information Act
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HBc	hepatitis B core protein
HBcrAg	hepatitis B core-related antigen
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBs	hepatitis B surface
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
HEV	hepatitis E virus
HIV(-1) (-2)	human immunodeficiency virus (type 1) (type 2)
HRQOL	Health-Related Quality of life
IA	interim analysis
IB	Investigator's Brochure
ICE	intercurrent event
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors

ICS	intracellular cytokine staining
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFLEP	Independent Flare Expert Panel
IFN	interferon
IFN-γ	gamma interferon
Ig	immunoglobulin
IgM	immunoglobulin M
IL	interleukin
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
ISR	injection site reaction
ITT	Intent-to-treat
IU/mL	International Units Per Milliliter
IWRS	interactive web response system
LLN	lower limit of normal
LLOQ	lower limit of quantitation
LSM	liver stiffness measurement
MAR	Missing At Random
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MRU	medical resource utilization
NA	nucleos(t)ide analog
NIMP	Non-Investigational Medicinal Product
NOAEL	no observed adverse effect level
PBMC	peripheral blood mononuclear cell
PCS	Physical Component Summary
PD	pharmacodynamic(s)
PegIFN-α	pegylated interferon-alpha
pgRNA	pre-genomic ribonucleic acid
PK	pharmacokinetic(s)
PQC	Product Quality Complaint
Q4W	every 4 weeks
qd	once daily
QTcF	QT interval corrected for heart rate according to Fridericia
RBC	red blood cell
RNA	ribonucleic acid
RNAi	ribonucleic acid interference
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SC	subcutaneous
SD	standard deviation
SoA	Schedule of Activities
siRNA	small interfering RNA
SUSAR	suspected unexpected serious adverse reaction
TAF	tenofovir alafenamide
TNF	tumor necrosis factor
ULN	upper limit of normal
US	United States
VCTE	vibration-controlled transient elastography
WBC	white blood cell

Definitions of Terms

Electronic source system	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in a CRF as determined by the protocol. Data in this system may be considered source documentation.
HBsAg seroclearance	HBsAg negativity based on the assay used
HBsAg seroconversion	HBsAg negativity and anti-HBs antibody positivity
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 following tests will be performed according to the Schedule of Activities by the central laboratory:

The actual date of assessment and, if required, the actual time of the assessment of laboratory samples will be recorded in the source documentation and in the eCRF or laboratory requisition form.

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
Reticulocyte count and index</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. A RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.</td></tr>
<tr><td rowspan="2">Clinical Chemistry</td><td colspan="2">Sodium
Potassium
Chloride
Bicarbonate
Blood urea nitrogen (BUN)
Creatinine
Glucose
Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic
Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic
Gamma-glutamyltransferase (GGT)</td><td>Total, conjugated, and non-conjugated bilirubin
Alkaline phosphatase
Creatine phosphokinase (CPK)
Lactic acid dehydrogenase (LDH)
Uric acid
Calcium
Phosphate
Albumin
Total protein
Cholesterol
Triglycerides
Magnesium</td></tr>
<tr><td colspan="3">Creatinine clearance (eGFR calculated by the CKD-EPI formula) will be assessed.

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

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

10.3.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country- or territory-specific requirements.

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

Protocol Amendments

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

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

Regulatory Approval/Notification

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

Required Prestudy Documentation

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

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

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

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

Independent Ethics Committee or Institutional Review Board

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

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

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

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

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

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

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

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

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

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

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

Country/Territory Selection

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

Other Ethical Considerations

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

10.3.2. Financial Disclosure

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

10.3.3. Informed Consent Process

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

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

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

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

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

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

10.3.4. Data Protection

Privacy of Personal Data

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

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

The informed consent obtained from the participant includes information about, and where required per applicable regulations, explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. The informed consent also provides information to address the lawful transfer of the data to other entities and to other countries/territories.

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

In the event of a data security breach, the sponsor will apply measures to adequately manage and mitigate possible adverse effects taking into consideration the nature of the data security breach as necessary to address other obligations such as notifying appropriate authorities in accordance with applicable data protection law.

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

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

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

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

10.3.6. Committees Structure

Independent Data Monitoring Committee

An IDMC will be established for continuous monitoring of SAEs, AEs leading to discontinuation, and ALT flares. In addition, at prespecified IA time points, the IDMC will review the unblinded results of efficacy parameters measured by different HBV/HDV disease blood markers (eg, HDV RNA, HBV DNA, HBeAg, HBsAg) during the double-blind phase. During the open-label phase, all data will be unblinded. When all participants are in the open-label phase or discontinued earlier, the IDMC responsibilities will be covered by the internal DRC.

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

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

Internal Data Review Committee

A DRC will be established for continuous monitoring of SAEs, AEs leading to discontinuation, and ALT flares when all participants have completed double-blind phase and IDMC has completed its review. This committee will consist of at least one medical expert in the relevant therapeutic area (hepatology) and at least one statistician; committee membership responsibilities, authorities, and procedures will be documented in the DRC charter. The committee will meet periodically to review data of the efficacy parameters measured by different HBV and HDV disease blood markers (eg, HDV RNA, HBV DNA, HBeAg, HBsAg, etc).

The DRC members will be appointed to review the interim data for both safety and efficacy and formulate recommendation(s) to the Sponsor Committee, who will make the final decision(s). The Sponsor Committee includes representatives from the sponsor's Clinical, Biostatistics, Global Medical Safety, and Virology departments. DRC and Sponsor Committee members will not be involved in the study conduct. Details on the roles and responsibilities of the DRC and Sponsor Committee, as well as the flows of communication, will be documented in the DRC charter.

Independent Flare Expert Panel

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

In order to allow for an unbiased assessment, members of the committee will not serve as study investigators or as members of the IDMC and will be blinded to the treatment assigned to each participant up to the time of Part 1 IA1, when the IFLEP will become unblinded to the Part 1 data. In Part 2, the IFLEP will also be blinded to the treatment assigned to each participant up to unblinding of the Part 2 clinical data.

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

10.3.7. Publication Policy/Dissemination of Clinical Study Data

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

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

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

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

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

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

Registration of Clinical Studies and Disclosure of Results

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

10.3.8. Data Quality Assurance

Data Quality Assurance/Quality Control

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

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

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

10.3.9. Case Report Form Completion

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

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

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

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

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

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

10.3.10. Source Documents

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

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

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

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

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

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

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

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

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

eSource system but information collected through eSource may not be limited to that found in the CRF.

10.3.11. Monitoring

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

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

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

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

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

10.3.12. On-site Audits

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

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator must immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.3.13. Record Retention

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

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

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

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

10.3.14. Study and Site Start and Closure

First Act of Recruitment

The first potential participant screened is considered the first act of recruitment and it becomes the study start date.

Study/Site Termination

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

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

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

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

10.4. Appendix 4: Adverse Events, 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

Adverse Event

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

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

Note: The sponsor collects AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

Serious Adverse Event

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

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

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

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

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

10.4.2. Attribution Definitions

Assessment of Causality

The causal relationship to study intervention is assessed by the investigator and documented in the Medical Records.

The assessment of causality must consider the following factors:

- Temporal relationship
- Clinical characteristics of event
- Pharmacological plausibility
- Confounding risk factors:
  - Concomitant medication
  - Underlying/concurrent disease
  - Family/social history
- Challenge:
  - De-challenge: Did the reaction improve when the investigational product was withdrawn, in the absence of any other treatment?
  - Re-challenge: What happens if participant is re-challenged with investigational product?
- Other considerations: Participant characteristics and past medical history, and quality of information

The following selection must be used to assess all AEs.

Related

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

Not Related

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

10.4.3. Severity Criteria

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

The investigator must use clinical judgement in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

10.4.4. Special Reporting Situations

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

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

Special reporting situations must be recorded in the CRF. Any special reporting situation that meets the criteria of an SAE must be recorded on the serious adverse event page of the CRF.

10.4.5. Procedures

All Adverse Events

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

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

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

Serious Adverse Events

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

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

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the study must be reported as a serious adverse event, except hospitalizations for the following:

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

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

Information regarding SAEs will be transmitted to the sponsor using a serious adverse event reporting form, which must be completed and signed by a physician from the study site, and transmitted in a secure manner to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

10.4.6. Product Quality Complaint Handling

Definition

A PQC is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

Procedures

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

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

10.4.7. Contacting Sponsor Regarding Safety, Including Product Quality

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

10.5. Appendix 5: Rash Management

Table 3: Management of Rash Events by Severity Grade

	Definition	Study Intervention Action	• Activities by Day[a]	Referral to Dermatologist and Dermatology Activities
Grade 1 rash (with or without pruritus)[b]	Erythema	Study intervention intake may be continued at the investigator's discretion	• Day 0: optional on-site visit for initial rash evaluation may be performed at the investigator's discretion. • Safety laboratory assessments may be performed at the investigator's discretion (recommended if visit occurs). • Digital pictures* of skin lesions may be taken at the investigator's discretion. • Determine if participant was adhering to the recommended sun-protective measures. If appropriate, provide sun protection counseling. • Day 1 and thereafter: appropriate follow-up visits at the investigator's discretion until resolution of rash. • Safety laboratory assessments and photography (digital pictures* of skin lesions) may be performed at the investigator's discretion. • * Digital pictures to be taken at the clinical site upon consent of the participant.	Not required

Table 3: Management of Rash Events by Severity Grade				
	Definition	**Study Intervention Action**	**Activities by Day[a]**	**Referral to Dermatologist and Dermatology Activities**
Grade 2 rash (with or without pruritus)[b]	Diffuse, maculopapular rash, or dry desquamation	Study intervention intake may be continued at the investigator's discretion	• Day 0: required on-site visit (if a visit is not possible, telephone contact with the participant should take place to collect information and give advice on the necessary measures to be taken). • Safety laboratory assessments may be performed at the investigator's discretion (recommended). • Digital pictures* of skin lesions may be taken at the investigator's discretion. Digital pictures* of skin lesions are recommended in case consultation of a dermatologist is required. Determine if participant was adhering to the recommended sun-protective measures. If appropriate, provide sun protection counseling. • Day 1 and thereafter: appropriate follow-up visits at the investigator's discretion until resolution of rash or until clinical stability is reached. • Safety laboratory assessments are required on Day 1 and are required thereafter only if the previous values were abnormal (but may be performed at the investigator's discretion). If the rash progresses to a higher grade, safety laboratory assessments of the higher grade should be followed. • Digital pictures* of skin lesions may be taken at the investigator's discretion. • * Digital pictures to be taken at the clinical site upon consent of the participant.	Referral to dermatologist at the discretion of the investigator[c] Biopsy not required, but may be performed at the dermatologist's discretion

Table 3: Management of Rash Events by Severity Grade

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

Table 3: 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; no rechallenge allowed NA treatment may be discontinued based on investigator judgement in consultation with the sponsor	• Day 0: required on-site visit. • Safety laboratory assessments required to be performed. • Digital pictures* of skin lesions may be taken at the investigator's discretion (recommended). • Determine if participant was adhering to the recommended sun-protective measures. If appropriate, provide sun protection counseling. • Day 1: required on-site visit. • Safety laboratory assessments required to be performed. • Digital pictures* of skin lesions may be taken at the investigator's discretion (recommended). • Further visit(s): appropriate follow-up required until resolution of rash or until clinical stability is reached. • Safety laboratory assessments and photography (digital pictures* of skin lesions) are recommended to be performed until the rash severity resolves to grade 2 or grade 1. • * Digital pictures to be taken at the clinical site upon consent of the participant.	Required[c] Biopsy required and to be performed as soon as possible after the onset of the rash.

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

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

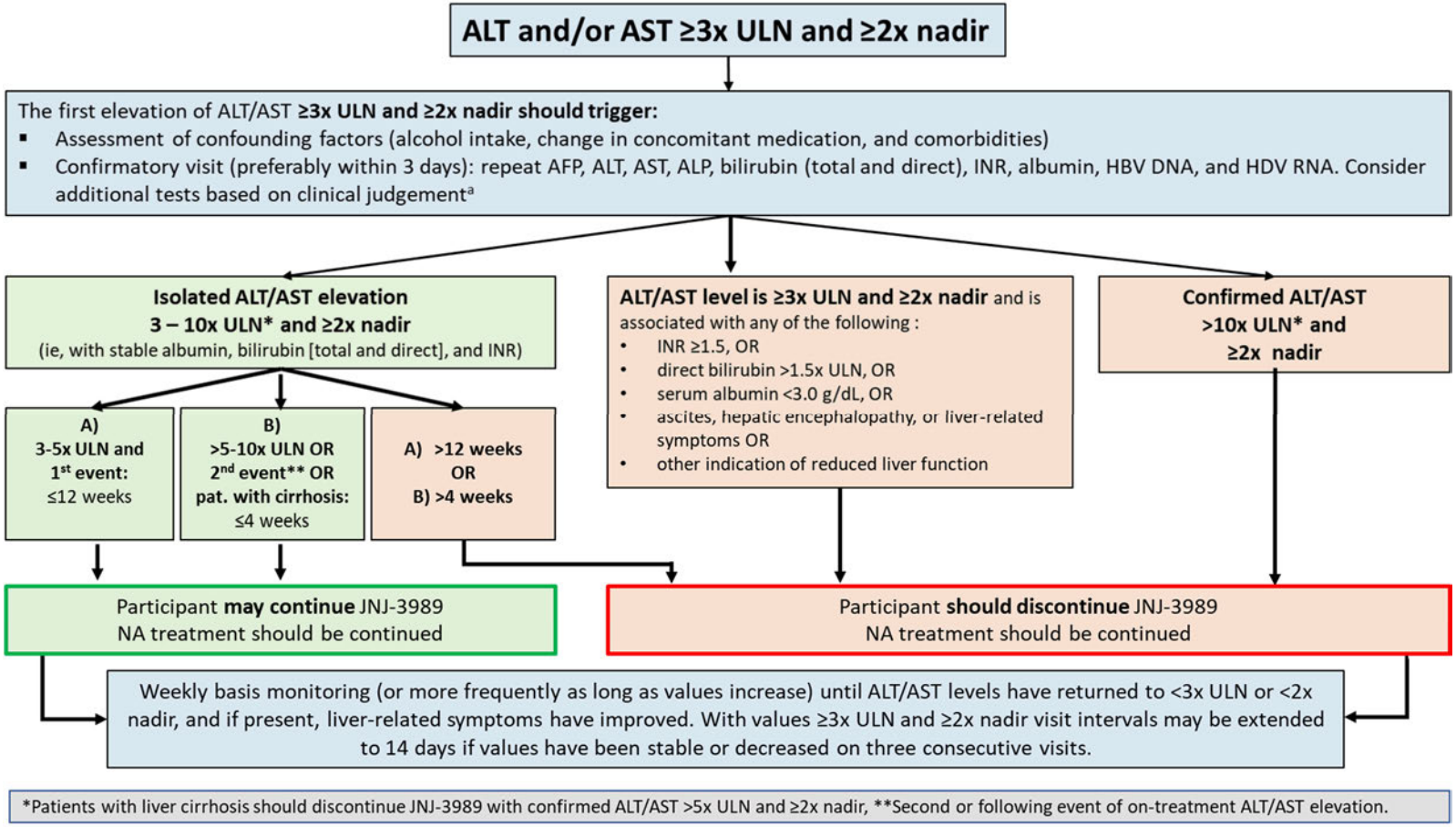
[b] The participant should be advised to contact the investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms appear, or if mucosal involvement develops. In case the rash evolves to a higher grade than that first observed, management of the rash should follow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

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

Note:

- Local laboratory assessments are to be used for rash management. Relevant laboratory assessment values are to be shared with the sponsor (if applicable and local regulations allow) as per the "Instructions for Investigators for sharing of Digital Pictures and Local lab reports" and should be de-identified.
- Digital pictures that are collected, dermatological consultation reports or biopsy reports that become available, should be de-identified and provided to the sponsor.

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



Note: please refer to Section 8.3.6.1, Intervention-emergent ALT/AST Elevations.
a: Additional tests may be considered based on clinical judgement in case of confirmed ALT flares
- Hepatitis A, C, E: IgM anti-HAV; delta IgM, IgG & PCR, HCV RNA, IgM & IgG anti-HEV, HEV RNA
- CMV, HSV, EBV infection: IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV, PCR
- HIV
- Ig –Electrophoresis

10.7. Appendix 7: Cardiovascular Safety – Abnormalities

ECG

All important abnormalities from the ECG readings will be listed.

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

ECG: electrocardiogram; NAP = not applicable

For absolute QTc parameters the categories are defined based on the ICH E14 GuidanceF[a]

Vital Signs[b]

The following abnormalities will be defined for vital signs:

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

DBP: diastolic blood pressure; SBP: systolic blood pressure

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

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

10.8. Appendix 8: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

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

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high 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. 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 (for the purpose of this study)**
  - Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.
  - Has congenital abnormalities resulting in sterility.

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

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

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

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

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED FOR MALE OR FEMALE PARTICIPANTS 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)
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception must 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.)*
NOT ALLOWED METHODS UNLESS USED TOGETHER WITH HIGHLY EFFECTIVE METHODS OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[b]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[b]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)
a) Typical use failure rates may differ from those when used consistently and correctly. Use must be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. b) Male condom and female condom must not be used together (due to risk of failure with friction).

10.9. Appendix 9: DAIDS Table

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

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

General Instructions

Grading Adult and Pediatric Adverse Events

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

Determining Severity Grade for Parameters Between Grades

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

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

Definitions

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

Estimating Severity Grade for Parameters not Identified in the Grading Table

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

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

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

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

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

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

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

AV: atrioventricular; NAP: not applicable; RBC: red blood cell; TdP: Torsades de Pointes

[b] Modified by the sponsor.

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

IV: intravenous; NAP: not applicable

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

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

NAP: not applicable

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

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

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

IV: intravenous; NAP: not applicable

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

IV: intravenous; NAP: not applicable

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

BMD: bone mineral density; NAP: not applicable

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

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

CNS: central nervous system; NAP: not applicable

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

NAP: not applicable

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

ID: identity, NAP: not applicable

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

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

NAP: not applicable

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

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

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

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

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

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: COVID-19 APPENDIX

10.10.1. Guidance on Study Conduct During the COVID-19 Pandemic

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

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

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

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

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 CSR.

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/territory-specific regulatory requirements.

Screening and Randomization

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

Dispensing/Administration of Study Intervention

- For participants able to visit the study site, but who request to reduce visit frequency, or for whom limited access to the site is expected, an additional supply of oral study intervention can be provided.
- For participants unable to visit the study site, direct-to-patient (DTP) shipment or handover to a caregiver or delegate of oral study intervention may be implemented, where allowed per local regulations and if requested by the investigator. Where DTP shipments or handover to delegates are deemed necessary, the process must be coordinated between the site and sponsor staff following standard DTP procedures for arranging shipment and adhering to associated approvals and documentation requirements.
- JNJ-3989/placebo should always be administered at the study site or, if site visits are not possible, at the participant's home (in consultation with the sponsor and taking into consideration participant safety). Of note, if a scheduled injection of JNJ-3989/placebo was missed, the injection should be given as soon as possible but within 3 weeks after the scheduled time. Otherwise, the injection should be skipped, and the next injection should be given at the next scheduled time point per the initial injection schedule.

Continuation of Study Intervention

- Any issue with continuation and/or provision of study intervention should be discussed with the sponsor and should be well documented.
- Study intervention should be continued if, in the assessment of the investigator, it does not result in risk to the participant. If at any time a participant's safety is considered at risk due to study intervention, study intervention will be temporarily or permanently discontinued, while every effort should be made to maintain follow-up on study. The benefit of continuing study intervention should be assessed by the investigator for each individual participant, considering the potential impact of reduced direct clinical supervision on participant safety.

- If a participant develops a SARS-CoV-2 infection, the investigator should contact the sponsor to discuss plans for study intervention and follow-up. A decision to continue study intervention should be made by the investigator depending on symptoms and concomitant medication used for the treatment of COVID-19. 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 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:

Locally approved COVID-19 vaccines (including those that received emergency use authorization or conditional marketing authorization) are allowed throughout the study.

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 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 maintain treatment blinding, HBV/HDV RNA, HBsAg, HBeAg, HBcrAg, anti-HBs, and anti-HBe antibody tests during the study intervention phase cannot be done locally (unless instructed otherwise by the sponsor).
- To safely maintain participants on study intervention while site capabilities are compromised by COVID-19-related restrictions, study visits may be performed by a nurse (who received study-specific training) at the patient's home (home health nurse) until such time that on-site visits can be resumed. The following activities may be completed as required per the Schedule of Activities and as feasible:
  - Sampling, processing and shipping of laboratory samples (as described above).
  - Checking study compliance: medication diary (if available), intake of oral study intervention, storage of oral study intervention
  - Performing ECGs
  - Collecting patient-reported outcomes (where appropriate translations and licensing are available)
  - JNJ-3989/placebo administration
  - Delivering oral study interventions
- Any data related to AE, concomitant medication, vital signs, and ECGs will be reviewed and assessed by the investigator.

- In addition, participants may have tele-health visits conducted by blinded qualified site personnel via phone or video conversation as per local regulation. Assessments may include review of AEs (including injection site reactions), concomitant medications, study intervention accountability. Key efficacy endpoint assessments should be performed as required and as feasible. 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 Adverse Event/Serious Adverse Event reporting requirements apply.

Informed Consent

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

Source Data Verification/Monitoring

- In case on-site monitoring visits are not possible, the site monitor may contact the investigator to arrange monitoring visits and activities remotely (in accordance with site and local requirements). Additional on-site monitoring visits may be needed in the future to catch up on source data verification.

Site Audits

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

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 4 (7 April 2023)

Overall Rationale for the Amendment:

Based on the observation that in Part 2 of the REEF-D study significant ALT elevations were more frequently observed in participants with HBsAg levels >10,000 IU/mL at screening or at baseline (irrespective of HDV RNA levels), a temporary halt of new enrollment into the study was implemented in December 2022. Since there was no immediate risk to the safety of participants already enrolled in the trial, treatment and monitoring of ongoing participants was continued as per current protocol.

In February 2023, the Sponsor has taken the strategic decision to discontinue further investment in its hepatitis B and D discovery and development programs. In light of this wider decision, which was not driven by safety concerns with JNJ-73763989 (JNJ-3989), enrollment of new participants into the REEF-D study will not be re-opened.

The overall reason for this amendment is to continue the study in a modified way for participants already enrolled and to describe the reduced sample size in the study. Per IDMC recommendation, it was added that in Part 2, participants with HBsAg values >10.000 IU/mL at screening or baseline, who were assigned to Arm 1 (placebo), will not roll-over to the open-label phase and will enter the follow-up phase. In addition, the stopping criteria for nucleos(t)ide analog (NA) treatment at Week 144/148 have been updated upon HA request.

The changes made to the clinical protocol 73763989HPB2004 as part of Protocol Amendment 4 are listed below, including the rationale of each change and a list of all applicable sections.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 4.1 Overall Design 4.2 Scientific Rationale for Study Design 6.3 Measures to Minimize Bias: Randomization and Blinding 7.1 Discontinuation of Study Intervention 9.2 Sample Size Determination 9.4.1 General Considerations 9.4.2.2 Analysis of The Main Estimator 9.5.2 Interim Analysis of Study Part 2 9.5.3 Independent Data Monitoring Committee	The sample size of Part 2 was reduced. The sample size re-estimation and related interim analysis during the double-blind phase of Part 2 were removed. Figure 1 was updated to reflect the reduced sample size in Part 2 of the study.	After the temporary halt of enrollment, the sponsor decided to not re-open enrollment and to continue the study in a modified way, ie, with reduced sample size.
1.1 Synopsis 3 Objectives and Endpoints 4.1 Overall Design 8.1.1 HBV and HDV Genotyping and Sequencing 9.1 Statistical Hypotheses 9.4.2.2 Analysis of The Main Estimator 9.4.3 Key Secondary Endpoints 9.4.4. Other Efficacy Endpoints 9.4.7.2 Pharmacokinetic/ Pharmacodynamic Analyses 9.4.7.3 Immune Analyses	The study was changed from confirmatory to descriptive. It was clarified that, if possible, the proportion of responders will be compared between the 2 arms using the stratum-adjusted Mantel-Haenszel test on the difference of proportions. Several analyses were now made optional, ie, subgroup analyses, pharmacokinetic/pharmacodynamic analyses, viral genome sequence analysis, and immune analyses.	The study will be continued in a modified way, ie, with reduced sample size and reduced statistical analyses.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3 Schedule of Activities 3 Objectives and Endpoints 8 Study Assessments and Procedures ~~8.1.3 Patient Reported Outcomes~~ ~~9.4.6 Patient Reported Outcomes (PRO)~~ ~~10.10: Appendix 10: Hepatitis B Quality of Life Instrument~~ ~~10.11 Appendix 11: Short Form 36 version 2 (SF-36v2) 2010 Questionnaire~~ ~~10.12 Appendix 12: 5 Level EuroQol 5 Dimension Questionnaire (EQ 5D 5L)~~ ~~10.13.1 Guidance on Study Conduct During the COVID 19 Pandemic~~ ~~10.13.2 Interview Version of the Short Form 36 version 2 (SF 36v2) 2010 Questionnaire~~ ~~10.13.3 Interview Version of the 5 Level EuroQol 5 Dimension Questionnaire (EQ5D5L)~~	PRO evaluations were removed.	The study will be continued in a modified way, ie, with reduced sample size and reduced study assessments.
1.1 Synopsis 1.3.3 Schedule of Activities – Follow-up Phase 2.3.3 Benefit-risk Assessment for Study Participation 4.1 Overall Design 6.4 Study Intervention Compliance 6.5 Re-treatment With NA During the Follow-up Phase ~~6.6 Continued Access to Study Intervention After the End of the Study~~ 8.3.6.1 Intervention-emergent ALT/AST Elevations	The re-treatment option for JNJ-3989 during the follow-up phase was removed. Removal of the posttrial access commitment for JNJ-3989.	Sponsor has taken the strategic decision to discontinue further investment in its hepatitis B and D discovery and development programs (this decision was not driven by safety concerns with JNJ-3989). As the shelf life of currently available batches is limited, re-treatment with JNJ-3989 during the follow-up phase and posttrial access cannot be offered.
2.3.3 Benefit-risk Assessment for Study Participation 7.1 Discontinuation of Study Intervention	It was added that in Part 2, participants with HBsAg values >10.000 IU/mL at screening or baseline, who were assigned to Arm 1 (placebo), will not roll-over to the open-label phase and will enter the follow-up phase.	Per IDMC recommendation to protect the safety of the participants.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3.2 Schedule of Activities – Open-label Study Intervention Phase (Weeks 52 – EOT) 1.3.3 Schedule of Activities – Follow-up Phase 2.3.3 Benefit-Risk Assessment for Study Participation 4.1 Overall Design 4.2 Scientific Rationale for Study Design 6.5 Re-treatment With JNJ-3989 and/or NA During the Follow-up Phase	The NA stopping criteria for non-cirrhotic participants during the follow-up phase were updated: 2 criteria were included in addition to HBsAg seroclearance, ie ALT <3x ULN and HBV DNA <LLOQ have to be achieved to consider NA cessation.	Upon HA request, the stopping criteria for NA treatment at study Week 144/148 were updated.
1.1 Synopsis 9.5.2 Interim Analysis of Study Part 2	The number of interim analyses during the open-label and follow-up phase of Part 2 was reduced: the interim analysis at Week 96 in the open-label phase and at Week 24 in the follow-up phase were removed.	The remaining interim analysis in the open-label phase of Part 2 at Week 148 (end of treatment), in addition to the final analysis (in the follow-up phase at Week 48), provides sufficient information to assess safety and evaluate the time course of different disease markers during study conduct.
1.1 Synopsis 2.3.3 Benefit-risk Assessment for Study Participation 6.3 Measures to Minimize Bias: Randomization and Blinding 8.3.6.1 Intervention-emergent ALT/AST Elevations	It was added that in case of IWRS participant unblinding and if the investigator requires to be unblinded in case of an emergent safety event (ie, study intervention discontinuation due to ALT flares) to allow further treatment of the participant, a sponsor request can be made to have the investigator and sponsor unblinded to all HDV RNA and HBsAg data from the double-blind phase.	To provide access of the double-blind phase laboratory data for HDV RNA and HBsAg to the investigator if required for medical/clinical patient management.
4.1 Overall Design 6.3 Measures to Minimize Bias: Randomization and Blinding 8.1 Efficacy Assessments	It was added that when a participant has completed the Week 48 visit or discontinued earlier, the investigator, site personnel, Sponsor, and participant will be unblinded for treatment allocation and all laboratory data, including HDV RNA and HBsAg data.	To provide access of the double-blind phase laboratory data for HDV RNA and HBsAg when a participant has completed the Week 48 visit or has discontinued earlier. This allows for a evaluation of the effect of treatment or placebo on HBV RNA and HBsAg on a participant level for clinical management.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 2.3.3 Benefit-risk Assessment for Study Participation 4.1 Overall Design 6.3 Measures to Minimize Bias: Randomization and Blinding 8.2 Safety Assessments 9.5.3 Independent Data Monitoring Committee 9.5.4 Internal Data Review Committee 9.5.5 Sponsor Committee 9.5.6 Independent Flare Expert Panel 10.3.6 Committees Structure	Continuous monitoring of SAEs, AEs leading to discontinuation, and ALT flares and review of unblinded efficacy parameters measured by HBV/HDV disease blood markers during the double-blind phase will be conducted by the IDMC. When all participants enter in the open-label phase, the IDMC responsibilities will be covered by the internal DRC. A description of the DRC was added to the protocol. It was added that in Part 2, the IFLEP will also be blinded to the treatment assigned to each participant up to unblinding of the Part 2 clinical data.	After unblinding of all data in the open-label phase, there is no need for a blinded data review anymore.
1.1 Synopsis 1.3 Schedule of Activities 3 Objectives and Endpoints 8.4 Pharmacokinetics 8.4.1 Evaluations 8.4.2 Analytical Procedures 8.4.3 Pharmacokinetic Parameters and Evaluations 8.5 Pharmacokinetics/Pharmacodynamics 8.4.7.1 Pharmacokinetic Analyses 9.4.7.2 Pharmacokinetics/Pharmacodynamics Analyses	The blood sampling for sparse PK of NA and blood sampling for intensive PK (PK subgroup) was removed. Only blood sampling for sparse PK of JNJ-3989 was kept. The PK/PD analyses are now optional.	To reduce the burden for the participants.
1.1 Synopsis 1.3 Schedule of Activities 8.6 Immune Assessments 9.4.7.3 Immune Analyses	A reduction in the number of samples for immune monitoring (immune cells [PBMCs]) was implemented (ie, reduction from 9 timepoints to 2 timepoints [ie, the Day 1 and Week 48 visits] for sample collection). It was clarified that additional PBMC samples may be taken until Week 48 in case of ALT flares.	To reduce the burden for the participants.
1.1 Synopsis 1.3 Schedule of Activities 4.1 Overall Design 8.7 Host Genetics 9.4.7.4 Pharmacogenomic Analyses	The collection of pharmacogenomic samples for epigenetic research was removed.	To reduce the burden for the participants.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3.1 Schedule of Activities – Screening and Double-blind Study Intervention Phase (First 48 Weeks) 8.1.2 Liver Biopsy and Fine Needle Aspirate Biopsy (Optional with Separate Consent, Part 2 Only)	Removal of the optional biopsy sample collections at an unscheduled visit.	To reduce the burden for the participants.
1.3 Schedule of Activities 8.8 Host Biomarkers	The separate lines for host serum protein sample collection were removed from the SoA. It was explained in a footnote that exploratory serology samples may be used for host serum protein testing as well.	To reduce the burden for the participants.
1.3 Schedule of Activities	A reduction in the number of samples for HBV and HDV virology and serology was implemented. The collection of exploratory biomarker samples for whole blood RNA gene expression and whole blood single cell profiling was removed.	To reduce the burden for the participants.
7.1 Discontinuation of Study Intervention	It was clarified that participants of the placebo group who develop cirrhosis at the end of the double-blind phase (based on the Week 48 FibroScan assessment) will not be eligible to receive JNJ-3989 during the open-label and follow-up phase.	To protect the safety of the participants.
1.3.1 Schedule of Activities – Screening and Double-blind Study Intervention Phase (First 48 Weeks) 2.3.3 Benefit-Risk Assessment for Study Participation	The requirement for a platelet aggregation test before FNAB collection was removed.	The platelet aggregation test is not part of the recommended pre fine needle aspiration work-up. Clinical data shows no changes in platelet numbers or function after treatment with JNJ-3989.
1.1 Synopsis 1.3.1 Schedule of Activities – Screening and Double-blind Study Intervention Phase (First 48 Weeks) 8.1 Efficacy Assessments	In addition to the qualitative anti-HDV antibody test, semi-quantitative IgM and total anti-HDV antibody data may be generated as well.	To clarify that semi-quantitative data for anti-HDV IgM and total antibody may be obtained in addition to the qualitative test result.
1.3 Schedule of Activities	The study protocol was updated to allow, in addition to evaluation of HBV, evaluation of virologic or serologic markers of HDV, including total anti-HDV antibodies and anti-HDV IgM antibodies throughout the study.	To clarify that exploratory Hepatitis D related tests are within the scope of this study.

Section number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	The language in footnotes a (for the double-blind phase, open-label phase, and follow-up phase SoA) was adapted to reflect that an early withdrawal visit should be scheduled as soon as possible and that in case these participants continue in the follow-up phase, the follow-up visits can be scheduled based on the withdrawal visit date.	Clarification.
2.3.1.2 Potential Risks	It was added that also in Part 2 a more sustained pattern of ALT elevations was observed and that in Part 2 of the study, the risk of ALT elevations was higher in participants with HBsAg levels >10,000 IU/mL at screening or baseline, and that a causal relationship between JNJ-3989 and ALT elevations is suspected, although the mechanism for this type of confirmed ALT elevations is not yet understood.	Clarification and update.
4.2.1 Study-specific Ethical Design Considerations	Updated that the total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study, ie, less than standard blood donation based upon recommendations of the World Health Organization, ie, 450 mL ± 10% for participants weighing at least 50 kg over a period of 12 weeks for male participants and 16 weeks for female participants, instead of based upon the standard of the American Red Cross.	Previous reference not valid anymore.
7.2.1 Withdrawal From the Use of Research Samples	For participants who withdraw consent for optional research samples (ie, host DNA samples), it was clarified that previously collected samples may be requested to be destructed, in which case no further use of the samples will take place.	To clarify what to do with the collected research samples in case of withdrawal of consent (aligned with ICF language).
8 Study Assessments and Procedures	Updated that the maximum amount of blood drawn from each participant in this study and during the follow-up phase will not exceed 3,210 mL. Added that with the removal of several sample collections, the amount of blood drawn, and the total blood volume needed will be less.	Updated to reflect removal of several sample collections.
8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting	It was clarified that all reported AEs will be coded according to MedDRA, with specific examples regarding ‘alanine aminotransferase increased’, ‘hepatitis B reactivation, and ‘viral load increased’.	Clarification upon HA request

Section number and Name	Description of Change	Brief Rationale
8.3.6.2 Rash 10.5 Appendix 5: Rash Management	The sentence 'The values of the local laboratory assessments need to be transcribed in the CRF by the study site personnel.' Has been replaced by 'Relevant laboratory assessment values are to be shared with the sponsor (if applicable and local regulations allow) as per the "Instructions for Investigators for sharing of Digital Pictures and Local lab reports" and should be de-identified.'	Clarification.
1.1 Synopsis 8.3.6.1 Intervention-emergent ALT/AST Elevations	Re-insertion of the sentence: 'The participant will be monitored (laboratory testing of ALT, AST, ALP, bilirubin [total and direct], INR, albumin, HBV DNA, and HDV RNA) on a weekly basis or more frequently until ALT and/or AST levels have returned to 50% of the maximal value.'.	Inadvertently deleted in Amendment 3.
5.2 Exclusion Criteria	The unit of platelet count was corrected in exclusion criterion 7: /µL instead of /dL.	Correction of an error.
7.1 Discontinuation of Study Intervention	'placebo' was added as part of the investigational study interventions to be discontinued in case of compliance with the listed criteria.	To correct that study intervention discontinuation applies to both JNJ-3989 and placebo.
2.2 Background 2.3 Benefit-risk Assessment 8.3.6.5 Hematologic Abnormalities	Sections were updated with the latest data from the Investigator's Brochure Edition 7.	To reflect the most up-to-date info for background and benefit-risk assessment.
1.3 Schedule of Activities 5.1 Inclusion Criteria	A note was added to clarify that if FibroScan is not available at the study site, acoustic radiation force impulse (ARFI) may be used at screening.	To clarify that participants can be enrolled using ARFI instead of FibroScan to rule out liver cirrhosis.
1.3.1 Schedule of Activities – Screening and Double-blind Study Intervention Phase (First 48 Weeks) 1.3.2 Schedule of Activities – Open-label Study Intervention Phase (Weeks 52 – EOT)	The language on the quantitative HBeAg assessment in footnotes dd (from the double-blind phase SoA) and r (from the open-label phase SoA) was aligned with footnote t (from the follow-up phase SoA).	To align language throughout the protocol.
6.7 Concomitant Therapy 10.10.1 Guidance on Study Conduct During the COVID-19 Pandemic	'prescribing information' was added to the sentence 'Refer to the COVID-19 vaccine prescribing information for more details'.	For completeness.

Section number and Name	Description of Change	Brief Rationale
Throughout the protocol	Changes to align with the sponsor's current protocol template wording.	Update to the most recent template.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 3 (6 December 2021)

Overall Rationale for the Amendment: Based on Part 1 interim study data, the sponsor in consultation with IDMC has decided to start enrollment into Part 2 of the study. The inclusion criteria for the participant population for Part 2 of the study have been updated. In addition, the JNJ-3989 stopping criteria in case of ALT elevation have been updated for Part 1 and Part 2 of the study. The Sponsor provided additional guidance to continue NA treatment until the last study visit.

Based on review of the HBsAg and HDV RNA data, the Sponsor determined that the predefined antiviral activity criteria for start of Part 2 of the study were met. In consultation with the IDMC and based on review of the antiviral activity and safety data, it was decided to open Part 2 of the study with changes to the inclusion criteria and to the safety management criteria for AST and/or ALT increases.

Part 1 interim data showed that one group of patients experienced no/minimal ALT elevations (<3x ULN) and had pronounced and consistent reductions of HDV RNA (1 to 3 $\log_{10}$ IU/mL at last available time point in the Part 1 interim data). In patients with ALT flare (>3x ULN), the HDV RNA kinetics were less consistent and did not show a clear benefit in terms of HDV RNA decline in all of those patients.

Given the prolonged ALT elevation seen in Part 1 of the study, mainly in participants with compensated cirrhosis, and the reduced functional hepatic reserve in patients with cirrhosis, the Sponsor decided that participants with liver cirrhosis will be excluded from Part 2 of the study.

Part 1 interim data showed a trend for a higher rate of ALT elevations in participants with high HDV RNA and HBsAg baseline levels. To reduce the risk of experiencing ALT flares, the Sponsor has updated the inclusion criteria for HBsAg and HDV RNA levels in Part 2 of the REEF-D study to select participants with lower risk for potential occurrence of ALT elevations in Part 2 of the study.

To further ensure the safety of the study participants the JNJ-3989 stopping criteria in case of ALT elevations have been made more stringent.

The Sponsor also amended the protocol to continue NA treatment at Week 144/148. In case of confirmed HBsAg seroclearance in non-cirrhotic participants, NA treatment may be discontinued upon discussion with the sponsor. For non-cirrhotic participants who discontinued treatment with NA, additional NA restart criteria were added. Furthermore, the Sponsor clarified that NA treatment should be continued in case of early discontinuation of JNJ-3989.

The Sponsor included in Part 2 of the study the option for liver biopsies (only in sites and in selected countries where this is feasible, and after all relevant approvals are in place and operational set-up is completed) to allow a better understanding of the impact of JNJ-3989 treatment on viral and immune markers in the liver in these HBV/HDV co-infected participants.

Other changes, clarifications and corrections were also made as detailed below.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 2.3.3 Benefit-risk Assessment for Study Participation 4.1 Overall Design 4.2 Scientific Rationale for Study Design 5.1 Inclusion Criteria 5.2 Exclusion Criteria 6.3 Measures to Minimize Bias: Randomization and Blinding 9.4.2.2 Analysis of The Main Estimator	The inclusion criteria have been updated to exclude participants with liver cirrhosis (LSM ≥12.5 kPa by VCTE [FibroScan] or core liver biopsy and platelet count ≤140,000/dL) from Part 2 of the study.	Given the reduced functional hepatic reserve in the cirrhotic participant population and the newly identified risk of on-treatment ALT elevation, the Sponsor decided that participants with liver cirrhosis will be excluded from Part 2 of the study to protect the safety of participants.
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS 9.4.3 Key Secondary Endpoints	The fixed sequence of key secondary endpoints was adjusted. The third key secondary endpoint '*Proportion of participants with ≥2 kPa reduction from baseline in liver stiffness measurement (LSM) assessed by vibration controlled transient elastography (VCTE) (FibroScan) at Week 48.*' has been moved to the fourth position.	Given participants with cirrhosis are excluded from Part 2 of the study, the probability of rejecting the null hypothesis for this endpoint will be reduced. Consequently, the fixed sequence procedure for multiple testing should be adjusted by moving this endpoint to the last position (4th).
2.3.3 Benefit-risk Assessment for Study Participation 5.1 Inclusion Criteria	The inclusion criteria for Part 2 of the study have been updated to include participants with HBsAg levels of ≤10,000 IU/mL or with HBsAg levels of >10,000 IU/mL if HDV RNA levels are ≤100,000 IU/mL In addition, for Part 2 of the study, participants must have HDV RNA values at screening ≥500 IU/mL.	Participants with HDV RNA and HBsAg levels above the thresholds at baseline were associated with increased risk of ALT elevations during treatment with JNJ-3989. To reduce the risk of experiencing an ALT flare, the Sponsor has updated the inclusion criteria.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis; 1.3.1 Schedule of Activities – Screening and Double-blind Study Intervention Phase (First 48 Weeks); 1.3.2 Schedule of Activities – Open-label Study Intervention Phase (Weeks 52 – EOT); 1.3.3 Schedule of Activities – Follow-up Phase; 6.5.2 Re-treatment With JNJ-3989 + NA 8.3.6.1 Intervention-emergent ALT/AST Elevations; 10.6 Appendix 6: Intervention-emergent ALT/AST Elevations	The algorithm for the management of intervention-emergent ALT and/or AST elevations has been updated. • The threshold value for defining the onset of an intervention-emergent ALT/AST elevation has become stricter, ie, from '≥3x ULN and ≥3x nadir' to '≥3x ULN and ≥2x nadir'. • The threshold value for discontinuation of JNJ-3989 for participants without cirrhosis has been modified to ALT >10x ULN and ≥2x nadir in the confirmatory sample and to ALT >5x ULN and ≥2x nadir for participants with cirrhosis. • Criteria for discontinuation of JNJ-3989 in case of prolonged ALT elevation have been updated to differentiate between participants with compensated liver cirrhosis, and participants without liver cirrhosis who experience a first or second ALT flare. Furthermore, the monitoring frequency for participants who experience an ALT/AST flare has been adjusted to weekly (or more frequently as long as values increase) until ALT and/or AST levels have returned to <3x ULN or <2x nadir, and if present, liver-related symptoms have improved. With ALT and/or AST values ≥3x ULN and ≥2x nadir, visit intervals may be extended to 14 days if values have been stable or decreasing on 3 consecutive visits. In addition, the visit window for confirmatory visits in case of any intervention-emergent elevation of ALT and/or AST ≥3x ULN and ≥2x nadir has been changed to "preferably within 3 days" of the receipt of the initial ALT/AST results.	To ensure the participant's safety and to gain a better understanding of the outcome of ALT flares with continued treatment as well as HDV RNA kinetics after ALT normalization.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3.2 Schedule of Activities – Open-label Study Intervention Phase (Weeks 52 – EOT) 1.3.3 Schedule of Activities – Follow-up Phase 2.3.3 Benefit-risk Assessment for Study Participation 4.1 Overall Design 4.2 Scientific Rationale for Study Design 6.5 Re treatment With JNJ 3989 and/or NA During the Follow up Phase 7.1 Discontinuation of Study Intervention	NA treatment has become mandatory for all study participants until the last study visit (FU Week 48). Only for non-cirrhotic participants, NA treatment can be discontinued during the Follow-up Phase of the study in case of a confirmed HBsAg seroclearance and upon discussion with the Sponsor. For non-cirrhotic participants who discontinued treatment with NA, additional NA restart criteria were added. Furthermore, it has been clarified that NA treatment should be continued in case of early discontinuation of JNJ-3989.	Upon Health Authority Request and to protect the safety of the participants.
1.1 Synopsis; 1.3.1 Schedule of Activities – Screening and Double-blind Study Intervention Phase (First 48 Weeks) 2.3.1.3 Risks Due to Study Procedures 2.3.3 Benefit-risk Assessment for Study Participation 3 OBJECTIVES AND ENDPOINTS 4.2 Scientific Rationale for Study Design 5.1 Inclusion Criteria 5.2 Exclusion Criteria 6.8 Concomitant Therapy 8 STUDY ASSESSMENTS AND PROCEDURES 8.1.2 Liver Biopsy and Fine Needle	The study protocol was updated to include in Part 2 of the study the option to perform liver biopsies in participants who consented separately to this procedure.	To allow a better understanding of the impact of JNJ-3989 treatment on viral and immune markers in the liver in HBV/HDV co-infected participants.

Section number and Name	Description of Change	Brief Rationale
Aspirate Biopsy (Optional with Separate Consent, Part 2 Only) 8.3.6.6 Complications From Liver Biopsy 9.4.8 Other Analyses		
1.3.3 Schedule of Activities – Follow-up Phase	Blood sampling for HBV DNA analysis was added during FU W30 and FU W42 visits for the non-cirrhotic participants who discontinue NA treatment	To protect the safety of the participants.
2.2 Background	The subsection 'Clinical Studies' of the background section of the protocol has been updated with a short summary of the REEF-D Part 1 efficacy and safety data (ie, HDV RNA and ALT results, respectively).	For completeness
6.8 Concomitant Therapy 10.13 Appendix 13: COVID-19 APPENDIX	Guidance was added on the concomitant use of COVID-19 vaccines and JNJ-3989/NA.	Clarification added for completeness.
8 STUDY ASSESSMENTS AND PROCEDURES	The maximum amount of blood drawn from each participant in this study and during the follow up phase has been corrected (from 2500 mL to 3210 mL).	Correction of inconsistency.
6.7 Treatment of Overdose	The definitions of an overdose for JNJ-3989 and NA have been corrected.	Correction of inconsistencies.
6.8 Concomitant Therapy	Anticoagulants have been removed from the list of disallowed medication; instead, they are listed as medication to be used with caution.	Preclinical and clinical data for JNJ-3989 do not show evidence of coagulopathy.
1.3.3 Schedule of Activities – Follow-up Phase	Footnote has been added to the HBeAg quantitative testing in the SoA table for the follow-up phase.	Clarification
1.3.1 Schedule of Activities – Screening and Double-blind Study Intervention Phase (First 48 Weeks)	HDV RNA testing was added to footnote u of the SoA.	Correction of inconsistency.

Section number and Name	Description of Change	Brief Rationale
1.3.1 Schedule of Activities – Screening and Double-blind Study Intervention Phase (First 48 Weeks) 1.3.2 Schedule of Activities – Open-label Study Intervention Phase (Weeks 52 – EOT) 1.3.3 Schedule of Activities – Follow-up Phase	It has been clarified that in case MRI monitoring is used per patient's standard of care, MRI may be used instead of abdominal ultrasound to follow-up on HCC or clinically relevant renal abnormalities.	Clarification
1.3.3 Schedule of Activities – Follow-up Phase	In case of early treatment discontinuation, it has been clarified that follow-up study visits are to be scheduled relative to the last originally planned JNJ-3989 treatment visit.	Clarification
6.3 Measures to Minimize Bias: Randomization and Blinding	The sentence 'Under normal circumstances, the blind should not be broken until all participants have completed the visit at which the primary endpoint is assessed.' has been removed as the protocol text clearly states that at Week 52 it will be communicated to investigators and participants to which treatment arm they were allocated to follow the correct visit schedule during the open-label phase.	Correction of inconsistency
1.3.1 Schedule of Activities – Screening and Double-blind Study Intervention Phase (First 48 Weeks) 1.3.2 Schedule of Activities – Open-label Study Intervention Phase (Weeks 52 – EOT)	It has been clarified that Antidrug antibodies samples should be collected prior to JNJ-3989 administration.	Clarification.
1.3.1 Schedule of Activities – Screening and Double-blind Study Intervention Phase (First 48 Weeks)	It has been clarified that a sample for HLA haplotyping should preferably be collected during the Day 1 visit, but may occur at any other study visit during the double-blind study intervention phase.	Clarification.
5.2 Exclusion Criteria	Exclusion criterion 1 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	Clarification.

Section number and Name	Description of Change	Brief Rationale
	positive results. They can be enrolled if they have a negative HIV RNA test at screening. It was also clarified that participants with evidence of HIV-1 or HIV-2 infection who are on antiretroviral treatment are excluded	
1.1 Synopsis 6.1 Study Interventions Administered	The dosage regimen of ETV for nucleoside-naïve participants has been removed and replaced by a dosage regimen for all participants.	Clarification.
1.3.1 Schedule of Activities – Screening and Double-blind Study Intervention Phase (First 48 Weeks) 1.3.2 Schedule of Activities – Open-label Study Intervention Phase (Weeks 52 – EOT) 1.3.3 Schedule of Activities – Follow-up Phase 8.3.6.1 Intervention-emergent ALT/AST Elevations	It has been clarified that local laboratory assessments could be considered for repeat laboratory testing in case central laboratory testing proves to be difficult or does not provide a result in a timely manner (except for HDV RNA and HBsAg assessment during treatment to protect the blind). Off-treatment local HDV RNA test can be done to exclude/assess for HDV driven flare.	Clarification.
5.1 Inclusion Criteria	It has been clarified that conventional imaging procedures and serum marker panels are not acceptable for exclusion of cirrhosis.	Clarification.
1.3.2 Schedule of Activities – Open-label Study Intervention Phase (Weeks 52 – EOT) 1.3.3 Schedule of Activities – Follow-up Phase	It has been clarified that for liver ultrasound, a window of 1 week is allowed before or after the scheduled visit	Clarification.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 2 (17 June 2021)

Overall Rationale for the Amendment: During conduct of Part 1 of this study, a higher-than-expected proportion of participants (approximately 50% of 22 participants enrolled in Part 1) experienced elevations of alanine aminotransferase (ALT) on treatment. Management of these acute elevations is following protocol defined criteria but some of the cases show a prolonged pattern of ALT elevation for which no management criteria were provided in the protocol.

To better characterize these observed ALT elevations and to protect participants from a potential risk, the Sponsor, after consultation with the Independent Data Monitoring Committee (IDMC), decided to implement the following changes:

1. Introduction of new discontinuation criteria
2. Sponsor unblinding for antiviral activity parameters to interpret the ALT flares
3. Planning an additional interim analysis (IA)

These changes were introduced with immediate effect to allow the Sponsor to provide guidance to sites on study treatment discontinuation.

The additional IA is planned after all participants of Part 1 have completed at least Week 16 (or discontinued earlier). This is taking the observed pattern of ALT elevations into account, where all ALT elevations occurred at or before treatment Week 16.

Part 2 of this study will only be initiated after the results of the additional IA are available and supporting initiation of Part 2.

Furthermore, a second IA during the double-blind phase of Part 1, after all participants of Part 1 have completed at least Week 48 (or discontinued earlier), was introduced, and additional clarifications were made for study conduct and the planned statistical analyses.

Changes Related to the Observed ALT Elevations		
Section number and Name	**Description of Change**	**Brief Rationale**
1.1 Synopsis; 1.3.2 Schedule of Activities – Open-label Study Intervention Phase (Weeks 52 – EOT); 1.3.3 Schedule of Activities – Follow-up Phase 8.1 Efficacy Assessments; 8.3.6.1 Intervention-emergent ALT/AST Elevations;	Criteria for discontinuation of JNJ-3989 in case of prolonged elevation of ALT were added. To allow accurate assessment of the discontinuation criteria, HDV RNA samples will be collected in case of intervention-emergent ALT/AST flares, also prior to the Week 52 visit.	To ensure the safety of participants during the treatment with JNJ-3989.

Changes Related to the Observed ALT Elevations		
Section number and Name	**Description of Change**	**Brief Rationale**
10.6 Appendix 6: Intervention-emergent ALT/AST Elevations		
1.1 Synopsis; 4.1 Overall Design; 6.3 Measures to Minimize Bias: Randomization and Blinding; 9.5 Interim ; 9.5.4 Sponsor Committee; 9.5.5 Independent Flare Expert Panel; 10.3.6 Committees Structure	Two IAs were added to the double-blind phase of Part 1. Part 1 IA1 was added to evaluate data from all participants of Part 1 who have completed at least Week 16 or discontinued earlier. Part 1 IA2 was added to evaluate data from all participants of Part 1 who have completed at least Week 48 or discontinued earlier. Sponsor personnel and members of the Independent Flare Expert Panel (IFLEP) will become unblinded to the Part 1 clinical data at the time of Part 1 IA1. The investigators, participants, site personnel, and operational Sponsor team members involved with the sites will remain blinded. For safety-related decisions, HDV RNA and hepatitis B surface antigen (HBsAg) data may be discussed with investigators on a case-by-case basis. The planned blinding of Part 2 will not be affected.	Part 1 IA1 is introduced to assess and characterize ALT elevations observed in hepatitis D virus (HDV) infected participants of Part 1, and to inform the decision to start Part 2. Part 1 IA2 is introduced to continue the comprehensive assessment of the benefit-risk ratio of the investigational regimen in HDV-infected participants with longer term data on participants of Part 1.

Additional Clarifications and Corrections		
Section number and Name	**Description of Change**	**Brief Rationale**
4.1 Overall Design; 6.3 Measures to Minimize Bias: Randomization and Blinding	It was clarified that unblinding will not occur at the time of early discontinuation for patients who discontinue early, before the Week 52 visit.	Clarification
1.3.1 Schedule of Activities – Screening and Double-blind Study Intervention Phase (First 48 Weeks)	Changes were made to avoid repetitive collection of liver ultrasounds at baseline and to allow flexibility in the scheduling of the ultrasound.	Clarification

Additional Clarifications and Corrections		
Section number and Name	**Description of Change**	**Brief Rationale**
1.1 Synopsis; 4.2 Scientific Rationale for Study Design; 6.3 Measures to Minimize Bias: Randomization and Blinding; 9.2 Sample Size Determination; 9.4.1 General Considerations; 9.4.2.2 Analysis of The Main Estimator; 9.5.2 Interim Analyses of Study Part 2	Text was added to clarify that the randomization ratio of 4:1 (active:control) will remain the same regardless of a potential sample size increase in Part 2, and that the determination of the exact fixed weights used to adjust the efficacy analyses for the sample size re-estimation will be made prior to the IA in Part 2.	Clarification on the fixed randomization ratio and technical details of the statistical method for sample size re-estimation.
9.3 Populations for Analysis Sets	A definition was added for the Modified intent-to-treat (mITT) analysis set.	Address the potential impact of the COVID-19 pandemic on the efficacy analyses.
1.1 Synopsis; 9.4.1 General Considerations; 9.4.2.1 Primary Estimand	Clarified the definition of the main estimand and its attributes for the primary efficacy endpoint.	Clarification of the attributes of the estimand for the primary efficacy endpoint in alignment with the estimand framework in the ICH E9-R1 guidance.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 1 (6 August 2020)

Overall Rationale for the Amendment: This amendment is written to address comments from Health Authorities, to allow for clarifications to be added, and for minor inconsistencies and errors to be corrected.

Changes Requested by Health Authorities		
Section number and Name	**Description of Change**	**Brief Rationale**
5.1 Inclusion Criteria	Inclusion criterion 6 was modified to include only participants who have elevated ALT levels (>ULN) at screening.	As normal ALT is part of the primary endpoint for this study, only participants with elevated ALT levels at screening will be eligible to participate. The threshold of >ULN is aligned with similar inclusion criteria of other drug candidates in development for treatment of HDV infection.
1.1 Synopsis Safety Evaluations; 1.3 Schedule of Activities; 8.3.6.1 Intervention-emergent ALT/AST Elevations; 10.6 Appendix 6: Intervention-emergent ALT/AST Elevations; 11 REFERENCES	The frequency of monitoring participants who experience intervention-emergent ALT/AST elevations was changed to allow for more frequent testing than on a weekly basis. It was highlighted that confirmatory visits should take place “as soon as possible within 7 days” of receipt of the initial ALT/AST results and “on weekly basis or more frequently” until ALT and/or AST levels have returned to 50% of the maximal value.	Based on review of data from chronic HBV patients by Fontana et al,[11] HBV patients who experience an ALT flare may need more frequent laboratory assessments than once a week.
1.1 Synopsis Safety Evaluations; 1.3.3 Schedule of Activities – Follow-up Phase; 8.3.6.1 Intervention-emergent ALT/AST Elevations; 10.6 Appendix 6: Intervention-emergent ALT/AST Elevations	HDV RNA has been added to the list of laboratory parameters to be measured at the confirmatory study visits for participants who experience an ALT flare.	Information on HDV RNA will be made available to the IDMC at any time during the study. HDV RNA results will be made available to the Sponsor and investigators from primary analyses (Week 52) onwards.

Changes Requested by Health Authorities		
Section number and Name	**Description of Change**	**Brief Rationale**
1.1 Synopsis Overall Design; Safety Evaluations; 1.3.3 Schedule of Activities – Follow-up Phase; 4.1 Overall Design; 6.4 Study Intervention Compliance; 6.5 Re treatment With JNJ 3989 and/or NA During the Follow up; 8.3.6.1 Intervention-emergent ALT/AST Elevations	A section was added on re-treatment with JNJ-3989 and/or NA during the follow-up phase in case of transaminase flares and HBV/HDV recurrence.	The original protocol only described management of on-treatment transaminase flares. To ensure the safety of participants during the follow-up phase as well, the management of off-treatment flares was further expanded and the possibility for re-treatment was added, provided that the participant fulfills the protocol-defined re-treatment criteria.
8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	The timing for reporting of SAEs using the Serious Adverse Event Form has been corrected.	Correction of inconsistency.
6.3 Measures to Minimize Bias: Randomization and Blinding	Additional wording was added with regards to breaking the blind to clarify that unblinding of a participant's treatment should not be stalled or delayed in case of an emergency.	Section was revised in order to emphasize unambiguously that the investigator has the primary right to break the blind in order to treat a participant in an emergency.
10.8 Appendix 8: Contraceptive and Barrier Guidance	The footnote on interactions with the study intervention was removed from the Examples of Contraceptives table.	No interaction is expected between JNJ-3989 or NA and oral contraceptives.
10.8 Appendix 8: Contraceptive and Barrier Guidance	The subtitle 'Not Allowed as Sole Method of Contraception During the Study' in the Examples of Contraceptives table was revised to clarify that these methods should be used together with highly effective methods of contraception.	Clarification that, although frequently practiced, less effective methods of contraception should not be used without highly effective methods of contraception.
1.1 Synopsis Overall Design, Statistical Methods; 4.1 Overall Design; 9.4 Statistical Analyses; 9.4.1 General Considerations; 9.4.2.1 Primary Estimand;	Removed the inferentially seamless feature of the study; stated a clear separation of efficacy analyses by study parts, with use of Part 2 data only as the pivotal part of the study.	To protect the study integrity and allow the involvement of the Sponsor Committee in making the decision to initiate Part 2 based on the assessment of antiviral activity criteria in Part 1.

Changes Requested by Health Authorities		
Section number and Name	**Description of Change**	**Brief Rationale**
9.4.2.2 Analysis of The Main Estimator; 9.4.3 Key Secondary Endpoints; 9.4.4 Other Efficacy Endpoints; 9.4.7 Safety Analyses; 9.5 Interim Analysis		
1.1 Synopsis Overall Design, Number of Participants; Statistical Methods; 1.2 Schema; 4.1 Overall Design; 6.3 Measures to Minimize Bias: Randomization and Blinding; 9.2 Sample Size Determination; 11 REFERENCES	The text on sample size calculation was clarified by adding the type of statistical test used, and the justification for the assumptions made in the power calculations and sample size re-estimation. Changed the planned sample size of Part 2 to 145 participants with a potential increase to a maximum of 170.	Clarification of assumptions for the sample size calculation and update of the sample size increase for Part 2 due to the inferential separation of Part 1 from Part 2.
1.1 Synopsis Statistical Methods; 9.4.2.1 Primary Estimand; 9.4.2.2 Analysis of The Main Estimator	Clarification of intercurrent events in the main estimand definition for the primary efficacy endpoint regarding the major protocol violations, and update of the missing data handling rule in presence of intercurrent events. Addition of sensitivity and supplementary estimators for the primary estimand. 'Primary estimator' was changed to 'main estimator' in alignment with the SAP.	Alignment of the missing data handling rule with the treatment policy strategy proposed for selected intercurrent events defined in the primary estimand in accordance with the ICH-E9-R1 guidance. To evaluate the robustness of the assumption of MAR and the type of missing data. Correction of inconsistency between documents.
4.2 Scientific Rationale for Study Design	The rationale for choosing a 4:1 randomization ratio was added.	Clarification.

Additional Changes, Clarifications, and Corrections		
Section number and Name	**Description of Change**	**Brief Rationale**
6.1 Study Interventions Administered	It was specified which NA treatment the participant should start (if treatment-naïve) or continue (if virologically suppressed) at baseline.	Clarification was needed on which NA treatment should be administered during the study to treatment-naïve participants, virologically suppressed participants, and participants who experienced toxicity to either of the NA treatment options prior to screening.
1.1 Synopsis Description of Interventions; 6.1 Study Interventions Administered	A footnote was added to the Description of Interventions table, stating that TAF will be one of the NA treatment options in countries where TAF is commercially available.	Clarification that TAF will only be an NA treatment option in countries where it is commercially available.
5.1 Inclusion Criteria; 5.2 Exclusion Criteria	The timing for assessing the Child-Pugh score was specified. In addition, the point-based indication of the Child-Pugh score in the exclusion criteria has been changed to a category-based indication (ie, category A, B, or C) for consistency throughout the protocol.	The timing for assessing the Child-Pugh score was missing in the original protocol.
5.1 Inclusion Criteria	Wording was added to clarify that the minimum age for inclusion in the study is 18 years, even if the legal age of consent in the participating country is <18 years.	Only participants ≥18 years to ≤65 years of age are eligible for participation in this study. The sentence “or the legal age of consent in the jurisdiction in which the study is taking place” had been added to inclusion criterion 2 of the protocol to exclude patients who cannot legally consent by themselves, as the legal age of consent in some of the participating countries is ≥19 years. For countries with a legal age of consent of <18 years, it was clarified that only patients ≥18 years of age can be enrolled in this study.
1.3.1 Schedule of Activities – Screening and Double-blind Study Intervention Phase (First 48 Weeks)	The timing of liver biopsy for staging of liver fibrosis at screening was corrected in the footnotes of the Schedule of Activities.	Clarification that liver biopsy, if no other method for staging of liver fibrosis is available, is not necessary to be done at screening. The biopsy can still be done at screening, unless it was done within one year from screening.

Additional Changes, Clarifications, and Corrections		
Section number and Name	**Description of Change**	**Brief Rationale**
1.3.3 Schedule of Activities – Follow-up Phase	The early withdrawal (WD) visit has been added to the Schedule of Activities for the follow-up phase.	The early withdrawal (WD) visit was erroneously missing from the Schedule of Activities for the follow-up phase.
1.1 Synopsis Safety Evaluations; 1.3 Schedule of Activities; 2.3.3 Benefit-Risk Assessment for Study Participation; 8.2 Safety Assessments; 8.2.1 Physical Examinations; 8.2.2 Vital Signs; 9.4.7 Safety Analyses	Assessment of body weight has been categorized under vital signs instead of under physical examinations.	Alignment of time points for body weight assessments with time points for assessment of other vital signs.
6.8 Concomitant Therapy	It was specified that any prior IFN use needs to be recorded at screening.	Prior IFN use needs to be recorded in the CRF in order to allow analysis of the data by prior IFN use.
6.8 Concomitant Therapy	In the table with disallowed medication, IFN was removed from the 'disallowed from 6 months prior to baseline until end of follow-up' category of medication.	IFN was erroneously listed in both the 'disallowed from 6 months prior to screening until end of follow-up' and the 'disallowed from 6 months prior to baseline until end of follow-up' categories of medication.
6.8 Concomitant Therapy	In the table with disallowed medication, nucleic acid polymers were added to the 'disallowed at any time prior to screening until end of follow-up' category of medication.	Nucleic acid polymers are another example of oligonucleotide-based treatment and are therefore disallowed at any time prior to screening until end of follow-up.
1.1 Synopsis Overall Design, Safety Evaluations; 1.3.1 Schedule of Activities – Screening and Double-blind Study Intervention Phase (First 48 Weeks); 1.3.3 Schedule of Activities – Follow-up Phase;	A footnote was added to clarify that, for sites in the US, HDV RNA tests used to determine the participant's eligibility for the study (inclusion criteria) and to decide on JNJ-3989 re-treatment during the follow-up phase should be performed by a local laboratory.	Clarification.

Additional Changes, Clarifications, and Corrections		
Section number and Name	**Description of Change**	**Brief Rationale**
6.5.1 Re-treatment With JNJ-3989; 8.3.6.1 Intervention-emergent ALT/AST Elevations		
6.6 Continued Access to Study Intervention After the End of the Study	The text was updated to reflect the possibility that participants might have continued access to JNJ-3989 after the end of the study through compassionate use.	JNJ-3989 might be made available after the end of the study through compassionate use to allow access for patients who are expected to benefit from further treatment with JNJ-3989.
4.1 Overall Design	Definition of the primary analysis in this section has been aligned with the same wording in other sections of the protocol.	Correction of inconsistency.
1.1 Synopsis Pharmacokinetic Evaluations; 8.4.3 Pharmacokinetic Parameters and Evaluations	It was clarified that other PK parameters than AUC may be calculated, if applicable. In addition, it was specified that population PK modeling may be used to enable the calculation of the PK parameter AUC also in participants who only underwent sparse PK sampling.	Clarification/specification of PK parameters.
8.4 Pharmacokinetics	Text was added to clarify that intensive PK testing is optional and will only be done for participants who consent separately to the intensive PK study.	Clarification.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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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	30-Mar-2024 19:40:32 (GMT)	Document Approval