Janssen Research & Development *

Clinical Protocol

Intervention-specific Appendix 6 to Clinical Protocol PLATFORMPAHPB2001

A Phase 2, Open-label, Multicenter Study to Assess Efficacy, Safety, Tolerability, and Pharmacokinetics of Treatment With JNJ-73763989, Nucleos(t)ide Analogs, and Pegylated Interferon Alpha-2a in Patients With Chronic Hepatitis B Virus Infection

The PENGUIN-2 Study

Protocol 73763989PAHPB2007; Phase 2
Amendment 1

JNJ-73763989

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

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY

Document	Date
Amendment 1	This document
Original Protocol	30 June 2021

Amendment 1 (This document)

Overall Rationale for the Amendment:

The primary reasons for this amendment are to include pre-specified nucleos(t)ide analog (NA) treatment completion criteria, and to add a new NA re-treatment criterion and more frequent monitoring for participants who meet the NA treatment completion criteria based on the Week 24 (or Follow-up Week 2) results and discontinue NA treatment during follow-up.

A severe clinical alanine aminotransferase (ALT) flare following discontinuation of NA treatment was reported in a virologically suppressed hepatitis B e antigen (HBeAg) negative participant on long-term tenofovir disoproxil fumarate (TDF) treatment, who was randomized to the control arm (placebo + placebo + NA) in the REEF-2 (73763989PAHPB2002) study. The participant presented with hepatitis B virus (HBV) DNA levels that increased rapidly, before any relevant changes in liver markers were noted. Discontinuation of NA treatment followed the protocol-defined criteria and was in line with recent European Association for the Study of the Liver (EASL) treatment guidelines (EASL 2017). Flares following NA discontinuation are not unexpected, but the rapid evolution and clinical deterioration seen in this participant who was anti-HBe antibody positive at screening and had no history or evidence of liver cirrhosis was unforeseeable. Therefore, to protect safety of participants, the protocol was amended as detailed below.

Other changes were made in this amendment to lower the limit of serum hepatitis B surface antigen (HBsAg) for inclusion from 100 to 5 IU/mL at screening, to adjust the primary endpoint to assess the proportion of participants with a reduction of at least 2 $\log_{10}$ IU/mL in HBsAg levels from baseline at Week 24, and to revise and add secondary objectives and endpoints to account for the introduction of NA treatment completion criteria.

In addition, the pegylated interferon alpha-2a (PegIFN-α2a) eligibility criteria, the PegIFN-α2a discontinuation criteria, and the monitoring of neuropsychiatric adverse events during PegIFN-α2a treatment were amended to be consistent with the PegIFN-α2a prescribing information.

Other clarifications and corrections were also made as detailed below.

Description of Change	Brief Rationale	Section Number and Name
A new NA re-treatment criterion was added for participants who discontinued NA treatment during follow-up.	To ensure that participants with significant HBV DNA increases during treatment free follow-up are monitored more frequently and/or immediately re-start NA treatment irrespective of ALT levels.	1.1 Synopsis, 1.3 Schedule of Activities, 2.3.2.2 Potential Risks, 4.2 Scientific Rationale for Study Design, 6.5.2 NA Re-treatment Criteria During Follow-up, 6.6 Continued Access to Study Intervention After the End of the Study, 8.3.6.2 Intervention-emergent ALT/AST Elevations,

Description of Change	Brief Rationale	Section Number and Name
		10.7 Appendix 7: Intervention-emergent ALT/AST Elevations , 10.12 Appendix 12: NA Re-treatment During Follow-up
Participants who discontinue NA treatment during follow-up, will be monitored more frequently, with a study visit at least once every 4 weeks. The visit frequency for participants who continue NA treatment or have restarted NA treatment during the follow-up period and for whom the HBV DNA and ALT values are stable remains at least once every 12 weeks. For participants with increased follow-up, the total blood volume to be collected during the study will increase.	To further protect the safety of participants.	1.1 Synopsis, 1.2 Schema, 1.3 Schedule of Activities 4.1 Overall Design, 6.5.1 NA Treatment Completion , 6.5.2 NA Re-treatment Criteria During Follow-up, 8 STUDY ASSESSMENTS AND PROCEDURES
NA treatment completion criteria, which take ALT, HBV DNA, HBeAg, and HBsAg levels into consideration, were added. If the NA treatment completion criteria are met based on the Week 24 or Follow-up (FU) Week 2 results, treatment with NA will be stopped at the next scheduled visit (ie, FU Week 2 or FU Week 4). Because of that, the FU Week 2 visit becomes a mandatory visit.	To ensure that only participants with a higher chance of achieving sustained off-treatment response are allowed to stop all study intervention.	1.1 Synopsis, 1.2 Schema, 1.3 Schedule of Activities, 2.3.3 Benefit-Risk Assessment for Study Participation, 4.1 Overall Design, 4.2 Scientific Rationale for Study Design, 6.5.1 NA Treatment Completion , 6.5.2 NA Re-treatment Criteria During Follow-up, 8.1 Efficacy Assessments, 11 REFERENCES
Inclusion criterion A13 was updated to lower the limit of serum HBsAg for inclusion from 100 to 5 IU/mL at screening.	To assess treatment response in participants with a wider range of HBsAg levels at baseline.	5.1 Inclusion Criteria
The primary endpoint was adjusted to assess the proportion of participants with a reduction of at least 2 $\log_{10}$ IU/mL in HBsAg levels from baseline at Week 24. The sample size section and the efficacy analyses section were revised accordingly.	To accommodate the updated Inclusion criterion A13.	1.1 Synopsis, 3 OBJECTIVES AND ENDPOINTS, 9.1 Statistical Hypotheses, 9.2 Sample Size Determination, 9.4.2.1 Primary Efficacy Endpoint, 9.4.2.3 Across ISAs Comparisons of Efficacy
One secondary objective to assess the efficacy of the study intervention was revised and 1 new secondary objective and endpoint was added.	To account for the newly introduced NA treatment completion criteria.	1.1 Synopsis, 3 OBJECTIVES AND ENDPOINTS
The PegIFN-α2a discontinuation criteria were updated to clarify that participants with moderate or severe depression or other psychiatric symptoms should	Upon Health Authority request and to be consistent with the PegIFN-α2a prescribing information	1.3 Schedule of Activities, 5.2 Exclusion Criteria, 7.1 Discontinuation of Study Intervention

Description of Change	Brief Rationale	Section Number and Name
immediately discontinue PegIFN-α2a treatment. In addition, participants will be closely monitored for neuropsychiatric adverse events during the PegIFN-α2a treatment period. Participants who develop a neuropsychiatric adverse event during PegIFN-α2a treatment will be monitored closely until the neuropsychiatric adverse event resolves, by frequent (at least weekly) follow-up phone calls. Furthermore, exclusion criterion A24 was amended to exclude participants with depression or psychiatric disorders that are not adequately controlled on a stable medication regimen.		
An additional TSH/T4 assessment and ophthalmologic examination was added at Week 20.	To ensure that participants in Arm 2 have these assessments after initiating PegIFN-α2a treatment.	1.3 Schedule of Activities
An additional hematology sample was added at Week 36.	To ensure sufficient hematology assessments during follow-up visits that are applicable to all participants.	1.3 Schedule of Activities
At sites collecting peripheral blood mononuclear cell (PBMC) samples, additional PBMC samples will be collected at Week 4 and Week 8.	To explore when the earliest changes in HBV-specific T cell responses and/or other immune cell changes, such as NK cells, can be observed following combination treatment of JNJ-3989, NA, and PegIFN-α2a.	1.3 Schedule of Activities
Recommendations regarding the use of live vaccines during the study were added.	Clarification regarding the use of live vaccines during the study	6.8 Concomitant Therapy, 10.10 Appendix 10: Study Conduct During a Natural Disaster
Exclusion criterion A06 concerning laboratory abnormalities at screening was updated.	Clarification	5.2 Exclusion Criteria
Exclusion criterion A01 was adapted to clarify that participants with a positive HIV-1 or HIV-2 antibody/antigen test at screening should have a confirmatory HIV RNA test, to rule out false positive results. They can be enrolled if they have a negative HIV RNA test at screening. It was also clarified that participants with evidence of HIV-1 or HIV-2 infection who are on antiretroviral treatment are excluded.	Clarification upon Health Authority request	5.2 Exclusion Criteria
It was clarified that a participant who prematurely discontinues PegIFN-α2a (ie, before Week 23	Clarification	4.1 Overall Design, 6.5.1 NA Treatment Completion

Description of Change	Brief Rationale	Section Number and Name
[Arms 1 and 2] or before Week 11 [Arm 3]) should continue treatment with JNJ-3989 and NA as planned.		7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL, 7.1 Discontinuation of Study Intervention
The contraceptive guidance from the Master Protocol was replaced by ISA-specific contraceptive guidance, which includes the following updates versus the Master Protocol version: the list of examples which are not allowed as sole method of contraception during the study and the footnote concerning possible interaction between hormonal contraception and the study intervention have been removed. Additional clarifications were also made.	Upon Health Authority request and to align with the latest version of the sponsor's protocol template.	1.3 Schedule of Activities, 5.1 Inclusion Criteria, 10.5 Appendix 5: Contraceptive and Barrier Guidance
It was clarified that urine pregnancy tests for at-home use are to be provided during the Follow-up period to participants who continue NA treatment or have restarted NA treatment during the follow-up period (provided that their HBV DNA and ALT values are stable).	To allow 4-weekly urine pregnancy testing in between scheduled site visits for participants with less frequent follow-up.	1.3 Schedule of Activities, 8.2.5 Pregnancy Testing
It was clarified that venous blood samples will be collected for measurement of JNJ-3989, NA, and PegIFN-α2a. Bioanalysis of NA and PegIFN-α2a is optional at the discretion of the sponsor.	Clarification	1.1 Synopsis, 1.3 Schedule of Activities, 4.1 Overall Design, 8.4.1 Evaluations
It was clarified that a copy of the dermatologist's report, biopsy, and/or digital pictures if performed for rash management, should be made anonymous and provided to the sponsor.	Clarification	10.6 Appendix 6: Rash Management
Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted	Throughout the protocol

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1. PROTOCOL SUMMARY

1.1. Synopsis

Clinical Protocol 73763989PAHPB2007: A Phase 2, Open-label, Multicenter Study to Assess Efficacy, Safety, Tolerability, and Pharmacokinetics of Treatment With JNJ-73763989, Nucleos(t)ide Analogs, and Pegylated Interferon Alpha-2a in Patients With Chronic Hepatitis B Virus Infection.

Protocol 73763989PAHPB2007 is an intervention-specific appendix (ISA) to Master Protocol PLATFORMPAHPB2001.

JNJ-73763989 (JNJ-3989) is a liver-targeted antiviral therapeutic for subcutaneous injection designed to treat chronic hepatitis B virus (HBV) infection via a ribonucleic acid interference (RNAi) mechanism. Engagement of the cellular RNAi machinery by JNJ-3989 results in specific cleavage of HBV RNA transcripts, thereby reducing the levels of HBV proteins and the pre-genomic ribonucleic acid (pgRNA), the precursor of viral relaxed circular deoxyribonucleic acid (rcDNA). The small interfering RNA (siRNA) triggers in JNJ-3989, JNJ-73763976 (JNJ-3976) and JNJ-73763924 (JNJ-3924), are designed to target all HBV ribonucleic acid (RNA) transcripts derived from covalently closed circular deoxyribonucleic acid (cccDNA), as well as transcripts derived from integrated HBV deoxyribonucleic acid (DNA). The latter has been suggested to be a significant source of hepatitis B surface antigen (HBsAg) in hepatitis B e antigen (HBeAg)-negative patients or patients on long-term (≥2 years) treatment with nucleos(t)ide analogs (NAs), the current standard of care.

The term "study intervention" throughout the protocol, refers to JNJ-3989, nucleos(t)ide analog (NA), and pegylated interferon alpha-2a (PegIFN-α2a)

OBJECTIVES AND ENDPOINTS

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

Objectives	Endpoints
Primary	
• To evaluate the efficacy in terms of HBsAg changes from baseline for the treatment regimens of 24 weeks of JNJ-3989 + 24 weeks of NA + 12 or 24 weeks of PegIFN-α2a (with immediate or delayed start of PegIFN-α2a treatment), as compared to NA standard of care treatment.	• Proportion of participants with a reduction of at least 2 $\log_{10}$ IU/mL in HBsAg levels from baseline at Week 24 (end of study intervention [EOSI]).
Secondary	
• To evaluate the safety and tolerability of the study intervention.	• Safety and tolerability including but not limited to the proportion of participants with (S)AEs and abnormalities in clinical laboratory tests (including hematology, blood biochemistry, blood coagulation, urinalysis, urine chemistry, renal biomarkers), 12-lead electrocardiograms (ECGs), vital signs, and ophthalmologic and physical examinations throughout the study.

Objectives	Endpoints
• To evaluate the efficacy of the study intervention at the end of the 24-week treatment period.	• Proportion of participants meeting the protocol-defined NA treatment completion criteria based on the Week 24 (EOSI) or FU Week 2 results.
• To evaluate the efficacy of the study intervention during the follow-up (FU) period in those participants who met the protocol-defined NA treatment completion criteria based on the Week 24 or FU Week 2 results.	• Proportion of participants with HBsAg seroclearance at FU Week 24 and 48 (ie, 24 and 48 weeks after completion of all study interventions at Week 24) without re-starting NA treatment. • Proportion of participants with HBV DNA <lower limit of quantification (LLOQ) at FU Week 24 and 48 (ie, 24 and 48 weeks after completion of all study interventions at Week 24) without re-starting NA treatment. • Frequency of virologic and/or biochemical flares. • Proportion of participants requiring NA re-treatment.
• To evaluate the efficacy of the study intervention as measured by blood markers (such as HBsAg, HBeAg, HBV DNA, and alanine aminotransferase [ALT]) during the study intervention and FU period.	• Proportion of participants with HBsAg, HBeAg, HBV DNA, and ALT levels below/above different cut-offs over time. • Proportion of participants with HBsAg seroconversion. • Change from baseline over time in HBsAg. • Time to achieve HBsAg seroclearance/ seroconversion, and/or HBV DNA <LLOQ.
• To evaluate the frequency of virologic breakthrough throughout the study.	• Proportion of participants with virologic breakthrough.
• To evaluate the pharmacokinetics (PK) of JNJ-3989 (JNJ-3924 and JNJ-3976), and optionally of NA and PegIFN-α2a.	• PK parameters of JNJ-3989 (JNJ-3924 and JNJ-3976). • Optionally, PK parameters of NA and/or PegIFN-α2a.
Exploratory	
• To explore host and viral baseline and on-treatment markers associated with end of study intervention and/or off-treatment response.	• Association of baseline characteristics and baseline/on-treatment viral and host blood markers with selected on or off-treatment efficacy variables.
• To explore changes in the severity of liver disease.	• Changes in fibrosis (according to Fibroscan liver stiffness measurements) at EOSI and the end of the FU period versus baseline.
• To explore efficacy of the study intervention in terms of changes in HBV RNA and hepatitis B core-related antigen (HBcrAg) levels during the study intervention and FU period.	• Changes from baseline in HBV RNA and HBcrAg levels over time.

Objectives	Endpoints
• To explore the relationship of PK with selected pharmacodynamic (PD) parameters of efficacy and safety.	• Relationship of various PK parameters with selected efficacy and safety endpoints.
• To explore the HBV genome sequence during the study intervention and FU period.	• Assessment of intervention-associated mutations over time.
• To explore HBV-specific T-cell responses during the study intervention and FU period.[a]	• Changes from baseline in HBV-specific peripheral blood T-cell responses over time.[a]
• To explore the efficacy of NA re-treatment in participants who meet the criteria for NA re-treatment.	• Proportion of participants who reach HBV DNA <LLOQ after re-start of NA treatment during the FU period.
• To explore medical resource utilization (MRU) to manage participants during study intervention and follow-up.	• Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient) • Duration of hospitalization (total days length of stay, including duration by wards; eg, intensive care unit) • Number and character of diagnostic and therapeutic tests and procedures • Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications)

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

Hypothesis

The primary hypothesis of this study is that at least one of the combination regimens of JNJ-3989+NA+PegIFN-α2a is more efficacious than NA treatment (standard of care), as measured by the primary efficacy endpoint, the proportion of participants with a reduction of at least 2 $\log_{10}$ IU/mL in HBsAg levels from baseline at Week 24. Because the study does not include a control arm, the hypothesis is formulated assuming a fixed external NA control response rate of 2% in terms of the primary efficacy endpoint.

OVERALL DESIGN

This ISA describes a Phase 2 study of the combination regimen of JNJ-3989 with NA and different durations of PegIFN-α2a, and with an immediate or delayed start of PegIFN-α2a treatment. It is a companion document to the Master Protocol PLATFORMPAHPB2001, which describes the common design elements of the Platform study in participants with chronic HBV infection. This ISA describes specific and/or additional protocol elements applicable to this open-label, 3-arm, multicenter, interventional study to evaluate the efficacy, safety, tolerability, and PK of the combination of JNJ-3989, NAs, and PegIFN-α2a in long-term (≥2 years of NA treatment) virologically suppressed, HBeAg-negative, chronic HBV-infected, adult participants.

This open-label study will be conducted in 3 periods:

- Screening Period (4 weeks [if necessary, eg, for operational reasons, can be extended to a maximum of 8 weeks decided on a case-by-case basis and in agreement with the Sponsor]).

- Treatment Period (24 weeks):

  Arm 1 (N=34): JNJ-3989 for 24 weeks + NA for 24 weeks + PegIFN-α2a for 24 weeks.

  Arm 2 (N=34): JNJ-3989 for 24 weeks + NA for 24 weeks + PegIFN-α2a from Week 12 till Week 24.

  Arm 3 (N=34): JNJ-3989 for 24 weeks + NA for 24 weeks + PegIFN-α2a from baseline till Week 12.

- Follow-up (FU) Period (48 weeks), starting at Week 24.

At baseline, participants who meet the eligibility criteria will be randomized in a 1:1:1 ratio to Arm 1, Arm 2, or Arm 3. Randomization will be stratified by absolute HBsAg level (<1,000 IU/mL versus ≥1,000 IU/mL) at baseline and country grouping as proxy for HBV genotype (GT) at enrollment, with 3 levels: Poland (predominantly GT-A) versus Russia (predominantly GT-D) versus all other countries (other or mixed GT prevalence)[a]. Participants in Arm 2 who no longer meet the PegIFN-α2a eligibility criteria at Week 12, based on available laboratory or clinical data, will continue JNJ-3989 and NA treatment until Week 24 without PegIFN-α2a.

All participants will receive the last dose of JNJ-3989 at Week 24 and the last dose of PegIFN-α2a at Week 23 (Arms 1 and 2) or Week 11 (Arm 3). They will start the FU Period after the Week 24 visit. If all of the following NA treatment completion criteria are met based on the Week 24 results, treatment with NA will be stopped at the next scheduled visit (ie, FU Week 2), otherwise NA treatment will continue during the complete FU Period:

- The participant has ALT <3x ULN, AND
- The participant has HBV DNA <60 IU/mL at Week 24 and HBV DNA <LLOQ at the previous visit, or HBV DNA <LLOQ at Week 24, AND
- The participant is HBeAg-negative, AND
- The participant has HBsAg <100 IU/mL.

Note: Participants who are close to meeting the protocol-defined NA treatment completion criteria with the Week 24 results, and do meet the criteria based on the FU Week 2 results may be allowed to stop NA at FU Week 4, after consultation with the Sponsor.

Participants who meet the protocol-defined NA treatment completion criteria based on the Week 24 or FU Week 2 results will be monitored closely during the 48-week FU Period with a study visit at least once every 4 weeks. NA treatment should be re-started in accordance with the NA re-treatment criteria (see below for more details).

Study intervention consists of:

- JNJ-3989: 200 mg subcutaneous injection every 4 weeks (Q4W)
- NA: tenofovir disoproxil (245 mg), or tenofovir alafenamide (TAF) (25 mg), or entecavir (ETV) (0.5 mg) tablets orally, daily (QD)
- PegIFN-α2a: 180 µg subcutaneous injection weekly (QW).

Assessments and sampling include efficacy (eg, HBsAg, HBeAg, and HBV DNA), safety (eg, [S]AEs, labs, ECGs, vital signs, physical examinations), PK, PK/ PD, viral genome sequencing, PBMC, human leukocyte

[a] Kim BK, Revill PA, Ahn SH, et al. HBV genotypes: relevance to natural history, pathogenesis and treatment of chronic hepatitis B. Antiviral Therapy. 2011;16:1169-1186

antigen (HLA) typing, immunogenicity and pharmacogenomic samples, blood sampling for exploratory analysis of host and viral markers, and medical resource utilization.

The total duration of individual participation will be up to 72 weeks (screening not included). Participants will be considered to have completed the study if they have completed all the assessments of the end of study (EOS) visit (ie, FU Week 48).

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

NA Re-treatment Criteria During Follow-up

Participants who meet the protocol-defined NA treatment completion criteria (based on the Week 24 or FU Week 2 results) will be monitored closely during the follow-up period with a study visit at least once every 4 weeks. They should re-start NA treatment immediately in the event of:

- Signs of decreasing liver function based on laboratory findings (eg, International Normalized Ratio [INR], direct bilirubin) or clinical assessment (eg, ascites, hepatic encephalopathy).
- HBV DNA value of >1,000,000 IU/mL (irrespective of confirmation and/or ALT increase).

  Note: A post-treatment HBV DNA value of >100,000 IU/mL should trigger re-testing of ALT/AST, HBV DNA, and total and direct bilirubin within a maximum of 7 days from receipt of the data and further repeats as necessary (ie, weekly until HBV DNA returns to <100,000 IU/mL). A post-treatment HBV DNA value of >20,000 IU/mL (but <100,000 IU/mL) should trigger a re-test within 14 days. At all times, additional re-testing of the above parameters should be performed at the investigator's discretion.

In addition, re-start of NA treatment should be considered in the following cases:

- Confirmed post-treatment HBeAg seroreversion (HBeAg positive after it was negative at NA completion), OR
- Confirmed (at least 4 weeks apart) post-treatment increases in HBV DNA >2,000 IU/mL and ALT >5x upper limit of normal (ULN), OR

  Note: A post-treatment ALT value of >5x ULN should trigger re-testing of ALT, AST, ALP, total and direct bilirubin, INR, albumin, and HBV DNA on a weekly basis until ALT and AST levels have returned to <5x ULN. At all times, additional re-testing of these parameters should be performed at the investigator's discretion.

- Confirmed (at least 4 weeks apart) post-treatment increases in HBV DNA >20,000 IU/mL.

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

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

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

NUMBER OF PARTICIPANTS

Approximately 102 long-term (≥2 years of NA treatment) virologically suppressed, HBeAg-negative, chronic HBV-infected, adult participants, ≥18 (or the legal age of consent in the jurisdiction in which the study is taking place) to 65 years of age (inclusive) will be enrolled in this study.

DESCRIPTION OF INTERVENTIONS

Intervention Name	JNJ-3989	PegIFN-α2a	Tenofovir disoproxil	Tenofovir alafenamide (TAF)*	Entecavir (ETV) monohydrate
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	180 µg/0.5 mL	245 mg	25 mg	0.5 mg
Dosage Level(s)	200 mg once every 4 weeks (Q4W)	180 µg once weekly (QW)	245 mg QD	25 mg QD	0.5 mg QD
Route of Administration	Subcutaneous injection (preferably in the abdomen)	Subcutaneous injection (in the thigh or abdomen)	Oral	Oral	Oral
Use	Investigational intervention	Investigational intervention	Background intervention	Background intervention	Background intervention
Investigational Medicinal Product (IMP)	Yes	Yes	Yes	Yes	Yes
Non-investigational Medicinal Product/ Auxiliary Medicinal Product (NIMP/AxMP)	No	No	No	No	No
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	Each unit will be labeled with unique medication ID number	Commercial supplies will be sourced. Each unit will be labeled with unique medication ID number.	Commercial supplies will be sourced. Each unit will be labeled with unique medication ID number.	Commercial supplies will be sourced. Each unit will be labeled with unique medication ID number.	Commercial supplies will be sourced. Each unit will be labeled with unique medication ID number.
		In child resistant packaging	In child resistant packaging	In child resistant packaging	In child resistant packaging
Food/Fasting Instructions	Regardless of food intake	Per the prescribing information	Per the prescribing information	Per the prescribing information	Per the prescribing information

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

* In countries where TAF is available, it will be one of the NA treatment options.

EFFICACY EVALUATIONS

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

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

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

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

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

Sequencing

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

SAFETY EVALUATIONS

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

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 injection site reactions (ISRs), alanine aminotransferase/aspartate aminotransferase (ALT/AST) elevations, and hematologic abnormalities. In addition, the following toxicities will also be carefully monitored: rash, renal complications, and acute systemic allergic reactions.

PHARMACOKINETIC EVALUATIONS

All participants will have sparse PK sampling during the treatment period.

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

Serum collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period.

PHARMACOKINETIC/PHARMACODYNAMIC EVALUATIONS

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

HOST GENETICS

An optional sample for HLA testing will be collected from participants who consent separately to this component of the study.

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

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

EXPLORATORY HOST BIOMARKERS

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

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

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

IMMUNE ASSESSMENTS

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

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

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

Blood samples taken at the time points indicated in the Schedule of Activities, can also be used to explore the emergence of antidrug antibodies to JNJ-3989 and optionally to PegIFN-α2a. Antidrug antibodies may

be analyzed using assays such as an enzyme-linked immunosorbent assay or functional assays. The analyses may also include gene expression and cytokine analyses assessing markers such as interferon-stimulated genes (ISGs), IFN-α, and interferon γ-induced protein 10 (IP-10).

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 duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days length of stay, including duration by wards; eg, intensive care unit)
- Number and character of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications)

STATISTICAL METHODS

Sample Size Determination

A sample size of 30 participants per arm yields >95% statistical power to detect a ≥30% difference in at least one arm in the proportions of participants with a reduction of at least 2 $\log_{10}$ IU/mL in HBsAg levels from baseline at Week 24 versus a fixed proportion of ≤2%, assumed for external control (NA treatment). Statistical power to test the primary hypothesis was assessed for each of the intervention arms, separately, using an exact test for single proportion with a one-sided Type 1 error rate of 0.05 and applying the Hochberg procedure for multiple comparisons adjustment. The assumed external control value is based on the data of the NA control arm in virologically suppressed HBeAg negative participants in study 73763989HPB2001 (REEF-1).

The total study sample size is 102 participants (34 per arm) with 1:1:1 randomization ratio to one of the three intervention arms, assuming an approximate 10% attrition rate.

For the secondary set of pairwise comparisons of the primary efficacy endpoint among the 3 study intervention arms (Arm 1 versus Arm 2, Arm 1 versus Arm 3, and Arm 2 versus Arm 3), the planned sample size yields about 68% power to detect a significant difference of 30%, assuming the lowest response rate at Week 24 to be 50% in one of the intervention arms, and 80% in one or both of the other 2 arms. The one-sided Type 1 error rate of 0.05 will be controlled for multiplicity by the Hochberg procedure.

Efficacy Analyses

The primary efficacy analysis will be performed when all participants have completed the Week 24 (EOSI) visit or discontinued earlier. The final analysis will be performed when all participants have completed the last study visit at Week 72 (FU Week 48) or discontinued earlier.

To evaluate the efficacy, the primary analysis set will be the Full Analysis Set (FAS; ie, all participants who were randomly assigned to an intervention arm in this ISA and received at least 1 dose of study intervention within this ISA). The IFN-FAS set will be used for sensitivity analyses of selected efficacy endpoints. (ie, all participants who were randomly assigned to an intervention arm in this ISA and received at least 1 dose of PegIFN-α2a within this ISA).

Primary Efficacy Endpoint

The proportion of participants who achieved a reduction of at least 2 $\log_{10}$ IU/mL in HBsAg levels from baseline at Week 24 will be summarized for each treatment arm paired with a two-sided, single arm 90% confidence interval (CI) based on the Clopper-Pearson method. The statistical comparison will be conducted using an exact binomial test against a fixed external control value of 2% at a one-sided Type 1 error rate of 0.05 and applying the Hochberg procedure for adjusting for multiple comparisons.

The Mantel-Haenszel (MH) test adjusted for the randomization stratification factors will be used in a secondary analysis comparing the primary endpoint between the study intervention arms at a one-sided alpha level of 0.05 and applying the Hochberg procedure for multiple comparisons adjustment.

Secondary Efficacy and Exploratory Endpoints

Descriptive statistics will be used for all efficacy endpoints, which will be summarized by intervention arm and by study period. Comparisons between intervention arms and 90% CIs will be done with no adjustment for multiplicity. Specific key selected endpoints may be analyzed using suitable categorical data approaches (eg, Mantel-Haenszel or logistic regression for proportions or other categorical type of endpoint), longitudinal repeated measures models (eg, for continuous types of variables), or survival analysis based on the Kaplan-Meier estimates (for time-to-event variables), as appropriate. Details will be described in the Statistical Analysis Plan (SAP).

Graphic data displays of different type (eg, bar charts, line plots, waterfall, and radar plots) will also be used to summarize the efficacy data by intervention arm and over time.

Across ISAs Comparisons of Efficacy

To further evaluate the impact of potential differences between ISAs, a virtual control arm will be generated for this ISA. Virtual control efficacy data will be defined as IFN-free regimen with JNJ-3989+NA at the dose level used in this ISA. Creating a virtual control arm by fitting the PK/PD model to the available HBsAg data can be performed for subjects with serum HBsAg >100 IU/mL at screening. The same approach may also be considered for subjects with serum HBsAg ≤100 IU/mL at screening, but as these subjects were typically not included in previous JNJ-3989 studies, the feasibility of this approach will be assessed based on the current analysis results.

For each participant in Arm 2 of this ISA, the HBsAg data for “virtual” control subjects will be generated using an appropriate longitudinal model (eg, kinetic pharmacodynamic model [KPD] or PK/PD model) developed and validated based on the data from the 73763989HPB2001 (REEF-1) study. In Arm 2, the first 12 weeks of HBsAg data under treatment with JNJ-3989+NA alone will enable to estimate individual parameters (ie, Empirical Bayes Estimates) describing each participant's specific HBsAg temporal kinetics. These individual parameters will be used further to extrapolate each participant’s individual HBsAg values over time, as if that participant had been treated with JNJ-3989+NA regimen (matching the same JNJ-3989 dose level) but without receiving PegIFN-α2a treatment. The observed HBsAg levels post PegIFN-α2a intake will be directly compared to virtual control model-generated data for this arm. Due to the randomization, the virtual control subjects derived for Arm 2 can be considered exchangeable with the participants of the other arms in this ISA. Therefore, the summary statistics at the group level of the virtual control subjects for Arm 2 constitute a virtual control arm for the other arms.

In addition, indirect comparisons of the primary endpoint between different regimens across ISAs will be performed in an exploratory fashion by selecting the similar subgroup of participants in other ISAs who match the most important inclusion/exclusion criteria and demographic characteristics in this ISA, such as for example the virologically suppressed participants who are HBeAg negative at screening.

More details on this approach and its application to secondary endpoints will be provided in a separate analysis plan document.

Safety Analyses

Safety analyses will be based on the safety population.

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

Other Analyses

Pharmacokinetic Analyses

Population PK analysis of concentration-time data of JNJ-3976 and JNJ-3924, and, optionally, of NA and PegIFN-α2a 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. 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.

Pharmacokinetic/Pharmacodynamic Analyses

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

Modeling of key PD parameters (eg, HBsAg, HBV DNA) may be performed using population PK/PD. If PK/PD modeling of key efficacy endpoints is performed, treatment effect and possible covariates may be investigated. Other biomarkers may be explored at the Sponsor's discretion. If applicable, the results will be described in a separate report.

Resistance analysis

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

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

Pharmacogenomic Analyses

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

Host Biomarker Analyses

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

Immune Analyses

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

Medical Resource Utilization

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

Interim Analyses

Interim analyses (IA) will be conducted to assess safety and evaluate the time course of different safety and efficacy markers to support the Sponsor's interactions with health authorities, as well as to inform internal decisions about additional studies and/or investigation of other treatment combinations.

The IAs are planned when:

- Approximately 50% of the randomized participants have completed Week 12 or discontinued earlier.
- Approximately 50% of the randomized participants have completed Week 24 or discontinued earlier.
- All randomized participants have completed Week 36 (FU Week 12) or discontinued earlier.
- All randomized participants have completed Week 48 (FU Week 24) or discontinued earlier.
- All randomized participants have completed Week 60 (FU Week 36) or discontinued earlier.

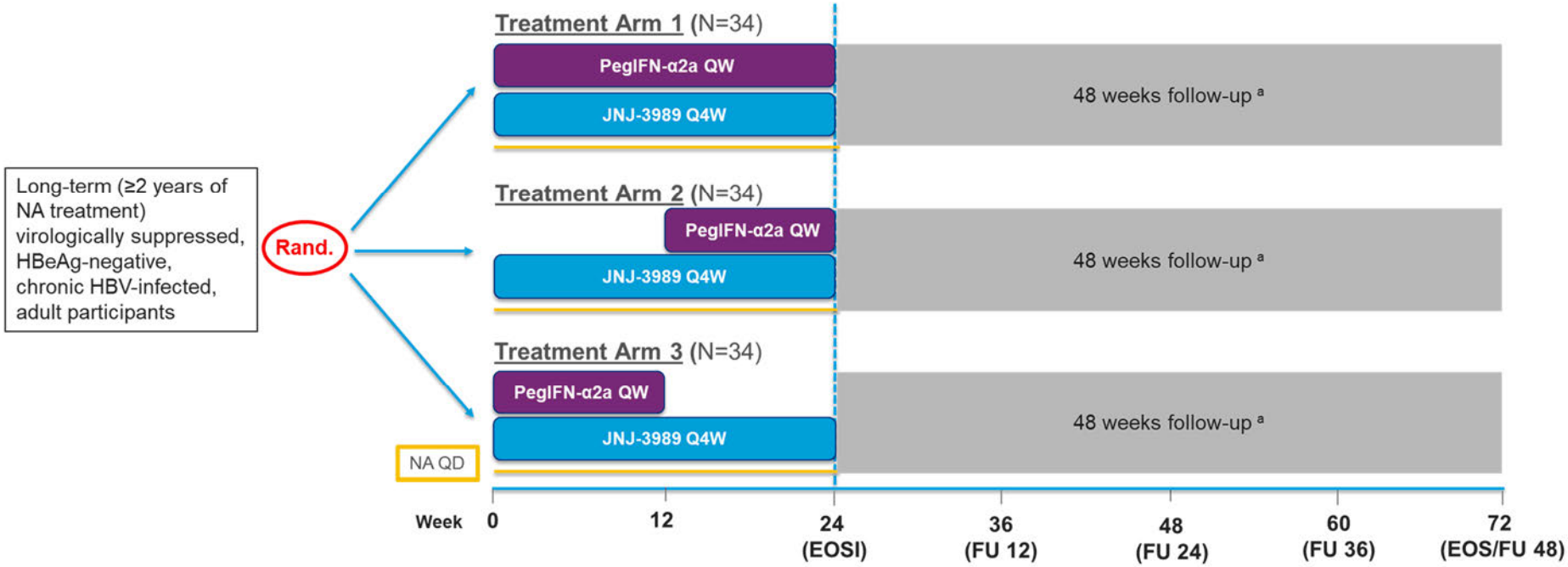
Depending on the enrollment rate, any of the above IAs may be skipped if it is too close to the predicted timing of any adjacent interim cutoffs and additional IAs may be performed by the Sponsor to support interactions with health authorities.

The study is open-label, and the Sponsor will conduct IA(s). Hence, the study team and the DRC will have access to the IA results, while the investigators and patients will not.

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

1.2. Schema

Figure 1: Schematic Overview of the Study



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

[a] If all of the NA treatment completion criteria (see Section 6.5.1, NA Treatment Completion, for more details) are met based on the Week 24 results, NA will be stopped at the next scheduled visit (ie, FU Week 2), otherwise NA treatment will continue during the complete FU period.

Note: Participants who are close to meeting the protocol-defined NA treatment completion criteria with the Week 24 results, and do meet the criteria based on the FU Week 2 results may be allowed to stop NA at FU Week 4, after consultation with the Sponsor.

Participants who meet the protocol-defined NA treatment completion criteria will be monitored closely during the 48-week FU Period with a study visit at least once every 4 weeks. NA treatment should be re-started in accordance with the NA re-treatment criteria (see Section 6.5.2, NA Re-treatment Criteria During Follow-up, for more details).

1.3. Schedule of Activities

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

Study Period	Screening	Treatment[a,b,c]									Follow-up[a,c,d]												
Visit Day (D)/Week (W)	W 4 to 0[e]	W0/ D1	W2[f]	W4	W8	W12	W14[g]	W16	W20	W24/ EOSI/ WD[c]	FU W2	FU W4	*FU W8*	FU W12	*FU W16*	*FU W20*	FU W24	*FU W28*	*FU W32*	FU W36	*FU W40*	*FU W44*	FU W48 /EOS /WD[e]
Study Day (Window)	28 to 0	1	15 +/ 2d	29 +/ 2d	57 +/ 2d	85 +/ 2d	99 +/ 3d	113 +/ 3d	141 +/ 3d	169 +/ 3d	15 +/ 4d	29 +/ 4d	*57 +/ 4d*	85 +/ 4d	*113 +/ 4d*	*141 +/ 4d*	169 +/ 4d	*197 +/ 4d*	*225 +/ 4d*	253 +/ 4d	*281 +/ 4d*	*309 +/ 4d*	337 +/ 4d
Screening/ Administrative																							
ICF[h]	X																						
ICF for optional pharmacogenomic samples	X																						
Inclusion/exclusion criteria[i]	X																						
PegIFN α2a eligibility	X					X[j]																	
Prestudy therapy (including prior anti HBV therapy)	X																						
Medical/surgical history and demographics[k]	X																						
Preplanned surgery/procedure(s)	X																						
Fibroscan or liver biopsy[l]	X																						
Ultrasound[m]	X																						
Study Intervention																							
Randomization		X																					
Administration of JNJ 3989		X		X	X	X		X	X	X													
Intake of NA[n,o]		X	X	X	X	X	X	X	X	X	(X)[p]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Dispensation of NA[o]		X		X	X	X		X	X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)[oo]
Administration of PegIFN α2a[q,o]:																							
Arm 1		*Weekly*																					
Arm 2						*Weekly*																	
Arm 3		*Weekly*																					
Dispensation of PegIFN α2a[q,o]:																							
Arm 1		X		X	X	X		X	X														
Arm 2						X		X	X														
Arm 3		X		X	X																		

Study Period	Screening	Treatment[a,b,c]									Follow-up[a,c,d]												
Visit Day (D)/Week (W)	W 4 to 0[e]	W0/ D1	W2[f]	W4	W8	W12	W14[g]	W16	W20	W24/ EOSI/ WD[c]	FU W2	FU W4	*FU W8*	FU W12	*FU W16*	*FU W20*	FU W24	*FU W28*	*FU W32*	FU W36	*FU W40*	*FU W44*	FU W48 /EOS /WD[e]
Study Day (Window)	28 to 0	1	15 +/ 2d	29 +/ 2d	57 +/ 2d	85 +/ 2d	99 +/ 3d	113 +/ 3d	141 +/ 3d	169 +/ 3d	15 +/ 4d	29 +/ 4d	*57 +/ 4d*	85 +/ 4d	*113 +/ 4d*	*141 +/ 4d*	169 +/ 4d	*197 +/ 4d*	*225 +/ 4d*	253 +/ 4d	*281 +/ 4d*	*309 +/ 4d*	337 +/ 4d
Provide PegIFN α2a self injection tracker[r]:																							
Arm 1		X				X																	
Arm 2						X																	
Arm 3		X																					
Review PegIFN α2a self injection tracker[r]:																							
Arm 1			*At every study visit*																				
Arm 2							*At every study visit*																
Arm 3			*At every study visit*																				
Study intervention accountability[o]			X	X	X	X	X	X	X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Assess NA treatment completion criteria[p,ww]											X	(X)											
Continuous assessment of NA re treatment criteria, as applicable[o]												(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Safety Assessments																							
Complete physical examination[s]	X									X													
Body weight and symptom directed physical examination		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmologic examination (including fundoscopy)[t]	X				X				X														
Vital signs[u]	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[v]	X	X		X		X				X		X											
Injection site reactions (for JNJ 3989 and/or PegIFN α2a)		X	X	X	X	X	X	X	X	X	X												
Liver ultrasound		(X)[w]								X							X						X
Medical resource utilization[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[y]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X		X		X	X
Blood chemistry (including cystatin C and liver function tests)[z,aa,bb]	X	X	X	X	X	X	X	X	X	X	X	X	X[cc]	X	X[cc]	X[cc]	X	X[cc]	X[cc]	X	X	X	X
Blood coagulation	X	X	X	X	X	X	X	X	X	X	X	X		X			X			X		X	X
Urinalysis[dd]	X	X	X	X	X	X	X	X	X	X	X[ee]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X
Urine chemistry[ff]	X	X	X	X	X	X	X	X	X	X	X[ee]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X
Renal biomarkers[gg]		X				X				X													

Study Period	Screening	Treatment[a,b,c]									Follow-up[a,c,d]												
Visit Day (D)/Week (W)	W 4 to 0[e]	W0/ D1	W2[f]	W4	W8	W12	W14[g]	W16	W20	W24/ EOSI/ WD[c]	FU W2	FU W4	*FU W8*	FU W12	*FU W16*	*FU W20*	FU W24	*FU W28*	*FU W32*	FU W36	*FU W40*	*FU W44*	FU W48 /EOS /WD[e]
Study Day (Window)	28 to 0	1	15 +/ 2d	29 +/ 2d	57 +/ 2d	85 +/ 2d	99 +/ 3d	113 +/ 3d	141 +/ 3d	169 +/ 3d	15 +/ 4d	29 +/ 4d	*57 +/ 4d*	85 +/ 4d	*113 +/ 4d*	*141 +/ 4d*	169 +/ 4d	*197 +/ 4d*	*225 +/ 4d*	253 +/ 4d	*281 +/ 4d*	*309 +/ 4d*	337 +/ 4d
Testing for hepatitis A, B, C, D, and E virus, HIV 1 and 2[bb]	X																						
Serum IgM anti HBc antibody test	X																						
FSH test (postmenopausal women only)[hh]	X																						
AFP test[bb,ii]	X									X							X						X
Hemoglobin A1c test	X																						
Serum pregnancy test (women of childbearing potential only)	X																						
Urine pregnancy test (women of childbearing potential)[ii]		X		X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
TSH and T4	X				X				X														
Efficacy Evaluations																							
Fibroscan[kk]		(X)								(X)							(X)						(X)
HBV Virology																							
Blood sampling for HBV DNA[ww]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV genotype[ll]		X																					
Blood sampling for HBV RNA[mm]	X	X		X	X	X		X	X	X		X		X			X						X
Sampling for viral genome sequencing[nn]		X				X				X				X		X		X		X			X
HBV Serology																							
Blood sampling for:																							
Anti HBs and anti HBe	X	X				X				X		X		X			X			X			X
HBsAg and HBeAg (qualitative)	X	X				X			X					X			X						X
HBsAg (quantitative)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBeAg (quantitative)	X					X			X		X	X	X	X	X	X	X	X	X	X	X	X	X
HBcrAg[mm]	X	X		X	X	X		X	X	X		X		X			X			X			X
Exploratory serology[pp]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X			X			X
Clinical Pharmacology Assessments																							
Blood sampling for sparse PK of JNJ 3989, NA and PegIFN α2a[qq]		X		X		X		X		X													
Exploratory Host Biomarkers																							
Whole blood RNA gene expression (RNA PAXgene tubes)		X[rr]	X	X		X[rr]	X	X		X													X

Study Period	Screening	Treatment[a,b,c]									Follow-up[a,c,d]												
Visit Day (D)/Week (W)	W 4 to 0[e]	W0/ D1	W2[f]	W4	W8	W12	W14[g]	W16	W20	W24/ EOSI/ WD[c]	FU W2	FU W4	*FU W8*	FU W12	*FU W16*	*FU W20*	FU W24	*FU W28*	*FU W32*	FU W36	*FU W40*	*FU W44*	FU W48 /EOS /WD[e]
Study Day (Window)	28 to 0	1	15 +/ 2d	29 +/ 2d	57 +/ 2d	85 +/ 2d	99 +/ 3d	113 +/ 3d	141 +/ 3d	169 +/ 3d	15 +/ 4d	29 +/ 4d	*57 +/ 4d*	85 +/ 4d	*113 +/ 4d*	*141 +/ 4d*	169 +/ 4d	*197 +/ 4d*	*225 +/ 4d*	253 +/ 4d	*281 +/ 4d*	*309 +/ 4d*	337 +/ 4d
Whole blood single cell profiling (Smart Tubes)		X[rr]	X		X	X[rr]	X			X		X	X	X			X			X			X
Host serum proteins (eg, cytokines)		X[rr]		X	X	X[rr]				X		X	X	X			X			X			X
Antidrug antibodies (to JNJ 3989 and PegIFN α2a)		X				X		X		X				X			X						X
Immune Monitoring																							
Immune cells (PBMCs) (selected sites only)[tt]		X		X	X	X		X		X			X				X						X
Pharmacogenomics (DNA)																							
HLA typing (optional)[ss]		X																					
Exploratory host genotyping (optional)[ss]		X																					
Epigenetic research (optional)[ss]		X[rr]				X[rr]				X		X		X			X						X
Ongoing Participant Review																							
Concomitant therapy[uu]	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[uu,vv]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

For Japan only: twice weekly visits are to be scheduled during the first week of treatment with PegIFN-α2a (ie, Week 0 for Arms 1 and 3; Week 12 for Arm 2), followed by weekly visits up to Week 12 (Arm 3) or Week 24 (Arms 1 and 2), for assessment of safety (injection site reactions, physical examination, ophthalmologic examination [when indicated], vital signs), concomitant therapy and adverse events. Hematology assessments are required during the first 8 weeks after initial PegIFN-α2a injection: twice in the first week and weekly afterwards.

AFP: alpha fetoprotein; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CKD EPI: Chronic Kidney Disease Epidemiology Collaboration; CRF: case report form; CT: computed tomography; D/d: day; DAIDS: Division of Acquired Immunodeficiency Syndrome; DBP: diastolic blood pressure; DNA: deoxyribonucleic acid; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; EOS: end of study; EOSI: end of study intervention; FSH: follicle stimulating hormone; FU: follow up; GI giga; HBc: hepatitis B core protein; HBe(Ag): hepatitis B e (antigen); HBcrAg: hepatitis B core related antigen; HBs(Ag): hepatitis B surface (antigen); HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HIV 1 (2): human immunodeficiency virus type 1 (type 2); HLA: human leukocyte antigen; ICF: informed consent form; IgM: immunoglobulin M; INR: International Normalized Ratio; ISA: intervention specific appendix; MRI: magnetic resonance imaging; NA: nucleos(t)ide analog; PBMC: peripheral blood mononuclear cells; PegIFN α2a: pegylated interferon alpha 2a; PK: pharmacokinetic; RBC: red blood cell; RNA: ribonucleic acid; SBP: systolic blood pressure; T4: thyroxine; TSH: thyroid stimulating hormone; ULN: upper limit of normal; W: week; WD: withdrawal.

a. All study visits are to be scheduled relative to the baseline (Day 1) visit date. All follow up study visits are to be scheduled relative to the Week 24/EOSI/WD visit. An unscheduled visit can be performed upon the investigator's discretion, in case of HBV DNA elevations, ALT elevations, other signs of worsening of liver disease, or for any other reason.

b. At all visits, blood samples should be collected before administration/intake of study intervention (JNJ 3989, PegIFN α2a, and NA), unless indicated otherwise.

c. Participants who discontinue study intervention early will have an early WD visit and will enter follow up unless they withdraw consent. Participants who withdraw consent will be offered an optional safety follow up visit to occur on the day of consent withdrawal. For the optional safety follow up visit, assessments are at the investigator's discretion and could be similar to the early WD visit.

d. Visits at follow up Week 8, 16, 20, 28, 32, 40, and 44 are optional for participants who continue NA treatment or have restarted NA treatment during the follow up period (provided that their HBV DNA and ALT values are stable) and mandatory for participants who do not continue NA treatment during the follow up period. Participants who experience

ALT/AST elevations as defined in Section 8.3.6.2, Intervention emergent ALT/AST Elevations, will be monitored on a weekly basis or more frequently until ALT and AST levels have returned to <5x ULN and HBV DNA is <20,000 IU/mL.

e. If necessary (eg, for operational reasons), the Screening Period may be extended up to a maximum of 8 weeks in agreement with the Sponsor.

f. Only applicable for participants of Arms 1 and 3.

g. Only applicable for participants of Arm 2.

h. Both the Platform Master ICF and the ISA ICF must be signed before the first study related activity.

i. Minimum criteria for the availability of documentation supporting the eligibility criteria are described in the source documents section in Attachment 3 of the Master Protocol PLATFORMPAHPB2001. Clinical status will be checked and documented at screening and again before first dose of study intervention. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study.

j. Only applicable for Arm 2: Exclusion criterion A24 regarding contraindications to the use of PegIFN α2a needs to be checked and documented again prior to the first dose of PegIFN α2a on Week 12. If an Arm 2 participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after randomization but before the first dose of PegIFN α2a is administered, such that he or she meets exclusion criterion A24, then the participant will continue treatment as planned but without PegIFN α2a (ie, JNJ 3989+NA until Week 24).

k. Medical history also includes mode of HBV transmission, stage of liver fibrosis, and alcohol consumption. Historical HBV DNA, ALT, HBsAg, and HBeAg data, if available, will be recorded in the CRF and/or source documents. Available historical data on previous HBV genotype assessments will also be collected in the CRF. HBeAg status should also be recorded.

l. 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).

m. Participants must have absence of signs of cirrhosis or portal hypertension (absence of nodules, smooth liver contour, normal portal vein, spleen size <12 cm) and absence of signs of HCC or clinically relevant renal abnormalities on an abdominal ultrasound performed within 3 months prior to screening or at the time of screening. In case of suspicious findings on conventional ultrasound the participant may still be eligible if HCC or clinically relevant renal abnormalities have been ruled out by a more specific imaging procedure (contrast enhanced ultrasound, CT or MRI).

n. In between study visits, participants will take NA at home and will bring their NA with them to each study visit. At study visits, the NA should be taken on site.

o. No JNJ 3989/PegIFN α2a will be administered or dispensed during follow up. Administration/Dispensation of NA is only applicable for participants who could not stop NA treatment at FU Week 2 or FU Week 4, or for those who met the NA re treatment criteria. Sufficient NA will need to be dispensed as visits during follow up only take place every 12 weeks for participants who continue or have restarted NA treatment.

p. If the NA treatment completion criteria are met based on the Week 24 results, treatment with NA will be stopped at the next scheduled visit (ie, FU Week 2). Participants who are close to meeting the protocol defined NA treatment completion criteria with the Week 24 results, and do meet the criteria based on the FU Week 2 results may be allowed to stop NA at FU Week 4, after consultation with the Sponsor.
Participants who meet the protocol defined NA treatment completion criteria will be monitored closely during the 48 week FU Period with a study visit at least once every 4 weeks. NA treatment should be re started in accordance with the NA re treatment criteria (see Section 6.5.2, NA Re treatment Criteria During Follow up, for more details).

q. The first administration of PegIFN α2a at Day 1 (Arms 1 and 3) or Week 12 (Arm 2) must be performed at the study site by the investigator or his/her designee. Thereafter, weekly PegIFN α2a administration should preferably be done on the same day of the week in the evening by self injection. For participants in Arm 1, a total of 24 injections should be administered, starting at Day 1, with the last injection during Week 23. For participants in Arm 2, a total of 12 injections should be administered, starting at Week 12, with the last injection during Week 23. For participants in Arm 3, a total of 12 injections should be administered, starting at Day 1, with the last injection during Week 11. If desired, participants can also choose to have the weekly administration of PegIFN α2a performed on site irrespective of the time of day. For countries that do not allow PegIFN α2a self injection: weekly administration of PegIFN α2a must be performed at the study site by the investigator or his/her designee.

r. Only applicable for participants who are administering PegIFN α2a by self injection. These participants will be requested to complete a self injection tracker. Each tracker covers a 12 week treatment period. Refer to Section 6.4, Study Intervention Compliance for more details.

s. Complete physical examination, including height (only at screening), body weight, skin examination, and other body systems.

t. For participants with a risk factor (eg, diabetes or hypertension), an ophthalmic examination at Week 8 (+/ 3 weeks) and Week 20 (+/ 3 weeks) of the treatment phase should be considered. Any participant experiencing a decrease or loss of vision at any time point during study participation, must have a prompt ophthalmic examination.

u. Vital signs include supine SBP, DBP, pulse rate, and body temperature.

v. All ECGs will be read centrally. Only on Day 1, an ECG will be collected and assessed locally prior to dosing. The ECG collected locally on Day 1 should be completed before any tests, procedures or other consultations for that visit.

w. The liver ultrasound does not need to be repeated at baseline if it was done at screening or within 3 months prior to screening. For any subsequent liver ultrasound, a window of 1 week is allowed before or after the scheduled visit.

x. The medical resource utilization data will include: number and duration of medical care encounters, duration of hospitalization, number and character of diagnostic and therapeutic tests and procedures, and outpatient medical encounters and treatments. For more details, refer to Section 8.8, Medical Resource Utilization.

y. The following criteria will trigger additional unscheduled visits: Platelet counts: <100,000 cells/mm^3 or <100 GI/L or reduction from baseline by at least 50%; Hemoglobin: Decrease of at least 2 g/dL from baseline or at least Grade 2 (DAIDS); Neutrophil count: Treatment emergent reduction to at least Grade 2 (DAIDS) (see also Section 8.3.6.3, Hematologic Abnormalities).

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

z. Biochemistry samples should be taken after fasting for at least 10 hours for measurement of phosphate, calcium, creatinine, and lipids. If applicable, participants should bring their study intervention with them to each visit and have that day's intake at the site with food.

aa. Creatinine clearance (eGFRcr calculated by the CKD EPI formula) will be assessed.

bb. Intervention emergent ALT/AST elevations (ie, ALT and/or AST ≥3x ULN and ≥3x nadir [ie, lowest value during study participation]), should trigger an assessment of confounding factors (alcohol intake, change in concomitant medication, and comorbidities). A confirmatory visit should be scheduled as soon as possible within 7 days of the receipt of the initial ALT/AST results, to repeat laboratory testing of AFP, ALT, AST, ALP, bilirubin (total and direct), INR, albumin, and HBV DNA. Additional tests should be considered based on clinical judgement. For more details and further management guidance, refer to Section 10.7, Appendix 7: Intervention emergent ALT/AST Elevations.

cc. Liver function tests only.

dd. Urinalysis by dipstick: specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic analysis if needed. The dipstick reading should be done as soon as possible and in accordance with the manufacturer's recommendation. In case of a positive dipstick result, a urine sample will be set aside for additional examination of the positive parameter (eg, quantification as applicable).

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

ff. Urine chemistry sample (quantitative measurement): creatinine, sodium, phosphate, glucose, protein, and albumin.

gg. Urine sample for selected renal biomarkers including retinol binding protein and beta 2 microglobulin (other biomarkers might be measured).

hh. For postmenopausal women only: An FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to confirm a woman is not of childbearing potential (see Section 10.5, Appendix 5, Contraceptive and Barrier Guidance).

ii. Additional samples may be collected for AFP testing in case of ALT flares.

jj. Urine pregnancy tests should be done at least every 4 weeks, preferably during a scheduled site visit. Given the less frequent follow up of participants who continue NA treatment or have restarted NA treatment during the follow up period (provided that their HBV DNA and ALT values are stable), pregnancy tests for at home use may be provided to these participants from Follow up Week 4 onwards to allow 4 weekly urine pregnancy testing in between scheduled site visits. Participants will report the results to the study site personnel at the next visit, and these will be added to the source documents. If positive, the participant should contact the site immediately.

kk. Only applicable to participants who are enrolled at a site with access to a Fibroscan device. A Fibroscan assessment will only be done at baseline if it was not done at screening.

ll. HBV genotype will be determined at baseline using a standard genotyping assay if HBV DNA levels are sufficiently high. Available historical data on a previous HBV genotype assessment will also be collected in the CRF. Exploratory genotyping may be performed.

mm. HBcrAg and HBV RNA samples may be batched and only selected samples may be tested at the Sponsor's request. Samples can be used for assessment of other serologic/virologic markers of HBV.

nn. Samples may be sequenced based on the Sponsor virologist's request, considering the HBV DNA levels. In case of a virologic breakthrough/flare, additional samples for viral sequencing may be taken.

oo. The investigator should consider to re start NA treatment per local standard of care at the EOS visit (Follow up Week 48) for participants who met the NA treatment completion criteria based on the Week 24 (or FU Week 2) results, who did not re start NA treatment during the follow up phase, and who did not achieve and maintain HBsAg seroclearance. NA will not be provided by the sponsor after the final study visit.

pp. Exploratory serology samples may be analyzed at the Sponsor's discretion. Samples may be used to assess virologic or serologic markers of HBV.

qq. All participants will have sparse PK sampling for JNJ 3989, NA, and PegIFN α2a at any time between 2 and 6 hours post dose, and an optional sample for JNJ 3989, NA, and PegIFN α2a may be taken 6 to 24 hours post dose. Bioanalysis of NA and PegIFN α2a is optional at the discretion of the sponsor.
For all samples, the date and time of the preceding 2 intakes of NA, the date and time of the previous JNJ 3989 and PegIFN α2a administration, as applicable, and the date and time of PK sampling should be recorded. Before leaving the study site, the participant's well being should be confirmed.

rr. Sample to be collected before and 4 6 hours after administration of study intervention (JNJ 3989 and PegIFN α2a) on Day 1 (Arms 1 and 3) or Week 12 (Arm 2).

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

tt. PBMC samples will be collected at selected sites only. Additional PBMC samples may be taken in case of ALT flares, upon discussion with the Sponsor, and may require an unscheduled visit. If a PBMC sample has been taken within the last 4 weeks prior to the unscheduled visit, no new PBMC sample is to be collected.

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

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

ww. A post treatment HBV DNA value of >100,000 IU/mL should trigger re testing of ALT/AST, HBV DNA, and total and direct bilirubin within a maximum of 7 days from receipt of the data and further repeats as necessary (ie, weekly until HBV DNA returns to <100,000 IU/mL). A post treatment HBV DNA value of >20,000 IU/mL (but <100,000 IU/mL) should trigger a re test within 14 days. A post treatment ALT value of >5x ULN should trigger re testing of ALT, AST, ALP, total and direct bilirubin, INR, albumin, and HBV DNA on a weekly basis until ALT and AST levels have returned to <5x ULN. At all times, additional re testing of the above parameters should be performed at the investigator's discretion. In these situations that require more frequent re testing, sites are encouraged to run local re testing in parallel with central re testing. Local test results are to be recorded in the CRF and/or source documents, including information on the HBV DNA assay used.
NA treatment should be re started in accordance with the NA re treatment criteria (see Section 6.5.2, NA Re treatment Criteria During Follow up, for more details). NA treatment should be re started immediately in the event of signs of decreasing liver function based on laboratory findings (eg, INR, direct bilirubin) or clinical assessment (eg, ascites, hepatic encephalopathy), or an HBV DNA value of >1,000,000 IU/mL (irrespective of confirmation and/or ALT increase).

2. INTRODUCTION

This intervention-specific appendix (ISA) describes a Phase 2 study of JNJ-73763989 (JNJ-3989) in combination with a nucleos(t)ide analog (NA) and pegylated interferon alpha-2a (PegIFN-α2a). It is a companion document to the Master Protocol PLATFORMPAHPB2001, which describes the Sponsor's Platform study in participants with chronic HBV infection. This ISA describes specific and/or additional protocol elements applicable to this intervention cohort.

JNJ-3989 is a liver-targeted antiviral therapeutic for subcutaneous injection designed to treat chronic hepatitis B virus (HBV) infection via a ribonucleic acid interference (RNAi) mechanism. Engagement of the cellular RNAi machinery by JNJ-3989 results in specific cleavage of HBV RNA transcripts, thereby reducing the levels of HBV proteins and the pre-genomic ribonucleic acid (pgRNA), the precursor of viral relaxed circular deoxyribonucleic acid (rcDNA). The small interfering RNA (siRNA) triggers in JNJ-3989, JNJ-73763976 (JNJ-3976) and JNJ-73763924 (JNJ-3924), are designed to target all HBV ribonucleic acid (RNA) transcripts derived from covalently closed circular deoxyribonucleic acid (cccDNA), as well as transcripts derived from integrated HBV deoxyribonucleic acid (DNA). The latter has been suggested to be a significant source of hepatitis B surface antigen (HBsAg) in hepatitis B e antigen (HBeAg)-negative patients or patients on long-term (≥2 years) treatment with NAs, the current standard of care (Wooddell 2017).

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

For the most comprehensive nonclinical and clinical information regarding JNJ-3989, refer to the latest version of the Investigator's Brochure (IB) for JNJ-3989 (IB JNJ-3989). For nonclinical and clinical information regarding NA and PegIFN-α2a, refer to their respective prescribing information.

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

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

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

2.1. Study Rationale

Combination treatment with JNJ-3989 and NA has the potential to specifically decrease HBV viral antigen levels and inhibit viral replication. Since HBsAg is immune suppressive, the direct reduction of HBsAg levels by JNJ-3989 is anticipated to contribute to the restoration of the immune response that is impaired in chronic HBV infection.

PegIFN is an approved drug for the treatment of chronic HBV infection and after a finite treatment duration of 48 weeks results in slightly increased HBsAg seroclearance rates compared to NA

alone (Slaets 2020). PegIFN with its dual mode of action (direct antiviral effect [Belloni 2012, Lucifora 2014, Xu 2010, Yan 2015] and immune boosting effect [Gill 2016]) is expected to contribute to additional HBsAg decline and restoration of immune response including natural killer (NK) cell activation.

The current study is designed to assess efficacy and safety of a treatment regimen of 24 weeks of JNJ-3989 and NA, and 3 different treatment schedules for PegIFN-α2a. PegIFN-α2a will be administered during the complete 24-week treatment period for participants in Arm 1, during the second half of the treatment period (Week 12 till Week 24) for participants in Arm 2, and during the first half (from baseline till Week 12) for participants in Arm 3.

Long-term (≥2 years of NA treatment) virologically suppressed, HBeAg-negative, chronic HBV-infected, adult patients will be enrolled.

The primary objective of the study will be to assess the effect of the study intervention (JNJ-3989+NA+PegIFN-α2a) versus NA standard of care treatment on HBsAg levels at end of study intervention (EOSI) at Week 24. In addition, off-treatment efficacy will be explored to evaluate if the study intervention results in functional cure in patients with chronic HBV infection, defined as HBsAg seroclearance 24-weeks after EOSI. The complete follow-up (FU) Period will be 48 weeks, starting at EOSI.

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

In mice transiently harboring the human HBV genome, treatment with JNJ-3989 led to dose-dependent reductions of serum HBsAg, HBeAg, and HBV DNA. Multiple doses of JNJ-3989 resulted in additional and prolonged antigen and HBV DNA reductions in a stepwise fashion when compared to a single dose. This was consistent with prolonged liver persistence of antisense strands, which, when loaded into the RNA-induced silencing complex (RISC), exert the pharmacologic RNAi activity. The ability of JNJ-3989 to reduce serum HBV DNA was additive

to synergistic with entecavir (ETV). ETV alone had no effect on serum HBsAg levels, and no negative effect on the ability of JNJ-3989 to reduce serum HBsAg was observed when given in combination.

2.2.2. Nonclinical Studies

2.2.2.1. JNJ-3989

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

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

Target organs/tissues in rats are the liver, injection site, kidney, and macrophages (in testes, lymph nodes, injection site) and in monkeys are the liver, injection site, and macrophages (lymph nodes, injection site). Most of the observed study intervention-related microscopic changes in these tissues/organs are well-known modality-related findings (Janas 2018a, Janas 2018b) related to intracellular presence of siRNA. Additionally, adverse findings were noted in the liver and subcutaneous injection site in rats.

Slight alteration of the renal tubular epithelium in rats was characterized by the presence of basophilic granules and/or microvacuolation of the cytoplasm of renal tubules in the outer cortex. After a recovery period of 4 months in rats, most of the kidney findings noted at the end of treatment had fully (tubular vacuolation) or partially (basophilic granules) resolved. These findings were considered not toxicologically meaningful since they were related to compound accumulation and were largely in line with published data for GalNAC-conjugated siRNA compounds (Henry 2012; Janas 2018a). There was no evidence of cellular damage (degeneration/necrosis) and no correlation to clinical pathology indicators of changes in renal function.

After 6 months of dosing with JNJ-3989 in both rat studies (Studies 8381085 and TOX13822), livers showed basophilic granules in Kupffer cells and hepatocytes, hepatocellular vacuolation, single-cell necrosis (SCN), increased mitoses, karyomegaly, and/or cytoplasmic alteration, but also an increased incidence/severity of foci of cellular alteration (FCA), oval cell proliferation and cholangiofibrosis. These findings accompanied with increased alkaline phosphatase (ALP) activity levels. The FCA (in combination with the magnitude of other microscopic findings in the liver) were considered adverse in males at ≥180 mg/kg and in females at ≥60 mg/kg. Following a 4-month treatment-free period, there was no clear evidence of recovery of the FCA in females (also no progression).

At suprapharmacologic doses, GalNAc-siRNA compounds are known to induce modality-related liver findings in the rat. These findings include basophilic granules in hepatocytes and Kupffer cells, Kupffer cell hyperplasia, hepatocellular vacuolation, degeneration, and SCN, and are

commonly associated with signs of regeneration, such as increased mitosis and karyomegaly. This may be accompanied by mild increases in hepatic transaminases related to accumulation of GalNAc-siRNA in the liver (Janas 2018b). Sensitivity to hepatic injury including SCN and sequelae as a result of GalNAc-siRNA accumulations are described to be largely specific to rats because they are not seen or occur at lower severity in other species (Janas 2018a). The hypothesis for the presence of FCA in rat livers is that at continuously high compound exposure/accumulation in hepatocytes, primary hepatotoxic events (supported by presence of SCN) occur at a higher incidence/severity in rats. This leads to secondary regenerative proliferative responses (mitoses, karyomegaly, oval cell proliferation), ultimately leading to FCA, which are potentially preneoplastic findings (Holsapple 2006; Cattley 2013). While the mechanism for the species differences is not known, the cascade of hepatotoxic events does not appear to occur in non-human primates (NHPs), as supported by the 9-month chronic study (Study 8381086) and data from other GalNAc-siRNA (Givlaari 2019; Janas 2018b). Such liver findings were not observed in NHPs (Study 8381086) despite exhibiting higher liver concentrations, confirming the higher sensitivity of rats to liver toxicities induced by JNJ-3989. As reported, NHPs are considered a more relevant species for testing pharmacologically-related toxicity and potency of RNAi therapeutics as they present better genomic homology with humans (Ebeling 2011; Janas 2018a; Setten 2019)

The subcutaneous injection of JNJ-3989 in rats resulted in chronic vacuolated macrophage response (phagocytosis of siRNA), mononuclear cell infiltration, and a low incidence of fibrosis at the end of the dosing period caused by the chronic subcutaneous presence of the compound, while in monkey only minimal infiltrates of macrophages were observed. In one male rat of the 300 mg/kg dose group (highest dose tested, Study TOX13822), a poorly differentiated sarcoma was noted at the left flank during the recovery period. This was not seen in males up to 180 mg/kg, corresponding to a rat/human plasma area under the plasma concentration-time curve (AUC) ratio of 59x and 21x for JNJ-3924 and JNJ-3976, respectively (human exposures originating from Study AROHBV1001). Subcutaneous sarcomas can occur spontaneously in rodents or can be induced by subcutaneous injection by a range of non-carcinogenic agents after varying periods of time. They can be induced in laboratory rodents by implanted chemical or inert substances and are typically associated with agents that elicit a tissue response characterized by severe inflammation, tissue damage, a macrophage response, fibroblastic proliferation and fibroplasia (Greaves 2012). The rats in this study were repeatedly injected at the same location (ie, 10 injections in the left flank).

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

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

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

Results of the non-Good Laboratory Practice (non-GLP) in vitro studies demonstrated there is no potential for induction of the innate immune system (cytokine and complement activation),

mitochondrial toxicity/cytotoxicity, or platelet aggregation associated with JNJ-3989 exposure at concentrations up to 250 µg/mL.

The animal-to-human exposure ratios were calculated using rat and monkey exposures at no observed adverse effect levels (NOAELs) from the 24-week studies in rat and the 37-week study in monkey, respectively, and human exposures after a single subcutaneous injection of 200 mg JNJ-3989 in human participants (AROHBV1001) (Table 1).

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 a NOAEL in male rats of CC mg/kg, and a NOAEL in female rats of CCI mg/kg.

Table 1: Animal-to-human Exposure Ratios at NOAEL for JNJ-3989

						Ratio Total Concentration	
		Sex	NOAEL (mg/kg)	C_{max} (ng/mL)	AUC[a] (ng·h/mL)	C_{max} A/H Ratio	AUC[a] A/H Ratio
JNJ-3976	Human exposure[b]		CCI	1,315	20,136	-	-
	24-week rat[c]	M		23,500	199,000	17.9	9.9
		F		12,200	31,400	9.3	1.6
	37-week monkey[d]	M		73,200	1,230,000	55.7	61.1
		F		65,800	988,000	50.0	49.1
JNJ-3924	Human exposure[b]			363	4,605	-	-
	24-week rat[c]	M		14,400	124,000	39.6	26.9
		F		7,780	20,600	21.4	4.5
	37-week monkey[d]	M		21,600	383,000	59.5	83.2
		F		23,000	392,000	63.4	85.1

AUC: area under the plasma concentration time curve; $AUC_{0\text{-}24h}$ area under the plasma concentration time curve from administration to 24 h; $AUC_{0\text{-}last}$ area under the plasma concentration time curve from administration to last quantifiable sampling point; A/H ratio animal/human ratio; C_{max}: maximum plasma concentration; F female; M male.
Source: 24 week rat study (Study 8381085); 24 week monkey (Study 8381086)

[a] $AUC_{0\text{-}last}$ for human exposure; $AUC_{0\text{-}24h}$ for rat exposures; $AUC_{0\text{-}24h}$ for monkey exposures.
[b] Single dose of 200 mg JNJ 3989 in healthy participants via subcutaneous injection (Study AROHBV1001; based on clean dataset with data cut off date 29 October 2019).
[c] Once weekly dosing for 5 weeks, followed by once monthly dosing up to a total of 24 weeks.
[d] Once weekly dosing for 5 weeks, followed by once monthly dosing, up to a total of 37 weeks.

For further information, refer to the latest version of the IB for JNJ-3989 (IB JNJ-3989).

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

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

In the chronic rat studies with JNJ-3989, slight alteration of the renal tubular epithelium was characterized by basophilic stippling and/or microvacuolation of the cytoplasm of renal tubules in the outer cortex in rats. These findings were not considered toxicologically meaningful since they were related to compound accumulation, there was no evidence of cellular damage (degeneration/necrosis) and there were no correlated clinical pathology indicators of changes in

renal function (Henry 2012; Janas 2018a). These kidney findings have been observed in both the 2-week and 6-month studies and did not worsen over time. No kidney findings were observed in monkeys.

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

For TAF, minimal renal cortical tubular karyomegaly and/or basophilia was seen in rats and dogs. In addition, minimal renal cortical tubular degeneration/regeneration were reported in dogs. No renal findings were reported in monkeys (EMA Vemlidy 2020).

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

2.2.2.3. Combination of JNJ-3989 and PegIFN-α2a

A 3-month combination toxicity study of JNJ-3989 and PegIFN-α2a (Pegasys®) was conducted in male and female Cynomolgus monkeys (Study TOX14273). JNJ-3989 was administered at 60 or 180 mg/kg (SC, monthly) in combination with PegIFN-α2a at 0.015 mg/kg (SC, twice weekly). In addition, 180 mg/kg JNJ-3989 (SC, monthly) or PegIFN-α2a (0.015 mg/kg; SC, twice weekly) were dosed in monotherapy groups. The study was conducted in monkeys as the toxicity profile of both PegIFN-α2a and JNJ-3989 were known in monkeys (rat studies were not performed with PegIFN-α2a).

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

Transient local reactions (edema and erythema) were observed at the administration site at 60 and/or 180 mg/kg JNJ-3989. These reactions were also observed with PegIFN-α2a alone and incidentally in control females (erythema only). They were not correlated with microscopic findings.

Administration of JNJ-3989 alone or combined with PegIFN-α2a elicited minimal to mild, transient (on Day 30 only), non-dose-related increases in neutrophils and total WBCs. Similar findings were observed in the group administered 0.015 mg/kg PegIFN-α2a alone.

The combination of JNJ-3989 with PegIFN-α2a did not induce any further effects on biomarkers (interferon gamma inducible protein 10 and interferon alpha) than the increases observed with PegIFN-α2a treatment alone on Day 1.

JNJ-3989-related microscopic findings were observed in the lymph nodes (minimal to mild vacuolation of macrophages) at ≥60 mg/kg and in the liver (minimal hypertrophy of Kupffer cells) at 180 mg/kg in single agent and combination groups. The microscopic changes were comparable between the animals administered with JNJ-3989 alone or combined with PegIFN-α2a indicating an absence of synergistic effect.

In conclusion, the intermittent SC administration of JNJ-3989 up to 180 mg/kg given alone or combined with PegIFN-α2a for 3 months was well tolerated in Cynomolgus monkeys at up to 180 mg/kg. Treatment only induced transient local reactions at the injection site, transient hematological changes and microscopic findings in liver and lymph nodes, all considered as non-adverse. In addition, the administration of PegIFN-α2a in combination with test item did not amplify any toxicological effect. Based on these results, there were no additive or synergistic effects on the toxicity profile and no drug-drug interactions when JNJ-3989 is combined with PegIFN-α2a.

For further information, refer to the latest version of the IB for JNJ-3989 (IB JNJ-3989).

2.2.3. Clinical Studies

2.2.3.1. JNJ-3989

At the time of protocol writing, JNJ-3989 is being evaluated in 11 clinical studies. Two Phase 1 studies (Study 73763989HPB1001 in healthy adult Japanese participants and Study 73763989HPB1002 in adult participants with or without hepatic impairment) and one Phase 1/2a study (Study AROHBV1001) with a single ascending dose part in healthy adult participants and a multiple ascending dose part in adult participants with chronic HBV infection are completed. Conduct of the following studies is ongoing: 3 Phase 1 studies (Study 73763989HPB1004 in healthy adult Chinese participants, 73763989HPB1003 [renal impairment] and 73763989HPB1005 [relative bioavailability]), 4 Phase 2 studies (Studies 73763989HPB2001 [REEF-1], 73763989PAHPB2002 [REEF-2], 73763989PAHPB2005 [REEF-IT], and 73763989PAHPB2006 [PENGUIN]) in adult chronic HBV-infected participants, and 1 Phase 2 study (Study 73763989HPB2004 [REEF-D]) in adult participants coinfected with hepatitis B and D virus. In total, 46 healthy, 84 chronic HBV-infected participants, and 8 participants with moderately impaired hepatic function have been dosed with JNJ-3989 in Studies AROHBV1001, 73763989HPB1001, and 73763989HPB1002.

Across studies, JNJ-3989 was generally safe and well tolerated with no deaths, serious adverse events (SAEs) considered at least possibly related to the study intervention, or adverse events

(AEs) leading to study intervention discontinuation. All AEs were mild to moderate, with exception of 1 severe blood creatine phosphokinase increased in 1 chronic HBV-infected participant. All reported injection site reactions (ISRs) were mild. Adverse events and laboratory abnormalities were distributed across all dose levels and also occurred on placebo treatment, except for mild ISRs, which were only reported in participants on JNJ-3989 treatment. Most reported laboratory abnormalities were isolated incidences and resolved while on study intervention.

Up to 48-week hematology data from the ongoing Phase 2 clinical study REEF-1 are available and overall around 5% of the participants experienced AEs or laboratory abnormalities related to hematologic abnormalities, the majority of mild to moderate severity. The hematologic abnormalities resolved on continued JNJ-3989+NA treatment.

Antiviral activity data are available for 56 chronic HBV-infected participants from Study AROHBV1001, who received 3 subcutaneous injections of 25 to 400 mg JNJ-3989 every 4 weeks (Q4W). The antiviral activity data showed that administration of JNJ-3989 at doses of 25 to 400 mg resulted, on average, in pronounced HBsAg decline which was generally sustained at least until Day 168 (ie, 16 weeks after last dose) across all doses. No apparent dose response was observed at doses between 100 and 400 mg JNJ-3989; a numerically smaller mean decline was observed at the lower doses of 25 and 50 mg, mainly apparent after end of JNJ-3989 dosing. Treatment status (ie, virologically suppressed or not treated) did not seem to affect HBsAg changes. Other measurable serological and virological markers (HBV DNA, HBV RNA, HBeAg, hepatitis B Core-related antigen [HBcrAg]) also showed responses to JNJ-3989, indicating that JNJ-3989 shows target activity on all detectable viral products.

2.2.3.2. Combination of JNJ-3989 and Entecavir, Tenofovir Disoproxil, or Tenofovir Alafenamide

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

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

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

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

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

Clinical data from the Phase 1/2a AROHBV1001 study (see Section 2.2.3.1, JNJ-3989) showed that dosing JNJ-3989 with NA for 12 weeks did not result in any clinically relevant changes in kidney parameters/glomerular function.

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

Overall Assessment of the Combination Therapy

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

- Available toxicology data (Section 2.2.2.2, Combination of JNJ-3989 and Entecavir, Tenofovir Disoproxil, or Tenofovir Alafenamide).
- No clinically relevant changes in kidney parameters/glomerular function for JNJ-3989 + NA in the completed Phase 1/2a Study AROHBV1001 (Section 2.2.3.2, Combination With Entecavir, Tenofovir Disoproxil, or Tenofovir Alafenamide).

2.2.3.3. Combination of JNJ-3989 and PegIFN-α2a

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

Treatment with PegIFN-α2a has been associated with decreases in platelet count (common adverse reaction). Of the 84 adult chronic HBV-infected participants that received 3 subcutaneous injections of JNJ-3989 in the Phase 1/2a AROHBV1001 study (see Section 2.2.3.1, JNJ-3989), 6 participants developed Grade 1 platelet reduction with no general trend towards a continuous decline.

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

At the time of protocol writing, 2 clinical studies using the combination of JNJ-3989 and PegIFN-α2a are ongoing: REEF-IT and PENGUIN. Nonclinical studies to investigate the effect on platelet count decreases were completed and results are summarized in Section 2.2.2.1, JNJ-3989. Up to 48-week hematology data from the ongoing Phase 2 clinical study REEF-1 are available and overall around 5% of the participants experienced AEs or laboratory abnormalities related to hematologic abnormalities, the majority of mild to moderate severity. The hematologic abnormalities resolved on continued JNJ-3989+NA treatment.

2.3. Benefit-Risk Assessment

More detailed information about the known and expected benefits and risks of JNJ-3989 may be found in the IB (IB JNJ-3989).

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

2.3.1. Benefits for Study Participation

2.3.1.1. Known Benefits

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

2.3.1.2. Potential Benefits

Results from clinical studies with JNJ-3989, NAs, and PegIFN-α2a may be useful for the development of a novel therapeutic approach for chronic HBV infection.

JNJ-3989 on a background of NAs would target different stages of the viral life cycle. While NA treatment reduces HBV DNA to levels close to or below the lower limit of quantification (LLOQ) of the HBV DNA assay, HBV replication is not completely inhibited, resulting in replenishment of the cccDNA pool. The addition of JNJ-3989 is expected to intensify viral suppression by downregulating levels of the HBV DNA precursor pgRNA. In addition, JNJ-3989 reduces levels of all viral proteins including HBsAg, which is known to interfere with the host immune responses (Fang 2015; Li 2018; Wang 2013). By acting on both viral replication and by reducing barriers to the host immune-responses, higher functional cure rates may be achieved.

The addition of PegIFN-α2a (12 or 24 weeks, with immediate or delayed start) to the regimen may lead to further improvement of the immune response (such as reactivation of NK-cells) and ultimately could lead to immune control of HBV (ie, functional cure). In addition, PegIFN-α2a has shown to have direct antiviral effects on HBV which could also contribute to the efficacy of the regimen. By adding PegIFN-α2a to the regimen, higher functional cure rates may be achieved.

2.3.2. Risks for Study Participation

2.3.2.1. Known Risks

Injection site reactions were the most frequently observed AEs assessed as related to JNJ-3989 by the investigator.

The side effect profile of PegIFN-α2a is well established and includes, but is not limited to, neuropsychiatric, autoimmune, ischemic, ophthalmologic, hematological, and infectious disorders. Exacerbations of hepatitis during hepatitis B therapy are common and characterized by transient and potentially severe increases in serum ALT. Marked increases in ALT were sometimes accompanied by bilirubin elevation and other liver test abnormalities. In many, but not all cases, these disorders resolve after stopping PegIFN-α2a therapy. For a full list of known risks for PegIFN-α2a, refer to the respective prescribing information and Summary of Product Characteristics.

2.3.2.2. Potential Risks

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

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

2.3.2.2.1. Potential Risks for JNJ-3989

ALT Elevations:

ALT elevation is considered an important potential risk for JNJ-3989. Two distinct patterns of ALT elevations have been observed: a rapidly rising and resolving ALT elevation, or a sustained pattern of ALT elevation. In a Phase 2 study involving chronic HBV-infected participants (REEF-1), ALT flares (ALT ≥3x ULN and ≥3x Nadir) were observed in 7% of participants treated with 200 mg JNJ-3989 every 4 weeks, compared to 0% of participants treated with NA and 0% to 2% of participants treated with lower doses of JNJ-3989. The majority of the ALT flares resolved rapidly on continued treatment; 1 was considered serious. In REEF-D, an ongoing study with HBV/HDV co-infected participants, 10 out of 22 (45%) participants have developed ALT elevations. Study treatment assignment remains blinded. Three participants have experienced prolonged elevation of ALT. In 2 participants the ALT elevation was considered serious. ALT elevation has led to discontinuation of blinded study treatment in 2 participants. A causal association of ALT elevations with JNJ-3989 has not been confirmed and the underlying mechanism for ALT elevations being more frequent in context of HBV HDV co-infection is not yet understood.

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.

Viral Resistance

Treatment with JNJ-3989 may lead to viral resistance, but resistance to JNJ-3989 is not anticipated to impact treatment with other siRNAs, unless they would have an overlapping trigger binding region. Note that none of the siRNAs in development have overlapping regions. Using these agents in combination, especially in combination with ETV or tenofovir, is expected to minimize the risk of emerging resistant viral variants.

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

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

Risks specific for this study design are listed below:

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

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 deemed acceptable for the following reasons:

- JNJ-3989 was generally safe and well tolerated during the Phase 1/2a Study AROHBV1001 (see Section 2.2.3.1, JNJ-3989). All but one AE were mild or moderate in severity. All ISRs, identified as adverse drug reactions for JNJ-3989, were mild in intensity.
- Based on pre-clinical and clinical data available today, the combination of JNJ-3989, NA (ETV, tenofovir disoproxil, or TAF), and PegIFN-α2a is considered safe. Data from nonclinical combination toxicity studies (Section 2.2.2.3, Combination of JNJ-3989 and PegIFN-α2a) confirmed that combination of PegIFN-α2a with JNJ-3989 did not induce any synergistic or additive effect in monkeys up to 3 months of treatment. Fourty-eight (48)-week hematology data of ongoing Phase 2 clinical study REEF-1 (Section 2.2.3.3, Combination of JNJ-3989 and PegIFN-α2a) has been reviewed and no safety concern has been identified.
- 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 for JNJ-3989 that will be carefully monitored during the study include ISRs, ALT/AST elevations, and hematologic abnormalities (see Section 8.3.6, Adverse Events of

Special Interest). In addition, the following toxicities will also be carefully monitored: rash, renal complications, and acute systemic allergic reactions (Section 8.3.7, Other Toxicities).

- Continued careful assessment of the safety, efficacy, and PK during treatment is included in this study.
- To minimize potential risk and stress to participants, the following measures are in place:

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

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

  At regular time points throughout the study (see Schedule of Activities), blood samples for biochemistry, blood coagulation, and hematology and urine samples for urinalysis, urine chemistry, and renal biomarkers will be collected. Vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature), height (only at screening), body weight, and electrocardiograms (ECGs) will be recorded throughout the study. Physical and ophthalmologic 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).

  The impact of PegIFN-α2a addition to JNJ-3989 on ALT elevations is not known in context of HBV monoinfection. Strict rules for management of ALT elevation are in place (refer to Section 8.3.6.2, Intervention-emergent ALT/AST Elevations).

  An internal Data Review Committee (DRC) will be established for continuous monitoring of SAEs, AEs leading to discontinuation, and ALT flares to ensure the continuing safety of the participants enrolled in the current study. In addition, an Independent Flare Expert Panel (IFLEP) will be appointed to characterize and adjudicate each ALT flare. See Section 10.3.6, Committees Structure.

  Participants will be monitored closely during the 48-week FU Period, with frequent follow-up visits. Participants who completed NA treatment after meeting the NA treatment completion criteria (Section 6.5.1, NA Treatment Completion) based on the Week 24 (EOSI) or FU Week 2 results, should re-start NA treatment if pre-defined NA re-treatment criteria are met (Section 6.5.2, NA Re-treatment Criteria During Follow-up).

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

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

3. OBJECTIVES AND ENDPOINTS

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

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

Objectives	Endpoints
• To evaluate the frequency of virologic breakthrough throughout the study.	• Proportion of participants with virologic breakthrough[a].
• To evaluate the PK of JNJ-3989 (JNJ-3924 and JNJ-3976), and optionally of NA and PegIFN-α2a.	• PK parameters of JNJ-3989 (JNJ-3924 and JNJ-3976). • Optionally, PK parameters of NA and/or PegIFN-α2a.
Exploratory	
• To explore host and viral baseline and on-treatment markers associated with end of study intervention and/or off-treatment response.	• Association of baseline characteristics and baseline/on-treatment viral and host blood markers with selected on or off-treatment efficacy variables.
• To explore changes in the severity of liver disease.	• Changes in fibrosis (according to Fibroscan liver stiffness measurements) at EOSI and the end of the FU period versus baseline.
• To explore efficacy of the study intervention in terms of changes in HBV RNA and hepatitis B core-related antigen (HBcrAg) levels during the study intervention and FU period.	• Changes from baseline in HBV RNA and HBcrAg levels over time.
• To explore the relationship of PK with selected pharmacodynamic (PD) parameters of efficacy and safety.	• Relationship of various PK parameters with selected efficacy and safety endpoints.
• To explore the HBV genome sequence during the study intervention and FU period.	• Assessment of intervention-associated mutations over time.
• To explore HBV-specific T-cell responses during the study intervention and FU period.[b]	• Changes from baseline in HBV-specific peripheral blood T-cell responses over time.[b]
• To explore the efficacy of NA re-treatment in participants who meet the criteria for NA re-treatment.	• Proportion of participants who reach HBV DNA <LLOQ after re-start of NA treatment during the FU period.
• To explore medical resource utilization (MRU) to manage participants during study intervention and follow-up.	• Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient) • Duration of hospitalization (total days length of stay, including duration by wards; eg, intensive care unit) • Number and character of diagnostic and therapeutic tests and procedures • Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications)

[a] For the definition of virologic breakthrough, refer to Section 10.1, Appendix 1: Abbreviations and Definitions.
[b] Peripheral blood mononuclear cell (PBMC) samples for immune analyses will be collected at selected sites only.

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

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

HYPOTHESIS

The primary hypothesis of this study is that at least one of the combination regimens of JNJ-3989+NA+PegIFN-α2a is more efficacious than NA treatment alone (standard of care), as measured by the primary efficacy endpoint, the proportion of participants with a reduction of at least 2 $\log_{10}$ IU/mL in HBsAg levels from baseline at Week 24. Because the study does not include a control arm, the hypothesis is formulated assuming a fixed external NA control response rate of 2% in terms of the primary efficacy endpoint.

4. STUDY DESIGN

4.1. Overall Design

This ISA describes a Phase 2 study of the combination regimen of JNJ-3989 with NA and different durations of PegIFN-α2a, and with an immediate or delayed start of PegIFN-α2a treatment. It is a companion document to the Master Protocol PLATFORMPAHPB2001, which describes the common design elements of the Platform study in participants with chronic HBV infection. This ISA describes specific and/or additional protocol elements applicable to this open-label, 3-arm, multicenter, interventional study to evaluate the efficacy, safety, tolerability, and PK of the combination of JNJ-3989, NAs, and PegIFN-α2a in long-term (≥2 years of NA treatment) virologically suppressed, HBeAg-negative, chronic HBV-infected, adult participants.

Approximately 102 long-term (≥2 years of NA treatment) virologically suppressed, HBeAg-negative, chronic HBV-infected, adult participants, ≥18 (or the legal age of consent in the jurisdiction in which the study is taking place) to 65 years of age (inclusive) will be enrolled in this study.

This open-label study will be conducted in 3 periods:

- Screening Period (4 weeks [if necessary, eg, for operational reasons, can be extended to a maximum of 8 weeks decided on a case-by-case basis and in agreement with the Sponsor]).
- Treatment Period (24 weeks):
    - Arm 1 (N 34): JNJ-3989 for 24 weeks + NA for 24 weeks + PegIFN-α2a for 24 weeks.
    - Arm 2 (N 34): JNJ-3989 for 24 weeks + NA for 24 weeks + PegIFN-α2a from Week 12 till Week 24.
    - Arm 3 (N 34): JNJ-3989 for 24 weeks + NA for 24 weeks + PegIFN-α2a from baseline till Week 12.
- Follow-up (FU) Period (48 weeks), starting at Week 24.

At baseline, participants who meet the eligibility criteria will be randomized in a 1:1:1 ratio to Arm 1, Arm 2, or Arm 3. Randomization will be stratified by absolute HBsAg level (<1,000 IU/mL

versus ≥1,000 IU/mL) at baseline and country grouping as proxy for HBV genotype (GT) at enrollment, with 3 levels: Poland (predominantly GT-A) versus Russia (predominantly GT-D) versus all other countries (other or mixed GT prevalence) (Kim 2011). Participants in Arm 2 who no longer meet the PegIFN-α2a eligibility criteria (see Exclusion Criterion A24 in Section 5.2, Exclusion Criteria) at Week 12, based on available laboratory or clinical data, will continue JNJ-3989 and NA treatment until Week 24 without PegIFN-α2a.

All participants will receive the last dose of JNJ-3989 at Week 24 and the last dose of PegIFN-α2a at Week 23 (Arms 1 and 2) or Week 11 (Arm 3). They will start the FU Period after the Week 24 visit. If the protocol-defined NA treatment completion criteria (see Section 6.5.1, NA Treatment Completion, for more details) are met based on the Week 24 results, NA will be stopped at the next scheduled visit (ie, FU Week 2), otherwise NA treatment will continue during the complete FU Period. ***Note:*** Participants who are close to meeting the protocol-defined NA treatment completion criteria with the Week 24 results, and do meet the criteria based on the FU Week 2 results may be allowed to stop NA at FU Week 4, after consultation with the Sponsor.

Participants who meet the protocol-defined NA treatment completion criteria will be monitored closely during the 48-week FU Period with a study visit at least once every 4 weeks. NA treatment should be re-started in accordance with the NA re-treatment criteria (see Section 6.5.2, NA Re-treatment Criteria During Follow-up, for more details).

Study intervention consists of:

- JNJ-3989: 200 mg subcutaneous injection Q4W
- NA: tenofovir disoproxil (245 mg), or TAF (25 mg), or ETV (0.5 mg) tablets p.o. QD
- PegIFN-α2a: 180 µg subcutaneous injection QW.

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

Assessments and sampling include:

- Safety and tolerability, based on AEs, laboratory assessments, ECGs, vital signs, ophthalmologic and physical examination, will be assessed throughout the study from the time that the ISA ICF is signed until the completion of the last study-related activity (see Section 8.2, Safety Assessments, and Section 8.3, Adverse Events and Serious Adverse Events).
- Efficacy will be evaluated using different parameters including HBsAg, HBeAg, and HBV DNA (see Section 8.1, Efficacy Assessments).
- Samples for HBV genome sequencing will be taken at the time points indicated in the Schedule of Activities (see Section 8.1.1, Sequencing). Samples may be sequenced based on the Sponsor virologist's request, considering the HBV DNA levels. In case of a virologic breakthrough/flare, additional samples for viral sequencing may be taken.

- The study includes collection of blood samples for exploratory analysis of viral markers (see Section 8.1, Efficacy Assessments) and host blood biomarkers at the host RNA, protein, and cell level (see Section 8.6, Exploratory Host Biomarkers).
- All participants will have sparse PK sampling during the treatment period. Venous blood samples will be collected for measurement of plasma or serum (as applicable) concentrations of JNJ-3989 (ie, JNJ-3976 and JNJ-3924), NA and PegIFN-α2a, at time points specified in the Schedule of Activities. Bioanalysis of NA and PegIFN-α2a is optional at the discretion of the sponsor (see Section 8.4, Pharmacokinetics).
- Peripheral blood mononuclear cell (PBMC) samples for immune analyses will be collected at selected sites at the time points indicated in the Schedule of Activities (see Section 8.7, Immune Assessments).
- Optional samples for human leukocyte antigen (HLA) testing, pharmacogenomics, and epigenetics will be collected from participants who consent separately to this component of the study (see Section 8.5, Host Genetics).
- Medical resource utilization will be assessed (see Section 8.8, Medical Resource Utilization).

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

The total duration of individual participation will be up to 72 weeks (screening not included). Participants will be considered to have completed the study if they have completed all the assessments of the end of study (EOS) visit (ie, FU Week 48).

If a participant prematurely discontinues JNJ-3989 (ie, before Week 24), the participant will have an early WD visit and will enter the 48-week follow-up period as per the Schedule of Activities, unless the participant withdraws consent.

If a participant prematurely discontinues PegIFN-α2a (ie, before Week 23 [Arms 1 and 2] or before Week 11 [Arm 3]), treatment with JNJ-3989 and NA should be continued as planned.

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

An internal Data Review Committee (DRC) will be commissioned for monitoring safety of participants enrolled in this study. In addition, an Independent Flare Expert Panel (IFLEP) will be appointed. See Section 10.3.6, Committees Structure.

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

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

4.2. Scientific Rationale for Study Design

Randomization

Randomization will be used to minimize bias in the assignment of participants to intervention arms, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment arms, and to enhance the validity of statistical comparisons across intervention arms. Randomization will occur at baseline.

Stratification Factors

Randomization will be stratified by absolute HBsAg level (<1,000 IU/mL versus ≥1,000 IU/mL) at baseline and country grouping as proxy for HBV GT at enrollment, with 3 levels: Poland (predominantly GT-A) versus Russia (predominantly GT-D) versus all other countries (other or mixed GT prevalence) (Kim 2011). The two stratification factors selected will provide a reasonably balanced representation of 2 baseline factors across all intervention arms.

Addition of PegIFN-α2a to Treatment Regimen

The combination of the treatment regimen of JNJ-3989 + NA with PegIFN-α2a is based on 2 different properties of IFN-α: a direct antiviral effect and an immune boosting effect. The direct antiviral activity against HBV replication, and in some cases HBsAg production, was demonstrated for PegIFN-α2a (Belloni 2012, Lucifora 2014, Xu 2010, Yan 2015). In addition, IFN-α is expected to act as immune booster with potential to reactivate NK-cells (Gill 2016). Addition of PegIFN-α2a (for 12 weeks [during the first or second half of the treatment period for Arms 3 and 2, respectively] or during the complete 24 week treatment period [Arm 1]) to the treatment regimen is expected to enhance antiviral activity of JNJ-3989 + NA and may lead to a shorter overall treatment duration (ie, 24 weeks) and might improve functional cure rates.

Criteria for NA Treatment Completion

All participants will receive the last dose of JNJ-3989 at Week 24 and the last dose of PegIFN-α2a at Week 23 (Arms 1 and 2) or Week 11 (Arm 3). They will start the FU Period after the Week 24 visit. If the protocol-defined NA treatment completion criteria (described in Section 6.5.1, NA Treatment Completion) are met based on the Week 24 results, treatment with NA will be stopped at the next scheduled visit (ie, FU Week 2), otherwise NA treatment will continue during the complete FU Period. ***Note:*** Participants who are close to meeting the protocol-defined NA treatment completion criteria with the Week 24 results, and do meet the criteria based on the FU Week 2 results may be allowed to stop NA at FU Week 4, after consultation with the Sponsor.

The NA treatment completion criteria which take ALT, HBV DNA, HBeAg, and HBsAg levels into consideration, have been selected to ensure that only participants with a higher chance of achieving sustained off-treatment response are allowed to stop all study intervention. Across a range of studies, HBsAg levels at end of treatment below 100 IU/mL were consistently associated with favorable off-treatment response (Jeng 2018; Papatheodoridis 2018).

Participants will be monitored closely during the 48-week FU Period and participants who completed NA treatment should re-start NA treatment if NA re-treatment criteria are met (see Section 6.5.2, NA Re-treatment Criteria During Follow-up, for more details).

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

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

Increases in ALT and HBV DNA are frequently seen in patients after discontinuation of NA treatment. These ALT elevations may be reflecting an activation of the host cellular immune response and can as such lead to functional cure. Cases of fulminant HBV reactivation with fatal outcome were described after cessation of NA treatment, but the vast majority of such cases were described in patients with cirrhosis or decompensated liver disease at the time of NA discontinuation. These patients are not eligible to participate in the study. Still, a vigilant follow-up of patients during this phase of the study is critical to ensure patient safety. Signs of decreased liver function, or an HBV DNA value of >1,000,000 IU/mL (irrespective of confirmation and/or ALT increase), will trigger immediate re-initiation of NA treatment based on protocol-defined NA re-treatment criteria (see Section 6.5.2, NA Re-treatment Criteria During Follow-up).

In the absence of signs of decompensation or an HBV DNA value of >1,000,000 IU/mL, the decision to re-start NA treatment should take into account that a too early re-initiation might reduce the chances of achieving functional cure. Re-initiation of NA treatment should be considered in case of confirmed HBeAg seroreversion (HBeAg positive after it was negative at NA completion), in case of confirmed ALT increase (>5x ULN) in combination with increased HBV DNA replication (>2,000 IU/mL), and in case of confirmed increased HBV DNA replication at higher levels (>20,000 IU/mL). If the kinetics of the ALT increase permit it, the confirmatory test should be performed at least 4 weeks after the initial test, except in the situations described below.

A post-treatment HBV DNA value of >100,000 IU/mL should trigger re-testing of ALT/AST, HBV DNA, and total and direct bilirubin within a maximum of 7 days from receipt of the data and further repeats as necessary (ie, weekly until HBV DNA returns to <100,000 IU/mL). A post-treatment HBV DNA value of >20,000 IU/mL (but <100,000 IU/mL) should trigger a re-test within 14 days. A post-treatment ALT value of >5x ULN should trigger re-testing of ALT, AST, ALP, total and direct bilirubin, INR, albumin, and HBV DNA on a weekly basis until ALT and AST levels have returned to <5x ULN. At all times, additional re-testing of the above parameters should be performed at the investigator's discretion.

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

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

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

NA re-treatment criteria during follow-up are presented graphically in Section 10.12, Appendix 12.

Host DNA and Exploratory Host Biomarker Collection

Refer to Section 4.2 of the Master Protocol PLATFORMPAHPB2001.

4.2.1. Study-Specific Ethical Design Considerations

Refer to Section 4.2.1 of the Master Protocol PLATFORMPAHPB2001.

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

4.3. Justification for Dose and Treatment Duration

The proposed dose and treatment duration for JNJ-3989 are selected to maximize the chance for patients to achieve functional cure and are supported by scientific understanding of available data. The same dose (ie, 200 mg of JNJ-3989) is currently being tested in ongoing Phase 2b studies REEF-1 (73763989HPB2001), REEF-2 (73763989PAHPB2002), REEF-IT (73763989PAHPB2005), and Penguin (73763989PAHPB2006). Addition of short-term PegIFN-α2a (12 or 24 weeks, with immediate or delayed start) to the treatment regimen is expected to enhance antiviral activity of JNJ-3989 + NA and may lead to a shorter overall treatment duration (ie, 24 weeks) needed to achieve functional cure.

Clinical data on PK, PD, safety, and efficacy of JNJ-3989 are available from the Phase 1/2a AROHBV1001 study. The study has been completed and the final study report is available. Twenty adult healthy participants have received single subcutaneous injections of JNJ-3989 (35, 100, 200, 300, and 400 mg) and 84 adult chronic HBV-infected participants have received multiple doses of JNJ-3989 (25, 50, 100, 200, 300, and 400 mg), administered as 3 subcutaneous injections separated by either 7-day, 14-day, or 28-day intervals. All participants either continued or started on ETV or tenofovir disoproxil on Day 1.

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

Antiviral activity data were available for 56 chronic HBV-infected participants who received 3 subcutaneous injections of 25 to 400 mg JNJ-3989 Q4W (Gane 2019; Yuen 2019; IB JNJ-3989). In general, mean HBsAg declines reached nadir at Day 113 (ie, 8 weeks after last JNJ-3989). Mean HBsAg levels remained suppressed (below baseline levels) at least until Day 392 (ie, 9 months after last dose) in a substantial proportion of patients. The HBsAg levels at Day 392 were variable with some patients having HBsAg levels close to baseline levels while a substantial proportion of

patients still had HBsAg levels >1 log_{10} IU/mL lower than the baseline levels. JNJ-3989 showed activity on other viral markers (HBV DNA, HBV RNA, HBeAg and HBcrAg), frequently with sustained reduction at least until Day 362. No apparent dose response was observed at doses between 100 mg and 400 mg JNJ-3989, a numerically smaller mean decline was observed at the lower doses of 25 mg and 50 mg, mainly apparent after end of JNJ-3989 dosing.

A dose of 200 mg JNJ-3989 Q4W is chosen based on the observed decline in HBsAg in Study AROHBV1001 at this dose over 3 injections, and the lack of a substantial incremental efficacy response at higher doses.

4.4. End of Study Definition

End of Study Definition

The EOS is considered as the last visit (FU Week 48 or early discontinuation) for the last participant in the study. The final data from the study site will be sent to the Sponsor (or designee) after completion of the final participant visit at that study site, in the time frame specified in the Clinical Trial Agreement.

Study Completion Definition

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

5. STUDY POPULATION

Screening for eligible participants will be performed within 4 weeks before administration of the study intervention. If necessary, eg, for operational reasons, the Screening Period may be extended up to a maximum of 8 weeks on a case-by-case basis and in agreement with the Sponsor. Refer to Section 5.4, Screen Failures, of the Master Protocol PLATFORMPAHPB2001 for conditions under which the repeat of any screening procedures is allowed.

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

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

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

Each potential participant must satisfy all inclusion and exclusion criteria from the Master Protocol PLATFORMPAHPB2001 (numbering prefixed by “M” in the list below) and all additional intervention-specific inclusion and exclusion criteria (numbering prefixed by “A” in the list below). The latter inclusion and exclusion criteria are highlighted (colored fill). For the few criteria

from the Master Protocol that are specified or more restricted in this ISA, the additional text is also highlighted (colored fill).

5.1. Inclusion Criteria

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

A01 (adapted from M01)	Adult male or female participants ≥18 (or the legal age of consent in the jurisdiction in which the study is taking place) to 65 years of age, inclusive.
M02	Participants must be medically stable based on physical examination, medical history, vital signs, and 12-lead ECG performed at screening. If there are abnormalities, they must be consistent with the underlying illness in the study population. This determination must be recorded in the participant's source documents and initialed by the investigator.
A03 (adapted from M03a)	Participants must have chronic HBV infection. HBV infection must be documented by serum HBsAg positivity at screening. In addition, chronicity must be documented by any of the following, at least 6 months prior to screening: serum HBsAg positivity, HBeAg positivity or HBV DNA positivity, ALT elevation above ULN without another cause than HBV infection, documented transmission event. If none of the above are available, the following ways of documenting chronicity are acceptable at the time of screening: liver biopsy with changes consistent with chronic HBV, or absence of marker for acute HBV infection such as positive immunoglobulin M (IgM) anti-hepatitis B surface (HBs) and anti-HBc antibodies. Participants should: • be HBeAg-negative, AND • be anti-HBe antibody-positive, AND • be on stable HBV treatment, defined as currently receiving NA treatment for at least 2 years prior to screening, and having been on the same NA treatment regimen (at the same dose) as used in this study for at least 3 months at the time of screening, AND • have documented serum HBV DNA <60 IU/mL on 2 sequential measurements at least 6 months apart (one of which is at screening), AND • have documented ALT values <2.0x ULN on 2 sequential measurements at least 6 months apart (one of which is at screening).
M04	Participants must have a body mass index (BMI; weight in kg divided by the square of height in meters) between 18.0 and 35.0 kg/m^2, extremes included.

A05 (adapted from M05)	Participants must sign a Master ICF (specific for the Master Protocol PLATFORMPAHPB2001) and must sign the ICF specific for this intervention cohort, indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.
M06	Participants must sign a separate ICF if he or she agrees to provide additional optional DNA samples for research (where local regulations permit). Refusal to give consent for the optional DNA research samples does not exclude a participant from participation in the study.
A07 (adapted from M07)	Criterion modified per Amendment 1 A07.1 Female participants must be (as defined in Section 10.5, Appendix 5, Contraceptive and Barrier Guidance): a. Not of childbearing potential, OR b. Of childbearing potential and practicing a highly effective, preferably user-independent method of contraception (failure rate of <1% per year when used consistently and correctly) for at least 30 days prior to screening and agrees to remain on a highly effective method while receiving study intervention and until 90 days after last dose of study intervention. Examples of highly effective methods of contraception are provided in Section 10.5, Appendix 5, Contraceptive and Barrier Guidance. ***Note:*** Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
M08	Female participants of childbearing potential must have a negative highly sensitive serum pregnancy test (β-human chorionic gonadotropin) at screening and a negative urine pregnancy test on Day 1 before the first dose of study intervention.
M09	In the investigator's opinion, the participant is able to understand and comply with protocol requirements, instructions, and study restrictions and is likely to complete the study as planned per ISA (including the procedures outlined in the Master Protocol PLATFORMPAHPB2001).
A10 (adapted from M10)	Male participants must agree to wear a condom when engaging in any activity that allows for passage of ejaculate to another person during the study intervention period and until 90 days after last dose of study intervention.
A11	Female participants must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study intervention period and until 90 days after last dose of study intervention.

A12	Male participants must agree not to donate sperm for the purpose of reproduction during the study intervention period and until 90 days after last dose of study intervention.
A13	Criterion modified per Amendment 1 A13.1 Participants must have serum HBsAg >5 IU/mL at screening, as assessed by quantitative HBsAg assay.
A14	Participants must have: a. Fibroscan liver stiffness measurement ≤9.0 kPa within 6 months prior to screening or at the time of screening, OR b. If a Fibroscan result is not available: a liver biopsy result classified as Metavir F0-F2 within 1 year prior to screening. ***Note:*** Other radiologic liver staging modalities (eg, acoustic radiation force impulse) might be used if standard practice at the site or if otherwise validated and agreed with the Sponsor. Results should be equivalent to Metavir F0-F2. ***Note:*** Conventional imaging procedures (eg, conventional liver ultrasound, computed tomography [CT] or magnetic resonance imaging [MRI]) and serum marker panels are not allowed to rule out severe fibrosis or cirrhosis.

5.2. Exclusion Criteria

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

A01 (adapted from M01)	Criterion modified per Amendment 1 A01.1 Participants with evidence of hepatitis A virus infection (hepatitis A antibody IgM), HCV infection (HCV antibody), hepatitis D virus (HDV) infection (HDV antibody), hepatitis E virus (HEV) infection (hepatitis E antibody IgM), or HIV-1 or HIV-2 infection (laboratory confirmed) at screening. ***Note:*** Participants with a positive HCV antibody test can be enrolled if they have negative HCV RNA at screening and documented negative HCV RNA at least 6 months prior to screening. Participants with a positive HDV antibody test may be enrolled after discussion with the Sponsor if an active HDV co-infection can be ruled out by documentation of negative HDV RNA.

	Participants with a positive IgM antibody test for HEV infection may be enrolled after discussion with the Sponsor if an active HEV infection can be ruled out by documentation of negative anti-HEV immunoglobulin G (IgG).[a] Participants with a positive HIV-1 or HIV-2 antibody/antigen test at screening should have a confirmatory HIV RNA test, to rule out false positive results. They can be enrolled if they have a negative HIV RNA test at screening. Participants with evidence of HIV-1 or HIV-2 infection who are on antiretroviral treatment are excluded.
A02 (adapted from M02)	Participants with evidence of hepatic decompensation at any time point prior to or at the time of screening: a. Total bilirubin >1.5x ULN[b], OR b. Direct bilirubin >1.2x ULN[b], OR c. Prothrombin time >1.3x ULN (unless caused by anticoagulation therapy or vitamin K deficiency)[b], OR d. Serum albumin <3.2 g/dL[b].
M03	History or evidence of clinical signs or symptoms of hepatic decompensation, including but not limited to: portal hypertension, ascites, hepatic encephalopathy, esophageal varices.
M04	Participants with evidence of liver disease of non-HBV etiology. This includes but is not limited to hepatitis infections mentioned in exclusion criterion A01, drug- or alcohol-related liver disease, autoimmune hepatitis, hemochromatosis, Wilson's disease, α-1 antitrypsin deficiency, primary biliary cholangitis, primary sclerosing cholangitis, Gilbert's syndrome (mild cases are allowed) or any other non-HBV liver disease considered clinically significant by the investigator.
A05 (adapted from M05)	Participants with history or signs of cirrhosis or portal hypertension (nodules, no smooth liver contour, no normal portal vein, spleen size ≥12 cm) or signs of hepatocellular carcinoma (HCC) or clinically relevant renal abnormalities on an abdominal ultrasound performed within 3 months prior to screening or at the time of screening. In case of suspicious findings on conventional ultrasound the participant may still be eligible if HCC or clinically relevant renal abnormalities have been ruled out by a more specific imaging procedure (contrast enhanced ultrasound, CT or MRI).

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

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

A06 (adapted from M06)	Criterion modified per Amendment 1 A06.1 Participants with one or more of the following laboratory abnormalities at screening as defined by the Division of Acquired Immunodeficiency Syndrome (DAIDS) Toxicity Grading Scale (see Section 10.9, Appendix 9: DAIDS Table): a. Estimated glomerular filtration rate based on serum creatinine (eGFRcr) ≥Grade 3 (ie, <60 mL/min/1.73 m^2) at screening, calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; b. Pancreatic lipase elevation ≥Grade 3; c. Pancreatic amylase elevation ≥Grade 3; d. Hemoglobin ≤10.9 g/dL (males), ≤10.4 g/dL (females); e. Platelet count ≤lower limit of normal (LLN); f. Alpha-fetoprotein (AFP) >100 ng/mL; Note: Participants with AFP >ULN but ≤100 ng/mL may be eligible if HCC can be ruled out based on a sensitive imaging study (eg, contrast-enhanced ultrasound, CT or MRI) during screening. g. Any other laboratory abnormality considered to be clinically significant by the investigator (also see exclusion criterion A02).
M07	Participants with hemoglobin A1c >8% at screening.
M08	Participants with a history of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy, which are considered cured with minimal risk of recurrence).
M09	Participants with abnormal sinus rhythm (heart rate <45 or >100 beats per minute [bpm]); QT interval corrected for heart rate according to Fridericia's formula (QTcF) >450 ms for males and >470 ms for females; QRS interval ≥120 ms; PR interval >220 ms; abnormal conduction; or any other clinically significant abnormalities on a 12-lead ECG at screening. ***Note:*** Retesting of an abnormal ECG that may lead to exclusion will be allowed once without prior asking approval from the Sponsor. Retesting will take place during an unscheduled visit in the screening phase. Participants not meeting the above exclusion criterion at retest may be included.

M10	Participants with a history of or current cardiac arrhythmias (eg, extrasystole, tachycardia at rest), history of risk factors for Torsade de Pointes syndrome (eg, hypokalemia, family history of long QT Syndrome) or history or other clinical evidence of significant or unstable cardiac disease (eg, angina, congestive heart failure, myocardial infarction, diastolic dysfunction, significant arrhythmia and/or coronary heart disease), moderate to severe valvular disease, or uncontrolled hypertension at screening.
M11	Participants with any current or previous illness for which, in the opinion of the investigator and/or Sponsor, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments. This may include but is not limited to significant vascular, pulmonary (eg, chronic obstructive pulmonary disease), gastrointestinal (eg, significant diarrhea, gastric stasis, or constipation that in the investigator's opinion could influence drug absorption or bioavailability), endocrine (eg, thyroid disease), neurologic, hematologic, rheumatologic, psychiatric, neoplastic, or metabolic disturbances. Any condition possibly affecting drug absorption (eg, gastrectomy or other significant gastrointestinal tract surgery, such as gastroenterostomy, small bowel resection, or active enterostomy) will also lead to exclusion.
M12	Participants who have received an organ transplant (except for skin, hair, or cornea transplants).
M13	Participants with any history of or current clinically significant skin disease requiring regular or periodic treatment.
M14	Participants with clinically relevant alcohol or drug abuse within 12 months of screening.
M15	Participants with history of clinically relevant drug rash.
A16 (adapted from M16)	Participants who have taken any disallowed therapies as noted in Section 6.8, Concomitant Therapy, before screening or baseline. Participants who have taken IFN within the last 3 years prior to screening. Participants with lamivudine-refractory chronic hepatitis B.
A17 (adapted from M17)	Participants having used any invasive investigational medical device within 6 months, or having received an investigational intervention or a biological product, immunoglobulin or other blood product not intended for the treatment of HBV within 6 months or 5 half-lives (whichever is longer), before the planned first dose of study intervention, or is currently enrolled in an interventional clinical study with an investigational product.

A18 (adapted from M18)	Female participants who are pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 90 days after the last dose of study intervention.
A19 (adapted from M19)	Male participants who plan to father a child while enrolled in this study or within 90 days after the last dose of study intervention.
M20	Participants who had major surgery (eg, requiring general anesthesia), excluding diagnostic surgery, within 12 weeks before screening; or will not have fully recovered from surgery; or have surgery planned during the time of expected participation in the study. ***Note:*** Participants with planned surgical procedures to be conducted under local anesthesia may participate.
M21	Participant is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.
M22	Vulnerable participants (eg, incarcerated individuals, individuals under a legal protection measure).
A23	Participants with known allergies, hypersensitivity, or intolerance to JNJ-3989 or its excipients (refer to the IB [IB JNJ-3989 2020]) and/or to NA and/or to PegIFN-α2a or their excipients (refer to the respective prescribing information).
A24	Criterion modified per Amendment 1 A24.1 Participants who meet any of the additional exclusion criteria for PegIFN-α2a as described in local prescribing information (eg, refer to Pegasys SmPC or Pegasys USPI) per the investigator's discretion. Key exclusion criteria for PegIFN-α2a include: 1. Participants with signs or symptoms compatible with autoimmune disorders. 2. Participants with bone marrow suppression. 3. Participants with hypoglycaemia, hyperglycaemia, and/or diabetes mellitus, who cannot be effectively controlled by medication. 4. Participants with pre-existing ophthalmologic disorders. 5. Participants with one or more of the following laboratory abnormalities:

- Absolute neutrophil count <1,500 cells/mm^3 (<1,000 cells/mm^3 for black or African American participants).
- Serum creatinine >1.5x ULN.
- Inadequately controlled thyroid function (thyroid stimulating hormone [TSH] and thyroxine [T4]).

6. Participants with a history of a severe psychiatric disorder, including severe depression, suicidal ideation and attempted suicide, or a current depression or other psychiatric disorder that is not adequately controlled on a stable medication regimen.

Note: Contraindications to the use of PegIFN-α2a need to be checked at screening and again at Week 12 for participants in Arm 2.

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

5.3. Lifestyle Considerations

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

1. Refer to Section 6.8, 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

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

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Intervention(s) Administered

Description of Interventions

Intervention Name	JNJ-3989	PegIFN-α2a	Tenofovir disoproxil	Tenofovir alafenamide (TAF)*	Entecavir (ETV) monohydrate
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	180 µg/0.5 mL	245 mg	25 mg	0.5 mg
Dosage Level(s)	200 mg once every 4 weeks (Q4W)	180 µg once weekly (QW)	245 mg QD	25 mg QD	0.5 mg QD
Route of Administration	Subcutaneous injection (preferably in the abdomen)	Subcutaneous injection (in the thigh or abdomen)	Oral	Oral	Oral
Use	Investigational intervention	Investigational intervention	Background intervention	Background intervention	Background intervention
Investigational Medicinal Product (IMP)	Yes	Yes	Yes	Yes	Yes
Non-investigational Medicinal Product/ Auxiliary Medicinal Product (NIMP/AxMP)	No	No	No	No	No
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	Each unit will be labeled with unique medication ID number	Commercial supplies will be sourced. Each unit will be labeled with unique medication ID number.	Commercial supplies will be sourced. Each unit will be labeled with unique medication ID number.	Commercial supplies will be sourced. Each unit will be labeled with unique medication ID number.	Commercial supplies will be sourced. Each unit will be labeled with unique medication ID number.
		In child resistant packaging	In child resistant packaging	In child resistant packaging	In child resistant packaging

Intervention Name	**JNJ-3989**	**PegIFN-α2a**	**Tenofovir disoproxil**	**Tenofovir alafenamide (TAF)***	**Entecavir (ETV) monohydrate**
Food/Fasting Instructions	Regardless of food intake	Per the prescribing information	Per the prescribing information	Per the prescribing information	Per the prescribing information

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

* In countries where TAF is available, it will be one of the NA treatment options.

Physical Description of Study Interventions

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

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

The NAs ETV, tenofovir disoproxil, and TAF formulated as oral film-coated tablets of 0.5-mg, 245-mg, and 25-mg strength, respectively, will be provided by the Sponsor. Refer to the prescribing information for a list of excipients.

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

Packaging and Labeling

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

NA and PegIFN-α2a treatment may be repackaged into child-resistant packaging if this is not already the case.

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

Study Intervention Administration

Study intervention administration must be captured in the source documents and the CRF.

JNJ-3989 injections will be administered subcutaneously (preferably in the abdomen) at the study site.

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

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

During the study, participants will continue the same NA treatment (ETV, tenofovir disoproxil, or TAF) they were receiving at the time of screening (and during at least 3 months prior to screening). In case participants experienced toxicity to ETV, tenofovir disoproxil, or TAF prior to screening, they should be treated with one of the other two NAs during this study. If clinically indicated, switching from one NA treatment (ETV, tenofovir disoproxil, or TAF) to another NA treatment (ETV, tenofovir disoproxil, or TAF) during the study is allowed after consultation with the Sponsor.

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

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

For a definition of study intervention overdose, refer to Section 6.7, Treatment of Overdose.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

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

Study site personnel will instruct participants on how to store study intervention for at home use as indicated for this protocol.

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

Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The dispensing of NA and PegIFN-α2a (if self-administered) to the participant, and the return of NA, and PegIFN-α2a (if self-administered) from the participant (if applicable), must be documented on the intervention accountability form. Participants must be instructed to return all original containers, whether empty or containing study

[a] For countries that do not allow PegIFN-α2a self-injection: weekly administration of PegIFN-α2a must be performed at the study site by the investigator or his/her designee.

intervention. The JNJ-3989 and PegIFN-α2a injections administered to the participant at the study site must be documented on the intervention accountability form. All study intervention will be stored and disposed of according to the Sponsor's instructions. Study site personnel must not combine contents of the study intervention containers.

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

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

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

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Participants will be randomly assigned to 1 of 3 intervention groups based on a computer-generated randomization schedule at baseline under the supervision of the Sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by absolute HBsAg level (<1,000 IU/mL versus >1,000 IU/mL) at baseline and country grouping as proxy for HBV GT at enrollment, with 3 levels: Poland (predominantly GT-A) versus Russia (predominantly GT-D) versus all other countries (other or mixed GT prevalence) (Kim 2011). Based on this randomization code, the study intervention will be packaged and labeled for each participant. Participant numbers will be preprinted on the study intervention labels and assigned as participants qualify for the study and are assigned to intervention.

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

Blinding

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

6.4. Study Intervention Compliance

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

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

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

- If an injection of JNJ-3989 was missed, the injection should be given as soon as possible but within 3 weeks after the scheduled time. Otherwise, the injection should be skipped and the next injection should be given at the next scheduled time point per the initial injection schedule.
- If a dose of NA is missed, the participant should follow the guidelines in the prescribing information.
- If an injection of PegIFN-α2a is missed, the participant should follow the guidelines in the prescribing information.

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

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

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

6.5. Dose Modification

Dose modifications of JNJ-3989 and NA (increase or decrease of dose level) are not permitted. For PegIFN-α2a, dose adjustment guidelines are recommended for participants who develop

[a] Not applicable for participants in countries that do not allow PegIFN-α2a self-injection, where weekly administration of PegIFN-α2a must be performed at the study site by the investigator or his/her designee.

laboratory abnormalities during PegIFN-α2a treatment, as recommended in the locally approved prescribing information for PegIFN-α2a. The Pegasys USPI has been provided as an example in Table 2 below.

Table 2: PegIFN-α2a Hematological Dose Modification Guidelines

Laboratory Values	Recommended Dose
ANC <750 cells/mm³	Reduce to 135µg
ANC <500 cells/mm³	Discontinue treatment until ANC values return to more than 1,000 cells/mm³. Reinstitute at 90µg and monitor ANC.
Platelet <50,000 cells/mm³	Reduce to 90µg
Platelet <25,000 cells/mm³	Discontinue treatment

ANC: absolute neutrophil count
Source: Pegasys USPI

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

6.5.1. NA Treatment Completion

All participants will receive the last dose of JNJ-3989 at Week 24 and the last dose of PegIFN-α2a at Week 23 (Arms 1 and 2) or Week 11 (Arm 3). They will start the FU Period after the Week 24 visit. If all of the following NA treatment completion criteria are met based on the Week 24 results, treatment with NA will be stopped at the next scheduled visit (ie, FU Week 2):

- The participant has ALT <3x ULN, AND
- The participant has HBV DNA <60 IU/mL at Week 24 and HBV DNA <LLOQ at the previous visit, or HBV DNA <LLOQ at Week 24, AND
- The participant is HBeAg-negative, AND
- The participant has HBsAg <100 IU/mL.

Note: Participants who are close to meeting the protocol-defined NA treatment completion criteria with the Week 24 results, and do meet the criteria based on the FU Week 2 results may be allowed to stop NA at FU Week 4, after consultation with the Sponsor. In case of ALT elevation ≥3x ULN at Week 24, the investigator must consider different potential causes of increased ALT to ensure appropriate work up and management as needed. If the ALT elevation is unrelated to HBV activity and/or <3x ULN by FU Week 2, NA completion may be considered at the discretion of the investigator and in consultation with the sponsor.

Participants who do not meet the above criteria based on the Week 24 or FU Week 2 results should continue NA treatment during the 48-week FU Period.

Participants who meet the above-mentioned NA treatment completion criteria will be monitored closely during the 48-week FU Period with a study visit at least once every 4 weeks. NA treatment should be re-started in accordance with the NA re-treatment criteria (see Section 6.5.2, NA Re-treatment Criteria During Follow-up, for more details).

The investigator should consider to re-start NA treatment per local standard of care at the EOS visit (Follow-up Week 48) for participants who met the NA treatment completion criteria based on the Week 24 (or FU Week 2) results, who did not re-start NA treatment during the follow-up phase, and who did not achieve and maintain HBsAg seroclearance. NA will not be provided by the sponsor after the final study visit.

If a participant prematurely discontinues JNJ-3989 (ie, before Week 24), follow-up assessments should be obtained as per the Schedule of Activities until 48 weeks after the end of JNJ-3989 treatment, unless the participant withdraws consent. NA treatment may be continued or, in consultation with the sponsor, discontinued, based on the above-mentioned NA treatment completion criteria.

If a participant prematurely discontinues PegIFN-α2a (ie, before Week 23 [Arms 1 and 2] or before Week 11 [Arm 3]), treatment with JNJ-3989 and NA should be continued as planned.

6.5.2. NA Re-treatment Criteria During Follow-up

Participants who meet the protocol-defined NA treatment completion criteria based on the Week 24 (or FU Week 2) results should complete NA treatment at FU Week 2 (or FU Week 4) as outlined in Section 6.5.1, NA Treatment Completion, and will be monitored closely during the follow-up period with a study visit at least once every 4 weeks. They should re-start NA treatment immediately in the event of:

- Signs of decreasing liver function based on laboratory findings (eg, International Normalized Ratio [INR], direct bilirubin) or clinical assessment (eg, ascites, hepatic encephalopathy).
- HBV DNA value of >1,000,000 IU/mL (irrespective of confirmation and/or ALT increase).

  Note: A post-treatment HBV DNA value of >100,000 IU/mL should trigger re-testing of ALT/AST, HBV DNA, and total and direct bilirubin within a maximum of 7 days from receipt of the data and further repeats as necessary (ie, weekly until HBV DNA returns to <100,000 IU/mL). A post-treatment HBV DNA value of >20,000 IU/mL (but <100,000 IU/mL) should trigger a re-test within 14 days. At all times, additional re-testing of the above parameters should be performed at the investigator's discretion.

In addition, re-start of NA treatment should be considered in the following cases:

- Confirmed post-treatment HBeAg seroreversion (HBeAg positive after it was negative at NA completion), OR
- Confirmed (at least 4 weeks apart) post-treatment increases in HBV DNA >2,000 IU/mL and ALT >5x ULN, OR

  Note: A post-treatment ALT value of >5x ULN should trigger re-testing of ALT, AST, ALP, total and direct bilirubin, INR, albumin, and HBV DNA on a weekly basis until ALT and AST levels have returned to <5x ULN. At all times, additional re-testing of these parameters should be performed at the investigator's discretion.

- Confirmed (at least 4 weeks apart) post-treatment increases in HBV DNA >20,000 IU/mL.

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

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

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

NA re-treatment criteria during follow-up are presented graphically in Section 10.12, Appendix 12.

Management of intervention-emergent ALT/AST elevations is discussed in Section 8.3.6.2, Intervention-emergent ALT/AST Elevations.

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

Refer to Section 6.7 of the Master Protocol PLATFORMPAHPB2001.

The investigator should consider to re-start NA treatment per local standard of care at the EOS visit (Follow-up Week 48) for participants who met the NA treatment completion criteria based on the Week 24 (of FU Week 2) results, who did not re-start NA treatment during the follow-up phase, and who did not achieve and maintain HBsAg seroclearance. NA will not be provided by the sponsor after the final study visit.

6.7. Treatment of Overdose

For this study, any dose of JNJ-3989 exceeding the protocol-specified dose with ≥25% and any dose of NA (ETV, tenofovir disoproxil, or TAF) greater than the prescribed dose (refer to Section 6.1, Study Intervention(s) Administered), will be considered an overdose. Any dose of PegIFN-α2a greater than the prescribed dose will be considered an overdose. The Sponsor does not recommend specific treatment for an overdose.

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

- Contact the Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for AE/SAE and laboratory abnormalities.

- Obtain a plasma sample for PK analysis as soon as possible from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

6.8. Concomitant Therapy

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

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

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

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

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

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

Table 3: Disallowed Medication

Disallowed from 3 years prior to screening until end of follow-up:
• IFN, other than the PegIFN-α2a taken in the context of this study.
Disallowed from 1 year prior to baseline until end of follow-up:
• Any oligonucleotide-based treatment (eg, siRNA, nucleic acid polymers, antisense oligonucleotides), other than the study intervention taken in the context of this study.
Disallowed from 6 months prior to screening until end of follow-up:
• Any investigational agent, investigational vaccine, invasive investigational medical device, or investigational biological product (other than the study intervention taken in the context of this study). ***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:
• Any systemically (eg, intravenously, intramuscularly, orally, subcutaneously) administered medication that directly or indirectly interferes with immune responses (eg, cyclosporine, interleukins, systemic corticosteroids exceeding 5 mg of prednisolone equivalent/day).
Disallowed from screening until end of follow-up:
• Any anti-HBV drug (including vaccines) other than the study intervention taken in the context of this study. ***Notes:*** o NA standard of care treatment is allowed between screening and baseline. o Prior hepatic treatment with herbal or nutritional products is allowed but should be stopped at screening.
Disallowed from screening until end of study intervention:
• Products containing *Hypericum perforatum* (St. John's wort). • 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.

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

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

If a participant prematurely discontinues JNJ-3989 (ie, before Week 24), the participant will have an early WD visit and will enter the 48-week follow-up period, unless the participant withdraws consent from study participation.

If a participant prematurely discontinues PegIFN-α2a (ie, before Week 23 [Arms 1 and 2] or before Week 11 [Arm 3]), treatment with JNJ-3989 and NA should be continued as planned.

If the reason for withdrawal from the study is withdrawal of consent, then the participant will be offered an optional safety follow-up visit (to occur on the day of consent withdrawal). Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant.

7.1. Discontinuation of Study Intervention

Treatment with JNJ-3989 (and PegIFN-α2a if applicable) must be discontinued prematurely if any of the discontinuation criteria listed below are met. Criteria specific for this ISA are highlighted (colored fill). For the few criteria from the Master Protocol that are specified or more restricted in this ISA, the changes compared to the Master Protocol are also highlighted (colored fill). If JNJ-3989 is prematurely discontinued, PegIFN-α2a (if applicable) should also be discontinued. If PegIFN-α2a is prematurely discontinued (ie, before Week 23 [Arms 1 and 2] or before Week 11 [Arm 3]), treatment with JNJ-3989 and NA should be continued as planned. NA treatment may be continued or, in consultation with the Sponsor, discontinued based on investigator judgement.

The discontinuation criteria are:

- The participant withdraws consent to receive study intervention.
- The investigator believes that for safety or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue JNJ-3989 (and PegIFN-α2a, if applicable).
- The participant becomes pregnant.
- The participant has a ≥Grade 3 rash (see Section 10.6, Appendix 6: Rash Management) or allergic reaction (see Section 8.3.7.3, Acute Systemic Allergic Reactions).
- The participant has signs of hepatic decompensation (ie, clinical evidence of ascites, bleeding varices, or hepatic encephalopathy) or an increase in direct bilirubin >1.5x ULN in combination with INR ≥1.5x ULN or albumin <3.0 g/dL. Treatment with JNJ-3989 should be discontinued and alternative treatment options (outside the study) should be considered in discussion with the Sponsor.
- The participant has a confirmed ≥Grade 3 eGFR abnormality and a drop from baseline of >10 mL/min/1.73 m^2, considered at least possibly related to JNJ-3989 (or PegIFN-α2a, if applicable) that persists despite changing tenofovir disoproxil to ETV or TAF (if the patient was receiving tenofovir disoproxil) (see Section 8.3.7.2, Renal Complications).
- The participant has a QTcF prolongation (defined as a QTcF value of >500 ms, or an increase from baseline of >60 ms) at any given time point.
- The participant requires ≥7 days of treatment with any of the disallowed medications listed in Section 6.8, Concomitant Therapy, and does not intend to discontinue treatment with the disallowed medication.
- The participant has confirmed HBV virologic breakthrough (ie, confirmed on-treatment HBV DNA increase by >1 $\log_{10}$ IU/mL from nadir or confirmed on-treatment HBV DNA level >200 IU/mL in participants who had HBV DNA level <LLOQ of the HBV DNA assay).

  If virologic breakthrough occurs during PegIFN-α2a administration, this does not automatically lead to stop of JNJ-3989 and/or PegIFN-α2a, but should be assessed/discussed with the Sponsor.

In case of virologic breakthrough, a viral sequencing sample will be collected during an unscheduled visit within 7 days of the DNA increase.

- The participant has ALT/AST elevations, as described in Section 8.3.6.2, Intervention-emergent ALT/AST Elevations.

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

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

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

Note: PegIFN-α2a treatment can be restarted when ANC values return to more than 1,000 cells/mm^3 (see details in Section 6.5, Dose Modification)

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

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

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

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

7.2. Participant Discontinuation/Withdrawal From the Study

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

Withdrawal of Consent

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

7.2.1. Withdrawal From the Use of Research Samples

Refer to Section 7.2.1 of the Master Protocol PLATFORMPAHPB2001.

7.3. Lost to Follow-up

Refer to Section 7.3 of the Master Protocol PLATFORMPAHPB2001.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

Refer to Section 8 of the Master Protocol PLATFORMPAHPB2001.

The total blood volume to be collected from each participant during planned assessments for the entire study will be up to approximately 1050 mL.[a] In addition, PBMC samples (at selected sites only; approximately 450 mL) and optional pharmacogenomic samples (approximately 25 mL) may be collected.

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

Sample Collection and Handling

Refer to Section 8 of the Master Protocol PLATFORMPAHPB2001.

Study-Specific Materials

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

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

[a] For participants in Japan only: the total blood volume to be collected during planned assessments for the entire study will be approximately 920 mL due to additional hematology assessments.

8.1. Efficacy Assessments

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

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

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

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

It is the responsibility of the investigator:

- To monitor HBV DNA results and assess whether JNJ-3989 (and PegIFN-α2a if applicable) are discontinued in participants with confirmed virologic breakthrough (see Section 7.1, Discontinuation of Study Intervention).
- To assess if the protocol-defined NA treatment completion criteria are met (see Section 6.5.1, NA Treatment Completion).
- To assess whether re-start of NA treatment during follow-up is needed (see Section 6.5.2, NA Re-treatment Criteria During Follow-up).

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

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

8.1.1. Sequencing

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

Sequencing of the HBV genome will be performed to monitor HBV variants present at the time points indicated in the Schedule of Activities. Samples may be sequenced based on the Sponsor virologist's request, considering the HBV DNA levels. In case of a virologic breakthrough/flare, additional samples for viral sequencing may be taken.

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

8.2. Safety Assessments

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

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

8.2.1. Physical Examinations

Refer to Section 8.2.1 of the Master Protocol PLATFORMPAHPB2001.

8.2.2. Vital Signs

Refer to Section 8.2.2 of the Master Protocol PLATFORMPAHPB2001.

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

8.2.3. Electrocardiograms

Refer to Section 8.2.3 of the Master Protocol PLATFORMPAHPB2001.

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

8.2.4. Clinical Safety Laboratory Assessments

Refer to Section 8.2.4 of the Master Protocol PLATFORMPAHPB2001.

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

8.2.5. Pregnancy Testing

For women of childbearing potential, a negative screening serum pregnancy test and a negative baseline urine pregnancy test must be obtained before the first dose of study intervention on Day 1.

Urine pregnancy tests should be done at least every 4 weeks, preferably during a scheduled site visit. Given the less frequent follow-up of participants who continue NA treatment or have restarted NA treatment during the follow-up period (provided that their HBV DNA and ALT values are stable), pregnancy tests for at-home use may be provided to these participants from Follow-up Week 4 onwards to allow 4-weekly urine pregnancy testing in between scheduled site

visits. Participants will report the results to the study site personnel at the next visit, and these will be added to the source documents. If positive, the participant should contact the site immediately.

8.2.6. Ophthalmologic Examinations

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

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

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

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

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

Refer to Section 8.3.1 of the Master Protocol PLATFORMPAHPB2001.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Refer to Section 8.3.2 of the Master Protocol PLATFORMPAHPB2001.

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

Refer to Section 8.3.3 of the Master Protocol PLATFORMPAHPB2001.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

Refer to Section 8.3.4 of the Master Protocol PLATFORMPAHPB2001.

8.3.5. Pregnancy

Refer to Section 8.3.5 of the Master Protocol PLATFORMPAHPB2001.

8.3.6. Adverse Events of Special Interest

Events of Special Interest are significant AEs that are judged to be of special interest because of clinical importance, known class effects or based on nonclinical signals. Events of Special Interest for JNJ-3989 that will be carefully monitored during the study include ISRs, ALT/AST elevations, and hematologic abnormalities.

For participants reporting ISRs, ALT/AST elevations, or hematologic abnormalities 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. Injection Site Reactions

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

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

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

8.3.6.2. Intervention-emergent ALT/AST Elevations

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

Management of intervention-emergent ALT/AST elevations is presented graphically in Section 10.7, Appendix 7: Intervention-emergent ALT/AST Elevations, and is described below.

Any intervention-emergent elevation of ALT and/or AST ≥3x ULN and ≥3x nadir (ie, lowest value during study participation) should trigger an assessment of confounding factors (alcohol intake, change in concomitant medication, and comorbidities) and should trigger a confirmatory study visit to repeat laboratory testing of AFP, ALT, AST, ALP, bilirubin (total and direct), INR, albumin, and HBV DNA. Additional tests should be considered based on clinical judgement (refer to Section 10.7, Appendix 7: Intervention-emergent ALT/AST Elevations). This confirmatory visit should be scheduled as soon as possible within 7 days of the receipt of the initial ALT/AST results. In case the repeat laboratory testing shows an isolated ALT/AST elevation (ie, with stable albumin, bilirubin [total and direct], and INR) the participant may continue study intervention. In case of confirmed ALT elevation >1,000 U/L and ≥3x the baseline value, JNJ-3989 (and PegIFN-α2a if applicable) should be discontinued. In both cases, NA treatment should be continued. The participant will be monitored (laboratory testing of AFP, ALT, AST, ALP, bilirubin [total and direct], INR, albumin, and HBV DNA) on a weekly basis or more frequently until ALT and AST levels have returned to <5x ULN and HBV DNA is <20,000 IU/mL. Additional PBMC and AFP samples may be taken in case of ALT flares, upon discussion with the Sponsor, which may require an unscheduled visit.

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

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

the participant should discontinue JNJ-3989 (and PegIFN-α2a if applicable) and should be monitored on a weekly basis or more frequently, or as per good clinical practice, until ALT and AST levels have returned to <5x ULN, HBV DNA is <20,000 IU/mL and, if present, liver-related symptoms have improved. NA treatment should be continued. Additional tests can be considered based on clinical judgement (refer to Section 10.7, Appendix 7: Intervention-emergent ALT/AST Elevations).

In case of prolonged ALT elevation >3x ULN AND >2x nadir, which lasts at least 12 weeks, the decision to continue JNJ-3989 and/or PegIFN-α2a should be based upon virologic parameters (eg, HBsAg, HBV DNA) and should be made in consultation with the sponsor.

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

8.3.6.3. Hematologic Abnormalities

In the Phase 1/2a AROHBV1001 study with JNJ-3989, mild (Grade 1) transient thrombocytopenia was observed in 6 out of 84 participants receiving 3 subcutaneous injections of JNJ-3989 alone over a period of up to 12 weeks with background of NAs. The transient thrombocytopenia was not considered clinically significant. No thrombocytopenia or pancytopenia was observed in 12 participants when JNJ-3989 was given in combination with JNJ-6379 over a 12-week period in the same study.

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

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

In case any of the above criteria are met, a confirmatory visit should be scheduled as soon as possible, preferably within 7 days of the receipt of the initial results. Confirmation of the results will trigger weekly or biweekly (every other week) unscheduled visits until improvement or

stabilization of the respective parameter(s). Stabilization is defined as no further significant reduction over two consecutive visits.

In case of confirmed Grade 3 or Grade 4 hematologic abnormalities, discontinuation of JNJ-3989 (and PegIFN-α2a if applicable) should be considered. In case of discontinuation, NA treatment should be continued.

8.3.7. Other Toxicities

The following toxicities will be carefully monitored: rash, renal complications, and acute systemic allergic reactions.

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

8.3.7.1. Rash

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

All rash events should be captured in the AE section of the CRF. Separate Rash pages will be completed in case of a rash event.

Monitoring of the evolution of rash events will be performed as described in Table 4 in Section 10.6, Appendix 6: Rash Management.

When safety blood samples are drawn as per the rash management guidelines, these should be processed by the local laboratory. The following parameters will need to be tested: AST, ALT, sedimentation rate, complete blood cell count (including hemoglobin, hematocrit, RBC count, WBC count, differential count [neutrophils, lymphocytes, monocytes, eosinophils, and basophils], and platelet count), and creatinine. The values of the local laboratory assessments need to be transcribed in the CRF by the study site personnel.

The participant may be treated symptomatically until the rash resolves. Oral antihistamines (eg, cetirizine, levocetirizine) and/or topical corticosteroids may provide symptomatic relief but effectiveness of these measures has not been established. If systemic corticosteroids exceeding 5 mg of prednisolone equivalent/day are required for treatment of rash, JNJ-3989 (and PegIFN-α2a if applicable) need to be permanently discontinued. NAs can be continued. If the rash is considered to be most likely due to concomitant illness or non-study interventions, standard management, including discontinuation of the likely causative agent, should be undertaken.

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

8.3.7.3. Acute Systemic Allergic Reactions

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

Participants may continue the intake of study interventions.

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

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

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

Participants may continue the intake of study interventions.

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

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

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

Participants will permanently discontinue the intake of JNJ-3989 (and PegIFN-α2a if applicable). Rechallenge is not allowed. The participant's NA treatment may be discontinued based on investigator judgement in consultation with the Sponsor.

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

8.4. Pharmacokinetics

Plasma or serum samples, as applicable, will be used to evaluate the PK of JNJ-3989. Serum collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period.

8.4.1. Evaluations

All participants will have sparse PK sampling during the treatment period.

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

8.4.2. Analytical Procedures

Pharmacokinetics

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

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

8.4.3. Pharmacokinetic Parameters and Evaluations

Parameters

Based on the individual plasma concentration-time data, using the actual dose taken and the actual sampling times, PK parameters and exposure information of JNJ-3989 may be derived using population PK modelling. Baseline covariates (eg, body weight, age, sex, CrCL, race) may be included in the model, if relevant.

Pharmacokinetic/Pharmacodynamic Evaluations

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

8.5. Host Genetics

An optional sample for HLA testing will be collected from participants who consent separately to this component of the study.

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

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

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

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

8.6. Exploratory Host Biomarkers

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

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

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

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

8.7. Immune Assessments

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

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

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

intervention (safety/efficacy), or to explore new functional immune assays, or for immune assay optimalization.

Blood samples taken at the time points indicated in the Schedule of Activities, can also be used to explore the emergence of antidrug antibodies to JNJ-3989 and optionally to PegIFN-α2a. Antidrug antibodies may be analyzed using assays such as an enzyme-linked immunosorbent assay or functional assays. The analyses may also include gene expression and cytokine analyses assessing markers such as interferon-stimulated genes (ISGs), IFN-α, and interferon γ-induced protein 10 (IP-10).

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

8.8. 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 duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days length of stay, including duration by wards; eg, intensive care unit)
- Number and character of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications)

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

The primary hypothesis of this study is that at least one of the combination regimens of JNJ-3989+NA+PegIFN-α2a is more efficacious than NA treatment alone (standard of care), as measured by the primary efficacy endpoint, the proportion of participants who achieved a reduction of at least 2 $\log_{10}$ IU/mL in HBsAg levels from baseline at Week 24. Because the study does not include a control arm, the hypothesis is formulated assuming a fixed external NA control response rate of 2% in terms of the primary efficacy endpoint.

9.2. Sample Size Determination

A sample size of 30 participants per arm yields >95% statistical power to detect a ≥30% difference in at least one arm in the proportions of participants with a reduction of at least 2 $\log_{10}$ IU/mL in

HBsAg levels from baseline at Week 24 versus a fixed proportion of ≤2%, assumed for external control (NA treatment). Statistical power to test the primary hypothesis was assessed for each of the intervention arms, separately, using an exact test for a single proportion with a one-sided Type 1 error rate of 0.05 and applying the Hochberg procedure for multiple comparisons adjustment. The assumed external control value is based on the data of the NA control arm in virologically suppressed HBeAg negative participants in study 73763989HPB2001 (REEF-1).

The total study sample size is 102 participants (34 per arm) with 1:1:1 randomization ratio to one of the three intervention arms, assuming an approximate 10% attrition rate.

For the secondary set of pairwise comparisons of the primary efficacy endpoint among the 3 study intervention arms (Arm 1 versus Arm 2, Arm 1 versus Arm 3, and Arm 2 versus Arm 3) and using a 2-sample binomial test, the planned sample size yields about 68% power to detect a significant difference of at least 30%. This is assuming the lowest response rate at Week 24 to be 50% in one of the intervention arms, and 80% in one or both of the other 2 arms and applying the Hochberg procedure to control the 1-sided Type 1 error rate at 0.05 level. The assumption of 50% response rate was derived from the analysis of 73763989HPB2001 (REEF-1) on-treatment data.

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Screened	All participants who signed the ICF for the Master Protocol and the ICF specific for this ISA.
Enrolled	All participants who were enrolled in this ISA.
Full Analysis Set (FAS)	All participants who were randomly assigned to an intervention arm in this ISA and received at least 1 dose of study intervention within this ISA. Participants will be analyzed according to the study intervention they were randomly assigned to.
IFN-FAS	All participants who were randomly assigned to an intervention arm in this ISA and received at least 1 dose of PegIFN-α2a within this ISA. Participants will be analyzed according to the study intervention they were randomly assigned to.
Safety	All participants who received at least 1 dose of study intervention within this ISA. Participants will be analyzed according to the study intervention they actually received.

9.4. Statistical Analyses

The statistical analysis plan will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

Refer to Section 9.4.1 of the Master Protocol PLATFORMPAHPB2001.

9.4.2. Efficacy Analyses

The primary efficacy analysis will be performed when all participants have completed the Week 24 (EOSI) visit or discontinued earlier. The final analysis will be performed when all participants have completed the last study visit at Week 72 (FU Week 48) or discontinued earlier.

To evaluate the efficacy, the primary analysis set will be the FAS (see Section 9.3, Populations for Analysis Sets). The IFN-FAS set will be used for sensitivity analyses of selected efficacy endpoints.

All efficacy summaries will be presented with descriptive statistics and 90% confidence intervals (CI) by intervention arm, when applicable. If the endpoint is continuous, the descriptive statistics will include the number of participants, mean, standard deviation (SD), median, and range. If the endpoint is binary or categorical, the frequency distribution with the number and percentage of participants in each category will be calculated. For time-to-event variables, a summary table based on the Kaplan-Meier method 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 the randomization stratification factors (ie, country grouping as proxy for HBV genotype (GT) at enrollment and absolute HBsAg value at baseline [<1,000 IU/mL versus ≥1,000 IU/mL]).

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

9.4.2.1. Primary Efficacy Endpoint

The proportion of participants who achieved a reduction of at least 2 $\log_{10}$ IU/mL in HBsAg levels from baseline at Week 24 will be summarized for each treatment arm paired together with a two-sided, single arm 90% confidence interval (CI) based on the Clopper-Pearson method. The statistical comparison will be conducted using an exact binomial test against a fixed external control value of 2% at a one-sided Type 1 error rate of 0.05 and applying the Hochberg procedure for adjusting for multiple comparisons.

Association of the stratification factors and other demographic and baseline disease characteristics with the primary endpoint will be explored using logistic regression analyses and classification and regression tree analysis (CART).

The Mantel-Haenszel (MH) test adjusted for the randomization stratification factors will be used in a secondary analysis comparing the primary endpoint between the study intervention arms at a one-sided alpha level of 0.05 and applying the Hochberg procedure for multiple comparisons adjustment.

The primary efficacy endpoint will be compared between Arm 2 and the "virtual" model-generated IFN-free JNJ-3989 control participants in Arm 2 using the McNemar test for the difference between paired matched case-control binomial proportions at 0.05 one-sided Type 1 error rate. The associated 2-sided 90% CI will be estimated to accompany the point estimate of the difference in proportions. No multiplicity adjustment will be used in this exploratory statistical comparison. Description of the virtual control generated data for Arm 2 is described in Section 9.4.2.3, Across ISAs Comparisons of Efficacy.

9.4.2.2. Secondary Efficacy and Exploratory Endpoints

Descriptive statistics will be used for all efficacy endpoints, which will be summarized by intervention arm and by study period. Comparisons between intervention arms and 90% CIs will be done with no adjustment for multiplicity. Specific key selected endpoints may be analyzed using suitable categorical data approaches (eg, Mantel-Haenszel or logistic regression for proportions or other categorical type of endpoint), longitudinal repeated measures models (eg, for continuous types of variables), or survival analysis based on the Kaplan-Meier estimates (for time-to-event variables), as appropriate. Details will be described in the SAP.

Graphic data displays of different type (eg, bar charts, line plots, waterfall, and radar plots) will also be used to summarize the efficacy data by intervention arm and over time.

9.4.2.3. Across ISAs Comparisons of Efficacy

Indirect comparisons between different regimens across multiple ISAs will be performed in an exploratory fashion by selecting the similar subgroup of participants who match the most important inclusion/exclusion criteria and demographic characteristics of this ISA, such as for example the virologically suppressed participants who are HBeAg negative at screening across 73763989PAHPB2007 (this ISA), 73763989PAHPB2002 (REEF-2), and 73763989PAHPB2006 (PENGUIN) ISAs.

To further evaluate the impact of potential differences between ISAs, a virtual control arm will be generated for this ISA. Virtual control efficacy data will be defined as IFN-free regimen with JNJ-3989+NA at the dose level used in this ISA. Creating a virtual control arm by fitting the PK/PD model to the available HBsAg data can be performed for subjects with serum HBsAg >100 IU/mL at screening. The same approach may also be considered for subjects with serum HBsAg ≤100 IU/mL at screening, but as these subjects were typically not included in previous JNJ-3989 studies, the feasibility of this approach will be assessed based on the current analysis results.

For each participant in Arm 2 of this ISA, the HBsAg data for “virtual” control subjects will be generated using an appropriate longitudinal model (eg, kinetic pharmacodynamic model [KPD] or PK/PD model) developed and validated based on the data from the 73763989HPB2001 (REEF-1) study. In Arm 2, the first 12 weeks of HBsAg data under treatment with JNJ-3989+NA alone will enable to estimate individual parameters (ie, Empirical Bayes Estimates) describing each participant's specific HBsAg temporal kinetics. These individual parameters will be used further to extrapolate each participant’s individual HBsAg values over time, as if that participant had been treated with JNJ-3989+NA regimen (matching the same JNJ-3989 dose level) but without receiving PegIFN-α2a treatment. The observed HBsAg levels post PegIFN-α2a intake in Arm 2 will be directly compared to virtual control model-generated data for this arm. Due to the randomization, the virtual control subjects derived for Arm 2 can be considered exchangeable with the participants of the other arms in this ISA. Therefore, the estimates of HBsAg efficacy endpoints at the group level of the virtual control subjects for Arm 2 will also be compared to the other arms in this ISA.

The evaluation of the comparisons within this ISA (virtual within-participant control versus regimens in this ISA) against the results from comparing the regimens in this ISA with those in the 73763989PAHPB2006 (PENGUIN) and 73763989PAHPB2002 (REEF-2) ISAs will provide an additional efficacy assessment of the treatment benefit of PegIFN-α2a.

More details on this approach and its application to secondary endpoints will be provided in a separate analysis plan document (eg, SAP or the Modeling and Simulation Report).

9.4.3. Safety Analyses

Safety analyses will be based on the safety population (see Section 9.3, Populations for Analysis Sets) and are specified in Section 9.4.3 of the Master protocol PLATFORMPAHPB2001.

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

Indirect descriptive comparisons of selected safety endpoints between different regimens across different ISAs will be performed in an exploratory fashion by selecting the similar subgroup of participants who match the most important inclusion/exclusion criteria and demographic characteristics of this ISA population.

9.4.4. Other Analyses

Pharmacokinetic analysis

Population PK analysis of concentration-time data of JNJ-3976 and JNJ-3924, and, optionally, of NA and PegIFN-α2a 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. 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.

Pharmacokinetic/pharmacodynamic analysis

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

Modeling of key PD parameters (eg, HBsAg, HBV DNA) may be performed using population PK/PD. If PK/PD modeling of key efficacy endpoints is performed, treatment effect and possible covariates may be investigated. Other biomarkers may be explored at the Sponsor's discretion. If applicable, the results will be described in a separate report.

Resistance analysis

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

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

Immune analysis

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

Pharmacogenomic analysis

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

Host Biomarker analysis

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

Medical Resource Utilization

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

9.5. Interim Analysis

Interim analyses (IA) will be conducted to assess safety and evaluate the time course of different safety and efficacy markers to support the Sponsor's interactions with health authorities, as well as to inform internal decisions about additional studies and/or investigation of other treatment combinations.

The IAs are planned when:

- Approximately 50% of the randomized participants have completed Week 12 or discontinued earlier.
- Approximately 50% of the randomized participants have completed Week 24 or discontinued earlier.
- All randomized participants have completed Week 36 (FU Week 12) or discontinued earlier.
- All randomized participants have completed Week 48 (FU Week 24) or discontinued earlier.
- All randomized participants have completed Week 60 (FU Week 36) or discontinued earlier.

Depending on the enrollment rate, any of the above IAs may be skipped if it is too close to the predicted timing of any adjacent interim cutoffs, and additional IAs may be performed by the Sponsor to support interactions with health authorities.

The study is open-label, and the Sponsor will conduct IA(s). Hence, the study team and the DRC will have access to the IA results, while the investigators and patients will not.

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

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

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Definitions

AE	adverse event
AFP	alpha-fetoprotein
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC_{∞}	area under the plasma concentration time curve to last sampling point from time zero extrapolated to infinity
AUC_{τ}	area under the plasma concentration time curve over the dosing interval (τ)
$AUC_{0\text{-last}}$	area under the plasma concentration time curve from administration to last quantifiable sampling point
$AUC_{0\text{-xh}}$	area under the plasma concentration time curve from administration to x hours
BMI	body mass index
bpm	beats per minute
C_{24h}	plasma concentration 24 hours after administration
CAM(-N)	(Class N) capsid assembly modulator
cccDNA	covalently closed circular deoxyribonucleic acid
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	total apparent oral clearance
C_{max}	maximum plasma concentration
CRF	case report form
CT	computed tomography
CV	coefficient of variation
CYP	cytochrome P450
DAIDS	Division of Acquired Immunodeficiency Syndrome
DC	dendritic cell
DDI	drug-drug interaction
DNA	deoxyribonucleic acid
DRC	Data Review Committee
EC_{90}	90% effective concentration
ECG	electrocardiogram
EFD	embryofetal development
$eGFR_{cr}$	estimated glomerular filtration rate based on serum creatinine
$eGFR_{cys}$	estimated glomerular filtration rate based on cystatin C
ELISpot	enzyme-linked immunospot
EOS	end of study
EOSI	end of study intervention
ETV	entecavir
FAS	full analysis set
FC	functional cure
FOIA	Freedom of Information Act
FU	follow-up
GLDH	glutamate dehydrogenase
GT	genotype
HBc	hepatitis B core protein
HBcrAg	hepatitis B core-related antigen
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBs	hepatitis B surface protein
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus

HEV	hepatitis E virus
HIV(-1/2)	human immunodeficiency virus (type 1/2)
HLA	human leukocyte antigen
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICS	intracellular cytokine staining
IFLEP	Independent Flare Expert Panel
IFN(-α/γ)	(alpha/gamma) interferon
IFN-FAS	interferon full analysis set
IgG	immunoglobulin G
IgM	immunoglobulin M
IL	interleukin
IMP	investigational medicinal product
INR	International Normalized Ratio
ISA	intervention-specific appendix
ISR	injection site reaction
KPD	kinetic pharmacodynamic model
LLN	lower limit of normal
LLOQ	lower limit of quantification
MDSC	myeloid-derived suppressor cell
MoA	mode of action
MRI	magnetic resonance imaging
MRU	medical resource utilization
NA	nucleos(t)ide analog
NIMP	non-investigational medicinal product
NK	natural killer
NOAEL	no observed adverse effect level
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PegIFN-α2a	pegylated interferon alpha-2a
pgRNA	pre-genomic ribonucleic acid
PK	pharmacokinetic(s)
PoC	proof of concept
Q4W	every 4 weeks
QW	weekly
QD	once daily
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RBC	red blood cell
rcDNA	relaxed circular deoxyribonucleic acid
RNAi	ribonucleic acid interference
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SDM	site-directed mutant
SE	standard error
siRNA	small interfering ribonucleic acid
$t_{1/2term}$	terminal half-life
T4	thyroxine
TAF	tenofovir alafenamide
TEAE	treatment-emergent adverse event
t_{max}	time to reach C_{max}
TND	target not detected
TNF	tumor necrosis factor
TSH	thyroid stimulating hormone
WBC	white blood cell

Definitions of Terms

ALT/AST nadir	Lowest ALT/AST value during study participation
End of study intervention (EOSI)	Time of the last administration of study intervention
Functional cure (FC)	HBsAg seroclearance at 24-weeks after EOSI
HBsAg or HBeAg seroclearance	HBsAg or HBeAg negativity, respectively, based on the assay used
HBsAg or HBeAg seroconversion	HBsAg or HBeAg negativity and anti-HBs or anti-HBe antibody positivity, respectively
IC_{50}	half maximal inhibitory concentration
Study intervention	JNJ-73763989 (JNJ-3989), NA (either ETV, tenofovir disoproxil, or TAF), and PegIFN-α2a
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 selected laboratory. The tests to be performed are discussed in Section 8.2.4 of the Master Protocol PLATFORMPAHPB2001.

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

Protocol-Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="3">Parameters</th></tr>
<tr><td rowspan="2">Hematology</td><td>Platelet count
Red blood cell count
Hemoglobin
Hematocrit</td><td><u>RBC Indices:</u>
MCV
MCH
% Reticulocytes</td><td><u>White Blood Cell (WBC) count with Differential:</u>
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td colspan="3">Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. An RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.</td></tr>
<tr><td>Clinical Chemistry</td><td colspan="2">Sodium
Potassium
Chloride
Bicarbonate
Blood urea nitrogen (BUN)
Creatinine
Cystatin C
Glucose
Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Gamma-glutamyltransferase (GGT)
α_1-acid glycoprotein
Fibrinogen (on blood)
eGFR calculation based on Creatinine (eGFRcr; by CKD EPI formula)
eGFR calculation based on Cystatin C (eGFRcys; by CKD EPI formula)</td><td>Total, direct, indirect bilirubin
Alkaline phosphatase
Creatine phosphokinase (CPK)
Lactic acid dehydrogenase (LDH)
Uric acid
Calcium
Phosphate
Albumin
Total protein
Total cholesterol
High-density lipoprotein cholesterol
Low-density lipoprotein cholesterol
Triglycerides
Magnesium
Lipase
Amylase (reflex testing of pancreatic amylase should be done in case of amylase or lipase increase from screening onwards)</td></tr>
</table>

Laboratory Assessments	Parameters	
Routine Urinalysis	Dipstick Specific gravity pH Glucose Protein Blood Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase	Sediment (if dipstick result is abnormal) Red blood cells White blood cells Epithelial cells Crystals Casts Bacteria
	In case of a positive dipstick result, a urine sample will be set aside for additional examination of the positive parameter (eg, quantification as applicable).	
Urine Chemistry (quantitative measurement)	Creatinine Sodium Phosphate	Glucose Protein Albumin
Renal Biomarkers	Retinol binding protein[a] Beta-2-microglobulin[a] ***Note:*** Other biomarkers might be measured.	
Other Tests	• At screening, a follicle-stimulating hormone (FSH) test will be performed for postmenopausal women (see Section 10.5, Appendix 5). • At screening, a HIV-1 and -2 test, and hepatitis A, B, C, D, and E tests will be performed. • At screening, hemoglobin A1c will be measured. • At screening and time points as indicated in the Schedule of Activities, alpha-fetoprotein (AFP) will be measured. • At screening and time points as indicated in the Schedule of Activities, tests for coagulation parameters will be performed. The international normalized ratio (INR) will be calculated by the central laboratory. • At screening serum pregnancy testing will be done for women of childbearing potential only. • At baseline (Day 1) and time points as indicated in the Schedule of Activities, a urine pregnancy test will be performed for women of childbearing potential only. • Testing for HBsAg, HBeAg, and anti-HBs, anti-HBc and anti-HBe antibodies at the time points indicated in the Schedule of Activities. • Thyroid function tests (TSH and T4) will be performed at screening and time points indicated in the Schedule of Activities. • Optional tests in response to ALT flare (refer to Section 10.7, Appendix 7): o Testing for HIV-1 and -2, and hepatitis A, C, D, and E o Testing for CMV, HSV, EBV infection o Ig-Electrophoresis o AFP sampling	

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

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

10.3.1. Regulatory and Ethical Considerations

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

10.3.2. Financial Disclosure

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

10.3.3. Informed Consent Process

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

10.3.4. Data Protection

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

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

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

10.3.6. Committees Structure

Data Review Committee

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

Independent Flare Expert Panel

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

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

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

10.3.7. Publication Policy/Dissemination of Clinical Study Data

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

10.3.8. Data Quality Assurance

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

10.3.9. Case Report Form Completion

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

10.3.10. Source Documents

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

10.3.11. Monitoring

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

10.3.12. On-Site Audits

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

10.3.13. Record Retention

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

10.3.14. Study and Site Start and Closure

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

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

10.4.1. Adverse Event Definitions and Classifications

Refer to Attachment 4 of the Master Protocol PLATFORMPAHPB2001.

10.4.2. Attribution Definitions

Refer to Attachment 4 of the Master Protocol PLATFORMPAHPB2001.

10.4.3. Severity Criteria

Refer to Attachment 4 of the Master Protocol PLATFORMPAHPB2001.

10.4.4. Special Reporting Situations

Refer to Attachment 4 of the Master Protocol PLATFORMPAHPB2001.

10.4.5. Procedures

Refer to Attachment 4 of the Master Protocol PLATFORMPAHPB2001.

10.4.6. Product Quality Complaint Handling

Refer to Attachment 4 of the Master Protocol PLATFORMPAHPB2001.

10.4.7. Contacting Sponsor Regarding Safety, Including Product Quality

Refer to Attachment 4 of the Master Protocol PLATFORMPAHPB2001.

10.5. Appendix 5: Contraceptive and Barrier Guidance

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

Definitions

Woman of Childbearing Potential (WOCBP)

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

Woman Not of Childbearing Potential

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

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

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

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

Examples of Contraceptives

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

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

10.6. Appendix 6: Rash Management

Table 4: Management of Rash Events by Severity Grade

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

Table 4: Management of Rash Events by Severity Grade

	Definition	Study Intervention Action	Activities by Day[a]	Referral to Dermatologist and Dermatology Activities
			performed at the investigator's discretion). If the rash progresses to a higher grade, safety laboratory assessments of the higher grade should be followed. Digital pictures[c] of skin lesions may be taken at the investigator's discretion.	
Grade 3 rash[b]	Vesiculation, moist desquamation, or ulceration OR Any cutaneous event with 1 of the following: - Elevations in AST/ALT >2×baseline value - Fever >38°C or 100°F - Eosinophils >1.00×10^3/μL - Serum sickness-like reaction	Must permanently discontinue JNJ-3989 and JNJ-6379 and PegIFN-α2a; no rechallenge allowed NA treatment may be discontinued based on investigator judgement in consultation with the Sponsor	Day 0: required on-site visit. Safety laboratory assessments required to be performed. Digital pictures[c] of skin lesions may be taken at the investigator's discretion (recommended). Determine if participant was adhering to the recommended sun-protective measures. If appropriate, provide sun protection counseling. Day 1: required on-site visit. Safety laboratory assessments required to be performed. Digital pictures[c] of skin lesions may be taken at the investigator's discretion (recommended). Further visit(s): appropriate follow-up required until resolution of rash or until clinical stability is reached. Safety laboratory assessments and photography (digital pictures[c] of skin lesions) are recommended to be performed until the rash severity resolves to Grade 2 or Grade 1.	Required[d] Biopsy not required, but may be performed at the dermatologist's discretion.
Grade 4 rash	Exfoliative dermatitis OR Mucous membrane involvement in at least 2 distinct sites OR Erythema multiforme major OR	Must permanently discontinue JNJ-3989 and JNJ-6379 and PegIFN-α2a; no rechallenge allowed	Day 0: required on-site visit. Safety laboratory assessments required to be performed. Digital pictures[c] of skin lesions may be taken at the investigator's discretion (recommended). Determine if participant was adhering to the recommended sun-protective measures. If appropriate, provide sun protection counseling.	Required[d] Biopsy required and to be performed as soon as possible after the onset of the rash.

Table 4: Management of Rash Events by Severity Grade

	Definition	Study Intervention Action	Activities by Day[a]	Referral to Dermatologist and Dermatology Activities
	Stevens-Johnson syndrome OR Toxic epidermal necrolysis OR Necrosis requiring surgery	NA treatment may be discontinued based on investigator judgement in consultation with the Sponsor	Day 1: required on-site visit. Safety laboratory assessments required to be performed. Digital pictures[c] of skin lesions may be taken at the investigator's discretion (recommended). Further visit(s): appropriate follow-up required until resolution of rash or until clinical stability is reached. Safety laboratory assessments and photography (digital pictures[c] of skin lesions) are recommended to be performed until the rash severity resolves to Grade 2 or Grade 1.	

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

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

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

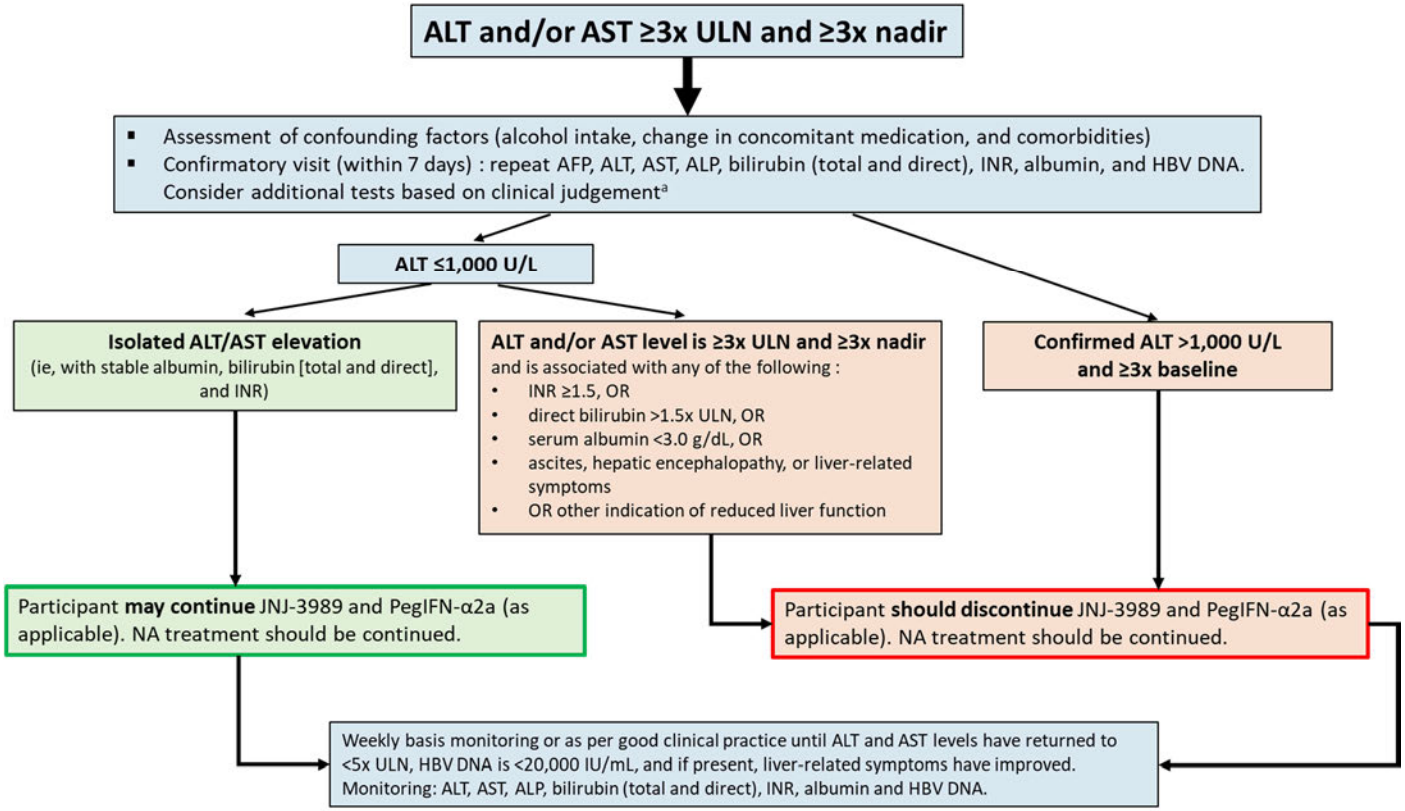
[c] Digital pictures to be taken at the clinical site upon consent of the participant.

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

Notes:

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

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



Note: In case of prolonged ALT elevation >3x ULN AND >2x nadir, which lasts at least 12 weeks, the decision to continue JNJ-3989 and/or PegIFN-α2a should be based upon virologic parameters (eg, HBsAg, HBV DNA) and should be made in consultation with the sponsor (refer to Section 8.3.6.2, Intervention-emergent ALT/AST Elevations)

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

- Hepatitis A, Delta, C, E: IgM anti-HAV; delta IgM, IgG and PCR, HCV RNA, IgM and IgG anti-HEV, HEV RNA
- CMV, HSV, EBV infection: IgM and IgG anti-CMV, IgM and IgG anti-HSV; IgM and IgG anti-EBV, PCR
- HIV-1 and -2
- Ig-Electrophoresis
- PBMC sampling
- AFP testing

10.8. Appendix 8: Cardiovascular Safety – Abnormalities

ECG

All important abnormalities from the ECG readings will be listed.

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

ECG: electrocardiogram; NAP = not applicable

For absolute QTc parameters the categories are defined based on the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E14 Guidance[a]

Vital Signs[b]

The following abnormalities will be defined for vital signs:

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

DBP: diastolic blood pressure; SBP: systolic blood pressure

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

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

10.9. Appendix 9: DAIDS Table

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

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

General Instructions

Grading Adult and Pediatric Adverse Events

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

Determining Severity Grade for Parameters Between Grades

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

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

Definitions

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

Estimating Severity Grade for Parameters not Identified in the Grading Table

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

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

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

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

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

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

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

AV: atrioventricular; NAP: not applicable; RBC: red blood cell; TdP: Torsades de Pointes

[b] Modified by the Sponsor.

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

IV: intravenous; NAP: not applicable

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

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

NAP: not applicable

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

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

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

IV: intravenous; NAP: not applicable

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

IV: intravenous; NAP: not applicable

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

BMD: bone mineral density; NAP: not applicable

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

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

CNS: central nervous system; NAP: not applicable

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

NAP: not applicable

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

ID: identity, NAP: not applicable

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

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

NAP: not applicable

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

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

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

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

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

IV: intravenous; NAP: not applicable

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

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

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

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

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

[k] WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007 bmi for age/en/ for participants aged >5 to 19 years and http://www.who.int/childgrowth/standards/chart catalogue/en/ for those aged ≤5 years.

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

NAP: not applicable

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

NAP: not applicable

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[s] Revised by the Sponsor.

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

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

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

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

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

NAP: not applicable; RBC: red blood cell

10.10. Appendix 10: Study Conduct During a Natural Disaster

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

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

The sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's travel to the study site is considered to be dangerous, study participation may be interrupted, and study follow-up conducted. If it becomes necessary to discontinue participation in the study, the procedures outlined in the protocol for discontinuing study intervention will be followed.

If, as a result of the COVID-19 pandemic, scheduled visits cannot be conducted in person at the study site, they will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

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

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

GUIDANCE SPECIFIC TO THIS PROTOCOL

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

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

Screening and Randomization:

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

Dispensing/Administration of Study Intervention:

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

Continuation of Study Intervention:

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

[a] Delivering PegIFN-α2a is not applicable for sites in countries that do not allow PegIFN-α2a self-injection.

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

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

COVID-19 vaccination during the study:

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

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

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

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

Study Visits and Assessments:

- If possible, central laboratory testing as outlined in the Schedule of Activities is to be continued. If central laboratory tests cannot be performed, the use of a local laboratory is allowed for study evaluations. A copy of the local laboratory report should be reviewed by the investigator and filed with the source documents, along with reference ranges.

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

Informed Consent:

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

Source Data Verification/Monitoring:

- In case on-site monitoring visits are not possible, the site monitor may contact the investigator to arrange monitoring activities remotely (in accordance with site and local requirements). Additional on-site monitoring visits may be needed in the future to catch up on source data verification.

[a] Delivering PegIFN-α2a is not applicable for sites in countries that do not allow PegIFN-α2a self-injection.

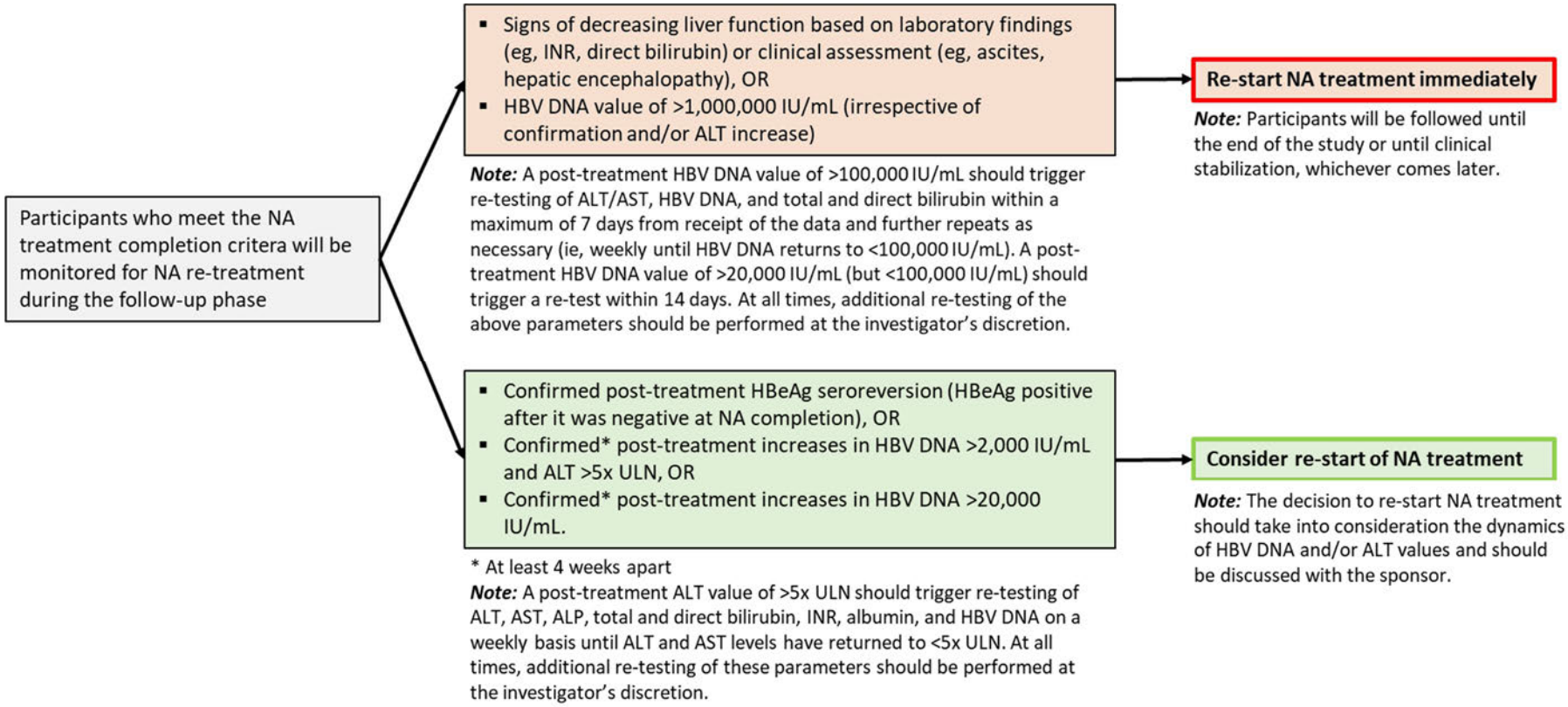
Site Audits:

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

10.11. Appendix 11: Protocol Amendment History

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

10.12. Appendix 12: NA Re-treatment During Follow-up



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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 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	06-Oct-2021 14:36:43 (GMT)	Document Approval