Janssen Research & Development *

Clinical Protocol

Intervention-specific Appendix 7 to Clinical Protocol PLATFORMPAHPB2001

A Phase 2 Open-label Trial to Evaluate Safety, Efficacy, Tolerability, and Pharmacodynamics of a Combination of JNJ-73763989, Nucleos(t)ide Analogs, and a PD-1 Inhibitor in Chronic Hepatitis B Patients.

OCTOPUS-1 Study

Protocol 73763989PAHPB2008; Phase 2
Version: Amendment 3

JNJ-73763989

*Janssen Research & Development is a global organization that operates through different legal entities in various countries/territories. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

EudraCT NUMBER: 2021-005132-33

Status: Approved
Date: 30 June 2023
Prepared by: Janssen Research & Development, a division of Janssen Pharmaceutica NV
EDMS number: EDMS-RIM-511735, 6.0

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLES

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	30 June 2023
Amendment 2	28 March 2023
Amendment 1	30 June 2022
Original Protocol	21 December 2021

Amendment 3 (30 June 2023)

Overall Rationale for the Amendment: The main reason for the protocol amendment is the discontinuation of PD-1 inhibitor (nivolumab) as study intervention as of 20 June 2023 as an urgent safety measure (USM). Based on the observation of two cases of potential hyperthyroidism, the sponsor decided on 20 June 2023, to halt further nivolumab dosing effective immediately. Both cases occurred in participants in treatment arm 1 who were randomized to receive a single dose of nivolumab administered at treatment week 16 of JNJ-3989 treatment. At treatment week 24, thyroid-stimulating hormone (TSH) was reduced in both patients. While the first patient had normal free T3 and free T4 values and TSH values returned to normal at follow-up visits, the second patient had fully suppressed TSH with elevation of free T3 and free T4. The testing frequency for thyroid parameters in the Schedule of Activities will not be changed. At the time of the USM, two participants in arm 2 were still scheduled for their third infusion with nivolumab. Both planned infusions were cancelled via direct communication with the study sites. Treatment with JNJ-3989 and/or nucleos(t)ide analog was continued as planned.

Also, additional clarifications were provided to the protocol sections about gastrointestinal adverse events and hematologic abnormalities.

Section number and Name	Description of Change	Brief Rationale
2.3.2.2 Potential Risks	Discontinuation of PD-1 inhibitor (nivolumab) as study intervention as of 20 June 2023 for the last two participants enrolled in treatment arm 2 who still had outstanding doses of nivolumab scheduled.	Two cases of potential hyperthyroidism were observed and therefore an urgent safety measure was implemented.
5.4 Screen Failures	It was clarified that the investigator will generate screening and enrollment logs.	To align with the company's most recent protocol template.
8.3.6.2.1 Gastrointestinal Adverse Events	It was clarified what is meant by lower endoscopy. In addition, bowel perforation was added as a contraindication to endoscopy.	For clarity and completeness
8.3.6.3.1 Hematologic Abnormalities	Autoimmune hemolytic anemia was added to the list of hematologic abnormalities reported with nivolumab in the oncology setting	For completeness

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 2 Open-label Trial to Evaluate Safety, Efficacy, Tolerability, and Pharmacodynamics of a Combination of JNJ-73763989, Nucleos(t)ide Analogs, and a PD-1 Inhibitor in Chronic Hepatitis B Patients.

Protocol 73763989PAHPB2008 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 ribonucleic acid (siRNA) triggers in JNJ-3989, JNJ-73763976 (JNJ-3976), and JNJ-73763924 (JNJ-3924), are designed to target all HBV RNA transcripts derived from covalently closed circular deoxyribonucleic acid (cccDNA), as well as transcripts derived from integrated HBV 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 programmed cell death protein receptor-1 (PD-1) inhibitor is nivolumab, which is a human immunoglobin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor, blocking the interaction between PD-1 and its ligand PD-L1. Nivolumab is approved for the treatment of certain cancers and for other indications at higher doses than intended in this study. The use of nivolumab in the treatment of HBV is investigational.

Nucleos(t)ide analogs are approved treatments of chronic HBV infection.

The term "study intervention" throughout the protocol, refers to JNJ-3989 and nivolumab.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 efficacy of the study intervention, based on HBsAg levels at Follow-up Week 24 (FU Week 24).	• Proportion of participants who achieve HBsAg seroclearance at FU Week 24.
Secondary	
To characterize the safety and tolerability of the study intervention.	• Proportion of participants who experienced adverse events (AEs) of interest. • Safety profile of JNJ-3989 with nivolumab throughout the study (safety parameters include but are not limited to the frequency and severity of AEs and immune-related AEs, vital signs measurements, physical examinations, clinical laboratory values, and 12-lead electrocardiograms [ECGs]).

Objectives	Endpoints
To evaluate efficacy in terms of changes in HBsAg levels from baseline over time during the study intervention and follow-up periods.	• Change from baseline in HBsAg levels during the study intervention and follow-up periods. • Proportion of participants with HBsAg levels below/above different cut-offs over time.
To evaluate efficacy in terms of HBsAg seroclearance/seroconversion during the study intervention and follow-up periods (as defined in the Definitions of Terms).	• Proportion of participants with HBsAg seroclearance/seroconversion during the study intervention and follow-up periods. • Time to achieve HBsAg seroclearance/ seroconversion.
To evaluate the efficacy as measured by blood markers (such as HBV DNA and HBeAg) during the study intervention and follow-up periods.	• Change from baseline in HBV DNA levels during the study intervention and follow-up periods. • Proportion of participants with HBV DNA and HBeAg levels below/above different cut-offs over time.
To evaluate the frequency of virologic breakthrough throughout the study.	• Proportion of participants with virological breakthrough throughout the study.
To evaluate the pharmacokinetics (PK) of JNJ-3989 (JNJ-3924 and JNJ-3976) and optionally of NA and/or nivolumab.	• PK parameters of JNJ-3989 (JNJ-3924 and JNJ-3976). • Optionally, PK parameters of NA and/or nivolumab.
Exploratory	
To characterize the pharmacodynamics (PD) of JNJ-3989 with nivolumab including quantification of receptor occupancy (RO) on peripheral T-cells.	• Relationship of various PK parameters with selected efficacy and safety endpoints. • Quantification of nivolumab RO on peripheral CD3+ T-cells by flow cytometry on whole blood.
To explore changes in the severity of liver disease.	• Changes in fibrosis (according to Fibroscan liver stiffness measurements) at end of study intervention (EOSI) and the end of the follow-up period versus baseline.
To explore HBV-specific T-cell responses throughout the study.*	• Changes from baseline in HBV-specific peripheral blood T-cell responses over time.
To explore efficacy of the study intervention in terms of changes in HBV RNA and hepatitis B core-related antigen (HBcrAg) levels throughout the study.	• Changes from baseline in HBV RNA and HBcrAg levels over time.
To explore the HBV genome sequence throughout the study.	• Assessment of intervention associated mutations over time.
To explore medical resource utilization to manage participants throughout the study.	• 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.

Objectives	Endpoints
	• Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications).

*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+nivolumab+NA is more efficacious than JNJ-3989+NA treatment, as measured by the primary efficacy endpoint (ie, the proportion of participants with HBsAg seroclearance at FU Week 24). Because the study does not include a regimen arm without nivolumab, the hypothesis is formulated assuming a fixed response rate for JNJ-3989+NA of 1% based on previous Study 73763989HPB2001 (REEF-1).

OVERALL DESIGN

This ISA describes a Phase 2 study of the combination regimen of JNJ-3989 with nivolumab and NA. It is a companion document to the Master Protocol PLATFORMPAHPB2001, which describes the common design elements of the Platform study in participants with chronic HBV infection. This ISA describes specific and/or additional protocol elements applicable to this randomized, open-label, parallel, multicenter, interventional study to evaluate safety, efficacy, tolerability, PK and PD of a combination of JNJ-3989, nivolumab, and NAs in virologically suppressed chronic HBV-infected adult participants.

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

- 6-week Screening Period (if necessary, eg, for operational reasons, this can be extended to a maximum of 8 weeks decided on a case-by-case basis and in agreement with the sponsor). During the Screening Period, the participants will continue the same NA treatment they were receiving before screening.
- 24-week Study Intervention Period:
  - Arm 1: JNJ-3989 once a week (Q1W) for the first 4 weeks then once every 4 weeks (Q4W) until Week 24 + nivolumab at Week 16 + NA once daily (QD)
  - Arm 2: JNJ-3989 Q1W for the first 4 weeks then Q4W until Week 24 + nivolumab Q4W at Weeks 16, 20, and 24 + NA QD.
- 48-week Follow-up Period: during which NA treatment will be continued.

At baseline, participants who meet the eligibility criteria will be randomized in a 1:1 ratio to Arm 1 or Arm 2. Randomization will be stratified by absolute HBsAg level (<100 IU/mL, 100 to <1,000 IU/mL, and ≥1,000 IU/mL) at screening, as assessed by quantitative HBsAg assay.

Assessments and sampling will be done for efficacy (eg, HBsAg, HBeAg, and HBV DNA), safety (eg, [S]AEs, immune-related AEs, laboratory evaluations, ECGs, vital signs, physical examinations), PK, PK/PD, viral genome sequencing, PBMC, human leukocyte antigen (HLA) typing, immunogenicity and pharmacogenomics, and for exploratory analysis of host and viral markers.

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

If a participant prematurely discontinues treatment with JNJ-3989 before Week 24, the participant will also discontinue further treatment with nivolumab and will have an early withdrawal (WD) visit. 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. The NA treatment will be continued until the end of the study.

If a participant prematurely discontinues nivolumab, treatment with JNJ-3989 and NA should be continued as planned, unless a treatment discontinuation rule for JNJ-3989 is also met. In that case, JNJ-3989 will also be discontinued but NA treatment should be continued as planned.

If a participant withdraws prematurely from the study, the reason for withdrawal (if known) should be documented. 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.

NUMBER OF PARTICIPANTS

Initially, 44 (22 per arm) virologically suppressed, HBeAg negative, adult chronic hepatitis B participants ≥18 (or the legal age of consent in the jurisdiction in which the study is taking place) to <56 years of age were planned to be enrolled in this study.

Due to the decision to not extend further enrollment beyond the planned enrollment period and proceed with a reduced sample size, the final sample size is 37 (18 in Arm 1 and 19 in Arm 2).

INTERVENTION GROUPS AND DURATION

The total duration of individual participation will be up to 72 weeks (screening not included) with a 24-week study intervention period and a 48-week follow-up period.

Description of Background Treatment

Background treatment consists of NAs tenofovir disoproxil (245 mg), tenofovir alafenamide (TAF) (25 mg), or entecavir (ETV) (0.5 mg) given as oral tablets QD for approximately 76 weeks (screening included).

Investigators should follow guidance detailed in the local prescribing information of NA.

Treatment Name	**Tenofovir disoproxil**	**Tenofovir alafenamide (TAF)***	**Entecavir (ETV) monohydrate**
Type	Drug	Drug	Drug
Dose Formulation	Film-coated tablets	Film-coated tablets	Film-coated tablets
Unit Dose Strength(s)	245 mg	25 mg	0.5 mg
Dosage Level(s)	245 mg QD	25 mg QD	0.5 mg QD
Route of Administration	Oral	Oral	Oral

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

Description of Study Intervention

Study intervention consists of:

- JNJ-3989: 200 mg given by subcutaneous (SC) injections Q1W for the first 4 weeks then Q4W until Week 24 (10 doses)
- Nivolumab: 0.3 mg/kg, one single intravenous (IV) infusion at Week 16 for Arm 1 or 3 IV infusions at Weeks 16, 20, and 24 for Arm 2.

Intervention Name	**JNJ-3989**	**Nivolumab**
Type	Drug	Drug
Dose Formulation	Solution for injection (G001)	Concentrate for solution for infusion
Unit Dose Strength(s)	200 mg/mL	40 mg/4 mL
Dosage Level(s)	200 mg Q1W for the first 4 weeks, then Q4W until Week 24	0.3 mg/kg (1 intravenous [IV] infusion for Arm 1 or 3 IV infusions Q4W for Arm 2)**
Route of Administration	Subcutaneous injection* (preferably in the abdomen; upper arm or thigh is also allowed)	IV infusion over 30 minutes
Use	Investigational intervention	Investigational intervention
Investigational Medicinal Product (IMP)	Yes	Yes
Non-investigational Medicinal Product/ Auxiliary Medicinal Product (NIMP/AxMP)	No	No
Sourcing	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
Food/Fasting Instructions	Regardless of food intake	Not Applicable

*Note: Administration into scar tissue or areas that are reddened, inflamed or swollen should be avoided. If injecting into the abdomen, avoid a 5 cm diameter circle around the navel.
**Note: a tolerance of +/- 5% around the theoretical dose of 0.3 mg/kg will be applied to consider the necessary rounding and standard practice for the preparation and intravenous administration of drugs dosed by weight.

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, HBeAg, anti-HBs antibodies, and

anti-HBe antibodies 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.

Adverse 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. Guidelines are in place for management of AEs of Special Interest.

PHARMACOKINETIC EVALUATIONS

All participants will have sparse PK sampling during the study intervention period.

Blood samples will be collected for measurement of plasma concentrations of JNJ-3989 (ie, JNJ-3976 and JNJ-3924) and NA, and serum concentrations of nivolumab at time points specified in the Schedule of Activities. Bioanalysis of NA and nivolumab 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 nivolumab, with RO, selected efficacy and/or safety endpoints may be evaluated, if applicable.

PHARMACODYNAMIC EVALUATIONS

Whole blood samples will be collected for assessment of nivolumab RO on circulating T-cells by flow cytometry analysis.

Pharmacodynamic biomarkers will be evaluated in all participants pretreatment, on-treatment, and posttreatment with study intervention as detailed in Section 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 in participants who consent. These samples could for example be used to assess changes in frequencies of immune cells.

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.

A fine needle aspiration (FNA) biopsy sample may be collected from participants who consent separately to this component of the study (as permitted by local regulations). If participants agree to undergo an optional FNA biopsy of the liver, following local standard practice, the biopsy location will be identified and/or guided with ultrasound and the FNA biopsy samples will be collected after application of local anesthesia to allow for exploratory biomarker research.

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 alanine aminotransferase (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. Leftover PBMC samples may be used at the sponsor's discretion for additional exploratory research 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/or nivolumab. Antidrug antibodies may be analyzed using assays such as an enzyme-linked immunosorbent assay or functional assays.

Medical Resource Utilization

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

- Number and 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 According to the initial protocol, the study aimed to have a sample size of 20 participants per intervention arm which yielded ≥85% statistical power to detect a ≥15% and ≥20% difference for the proportions of participants with HBsAg seroclearance at FU Week 24 in the 2 intervention arms, respectively, vs a fixed proportion of ≤1%. Statistical power to test the primary hypothesis was assessed for each of the intervention arms, 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 fixed rate assumed for the external active control (JNJ-3989 [200 mg]+NA treatment) is based on the data of Study 73763989HPB2001 (REEF-1).

The total study sample size was adjusted to 44 participants (22 per arm), with 1:1 randomization ratio to each of the intervention arms, to account for an approximate 10% attrition rate.

Due to the decision to not extend further enrollment beyond the planned enrollment period and proceed with a reduced sample size, the final sample size is 37 (18 in Arm 1 and 19 in Arm 2). Under the same assumptions and methods of the initial protocol, an approximate sample size of 16 participants per intervention arm (assuming 10% attrition) yields ≥75% statistical power to detect the same differences in HBsAg seroclearance at FU Week 24.

Efficacy Analyses

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

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

Primary Efficacy Endpoint

The proportion of participants who achieved HBsAg seroclearance at FU Week 24 will be summarized for each intervention 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 1% 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 may be explored using logistic regression analyses and classification and regression tree analysis (CART).

The Mantel-Haenszel test adjusted for the randomization stratification factors will be used in a secondary analysis comparing the primary endpoint between the 2 study intervention arms at a one-sided alpha level of 0.05.

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 may 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, and waterfall plots) will also be used to summarize the efficacy data by intervention arm and over time.

Across ISAs Comparisons of Efficacy

Indirect comparisons between different regimens across multiple ISAs may 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.

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

Safety Analyses

Safety analyses will be based on the safety population. Safety will be evaluated by means of descriptive summaries of AEs including AEs of Special Interest to any of the study interventions, clinical laboratory tests, ECGs, vital signs, and physical examinations. The safety analysis will be done by study 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/or nivolumab 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/or nivolumab, with RO, selected efficacy and/or 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.

Pharmacodynamic Analyses

Descriptive statistics by treatment will be used to summarize PD parameters at each applicable time point. Statistics include sample size (n), mean, standard deviation (SD), coefficient of variation (CV), geometric mean, median, minimum, and maximum. Additional PD analyses may be performed, as deemed necessary.

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, SD, CV, geometric mean, median, minimum, and maximum) may be used to describe the magnitude of the IFN-γ T-cell response or the CD4+ and CD8+ T-cell responses (expressing at least 1 cytokine such as IL-2, TNF-α or IFN-γ specific to any HBV antigen) as defined by ELISpot and/or ICS, respectively. Changes from baseline (or positivity threshold) 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 over time.

Interim Analyses

Interim analyses (IAs) 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.

Optional IAs are planned when:

- All randomized participants have completed Week 24 or discontinued earlier.
- All randomized participants have completed FU Week 12 or discontinued earlier.

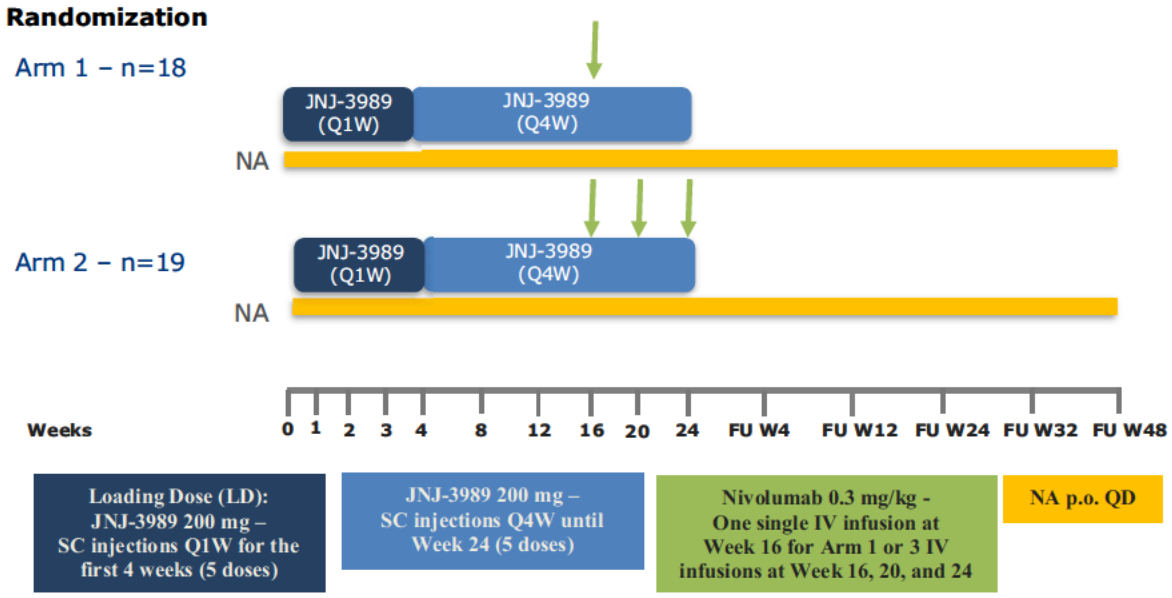
Depending on the enrollment rate, any of the above IAs may be skipped if it is too close to the predicted timing of any adjacent interim cut-offs and additional IAs may be performed by the sponsor to support interactions with health authorities.

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 participants 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



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 10.9 Appendix 9: Study Conduct During a Natural Disaster.

1.3.1. Schedule of Activities – Screening Phase and Study Intervention Phase

Study Period	**Screening**	**Study Intervention[a,b,c,d]**									
Visit Day (D)/Week (W)	W-6 to 0[e]	W0/D1	W1	W2	W3	W4	W8	W12	W16	W20	W24/ EOSI/WD[c]
Study Day (Window)	-42 to 0	1	8 +/-2d	15 +/-2d	22 +/-2d	29+/-2d	57+/-2d	85+/-2d	113+/-3d	141+/-3d	169+/-3d
Screening/ Administrative											
ICF[f]	X										
ICF for optional pharmacogenomic samples[g]	X										
ICF for optional FNA biopsy of the liver[g]	X										
Inclusion/exclusion criteria[h]	X										
Prestudy therapy (including prior anti-HBV therapy)	X										
Medical/surgical history and demographics[i]	X										
Preplanned surgery/procedure(s)	X										
Fibroscan or liver biopsy[j]	X										
Abdominal ultrasound[k]	X										
Study Intervention / Background Treatment											
Randomization		X									
Administration of JNJ-3989[l,m]		X	X	X	X	X	X	X	X	X	X
Intake of NA[n]		X	X	X	X	X	X	X	X	X	X
Administration of nivolumab[l,m] (A2=Arm 2)									X[o]	A2	A2
Study intervention accountability			X	X	X	X	X	X	X	X	X
Safety Assessments											
Complete physical examination[p]	X										X
Body weight and symptom-directed physical examination		X	X	X	X	X	X	X	X	X	
Vital signs[q]	X	X	X	X	X	X	X	X	X	X	X
Triplicate 12-lead ECG[r]	X	X				X					X

Study Period	Screening	Study Intervention[a,b,c,d]									
Visit Day (D)/Week (W)	W-6 to 0[e]	W0/D1	W1	W2	W3	W4	W8	W12	W16	W20	W24/ EOSI/WD[c]
Study Day (Window)	-42 to 0	1	8 +/-2d	15 +/-2d	22 +/-2d	29+/-2d	57+/-2d	85+/-2d	113+/-3d	141+/-3d	169+/-3d
Injection site reactions for JNJ-3989 and infusion-related reactions for nivolumab as applicable		X	X	X	X	X	X	X	X	X	X
Liver ultrasound[s]											X
Medical resource utilization[t]	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests											
Hematology[u]	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry (including cystatin C and liver function tests)[v,w,x]	X	X	X	X	X	X	X	X	X	X	X
CRP	X					X		X	X		X
Blood coagulation	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[y]	X	X		X		X	X	X	X	X	X
Urine chemistry[z]	X	X		X		X	X	X	X	X	X
Renal biomarkers[aa]		X		X		X		X			X
Testing for hepatitis A, B, C, D, and E virus, HIV-1 and -2	X										
Serum IgM anti-HBc antibody test	X										
Autoantibodies[pp]	X							X			X
FSH test (postmenopausal women only)[bb]	X										
AFP test[cc]	X										X
Hemoglobin A1c test	X										
Serum pregnancy test (women of childbearing potential only)	X										
Urine pregnancy test (women of childbearing potential)[dd]		X				X	X	X	X	X	X
TSH, T3, and T4	X						X		X		X
Efficacy Evaluations											
Fibroscan[ee]		(X)									X
HBV Virology											
Blood sampling for HBV DNA	X	X		X		X	X	X	X	X	X
HBV genotype[ff]		X									
Blood sampling for HBV RNA[gg]	X	X		X		X	X	X	X	X	X
Sampling for viral genome sequencing[hh]		X						X			X
HBV Serology											
Blood sampling for:											
Anti-HBs and anti-HBe	X	X						X			X

Study Period	Screening	Study Intervention[a,b,c,d]									
Visit Day (D)/Week (W)	W-6 to 0[e]	W0/D1	W1	W2	W3	W4	W8	W12	W16	W20	W24/ EOSI/WD[c]
Study Day (Window)	-42 to 0	1	8 +/-2d	15 +/-2d	22 +/-2d	29+/-2d	57+/-2d	85+/-2d	113+/-3d	141+/-3d	169+/-3d
HBsAg and HBeAg (qualitative)	X	X									
HBsAg (quantitative)	X	X	X	X	X	X	X	X	X	X	X
HBeAg (quantitative)	X	X		X		X	X	X		X	X
HBcrAg[gg]	X	X		X		X	X	X	X	X	X
Exploratory serology[ii]	X	X		X		X	X	X	X	X	X
Clinical Pharmacology Assessments											
Blood sampling for:[jj]											
JNJ-3989/NA sparse PK: 2-6 hours post-dose		X		X		X		X	X	X	X
JNJ-3989/NA sparse PK: 6-24 hours post-dose		(X)		(X)		(X)		(X)	(X)	(X)	(X)
Nivolumab sparse PK: pre-dose (Arm 2 only)										X	X
Nivolumab sparse PK: 2-6 hours post-dose									X	X	X
Nivolumab sparse PK: 6-24 hours post-dose (Arm 2 only)									(X)	(X)	(X)
Exploratory Host Biomarkers											
Whole blood RNA gene expression		X					X		X		X
Whole blood single-cell profiling		X					X		X		X
Host serum proteins		X					X		X		X
Optional FNA collection[kk]		X[ll]									X
Antidrug antibodies to JNJ-3989		X						X			X
Antidrug antibodies to nivolumab								X	X	X	X
Blood sample collection for RO assay (nivolumab):[mm]											
Arm 1, pre-dose and 2h +/-10 min post-dose									X		
Arm 1, any time										X	X
Arm 2, pre-dose and 2h +/-10 min post-dose									X	X	X
Immune Monitoring											
Immune cells (PBMCs) (selected sites only)[nn]		X							X	X	X
Pharmacogenomics (DNA)											
HLA typing (optional)[kk]		X									
Exploratory host genotyping (optional)[kk]		X									
Epigenetic research (optional)[kk]		X						X			X
Ongoing Participant Review											
Concomitant therapy[oo]	X	X	X	X	X	X	X	X	X	X	X
Adverse events[oo]	X	X	X	X	X	X	X	X	X	X	X

(X): optional or conditional sample; AFP: alpha-fetoprotein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CRF: case report form; CRP: C-reactive protein; 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; EOSI: end of study intervention; FNA: fine needle aspiration; 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; PK: pharmacokinetic; RNA: ribonucleic acid; RO: receptor occupancy; SBP: systolic blood pressure; T3: triiodothyronine; T4: thyroxine; TSH: thyroid-stimulating hormone; ULN: upper limit of normal; W: week; WD: withdrawal.

a. All study intervention visits are to be scheduled relative to the baseline (Day 1) visit date. 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, nivolumab) and NA, unless indicated otherwise.
c. Participants who discontinue treatment with JNJ-3989 early will also discontinue further treatment with nivolumab. The participants will have an early WD visit and will enter follow-up period 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. Participants who prematurely discontinue nivolumab should continue treatment with JNJ-3989 and NA as planned unless a treatment discontinuation rule for JNJ-3989 is also met. In that case, JNJ-3989 will also be discontinued but NA treatment should be continued as planned.
d. Refer to Section 8.3.6.1 for management of intervention-emergent ALT/AST elevations.
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. Both the Platform Master ICF and the ISA ICF must be signed before the first study-related activity.
g. ICF for optional pharmacogenomic samples or FNA biopsy of the liver must be signed before the genetic or FNA biopsy samples are taken from participants, respectively.
h. 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.
i. Medical history also includes mode of HBV transmission, stage of liver fibrosis, and alcohol consumption. Available historical HBV DNA, ALT, HBsAg, and HBeAg data will be recorded in the CRF and/or source documents. Available historical data on previous HBV genotype assessments and on HBeAg status before start of NA treatment will also be collected in the CRF.
j. 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).
k. Participants must have absence of signs of cirrhosis or portal hypertension (absence of nodules, smooth liver contour, normal portal vein, spleen size <12 cm) 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).
l. When both JNJ-3989 and nivolumab are administered at the same visit, JNJ-3989 should be administered first (preferably in abdomen) followed within approximately 30 minutes by IV infusion of nivolumab. No JNJ-3989/nivolumab will be administered or dispensed during follow-up.
m. Before each administration of study intervention, the participant will be evaluated for possible toxicities that may have occurred since the previous dose of study intervention. The most recent laboratory results and general physical status must be reviewed. If immune-related toxicity has occurred, the criteria outlined in Section 8.3.6 must be followed for management.
n. NA prescription should follow the standard of care. 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. Compliance will be assessed by the investigator based on participant interview.
o. Prior to starting nivolumab treatment, the participant's most recent ALT value (tested by local or central lab) should be <3x ULN with no change in autoimmune status. In case the injection of nivolumab would not be in the interest of the participant, this should be discussed with the sponsor.
p. Complete physical examination, including height (only at screening), body weight, skin and other body systems examination.
q. Vital signs include supine SBP, DBP, pulse rate, and body temperature. Vital signs should preferably be assessed prior to any blood sampling.

r. ECGs should be completed before any tests, procedures or other consultations for that visit. All ECGs will be read centrally. Only on Day 1, an ECG will also be assessed locally prior to dosing.
s. For liver ultrasound, a window of 1 week is allowed before or after the scheduled visit.
t. 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 8.9.
u. 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) (Refer to Section 8.3.6.3.1).
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 2 consecutive visits.
v. Biochemistry samples should be taken after fasting for at least 10 hours for measurement of phosphate, calcium, creatinine, and lipids. Participants should bring their NA with them to each visit and have that day's intake at the site with food (as applicable), after the sample was taken.
w. Creatinine clearance (eGFR calculated by the CKD-EPI formula) will be assessed.
x. Refer to Section 8.3.6.1 for management of treatment-emergent ALT/AST elevations.
y. 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).
z. Urine chemistry sample (quantitative measurement): creatinine, sodium, phosphate, glucose, protein, and albumin.
aa. Urine sample for selected renal biomarkers including retinol binding protein and beta-2-microglobulin (other biomarkers might be measured).
bb. 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).
cc. Additional samples may be collected for AFP testing in case of ALT flares.
dd. Urine pregnancy tests should be done at least every 4 weeks. On days of study intervention administration (JNJ-3989 +/- nivolumab), the urine pregnancy test should be performed pre-dose.
ee. 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.
ff. HBV genotype will be determined at baseline using a standard genotyping assay if HBV DNA levels are sufficiently high. Exploratory genotyping may be performed.
gg. 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.
hh. 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.
ii. Exploratory serology samples may be analyzed at the sponsor's discretion. Samples may be used to assess virologic or serologic markers of HBV.
jj. All participants will have sparse PK samples taken 2 to 6 hours after administration of the study intervention(s). An optional sample may be taken 6 to 24 hours after administration of the study intervention(s). When both JNJ-3989 and nivolumab are administered at the same visit, the sparse PK samples will be collected 2-6 hours (mandatory samples) and 6-24 hours (optional sample) after the end of nivolumab infusion. In addition, for Arm 2, a pre-dose PK sample will be taken prior to administration of nivolumab at Weeks 20 and 24. For all samples, the date and time of the preceding 2 intakes of NA, the date and time of the previous JNJ-3989 and nivolumab 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.
kk. 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.
ll. If the FNA biopsy cannot be completed on Day 1, it may be completed at a later visit without constituting a protocol deviation. A separate visit may be scheduled for FNA biopsies and blood sample collections for safety labs required prior to FNA biopsy procedures. Participants may stay overnight at the study site after the FNA biopsy procedures at the investigator's discretion. Prior to each FNA biopsy, a recent (≤2 weeks) coagulation and hematology panel are required, to ensure normal platelet count and normal coagulation parameters.
mm. On the days of nivolumab infusion, whole blood samples for RO assay will be taken before nivolumab infusion (pre-dose) and 2 hours +/- 10 minutes after the end of nivolumab infusion (post-dose). At the visits without nivolumab infusion, the sample will be taken at any time during the visit.

nn. 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. PBMC whole blood samples need to be collected before starting nivolumab infusion.

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

pp. Autoantibodies tests include antinuclear antibodies; anti-smooth muscle antibodies; anti-mitochondrial antibodies; anti-thyroid peroxidase antibodies; anti-neutrophil cytoplasmic antibodies and rheumatoid factor.

1.3.2. Schedule of Activities – Follow-up Phase

Study Period	Follow-up[a,b,c,d]								
Visit Week (W)	FU W4	FU W8	FU W12	FU W16	FU W20	FU W24	FU W32	FU W40	FU W48 / WD[c]
Study Day (Window)	29 +/-4d	57 +/-4d	85 +/-4d	113 +/-4d	141 +/-4d	169 +/-4d	225 +/-4d	281 +/-4d	337 +/-4d
Study Intervention / Background Treatment									
Intake of NA[e]	X	X	X	X	X	X	X	X	X
Safety Assessments									
Body weight and symptom-directed physical examination	X	X	X	X	X	X	X	X	X
Vital signs[f]	X	X	X	X	X	X	X	X	X
Triplicate 12-lead ECG[g]	X								
Liver ultrasound[h]						X			X
Medical resource utilization[i]	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests									
Hematology[j]	X	X	X	X	X	X	X	X	X
Blood chemistry (including cystatin C and liver function tests)[k,l,m]	X	X[n]	X	X[n]	X[n]	X	X	X	X
CRP			X			X			X
Blood coagulation	X		X			X			X
Urinalysis[o]	X[p]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X[p]
Urine chemistry[q]	X[p]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X[p]
Autoantibodies[bb]						X			X
AFP test[r]						X			X
Urine pregnancy test (women of childbearing potential)[s]	X	X	X	X	X	X	X	X	X
TSH, T3, and T4		X				X			X
Efficacy Evaluations									
Fibroscan[t]						X			X
HBV Virology									
Blood sampling for HBV DNA	X	X	X	X	X	X	X	X	X
Blood sampling for HBV RNA[u]			X			X			X
HBV Serology									
Blood sampling for:									
Anti-HBs and anti-HBe						X			X
HBsAg (quantitative)		X	X	X	X	X	X	X	X
HBeAg (quantitative)			X			X			X
HBcrAg[u]			X			X			X
Exploratory serology[v]			X			X			X

Study Period	Follow-up[a,b,c,d]								
Visit Week (W)	FU W4	FU W8	FU W12	FU W16	FU W20	FU W24	FU W32	FU W40	FU W48 / WD[c]
Study Day (Window)	29 +/-4d	57 +/-4d	85 +/-4d	113 +/-4d	141 +/-4d	169 +/-4d	225 +/-4d	281 +/-4d	337 +/-4d
Exploratory Host Biomarkers									
Whole blood RNA gene expression									X
Whole blood single-cell profiling			X						X
Host serum proteins			X						X
Optional FNA collection[w,x]									(X)[cc]
Antidrug antibodies to JNJ-3989			X			X			X
Antidrug antibodies to nivolumab			X			X			X
Blood sample collection for RO assay (nivolumab):[y]									
Arm 1			X						
Arm 2			X			X			
Immune Monitoring									
Immune cells (PBMCs) (selected sites only)[z]		X							
Ongoing Participant Review									
Concomitant therapy[aa]	X	X	X	X	X	X	X	X	X
Adverse events[aa]	X	X	X	X	X	X	X	X	X

(X): optional or conditional sample; AFP: alpha-fetoprotein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CRP: C-reactive protein; d: day; DAIDS: Division of Acquired Immunodeficiency Syndrome; DBP: diastolic blood pressure; DNA: deoxyribonucleic acid; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; EOSI: end of study intervention; FNA: fine needle aspiration; 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; ICF: informed consent form; ISA: intervention-specific appendix; NA: nucleos(t)ide analog; PBMC: peripheral blood mononuclear cells; PK: pharmacokinetic; RNA: ribonucleic acid; RO: receptor occupancy; SBP: systolic blood pressure; T3: triiodothyronine; T4: thyroxine; TSH: thyroid-stimulating hormone; W: week; WD: withdrawal.

a. All follow-up study visits are to be scheduled relative to the Week 24/EOSI/WD visit (see Section 1.3.1). 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 intake of NA, unless indicated otherwise.
c. Participants who discontinue study prematurely will have an early WD visit. 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. Refer to Section 8.3.6.1 for management of intervention-emergent ALT/AST elevations.
e. NA prescription should follow the standard of care. 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. Compliance will be assessed by the investigator based on participant interview.
f. Vital signs include supine SBP, DBP, pulse rate, and body temperature. Vital signs should preferably be assessed prior to any blood sampling.
g. ECGs should be completed before any tests, procedures or other consultations for that visit. All ECGs will be read centrally.
h. For liver ultrasound, a window of 1 week is allowed before or after the scheduled visit.
i. 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 8.9.
j. 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) (Refer to Section 8.3.6.3.1).

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 2 consecutive visits.

k. Biochemistry samples should be taken after fasting for at least 10 hours for measurement of phosphate, calcium, creatinine, and lipids. Participants should bring their NA with them to each visit and have that day's intake at the site with food (as applicable), after the sample was taken.
l. Creatinine clearance (eGFR calculated by the CKD-EPI formula) will be assessed.
m. Refer to Section 8.3.6.1 for management of treatment-emergent ALT/AST elevations.
n. Liver function tests only.
o. 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).
p. A urinalysis and urine chemistry sample will be taken at FU Week 4 and FU Week 48. In case of abnormalities at FU Week 4, the tests should be repeated at the following visits (from FU Week 8 to FU Week 40).
q. Urine chemistry sample (quantitative measurement): creatinine, sodium, phosphate, glucose, protein, and albumin.
r. Additional samples may be collected for AFP testing in case of ALT flares.
s. Urine pregnancy tests should be done at least every 4 weeks, preferably during a scheduled site visit. Pregnancy tests for at-home use will be provided to the participants from Follow-up Week 24 onwards to allow 4-weekly urine pregnancy testing in between scheduled site visits. If positive, the participant should contact the site immediately.
t. Only applicable to participants who are enrolled at a site with access to a Fibroscan device.
u. 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.
v. Exploratory serology samples may be analyzed at the sponsor's discretion. Samples may be used to assess virologic or serologic markers of HBV.
w. These samples are optional and will only be collected from participants who consent separately to this component of the study.
x. A separate visit may be scheduled for FNA biopsies and blood sample collections for safety labs required prior to FNA biopsy procedures. Participants may stay overnight at the study site after the FNA biopsy procedures at the investigator's discretion. Prior to each FNA biopsy, a recent (≤2 weeks) coagulation and hematology panel are required, to ensure normal platelet count and normal coagulation parameters.
y. During the follow-up period, whole blood samples for RO assay will be taken at any time during the visit.
z. 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.
aa. 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.
bb. Autoantibodies tests include antinuclear antibodies; anti-smooth muscle antibodies; anti-mitochondrial antibodies; anti-thyroid peroxidase antibodies; anti-neutrophil cytoplasmic antibodies; and rheumatoid factor.
cc. Optional FNA collection at follow-up Week 48 should be confirmed ahead of the visit with the Sponsor.

2. INTRODUCTION

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

The programmed cell death protein receptor-1 (PD-1) inhibitor is nivolumab, which is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor, blocking the interaction between PD-1 and its ligand PD-L1. Nivolumab is approved for the treatment of certain cancers at higher doses than intended in this study. The use of nivolumab in the treatment of HBV is investigational.

The nucleos(t)ide analogs (NAs) 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) and Addenda for JNJ-3989 (IB JNJ-3989). For nonclinical and clinical information regarding nivolumab and NA, refer to the respective prescribing information.

The term "study intervention" throughout the protocol, refers to JNJ-3989 and nivolumab 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 shown to specifically decrease HBV viral antigen levels and inhibit viral replication. Since hepatitis B surface antigen (HBsAg) is immune-suppressive, the direct reduction of HBsAg levels by JNJ-3989 is aimed at contributing to the restoration of the immune response that is impaired in chronic HBV infection. The restoration of immune response may not be sufficient and therefore addition of immunomodulatory agents is being investigated.

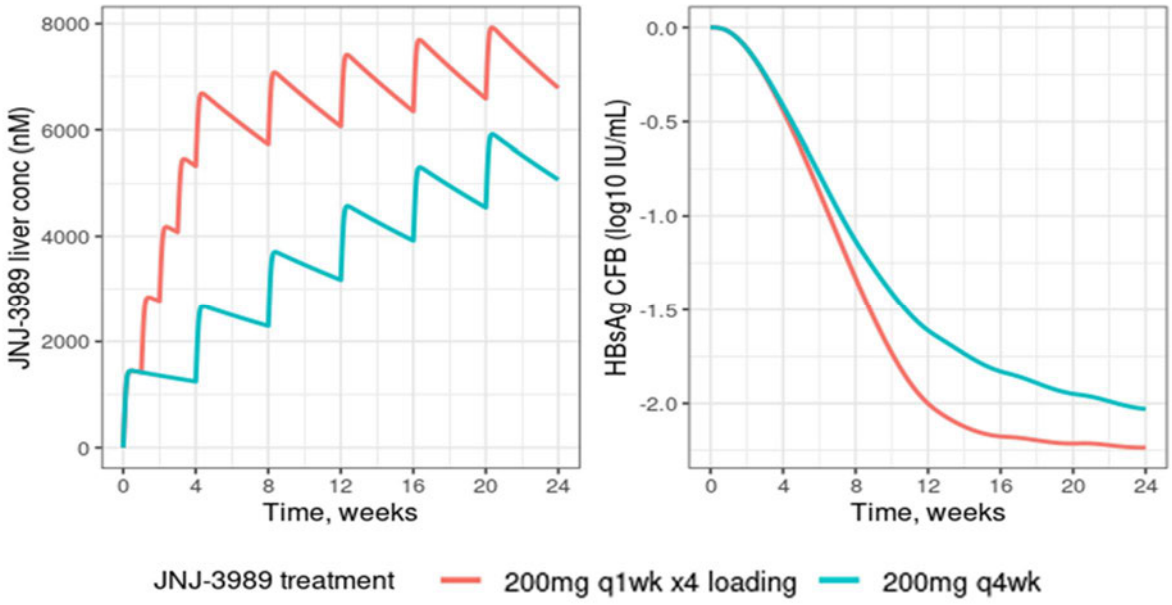
The current study is designed to assess efficacy and safety of a treatment regimen of 24 weeks of JNJ-3989 (200 mg administered Q1W for the first 4 weeks then Q4W until Week 24), in combination with 1 or 3 doses of nivolumab every 4 weeks (Q4W) as of Week 16 and with NA.

Virologically suppressed chronic HBV-infected HBeAg negative patients will be enrolled in this study.

The primary objective of the study will be to explore the proportion of participants who achieve HBsAg seroclearance at Follow-up (FU) Week 24. The complete follow-up period will be 48 weeks.

Pharmacokinetic-pharmacodynamic (PK/PD) modeling of JNJ-3989 using a transporter-mediated drug disposition (TMDD) and indirect response model (IRM) based on REEF-1 data suggests that applying a loading dose (Q1W) regimen for JNJ-3989 will result in higher liver concentrations more rapidly than with a Q4W dosing regimen. Higher liver concentrations are expected to result in a more pronounced and faster decline in HBsAg and may improve the likelihood of achieving functional cure. Figure 2 illustrates the model-predicted liver concentrations of JNJ-3989 and corresponding predicted change from baseline in HBsAg, comparing a 200 mg JNJ-3989 Q4W regimen with a 200 mg JNJ-3989 loading dose regimen (Q1W for the first 4 weeks and then Q4W). The deterministic prediction was performed using a typical subject of the REEF-1 study, being virologically suppressed and HBeAg negative, representative of the (median) population.

Figure 2: TMDD-IRM Predicted Liver Concentrations of JNJ-3989 (Left) and Corresponding Predicted Change From Baseline (CFB) in HBsAg (Right) With (Red) and Without (Cyan) Loading Dosing (200 mg JNJ-3989 Weekly for 4 Weeks) Prior to the 200 mg JNJ-3989 Q4W Regimen

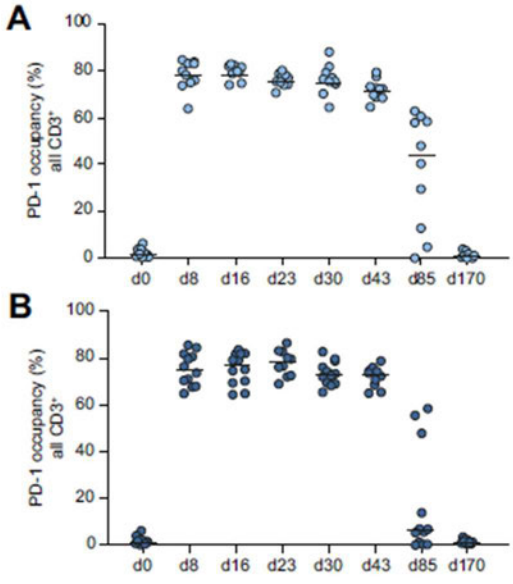


A major barrier to achieving functional cure of HBV is the dysfunctional immune response to viral infection. In patients with chronic hepatitis B (CHB), HBV antigen-specific T-cells are depleted or exhausted and therefore, incapable of controlling and eliminating virus. HBsAg-specific B-cells are also deficient in producing antibodies. The primary cause of immune dysfunction is excessive antigen (eg, HBsAg) stimulation from ongoing viral replication which induces epigenetic reprogramming of CD8+ T-cells and subsequently increased expression of multiple inhibitory receptors, such as PD-1. Expression of the corresponding ligands (eg, PDL-1) is also increased. In vitro, checkpoint blockade with PD(L)-1 inhibitors can reinvigorate cytokine production of the immune dysfunction from HBV and proliferation potential of exhausted T-cells (Yang 2021).

In 51 CHB patients with advanced hepatocellular carcinoma (HCC) treated with the humanized monoclonal antibody (mAb, IgG4) PD-1 inhibitor nivolumab dosed 3 mg/kg every 2 weeks (Q2W) during the dose expansion phase of CHECKMATE 040, 3 patients (6%) had ≥1 $\log_{10}$ decline in HBsAg – there were no HBsAg seroconversions or HBV reactivation in this cohort (El-Khoueiry 2017).

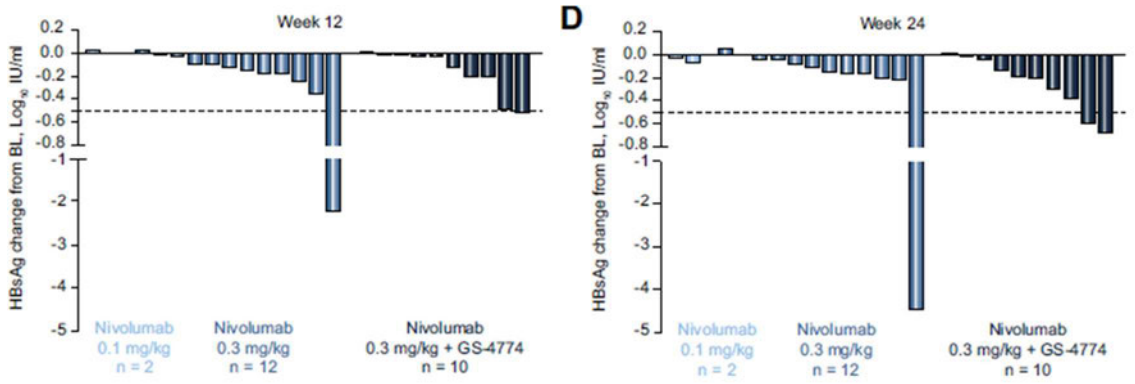
In the initial dose-ranging study of nivolumab, doses of 0.1 to 10 mg/kg IV were used – no serious adverse events (SAEs), fewer treatment-related Grade 3-4 adverse events (AEs), and no autoimmune disorders were reported in cancer patients who received single or multiple doses <1 mg/kg IV (Brahmer 2010, Topalian 2012). Based on these data, Gane 2019 evaluated single-dose nivolumab 0.1 or 0.3 mg/kg IV alone or with GS-4774 (therapeutic HBV vaccine) in virologically suppressed CHB patients who were HBeAg negative on current anti-HBV treatment. Maximum receptor occupancy (RO) measured in peripheral blood mononuclear cell (PBMCs) was 68.9-88.2% across the 2 doses, similar to levels seen in prior evaluations of nivolumab (from 0.1 to 10 mg/kg) and were maintained up to Day 43 post-dose (see Figure 3).

Figure 3: Receptor Occupancy: (A) Nivolumab 0.1 mg/kg or 0.3 mg/kg, and (B) Nivolumab 0.3 mg/kg + GS-4774



No difference in HBsAg was observed after 12 weeks in the 2 patients dosed 0.1 mg/kg IV. The mean (95% confidence interval [CI]) change in HBsAg from baseline to Week 12 was -0.30 (-0.46 to -0.14) log_{10} IU/mL for 12 patients treated with nivolumab 0.3 mg/kg IV and -0.16 (-0.33 to 0.01) log_{10} IU/mL for 10 patients treated with nivolumab 0.3 mg/kg IV and GS-4774 40 yeast units (YU); change in HBsAg from baseline to Week 24 was -0.48 (-0.83 to -0.13) and -0.25 (-0.64 to 0.13), respectively. Individual change in HBsAg is shown in Figure 4 (Gane 2019).

Figure 4: Individual Patient Changes in HBsAg From Baseline to Week 12 (Left) or Week 24 (Right) by Nivolumab Treatment



AEs were reported in 15 patients: 1 (50%) receiving nivolumab 0.1 mg/kg IV, 7 (58%) receiving nivolumab 0.3 mg/kg IV, and 7 (70%) receiving nivolumab 0.3 mg/kg IV with GS-4774 40 YU. Most AEs were Grade 1 in severity and were considered not related to nivolumab. One patient receiving GS-4774 + nivolumab 0.3 mg/kg experienced an AE (injection site pain) considered by the investigator as related to GS-4774, and 3 patients receiving nivolumab 0.3 mg/kg experienced an AE (mild fatigue, mild headache, mild cough [1 patient each]) considered by the investigator as related to nivolumab. The most common AEs were fatigue (3 patients [nivolumab 0.3 mg/kg group]), upper respiratory tract infection (2 patients [GS-4774 + nivolumab 0.3 mg/kg group]), and nasal congestion (2 patients [GS-4774 + nivolumab 0.3 mg/kg group]). There were no Grade 3 or 4 AEs or SAEs. There were no AEs of autoimmune disorders (eg, pneumonitis, colitis, rash, or endocrinopathies). One patient in the 0.3 mg/kg nivolumab group had a baseline alanine aminotransferase (ALT) of 49 IU/mL which increased to 275 IU/mL at Week 4 (Grade 3 elevation) after nivolumab administration before returning to 54 IU/mL by the end of study. The ALT elevation was accompanied by a 3-log_{10} reduction in HBsAg level and subsequent HBsAg seroconversion.

Two other patients (1 in the nivolumab 0.3 mg/kg group and 1 in the GS-4774 + nivolumab group) experienced Grade 1 ALT elevations with peak ALT values of 59 IU/mL and 61 IU/mL, respectively, both accompanied by >0.5 log_{10} reduction in serum HBsAg levels at 24 weeks. The association of these transient ALT elevations with HBsAg responses in all 3 patients suggested that these were immune-mediated HBV flares rather than de novo autoimmune hepatitis.

There were no clinically significant abnormal findings for electrocardiograms or vital signs (Gane 2019).

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 SC 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 (QW) 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 supra-pharmacologic 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 SC 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 SC 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 SC 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 CCI and a NOAEL in female rats of CCI

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

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

Nivolumab is a fully human IgG4 monoclonal antibody targeting PD-1. Nivolumab is able to bind PD-1 from both humans and cynomolgus monkeys and to prevent the interaction of PD-1 with its ligands, PD-L1 and PD-L2. This interaction plays an important role in the maintenance of self-tolerance and the prevention of unnecessary tissue damage following immune activation after acute infection by downregulating the immune response. General toxicology studies with nivolumab administered either weekly (4-week study) or twice weekly (13-week study) were conducted in cynomolgus monkeys to investigate the safety of nivolumab. In both monkey studies, exposure of nivolumab at all dose levels tested exceeded that measured in humans at the intended clinical dose and schedule of 3 mg/kg once every 2 weeks. Toxicities noted in these monkey studies were limited to mild increases in monocytic and lymphocytic infiltration in tissues. These changes are consistent with the pharmacologic activity of the antibody: blocking signaling through the immune-inhibitory PD-1 pathway. Immunophenotyping performed on samples from monkeys administered nivolumab during the 13-week study showed a trend towards increases in the percentage of CD4+ and CD8+ effector and central memory cells; this trend was clearer for the CD8+ T-cell population. Monkeys did not develop any clear signs of the autoimmune toxicity seen in clinical trials with nivolumab; however, the generalized lymphocytic infiltration and increases in memory T-cells do hint at the possibility of these types of toxicities. Given nivolumab's mechanism of action, the possibility exists that greater exposure in treated monkeys would result in a more serious inflammatory pattern closer to that seen clinically (Memorandum 2014).

2.2.2.3. Combination Nivolumab + JNJ-3989

Due to the distinct mechanism of action and safety profile of JNJ-3989 and nivolumab, it is not expected that they will have additive or synergistic effects on toxicology parameters. Therefore, a combination study with these 2 compounds is not warranted.

2.2.3. Clinical Studies

2.2.3.1. JNJ-3989

At the time of protocol writing, JNJ-3989 is being evaluated in 13 clinical studies. Three Phase 1 studies (Study 73763989HPB1001 in healthy adult Japanese participants, Study 73763989HPB1002 in adult participants with or without hepatic impairment, and Study 73763989HPB1004 in healthy adult Chinese participants) 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: 2 Phase 1 studies (73763989HPB1003 [renal impairment], 73763989HPB1005 [relative bioavailability], and 73763989PAHPB1006 [OSPREY], 5 Phase 2 studies (Studies 73763989HPB2001 [REEF-1], 73763989PAHPB2002 [REEF-2], 73763989PAHPB2003 [INSIGHT], 73763989PAHPB2005 [REEF-IT], 73763989PAHPB2006 [PENGUIN], and 73763989PAHPB2007 [PENGUIN-2]) in adult chronic HBV-infected participants, and 1 Phase 2 study (Study 73763989HPB2004 [REEF-D]) in adult participants co-infected with hepatitis B and D virus. In total, 64 healthy, 84 chronic HBV-infected participants, and 8 participants with moderately impaired hepatic function have been dosed with JNJ-3989 in completed Studies AROHBV1001, 73763989HPB1001, 73763989HPB1002, and 73763989HPB1004.

Across these completed studies, JNJ-3989 was generally safe and well tolerated with no deaths, SAEs considered at least possibly related to the study intervention, or AEs leading to study intervention discontinuation. All treatment-emergent 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 occurred also 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.

In the primary REEF-1 analysis (Week 48, end of treatment), the primary endpoint (ie, proportion of participants meeting NA completion criteria at Week 48 [assessments performed at Week 44]: HBsAg <10 IU/mL, <3x upper limit of normal [ULN] ALT, HBV DNA < lower limit of quantification [LLOQ] and HBeAg negative) was most commonly met in the HBeAg negative virologically suppressed subgroup for all regimens containing JNJ-3989. The numerically largest NA treatment completion rate was observed in the virologically suppressed HBeAg negative subgroup (200 mg dose group). The main reason for not meeting the primary endpoint criteria in the HBeAg positive subgroup was the persistence of HBeAg positivity.

A dose-response pattern was shown across the 3 dose levels of JNJ-3989 in mean HBsAg (log_{10}) decline from baseline over time. Overall, mean HBsAg levels in treatment arms containing JNJ-3989 show the greatest magnitude of decline during the first 24 weeks.

In the REEF-1 Week 48 analysis, no deaths were reported. Ten SAEs were reported of which 2 were considered related to study drug by the investigator. Two participants experienced SAEs related to study treatment: 1 ALT/aspartate aminotransferase (AST) increased in the triple regimen (JNJ-3989 100 mg + JNJ-6379 250 mg QD [capsid assembly modulator] + NA) arm and 1 CK elevation reported as rhabdomyolysis in the JNJ-3989 200 mg + NA arm. The CK elevation was confounded by recent strenuous exercise. The elevated CK levels returned to normal and did not recur with subsequent administrations of study treatment.

Overall, 5 (1.1%) participants discontinued investigational treatment due to an AE: 2/95 participants in the triple regimen arm, 2/93 participants in the JNJ-3989 40mg + NA arm, and 1/48 participant in the JNJ-6379 + NA arm.

Of the 29 (6.2%) participants who experienced any Grade 3 or 4 AEs, the largest incidence was observed in the in JNJ-6379+NA arm (14.6% [7/48]) and the triple regimen arm (7.4% [7/95]). The most frequent (8 participants) Grade 3 or 4 AEs were alanine aminotransferase increased: 3 participants each in the triple regimen arm and the JNJ-6379 + NA arm, and 2 participants in the JNJ-3989 200 mg + NA.

Events related to renal function were the most frequently reported AE of Special Interest (14.7% [14/95] in triple regimen arm and 8.3% [4/48] in JNJ-6379 + NA arm), followed by ISRs (10.8% [10/93] in JNJ-3989 100mg + NA arm) and ALT/AST elevations (8.3% [4/48] in JNJ-6379 + NA arm and 7.4% [7/95] in triple regimen arm).

Laboratory Abnormalities and Grade 3/4 ALT Elevations

No eGFR Grade 4 abnormalities were observed. No meaningful changes over time in mean estimated glomerular filtration rate based on serum creatinine (eGFRcr) are seen in JNJ-3989 + NA regimens.

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.

Treatment-emergent increases in mean ALT values were mild and remained within the normal range in all treatment arms. Currently not treated participants were required to have ALT >ULN at study entry to be eligible while virologically suppressed participants were required to have ALT ≤2x ULN. In currently not treated participants, an increase of mean ALT values early on treatment was observed, followed by a gradual reduction towards normal values across all treatment arms.

For the virologically suppressed participants an immediate increase of mean ALT values is seen in both arms containing JNJ-6379 and a delayed and gradual increase is seen in JNJ-3989 200 mg group.

Thirteen cases of ALT flare (3.1% [13 of 425]) (confirmed treatment-emergent elevation of ALT and/or AST ≥3x ULN and ≥3x nadir) were observed across the active treatment arms, primarily in currently not treated participants (11 of 13). No ALT flares were observed in the control arm. Seven ALT flares were observed in the JNJ-3989 200 mg + NA arm (7.3% [7 of 96]), followed by 2 flares each in the JNJ-3989 (100 mg) + NA (2.2% [2 of 93]), JNJ-3989 (100 mg) + JNJ-6379 (250 mg) + NA (2.1% [2 of 95]) and the JNJ-6379 250 mg + NA arms (4.1% [2 of 48]). Majority of the ALT flares occurred early during the study (61.5% [8 of 13]), between 1-12 weeks, one ALT flare occurred between 13-24 weeks (7.7% [1 of 13]) and the remainder occurred between 25-48 weeks (30.7% [4 of 13]). Declines in virologic parameters were similar between participants with and without ALT flare. The ALT elevations were without concurrent bilirubin elevations or signs and symptoms of hepatic dysfunction. All ALT flares resolved or stabilized on continued treatment.

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 (ALT or 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 (IB JNJ-3989).

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

Based on available clinical and nonclinical data, no clinically relevant drug-drug interactions are expected between JNJ-3989, nivolumab, and NAs. No specific concerns about additive or synergistic toxicities in the kidney are expected when JNJ-3989 is combined with ETV, tenofovir disoproxil, or TAF.

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 nivolumab and NA, refer to the respective prescribing information.

Weekly dosing of JNJ-3989 was tested in study AROHBV1001 at doses ranging from 100 mg to 300 mg Q1W for 3 doses and no safety concerns were identified. For more details, refer to the IB (IB JNJ-3989).

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 and NAs 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 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 pgRNA levels and therefore also HBV DNA. 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.

Gane et al has shown, among the 12 participants who received one dose of 0.3 mg/kg nivolumab, 92% (11/12) had a reduction in HBsAg from baseline during the study. One participant achieved a $\geq$0.5 $\log_{10}$ IU/mL decrease in HBsAg at Week 12 that continued to decline and became undetectable at Week 16 and had an associated ALT flare from Week 3 to Week 8. This participant developed an anti-HBs response 10 weeks after the end of the study, which is the ultimate goal of HBV treatment.

2.3.2. Risks for Study Participation

2.3.2.1. Known Risks

In the AROHBV1001 study, ISRs were the most frequently observed AEs assessed by the investigator as related to JNJ-3989 administered subcutaneously.

Immune checkpoint inhibitors (ICIs), such as anti-PD-1 monoclonal antibodies, target proteins that enhance the response of the immune system to tumor cells or HBV-infected hepatocytes. By stimulating the endogenous immune system however, there is the potential for adverse effects on other tissues by way of immune cell activation and inflammatory mechanisms. The potential immune-related AEs (irAEs) require close and more frequent monitoring, and early intervention such as administration of corticosteroids.

Safety risks for nivolumab are based on results from nonclinical toxicology studies and oncology clinical studies conducted with nivolumab, the known mechanism of action of nivolumab (ie, anti-PD-1 antibody), and the route of administration. irAEs and infusion-related reactions (IRRs) have been identified as important identified risks for nivolumab (ie, immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related nephritis and renal dysfunction, immune-related endocrinopathies, immune-related skin adverse reactions, other irAEs, and severe infusion reactions (NSPC).

The safety profile of nivolumab is manageable with the majority of AEs being Grade 1 or Grade 2 in severity based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE). irAEs typically resolve after systemic treatment with corticosteroids or discontinuation of nivolumab treatment. Immune-related endocrinopathies such as hypothyroidism and adrenal insufficiency may require endocrine replacement therapy.

Treatment with anti-PD-1 medications is associated with a risk of HBV reactivation in CHB patients. This risk is reduced with concurrent NA treatment or continuation of ongoing NA treatment.

In a case series of cancer patients with HIV, HBV, or hepatitis C virus (HCV) infection treated with ICI therapy including chemotherapy plus immunotherapy, it was found that the safety and efficacy profile of ICI therapy is similar to that observed in those without chronic viral illness, suggesting that ICI therapy is a safe and effective treatment option for patients with HIV, HBV, or HCV infection suffering from advanced-stage cancer (Shah 2019).

2.3.2.2. Potential Risks

All therapies have the potential to cause adverse experiences.

Patients with positive HBV DNA and positive HBsAg can always experience increases in liver transaminases which may indicate immune activation and may result in the reduction of viral parameters such as HBV DNA and/or HBsAg. Whether this occurs at higher frequency during or after treatment with JNJ-3989 is not known.

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 Q4W, compared to 0% of participants treated with NA and 0% to 2% of participants treated with lower doses of JNJ-3989.Those ALT flares seen primarily early during

treatment with JNJ-3989, were observed in currently not treated HBeAg positive participants. The majority of the ALT flares resolved rapidly on continued treatment; 1 was considered serious. In REEF-D, an ongoing study with HBV/hepatitis D virus (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.

Important potential risks of nivolumab include embryofetal toxicity and immunogenicity (NSPC).

Optional fine needle aspiration (FNA) biopsy of the liver will be performed during this study only for participants who consent to this procedure. The related risks and complications will be described in a separate informed consent form (ICF) and may include pain and discomfort located at or near the puncture site (Tang 2003). No complications were seen in a series of more than 1000 FNA biopsies performed as part of monitoring of liver allografts (Lautenschlager 1991).

During the conduct of this OCTOPUS-1 study, two cases of possible hyperthyroidism were reported. Both cases occurred in participants in treatment Arm 1 who were randomized to receive a single dose of nivolumab administered at treatment week 16 of JNJ-73763989 treatment. At treatment week 24, thyroid-stimulating hormone (TSH) was reduced in both patients. While the first patient had normal free T3 and free T4 and TSH values returned to normal at follow-up visits, the second patient had fully suppressed TSH with elevation of free T3 and free T4. In light of this observation, the Sponsor decided on 20 June 2023 to not further expose any patients in the OCTOPUS-1 study to nivolumab. Two patients were concerned by this USM and did not receive their third dose of nivolumab.

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

2.3.3. Benefit-Risk Assessment for Study Participation

Based on the available data and proposed safety measures, the overall risk/benefit assessment for JNJ-3989 and nivolumab clinical studies is deemed acceptable for the following reasons:

- Efficacy and safety of JNJ-3989 with NA as assessed in CHB patients in the REEF-1 study over a 48-week period was generally considered safe and well tolerated. Robust reductions of HBsAg levels were seen in all JNJ-3989 arms, however, HBsAg seroclearance occurred only in a few participants. In the current study, JNJ-3989 is being combined with nivolumab, a PD-1 inhibitor, which may lead to higher seroclearance rates.
- The toxicities associated with JNJ-3989, nivolumab and NAs are manageable with guidance provided in this protocol, the IB, and approved prescribing information. ALT/AST elevations is an important potential risk associated for JNJ-3989 and has been observed in the REEF-1 study. These ALT/AST elevations were not associated with signs of reduced liver function. Nivolumab is a PD-1 inhibitor administered intravenously and is associated with irAEs and

IRRs. Nivolumab may cause fetal harm when administered to pregnant women. NAs are established treatment for chronic hepatitis B and well tolerated; discontinuation of NA treatment may lead to reactivation of hepatitis.

- Continued careful assessment of the safety, efficacy, and PK during treatment is included in this study.
- Events of Special Interest are significant AEs that are judged to be of special interest because of clinical importance, known class effects or based on nonclinical signals. Events of Special Interest that will be carefully monitored during the study include ALT/AST elevations including immune-related hepatic AEs, IRRs and other irAEs (including gastrointestinal AEs, neurological AEs, pulmonary AEs, renal AEs, endocrinopathies, rash, uveitis and visual complaints, lipase/amylase elevations, and infection; see Section 8.3.6.1 and Section 8.3.6.2). Other AEs of Special Interest related to JNJ-3989 that will be carefully monitored during the study include hematological abnormalities and ISRs (see Section 8.3.6.3).
- 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 will be offered an optional safety follow-up visit.
  - At regular time points throughout the study (see Schedule of Activities), blood samples for biochemistry, blood coagulation, and hematology and urine samples for urinalysis, urine chemistry, and renal biomarkers will be collected. Vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature), height (only at screening), body weight, and electrocardiograms (ECGs) will be recorded throughout the study. Physical examinations will be performed, and AEs will be assessed (see Section 8.2, Safety Assessments). AEs of Special Interest will be closely monitored (Section 8.3.6, Guidelines for Management of Adverse Events of Special Interest Including Immune-Related Adverse Events).
  - An internal Data Review Committee (DRC) will be established for continuous monitoring of safety data including 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 regularly monitored for HBV reactivation and virologic breakthroughs throughout the study.
  - Participants will be monitored closely during the 48-week follow-up period, with frequent follow-up visits.
  - JNJ-3989 will be administered using a proper SC technique to decrease the risk of ISRs. ISRs will be managed as outlined in Section 8.3.6, Guidelines for Management of Adverse Events of Special Interest Including Immune-Related Adverse Events. Nivolumab will be administered by IV infusion and participants will be carefully monitored for IRRs.

- Female participants will be monitored for pregnancy due to risk of embryofetal toxicity associated with PD-1 inhibitors. Participants of childbearing potential are required to use a highly effective user-independent contraceptive method while receiving study intervention and until 5 months after the last dose of study intervention.
- 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).

More detailed information about the benefits and risks of JNJ-3989 may be found in the IB. For nivolumab and NA, refer to the respective prescribing information.

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 efficacy of the study intervention, based on HBsAg levels at FU Week 24.	• Proportion of participants who achieve HBsAg seroclearance at FU Week 24.
Secondary	
To characterize the safety and tolerability of the study intervention.	• Proportion of participants who experienced AEs of interest. • Safety profile of JNJ-3989 with nivolumab throughout the study (safety parameters include but are not limited to the frequency and severity of AEs and immune-related AEs, vital signs measurements, physical examinations, clinical laboratory values, and 12-lead electrocardiograms [ECGs]).
To evaluate efficacy in terms of changes in HBsAg levels from baseline over time during the study intervention and follow-up periods.	• Change from baseline in HBsAg levels during the study intervention and follow-up periods. • Proportion of participants with HBsAg levels below/above different cut-offs over time.
To evaluate efficacy in terms of HBsAg seroclearance/seroconversion during the study intervention and follow-up periods (as defined in the Definitions of Terms).	• Proportion of participants with HBsAg seroclearance/seroconversion during the study intervention and follow-up periods. • Time to achieve HBsAg seroclearance/ seroconversion.

Objectives	Endpoints
To evaluate the efficacy as measured by blood markers (such as HBV DNA and HBeAg) during the study intervention and follow-up period.	• Change from baseline in HBV DNA levels during the study intervention and follow-up periods. • Proportion of participants with HBV DNA and HBeAg levels below/above different cut-offs over time.
To evaluate the frequency of virologic breakthrough throughout the study.	• Proportion of participants with virological breakthrough throughout the study.
To evaluate the pharmacokinetics (PK) of JNJ-3989 (JNJ-3924 and JNJ-3976), and optionally of NA and/or nivolumab.	• PK parameters of JNJ-3989 (JNJ-3924 and JNJ-3976). • Optionally, PK parameters of NA and/or nivolumab.
Exploratory	
To characterize the pharmacodynamics (PD) of JNJ-3989 with nivolumab including quantification of RO on peripheral T-cells.	• Relationship of various PK parameters with selected efficacy and safety endpoints. • Quantification of nivolumab RO on peripheral CD3+ T-cells by flow cytometry on whole blood.
To explore changes in the severity of liver disease.	• Changes in fibrosis (according to Fibroscan liver stiffness measurements) at end of study intervention (EOSI) and the end of the follow-up period versus baseline.
To explore HBV-specific T-cell responses throughout the study.*	• Changes from baseline in HBV-specific peripheral blood T-cell responses over time.
To explore efficacy of the study intervention in terms of changes in HBV RNA and hepatitis B core-related antigen (HBcrAg) levels throughout the study.	• Changes from baseline in HBV RNA and HBcrAg levels over time.
To explore the HBV genome sequence throughout the study.	• Assessment of intervention-associated mutations over time.

Objectives	Endpoints
To explore medical resource utilization to manage participants throughout the study.	• 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).

*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.

HYPOTHESIS

The primary hypothesis of this study is that at least one of the combination regimens of JNJ-3989+nivolumab+NA is more efficacious than JNJ-3989+NA treatment, as measured by the primary efficacy endpoint (ie, the proportion of participants with HBsAg seroclearance at FU Week 24). Because the study does not include a regimen arm without nivolumab, the hypothesis is formulated assuming a fixed response rate for JNJ-3989+NA of 1% based on previous Study 73763989HPB2001 (REEF-1).

4. STUDY DESIGN

4.1. Overall Design

This ISA describes a Phase 2 study of the combination regimen of JNJ-3989 with nivolumab and NA. It is a companion document to the Master Protocol PLATFORMPAHPB2001, which describes the common design elements of the Platform study in participants with chronic HBV infection. This ISA describes specific and/or additional protocol elements applicable to this randomized, open-label, parallel, multicenter, interventional study to evaluate safety, efficacy, tolerability, PK and PD of a combination of JNJ-3989, nivolumab, and NAs in virologically suppressed chronic HBV-infected adult participants.

Initially, a target of approximately 44 virologically suppressed, HBeAg negative, adult chronic hepatitis B participants ≥18 (or the legal age of consent in the jurisdiction in which the study is taking place) to <56 years of age were planned to be randomly assigned in this study with 22 participants planned per arm.

Due to the decision to not extend further enrollment beyond the planned enrollment period and proceed with a reduced sample size, the final sample size is 37 (18 in Arm 1 and 19 in Arm 2).

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

- 6-week Screening Period (if necessary, eg, for operational reasons, this can be extended to a maximum of 8 weeks decided on a case-by-case basis and in agreement with the sponsor). During the Screening Period, the participants will continue the same NA treatment they were receiving before screening.
- 24-week Study Intervention Period:
  - Arm 1: JNJ-3989 Q1W for the first 4 weeks and then Q4W until Week 24 + nivolumab at Week 16 + NA QD
  - Arm 2: JNJ-3989 Q1W for the first 4 weeks and then Q4W until Week 24 + nivolumab Q4W at Weeks 16, 20, 24 + NA QD.
- 48-week Follow-up Period, during which NA treatment will be continued.

At baseline, participants who meet the eligibility criteria will be randomized in a 1:1 ratio to Arm 1 or Arm 2. Randomization will be stratified by absolute HBsAg level (<100 IU/mL, 100 to <1,000 IU/mL, and ≥1,000 IU/mL) at screening, as assessed by quantitative HBsAg assay.

Background treatment consists of:

- NA: tenofovir disoproxil (245 mg), TAF (25 mg), or ETV (0.5 mg) given as oral tablets QD for approximately 76 weeks (screening included).

Study intervention consists of:

- JNJ-3989: 200 mg given by SC injections Q1W for the first 4 weeks and then Q4W until Week 24 (10 doses)
- Nivolumab: 0.3 mg/kg, one single IV infusion at Week 16 for Arm 1 or 3 IV infusions at Weeks 16, 20, and 24 for Arm 2.

Assessments and sampling will be done for efficacy (eg, HBsAg, HBeAg, and HBV DNA), safety (eg, [S]AEs, irAEs, laboratory evaluations, ECGs, vital signs, physical examinations), PK, PK/PD, viral genome sequencing, PBMC, human leukocyte antigen (HLA) typing, immunogenicity and pharmacogenomics, and for exploratory analysis of host and viral markers.

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 final study visit (ie, FU Week 48).

If a participant prematurely discontinues treatment with JNJ-3989 before Week 24, the participant will also discontinue further treatment with nivolumab and will have an early withdrawal (WD) visit. 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. The NA treatment will be continued until the end of the study.

If a participant prematurely discontinues nivolumab, treatment with JNJ-3989 and NA should be continued as planned, unless a treatment discontinuation rule for JNJ-3989 is also met. In that case, JNJ-3989 will also be discontinued but NA treatment should be continued as planned.

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

An internal DRC will be commissioned for monitoring safety of participants enrolled in this study. In addition, an IFLEP will be appointed. Refer to Committees Structure in Appendix 3: Regulatory, Ethical, and Study Oversight Considerations for details.

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 intervention 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 (<100 IU/mL, 100 to <1,000 IU/mL, and ≥1,000 IU/mL) at screening, as assessed by quantitative HBsAg assay.

Host DNA and Exploratory Host Biomarker Collection

Refer to Section 4.2 of the Master Protocol PLATFORMPAHPB2001.

Optional FNA biopsy samples may be collected to assess intrahepatic immune responses which can be compared to responses in PBMCs.

4.2.1. Study-Specific Ethical Design Considerations

Refer to Section 4.2.1 of the Master Protocol PLATFORMPAHPB2001. Differences with the Master Protocol PLATFORMPAHPB2001 are highlighted (colored fill).

Written consent may be obtained through various sources (eg, paper or electronic such as eConsent, eSignature, or digital signature) as determined by regulations as well as study and/or patient preferences.

FNA biopsies may be performed during this study only for participants who consent to this procedure. The risks and complications related to these procedures are described in Section 2.3.2.2. These risks and complications will be described in the ICF and will be clearly explained to potential participants prior to enrollment.

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.

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

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

Antiviral activity data are available for 56 chronic HBV-infected participants who received 3 SC 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 injection). 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.

Clinical data on efficacy and safety of JNJ-3989 are available from the Phase 2b 73763989HPB2001 (REEF-1) study. One of the objectives of this ongoing study is to assess the dose-response relationship for antiviral activity of 3 doses (40 mg, 100 mg and 200 mg, administered Q4W) of JNJ-3989 in combination with NA.

A dose of 200 mg JNJ-3989 is chosen based on the dose-response pattern that was observed across the 3 dose levels of JNJ-3989 in mean HBsAg ($\log_{10}$) decline from baseline over time in Study REEF-1. Furthermore, a dose of 200 mg JNJ-3989 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.

A JNJ-3989 dosing interval of Q1W for the first 4 weeks and then Q4W until Week 24 is chosen based on PK/PD modeling of JNJ-3989 using a TMDD and IRM based on REEF-1 data, suggesting that a loading dose (Q1W) regimen for JNJ-3989 will result in higher liver concentrations more rapidly than a Q4W dosing regimen. Higher liver concentrations are expected to result in a more pronounced and faster decline in HBsAg and may improve the likelihood of achieving functional cure.

The proposed dose of nivolumab, 0.3 mg/kg, is based on available data for the use of nivolumab in CHB patients (refer to Section 2.1 for further information). The frequency of dosing in Arm 2, Q4W, is based on the estimated geometric mean half-life of nivolumab (25 days) and frequency of administration for its approved indications in oncology (for more details, refer to the nivolumab prescribing information).

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last scheduled study 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.

Participant Study Completion Definition

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

5. STUDY POPULATION

Screening for eligible participants will be performed within 42 days 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 decided on a case-by-case basis and in agreement with the sponsor.

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

Exceptional and limited retesting of abnormal screening values that lead to exclusion is allowed once, using an unscheduled visit during the Screening Period (to reassess eligibility).

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 <56 years of age.
M02	Participants must be medically stable based on physical examination, medical history, vital signs, and 12-lead ECG performed at screening. If there are abnormalities, they must be consistent with the underlying illness in the study population. This determination must be recorded in the participant's source documents and initialed by the investigator.
A03 (adapted from M03a)	Participants must have chronic HBV infection. HBV infection must be documented by serum HBsAg positivity at screening. In addition, chronicity must be documented by any of the following, at least 6 months prior to screening: serum HBsAg positivity, HBeAg positivity or HBV DNA positivity, ALT elevation >ULN without another cause than HBV infection, documented transmission event, liver biopsy with changes consistent with chronic HBV, or absence of marker for acute HBV infection at screening such as positive immunoglobulin M (IgM) anti-HBc antibodies. Participants should: • Be HBeAg negative at screening, AND • Be on stable HBV treatment, defined as currently receiving NA treatment (ie, entecavir, tenofovir disoproxil, or tenofovir alafenamide) for at least 12 months prior to screening, and having been on the same NA treatment regimen (at the same dose) as used in this study (see Table 4) for at least 3 months at the time of screening, AND • Have serum HBV DNA <60 IU/mL on 2 sequential measurements at least 6 months apart (one of which is at screening), AND • Have documented ALT values <2.0x ULN on 2 sequential measurements at least 6 months apart (one of which is at screening).
A04 (adapted from M04)	Participants must have a body mass index (BMI; weight in kg divided by the square of height in meters) between 18.0 and 30.0 kg/m^2, extremes included.
A05 (adapted from M05)	Participants must sign a Master ICF (specific for the Master Protocol PLATFORMPAHPB2001) and must sign an ICF specific for this intervention cohort, indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.
A06 (adapted from M06)	Participants must sign a separate ICF if he or she agrees to provide additional optional DNA samples and/or FNA biopsy samples for research (where local regulations permit). Refusal to give consent for the optional DNA and/or FNA biopsy research samples does not exclude a participant from participation in the study.

A07 (adapted from M07)	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, 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 5 months after the last dose of study intervention. The investigator must evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the dose of study intervention. Examples of user-independent 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 (with or without spermicidal foam/gel/film/cream/suppository) when engaging in any activity that allows for passage of ejaculate to another person while receiving study intervention and until 5 months after the last dose of study intervention. Female partners of male participants, if of childbearing potential, must also be practicing a highly effective method of contraception (as defined in Section 10.5). If the male participant is vasectomized, he still must wear a condom (with or without spermicidal foam/gel/film/cream/ suppository), but his female partner is not required to use contraception.
A11	Female participants must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction while receiving study intervention and until 5 months after the last dose of study intervention.
A12	Male participants must agree not to donate sperm for the purpose of reproduction while receiving study intervention and until 5 months after the last dose of study intervention.
A13	Participants must have serum HBsAg from ≥5 to ≤10,000 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)	Participants with evidence of hepatitis A virus infection (hepatitis A antibody IgM), HCV infection (HCV antibody), 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 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.

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

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[a], 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 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).
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 10.8, Appendix 8: DAIDS Table with Modifications): 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. Absolute neutrophil count <1,500/mm^3 (<1,000/mm^3 for participants of African ancestry); g. Alpha-fetoprotein (AFP) >100 ng/mL;

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

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.

h. Abnormal thyroid function (including TSH, free triiodothyronine [T3] and free thyroxine [T4])

i. Positive autoantibody test results for at least one of the following:

- Anti-nuclear antibodies (ANA) titer ≥1:80;
- Anti-smooth muscle antibodies (ASMA) titer ≥1:80;
- Anti-mitochondrial antibodies (AMA) titer ≥1:80;
- Anti-thyroid peroxidase antibodies ≥35 IU/mL;
- Anti-Neutrophil Cytoplasmic Antibody (ANCA) titer ≥1:20;
- Rheumatoid factor ≥14 IU/mL.

Note: In case of ≥2 positive tests but below the exclusionary cut-off, participant may be enrolled if approved by the sponsor before randomization.

j. 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; or any other clinically significant abnormalities on a 12-lead ECG at screening (eg, significant abnormal conduction).

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

M11	Participants with any current or previous illness for which, in the opinion of the investigator and/or sponsor, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments. This may include but is not limited to significant vascular, pulmonary (eg, chronic obstructive pulmonary disease), gastrointestinal (eg, significant diarrhea, gastric stasis, or constipation that in the investigator's opinion could influence drug absorption or bioavailability), endocrine (eg, thyroid disease), neurologic, hematologic, rheumatologic, psychiatric, neoplastic, or metabolic disturbances. Any condition possibly affecting drug absorption (eg, gastrectomy or other significant gastrointestinal tract surgery, such as gastroenterostomy, small bowel resection, or active enterostomy) will also lead to exclusion.
M12	Participants who have received an organ transplant (except for skin, hair, or cornea transplants).
M13	Participants with any history of or current clinically significant skin disease requiring regular or periodic treatment.
M14	Participants with clinically relevant alcohol or drug abuse within 12 months of screening.
M15	Participants with history of clinically relevant drug rash.
M16	Participants who have taken any disallowed therapies as noted in Section 6.5, Concomitant Therapy before screening.
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, until 5 months after last dose of study intervention.
A19 (adapted from M19)	Male participants who plan to father a child while enrolled in this study, until 5 months after 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]) and/or NA and/or nivolumab or their excipients (refer to the respective prescribing information).
A24	Participants with personal/familial history/indicative of immune-mediated disease risk.
A25	Participants with a history of tuberculosis (TB) or latent TB that has not been adequately treated, known active TB, suspected or known extrapulmonary TB based on medical history and/or concomitant medication, or recent close contact with a person with known active TB.
A26	Participants with symptomatic herpes zoster within 3 months prior to screening.
A27	Participants with contraindications to the use of anti-PD-1 antibody, anti-PD-L1 antibody or anti-PD-L2 antibody per local prescribing information.
A28	Participants who received or plans to receive any live vaccine within 28 days before the planned first dose of study intervention until the end of the study. **Note:** Non-live vaccines approved or authorized for emergency use by local health authorities are allowed. For this study, the second dose of Sputnik V COVID-19 vaccine is considered a live vaccine.
A29	Participants or their first-degree relatives (including parents, siblings, and children) have an active autoimmune disease or a documented history of autoimmune disease. **Note:** Participants with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Participants that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Participants with a history of transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent (eg, acute Lyme arthritis) will not be excluded from the study.

NOTE: Investigators must ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that the participant no longer meets all eligibility criteria, then the participant must be excluded from participation in the study. The required source documentation to support meeting the enrollment criteria are noted in Appendix 3: Regulatory, Ethical, and Study Oversight Considerations 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. Agree to follow all requirements outlined in Section 6.5, Concomitant Therapy, regarding prohibited and restricted therapy during the study.

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

5.4. Screen Failures

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

This study will use IWRS. The investigator will generate screening and enrollment logs directly from IWRS.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Intervention(s) Administered

Description of Study Intervention

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 SC injection, containing 0.5 mM sodium phosphate monobasic and 0.5 mM sodium phosphate dibasic in water as inactive ingredients (formulation G001). 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 nivolumab formulated as concentrate for solution for infusion will be supplied for this study by the sponsor as a 40 mg/4 mL solution for IV infusion. Refer to the prescribing information for a list of excipients.

Table 2: Description and Administration of Study Intervention

Intervention Name	**JNJ-3989**	**Nivolumab**
Type	Drug	Drug
Dose Formulation	Solution for injection (G001)	Concentrate for solution for infusion
Unit Dose Strength(s)	200 mg/mL	40 mg/4 mL
Dosage Level(s)	200 mg Q1W for the first 4 weeks, then once every Q4W until Week 24	0.3 mg/kg (1 intravenous [IV] infusion for Arm 1 or 3 IV infusions Q4W for Arm 2)**
Route of Administration	Subcutaneous injection* (preferably in the abdomen; upper arm or thigh is also allowed)	IV infusion over 30 minutes
Use	Investigational intervention	Investigational intervention
Investigational Medicinal Product (IMP)	Yes	Yes
Non-investigational Medicinal Product/ Auxiliary Medicinal Product (NIMP/AxMP)	No	No
Sourcing	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
Food/Fasting Instructions	Regardless of food intake	Not Applicable

*Note: Administration into scar tissue or areas that are reddened, inflamed or swollen should be avoided. If injecting into the abdomen, avoid a 5 cm diameter circle around the navel.
**Note: a tolerance of +/- 5% around the theoretical dose of 0.3 mg/kg will be applied to consider the necessary rounding and standard practice for the preparation and intravenous administration of drugs dosed by weight.

Packaging and Labeling of Study Intervention

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

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 case report form (CRF).

JNJ-3989 injections will be administered SC (preferably in the abdomen) at the study site and the approximate location should be recorded.

Prior to starting nivolumab treatment, the participant's most recent ALT value (tested by local or central lab) should be <3x ULN with no change in autoimmune status. In case the administration of nivolumab would not be in the interest of the participant, this should be discussed with the sponsor.

Nivolumab injections will be administered as an IV infusion at the study site. The duration of the IV infusion will be approximately 30 minutes.

When both JNJ-3989 and nivolumab are administered at the same visit, JNJ-3989 should be administered first (preferably in abdomen) followed within approximately 30 minutes by IV infusion of nivolumab.

For a definition of study intervention overdose, refer to Section 6.8, Treatment of Overdose.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

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

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

Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The dispensing of study intervention to the participant, and the return of study intervention from the participant (if applicable), must be documented on the intervention accountability form. Participants must be instructed to return all original containers, whether empty or containing study intervention. The study intervention administered to the participant must be documented on the intervention accountability form. All study intervention will be stored and disposed of according to the sponsor's instructions. Study site personnel must not combine contents of the study intervention containers.

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

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

Study intervention must be dispensed under the supervision of the investigator or a qualified member of the study site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to participants participating in the study. 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 intervention is 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 2 intervention groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by absolute HBsAg level (<100 IU/mL, 100 to <1,000 IU/mL, and ≥1,000 IU/mL) at screening, as assessed by quantitative HBsAg assay. 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 and nivolumab will be administered at the study site by qualified study site personnel as an SC injection and IV infusion, respectively, to assure compliance with study requirements. The details of each administration will be recorded in the source document and CRF (including date, start and stop times of the IV infusion or SC injection, volume prepared, and volume administered).

The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site personnel other than the person administering the study intervention. The study intervention may not be used for any purpose other than that outlined in this protocol, including other human studies, animal investigations, or in vitro testing. Study site personnel will maintain a log of all study interventions administered. Study intervention supplies for each participant will be inventoried and accounted for.

Every effort should be made to have the study interventions administered as indicated in the Schedule of Activities, especially during the first 4 weeks of dosing.

If a SC injection of JNJ-3989 was missed during the loading dose period (Week 1-4), the injection should be given as soon as possible but within 3 days after the scheduled time and with a minimum of 3 days between injections. Otherwise, the dose should be skipped and the next dose should be given at the next scheduled time point per the initial dosing schedule.

If after the loading dose period a SC injection of JNJ-3989 was missed or an IV infusion of nivolumab was missed, the injection or infusion should be given as soon as possible but within 2 weeks after the scheduled time. Otherwise, the dose should be skipped and the next dose should be given at the next scheduled time point per the initial dosing schedule.

In case of ALT elevation ≥3x ULN during the first 4 weeks of dosing, administration of JNJ-3989 should be discussed with the sponsor.

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.

6.5. Concomitant Therapy

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

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

For participants who consent to complete the optional FNA biopsy of the liver, any anticoagulants and antiplatelets are disallowed from baseline to at least 2 weeks after the completion of the last FNA biopsy. Use of low-dose aspirin is allowed except during the 7 days period preceding the FNA biopsies.

Note that locally approved COVID-19 vaccines (including those that received emergency use authorization or conditional marketing authorization) are allowed throughout the study, with the exception of the second dose of Sputnik V (which contains rAd5). Sputnik light which is the first dose of Sputnik V (with rAd26) is allowed.

During nivolumab treatment, the following recommendations should be applied to accommodate COVID-19 vaccination:

- COVID-19 vaccine and nivolumab should not be administered on the same day. If required, nivolumab administration can be delayed by 2-5 days.
- The next nivolumab administration should be performed at the scheduled time.
- If required, skipping a nivolumab administration may be considered after consultation with the sponsor.

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 nivolumab prescribing information for more details.

Table 3: Disallowed Medication

Disallowed from 12 months prior to screening until end of follow-up:
• IFN. • Any oligonucleotide-based treatment (eg, siRNA, nucleic acid polymers, antisense oligonucleotides), other than the study intervention taken in the context of this study. • Any prior treatment with an anti-PD-1 antibody, anti-PD-L1 antibody or anti-PD-L2 antibody, 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. • Any systemically (eg, intravenously, intramuscularly, orally, subcutaneously) administered medication that directly or indirectly interferes with immune responses (eg, cyclosporine, interleukins, systemic corticosteroids at doses exceeding 5 mg/day of prednisone or its equivalent). Use of systemic immunosuppressive medications for the management of irAEs, ISRs, or IRRs, or in participants with contrast allergies is acceptable, ie, it will not be considered a protocol deviation, but it will lead to nivolumab discontinuation and/or JNJ-3989 discontinuation if criteria relative to the use of prohibited medication (including systemic corticosteroids) detailed in Sections 7.1.1 and 7.1.2 are met. In addition, use of inhaled, topical, local, and intranasal corticosteroids is permitted.
Disallowed from screening until end of follow-up:
• Any anti-HBV drug (including vaccines) other than the study intervention and the NA background regimen taken in the context of this study. ***Notes:*** o Prior hepatic treatment with herbal or nutritional products is allowed but should be stopped at screening. • 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 nivolumab should be consulted for any additional prohibited medication.

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

6.6. Dose Modification

Any dose/dosage adjustment must be overseen by medically-qualified study site personnel (principal or subinvestigator unless an immediate safety risk appears to be present).

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

Refer to Section 6.7 of the Master Protocol PLATFORMPAHPB2001.

6.8. Treatment of Overdose

For this study, any dose of JNJ-3989 exceeding the protocol-specified dose with ≥25% and any dose of nivolumab exceeding the protocol-specified dose (0.3 mg/kg) with >5%; refer to Section 6.1, Study Intervention(s) Administered), will be considered 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 must 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.

6.9. Background Treatment

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

Table 4: Description and Administration of Background Treatment

Treatment Name	Tenofovir disoproxil	Tenofovir alafenamide (TAF)*	Entecavir (ETV) monohydrate
Type	Drug	Drug	Drug
Dose Formulation	Film-coated tablets	Film-coated tablets	Film-coated tablets
Unit Dose Strength(s)	245 mg	25 mg	0.5 mg
Dosage Level(s)	245 mg QD	25 mg QD	0.5 mg QD
Route of Administration	Oral	Oral	Oral

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

Investigators should follow guidance detailed in the local prescribing information of NA, including special warnings and precaution for use.

Participants are instructed to take their NA at home in between study visits, and to bring their NA with them to each study visit. Study site personnel will instruct participants on how to take their NA at home and how to store NA for at-home use. At study visits, the NA should be taken on site to allow biochemistry and renal biomarker samples to be taken in fasted conditions.

NA prescription should follow the standard of care. Compliance will be assessed by the investigator based on participant interview.

During the study, participants will continue the same NA treatment (ETV, tenofovir disoproxil, or TAF) at the same dose 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 2 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. NA combination treatment is not allowed in this study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

If a participant prematurely discontinues treatment with all study intervention (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. NA treatment will be continued until the end of the study.

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 should not be assigned to another participant.

7.1. Discontinuation of Study Intervention

Treatment with JNJ-3989 and/or nivolumab must be discontinued if any of the discontinuation criteria listed in Sections 7.1.1 and 7.1.2 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 and/or nivolumab are discontinued, NA treatment should be continued until study completion.
- If JNJ-3989 is discontinued, further treatment with nivolumab should also be discontinued.
- If nivolumab is discontinued, treatment with JNJ-3989 and NA should be continued as planned unless a treatment discontinuation rule for JNJ-3989 is also met. In that case, JNJ-3989 will also be discontinued, but NA treatment should be continued as planned.

No rechallenge is allowed after discontinuation of study intervention (JNJ-3989 and/or nivolumab).

Note: The grades are based on the DAIDS Toxicity Grading Scale and NCI-CTCAE (see Section 10.8, Appendix 8: DAIDS Table with Modifications).

7.1.1. Discontinuation of JNJ-3989

Treatment with JNJ-3989 must be discontinued if any of the following occurs:

- The participant withdraws consent to receive study intervention.
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue JNJ-3989.
- The participant becomes pregnant.
- The participant has ≥Grade 3 rash (see Section 10.6, Appendix 6: Rash Management).
- The participant has ≥Grade 3 allergic reaction or worsening of Grade 2 allergic reaction (see Section 8.3.6.4.1, 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. Alternative treatment options (outside the study) should be considered in consultation with the sponsor.
- The participant has treatment-emergent ALT/AST elevations, as described in Section 8.3.6.1, Intervention-emergent ALT/AST Elevations including immune-related hepatic AEs.
- The participant has a confirmed ≥Grade 3 eGFR abnormality and a drop from baseline of >10 mL/min/1.73 m^2, based on creatinine (calculated by the CKD-EPI formula), that persists despite changing tenofovir disoproxil to ETV or TAF (if the participant was receiving tenofovir disoproxil) and that is considered at least possibly related to JNJ-3989.
- The participant has a QTcF prolongation (defined as a QTcF value of >500 ms, or an increase from baseline of >60 ms) at any given time point.
- The participant requires ≥7 days of treatment with any of the disallowed medications listed in Section 6.5, Concomitant Therapy, and does not intend to discontinue treatment with the disallowed medication.
- The participant has confirmed HBV virologic breakthrough (ie, confirmed on-treatment HBV DNA increase by >1 $\log_{10}$ IU/mL from nadir or confirmed on-treatment HBV DNA level >200 IU/mL in participants who had HBV DNA level <LLOQ of the HBV DNA assay). If virologic breakthrough occurs during nivolumab administration, this does not automatically lead to stop of JNJ-3989 and/or nivolumab, but should be assessed/discussed with the sponsor.

  In case of virologic breakthrough, a viral sequencing sample may be collected at the next visit.

7.1.2. Discontinuation of Nivolumab

Treatment with nivolumab should be discontinued if any of the following occurs:

- Participant meets any of the JNJ-3989 discontinuation criteria listed in Section 7.1.1.
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue nivolumab.

- Participant experiences an irAE that requires systemic treatment with corticosteroids (refer to Section 8.3.6.2, Infusion-related Reactions and Other Immune-related AEs) or has treatment-emergent ALT/AST elevations, as described in Section 8.3.6.1, Intervention-emergent ALT/AST Elevations including immune-related hepatic AEs.
- Participant experiences Grade 3 or 4 irAE.
- Participant experiences Grade 3 or 4 IRR.

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

Withdrawal From the Study

A participant who withdraws from the ISA/Platform study will have the following options regarding the optional research samples (ie, pharmacogenomic and FNA samples):

- The collected samples will be retained and used in accordance with the participant's original informed consent for optional research samples.
- The participant may withdraw consent for optional research samples, in which case the samples will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

Withdrawal From the Optional Research Samples While Remaining in the ISA/Platform Study

The participant may withdraw consent for optional research samples (ie, pharmacogenomic and/or FNA samples) while remaining in the study. In such a case, the participant will have to indicate:

- Whether he/she withdraws from further collection only, and he/she agrees the previously collected samples will be retained and used in accordance with the participant's original informed consent for optional research samples.

- Or if he/she also requires that previously collected samples are destroyed and no further testing is done. The sample destruction process will proceed as described above.

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for future research (refer to the paragraphs on long-term retention of samples for additional future research in Attachment 3 of the Master protocol). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for future research are presented in the main ICF, and in the separate ICF for optional research samples.

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 Schedule of Activities summarizes the frequency and timing of efficacy, safety, PK, PD, pharmacogenomic, biomarker, medical resource utilization, and immune assessments applicable to this study.

The total blood volume to be collected from each participant during planned assessments for the entire study will be up to approximately 875 mL. In addition, PBMC samples (at selected sites only; approximately 250 mL) and optional pharmacogenomic samples (approximately 15 mL) may be collected.

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, and TAF, and nivolumab.
- Contact information page(s).

8.1. Efficacy Assessments

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

Qualitative and quantitative HBsAg and HBeAg, and quantitative HBcrAg as well as anti-hepatitis B surface (HBs) and anti-hepatitis B e (HBe) antibodies will be determined using validated serologic assays in a central laboratory. Samples for the determination of HBsAg, HBeAg, anti-HBs antibodies, and anti-HBe antibodies 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 is discontinued in participants with confirmed virologic breakthrough (see Section 7.1, Discontinuation of Study Intervention).

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 may be performed to monitor HBV variants using any of the virology/serology samples collected 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.

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

The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities.

8.2.1. Physical Examinations

Refer to Section 8.2.1 of the Master Protocol PLATFORMPAHPB2001.

In addition, physical examination will include neck and thyroid gland check.

8.2.2. Vital Signs

Refer to Section 8.2.2 of the Master Protocol PLATFORMPAHPB2001.

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

8.2.3. Electrocardiograms

Refer to Section 8.2.3 of the Master Protocol PLATFORMPAHPB2001.

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

8.2.4. Clinical Safety Laboratory Assessments

Refer to Section 8.2.4 of the Master Protocol PLATFORMPAHPB2001.

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

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. Pregnancy tests for at-home use may be provided to the participants from FU Week 24 onwards to allow 4-weekly urine pregnancy testing in between scheduled site visits. If positive, the participant should contact the site immediately.

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.

Further details on AEs, SAEs, and Product Quality Complaints (PQCs) can be found in Attachment 4 of the Master Protocol PLATFORMPAHPB2001.

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

- AE reporting an ALT flare in relation to laboratory test elevation will be coded to the MedDRA preferred term alanine aminotransferase increased.
- AE reporting a reactivation of hepatitis B in patients who are HBV DNA suppressed and have, when a patient is off NA treatment[a], a sudden HBV DNA increase (virologic flare) will be coded to MedDRA preferred term hepatitis B reactivation.
- AE reporting a viral breakthrough in the context of laboratory data will be coded to the MedDRA preferred term viral load increased.

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

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

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

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. Differences with the Master Protocol PLATFORMPAHPB2001 are highlighted (colored fill).

[a] Note that in the current study, participants will continue their NA background regimen during the study intervention and the follow-up periods.

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

8.3.6. Guidelines for Management of Adverse Events of Special Interest Including Immune-Related Adverse Events

Adverse events of interest are significant AEs that are judged to be of special interest because of clinical importance, known class effects or based on nonclinical signals. Immune-related AEs of interest that will be carefully monitored during the study include ALT/AST elevations including immune-related hepatic AEs, IRRs and other irAEs (including gastrointestinal AEs, neurological AEs, pulmonary AEs, renal AEs, endocrinopathies, rash, uveitis and visual complaints, lipase/amylase elevations, and infection). Other AEs of Special Interest related to JNJ-3989 that will be carefully monitored during the study include hematological abnormalities and ISRs.

AEs of Special Interest should be identified and reported to the sponsor's Medical Monitor and reported as an SAE if SAE criteria are met.

8.3.6.1. Intervention-emergent ALT/AST Elevations Including Immune-related Hepatic AEs

Elevated liver enzyme activity can be triggered by the underlying HBV disease as well as potentially by the study intervention. Management of intervention-emergent ALT/AST elevations is described below.

Hepatic AEs, including elevated liver function tests and, infrequently, drug-induced-liver-injuries (DILI) have been observed following treatment with anti-PD-1 therapies. Early recognition and treatment of elevated liver function tests and DILI are critical to their management. Participants should be advised to seek medical evaluation if they notice jaundice (yellow appearance of skin or sclera) or if they develop bruising, bleeding, or right-sided abdominal pain. Investigators should monitor liver function tests (included in chemistry laboratory test) during the study.

Any treatment-emergent elevation of ALT and/or AST ≥3x ULN and ≥3x nadir (ie, lowest value during study participation) should trigger an assessment of confounding factors (alcohol intake, change in concomitant medication, and comorbidities), and should trigger a confirmatory study visit to repeat laboratory testing of ALT, AST, ALP, bilirubin (total and direct), INR, albumin, HBV DNA. After nivolumab initiation, antinuclear antibodies, anti-smooth muscle antibodies, anti-neutrophil cytoplasmic antibodies, and gamma globulin should be added as part of the confirmatory laboratory testing to assess potential immune-related hepatic AEs. Additional tests should be considered based on clinical judgement: Hepatitis A, Delta, C, E: IgM anti-HAV; delta IgM, IgG and polymerase chain reaction (PCR), HCV RNA, IgM and IgG anti-HEV, HEV RNA; CMV, herpes simplex virus (HSV), Epstein-Barr virus (EBV) infection; IgM and IgG anti-CMV, IgM and IgG anti-HSV; IgM and IgG anti-EBV, PCR; HIV; Ig electrophoresis. The confirmatory visit should be scheduled as soon as possible within 7 days of the receipt of the initial ALT/AST results. Additional PBMC and AFP samples may be taken in case of ALT flares, upon discussion with the sponsor, which may require an unscheduled visit.

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.

JNJ-3989 (and nivolumab if already started) should be discontinued in case of:

- confirmed ALT elevation >1,000 U/L, OR
- ALT and/or AST ≥3x ULN and ≥3x nadir 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.

NA treatment should be continued. The participant should be monitored (laboratory testing of ALT, AST, ALP, bilirubin [total and direct], INR, albumin, and HBV DNA) on a weekly basis or more frequently, or as per clinical judgement until ALT and AST levels have returned to 50% of the maximal value and, if present, liver-related symptoms have improved.

In case of ALT elevation ≥3x ULN during the first 4 weeks, administration of JNJ-3989 should be discussed with the sponsor.

Prior to starting nivolumab treatment, the participant's most recent ALT value (tested by local or central lab) should be <3x ULN with no change in autoimmune status. In case the administration of nivolumab would not be in the interest of the participant, this should be discussed with the sponsor.

In case of suspicion of immune-related hepatic events, please refer to Table 5 for more frequent visit monitoring and nivolumab discontinuation criteria. JNJ-3989 might be continued after nivolumab discontinuation following discussion with the sponsor. NA treatment should be continued.

Table 5: Management of Immune-Related Hepatic Adverse Events

Grade	Recommended Actions
Grade 1 AST and/or ALT (<3xULN)	Monitor liver function tests (included in chemistry laboratory test) as outlined in the Schedule of Activities;
• **Grade 2 AST and/or ALT (≥3xULN to <5xULN), or** • **Grade 2 ALP (≥2.5xULN to <5xULN),** **with total bilirubin <2.5 mg/dL and INR<1.5**	Monitor within 7 days and on a weekly basis until return to 50% of the maximal value;

Grade	Recommended Actions
• **Grade 3-4 ALT and/or AST (≥5xULN) or** • **Grade 3-4 ALP (≥5xULN) or** • **total bilirubin ≥2.5mg/dL or** • **INR≥1.5**	Monitor every 2-3 days; **In case:** • Liver tests (ALT, AST or ALP) worsen within 7 days +/- histological confirmation of immune-mediated hepatitis or • Total bilirubin ≥2.5 mg/dL or • INR ≥1.5 **Immediately** • Start steroids 0.5 mg/kg/d (or 1 mg/kg/d if severe) • **Discontinue nivolumab** **No improvement:** Increase steroids to 1 or 2 mg/kg/d depending on previous dose If no improvement within 7 days at 2 mg/kg/d, add 1 steroid pulse of 500 mg **(repeat 3 times according to liver test evolution)** **Improvement LFT return to ≤Grade 1:** taper steroids over 6-8 weeks to 10-12 weeks depending on the dose given. **No improvement: consider** adding mycophenolate mofetil 1 g bid; if no response within 5 days consider other immunosuppressants per local guidelines

8.3.6.2. Infusion-related Reactions and Other Immune-related Adverse Events

Therapy with immunomodulator agents such as nivolumab can lead to specific irAEs that differ in nature, severity and duration as compared to AEs caused by agents with a different mode of action. Early recognition and management of these irAEs may mitigate more severe/subsequent toxicity. However, differential diagnoses including non-inflammatory etiologies and/or concomitant medication should be evaluated according to standard medical practice.

Management algorithms have been developed to assist investigators in assessing and managing specific irAEs following administration of nivolumab (NSPC; NUSPI 2016). These guidelines are presented below and should be followed for nivolumab:

1. Participants should be evaluated to identify any alternative etiology.
2. In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered immune-related.
3. Symptomatic and topical therapy should be considered for low-grade events.
4. Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event.
5. More potent immunosuppressives should be considered for events not responding to systemic corticosteroids (eg, anti-tumor necrosis factor [TNF] agents or mycophenolate).

Refer to Section 7.1 Discontinuation of study intervention for stopping rules.

8.3.6.2.1. Gastrointestinal Adverse Events

Diarrhea and colitis have been observed in participants receiving anti-PD-1 therapies. Early recognition and treatment of diarrhea and colitis are critical to their management. Participants should be advised to seek immediate medical evaluation if they develop new-onset diarrhea, blood in stool, or severe abdominal pain or if they have worsening of baseline diarrhea. In case of

treatment-emergent colitis ≥Grade 2, medical assessment should include testing for cytomegalovirus (CMV). In participants with pre-existing diverticulosis and/or diverticulitis receiving concomitant medication with corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioid analgesics together with anti-PD-1 therapies, diverticular perforation has been observed. Refer to Table 6 for the management of immune-related gastrointestinal AEs.

Table 6: Management of Immune-Related Gastrointestinal Adverse Events

Grade	Recommended Actions
Grade 1	Symptomatic treatment according to institutional standards Close monitoring; instruct participant to report worsening immediately and treat as Grade ≥2
Grade 2	**≤5 days:** Symptomatic treatment according to institutional standards **>5 days or recurrence:** 0.5–1.0 mg/kg/d methylprednisolone; consider prophylactic antibiotics; discontinue nivolumab **Persistence or worsening despite steroids >3 days:** treat as Grade 3/4 **Improvement to ≤Grade 1:** taper steroids over at least 4 weeks, consider prophylactic antibiotics for opportunistic infections, resume study therapy per protocol
Grade 3-4	**Immediately:** 1.0–2.0 mg/kg/d methylprednisolone IV; consider prophylactic antibiotics and lower endoscopy (ie, proctoscopy, sigmoidoscopy or full colonoscopy depending on the participant's symptoms; discontinue nivolumab Note that known or suspected bowel perforation is a contraindication to endoscopy. **Persistence >3 days or recurrence:** add infliximab 5 mg/kg (if no contraindication such as perforation or sepsis) **Improvement to ≤Grade 2 within ≤3 days:** taper steroids over at least 4 weeks
General	The oral corticosteroid equivalent of the recommended IV dose may be considered for ambulatory patients; the lower bioavailability of oral corticosteroids needs to be considered. Clinical caution should be exercised, for participants receiving concomitant medications of corticosteroids, NSAID, or opioid analgesics. In addition, monitor for signs and symptoms of potential perforation, especially in participants with known diverticular disease. Narcotics should be used with caution as pain medicines may mask the signs of colonic perforation

8.3.6.2.2. Neurological Adverse Events

Neurological AEs have been uncommonly observed following treatment with anti-PD-1 therapies. Neurological AEs can manifest as central abnormalities (eg, aseptic meningitis or encephalitis) or peripheral sensory/motor neuropathies (eg, Guillain-Barre Syndrome). The onset has been observed as early as after a single treatment. Early recognition and treatment of neurologic AEs is critical to their management (refer to Table 7). Participants should be advised to seek medical evaluation if they notice impairment in motor function (eg, weakness), changes in sensation (eg, numbness), or symptoms suggestive of possible central nervous system abnormalities such as new headache or mental status changes.

Table 7: Management of Neurological Adverse Events

Grade	Recommended Actions
Grade 1	Monitor per protocol **Worsening:** treat as ≥Grade 2
Grade 2	**Immediately:** treat symptoms according to institutional standards; consider 0.5-1.0 mg/kg/d methylprednisolone IV or oral equivalent; discontinue nivolumab **Worsening:** treat as Grade 3-4
Grade 3-4	**Immediately:** consult neurologist; treat symptoms according to institutional standards; start 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; prophylactic antibiotics; discontinue nivolumab

Grade	Recommended Actions
	Worsening or atypical presentation: consider immunoglobulins IV (IVIG) or other immunosuppressive therapies according to institutional standards **Improvement to ≤Grade 2:** taper steroids over at least 4 weeks
General	Participants on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids needs to be considered

8.3.6.2.3. Pulmonary Adverse Events

Pulmonary AEs including radiographic changes (eg, focal ground glass opacities and patchy infiltrates) indicative of drug-related pneumonitis have been observed in participants receiving anti-PD-1 therapies. These pulmonary AEs were either asymptomatic or associated with symptoms such as dyspnea, cough, or fever. The initial occurrence of pulmonary AEs may be as early as after a single dose of anti-PD-1 therapies or delayed after prolonged therapy. Early recognition and treatment of pneumonitis is critical to its management (refer to Table 8). Participants should be advised to seek medical evaluation promptly if they develop new-onset dyspnea, cough, or fever or if they have worsening of these baseline symptoms.

Table 8: Management of Pulmonary Adverse Events

Grade	Recommended Actions
Grade 1	Monitor for symptoms every 2-3 days; consider pulmonary and infectious-disease consult; re-image every 3 weeks **Worsening:** treat as ≥Grade 2
Grade 2	Monitor symptoms daily; re-image every 1-3 days; pulmonary and infectious-disease consultation; consider bronchoscopy and lung biopsy; consider hospitalization **Immediately:** start 1.0 mg/kg/d methylprednisolone IV or oral equivalent; prophylactic antibiotics; discontinue nivolumab **Persistence for 2 weeks or worsening:** treat as Grade 3-4 **Improvement to ≤ Grade 1 or baseline:** taper steroids over at least 4 weeks
Grade 3-4	Hospitalize; pulmonary and infectious-disease consult; consider bronchoscopy and lung biopsy **Immediately:** 2-4 mg/kg/d methylprednisolone or IV equivalent; add prophylactic antibiotics; discontinue nivolumab **Persistence for 2 days or worsening:** add immunosuppression (eg, infliximab, cyclophosphamide, IVIG, or mycophenolate mofetil) **Improvement to ≤ Grade 2:** taper steroids over at least 6 weeks
General	Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids needs to be considered

8.3.6.2.4. Renal Adverse Events

Elevated creatinine and biopsy-confirmed tubulointerstitial nephritis and allergic nephritis have been infrequently observed following treatment with anti-PD-1 therapies. Investigators should monitor creatinine regularly.

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.

In case of suspicion of immune-related renal events, please refer to Table 9 for guidance.

Table 9: Management of Renal Adverse Events

Grade	Recommended Actions
Grade 1	Monitor creatinine weekly **Creatinine returns to baseline:** continue monitoring per protocol **Creatinine increases:** treat as Grade ≥2
Grade 2-3	Monitor creatinine every ≤3 days **Immediately:** start 0.5-1.0 mg/kg/d methylprednisolone IV or oral equivalent; consider prophylactic antibiotics; consider renal biopsy; discontinue nivolumab **Improvement to ≤Grade 1:** taper steroids over at least 4 weeks **Persistence >7 days or worsening:** treat as Grade 4
Grade 4	Monitor creatinine daily **Immediately:** consult nephrologist; consider renal biopsy; start 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; add prophylactic antibiotics; discontinue nivolumab **Improvement to ≤Grade 1:** taper steroids over at least 4 weeks
General	Participants on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids needs to be considered.

8.3.6.2.5. Endocrinopathies

Endocrinopathies have been observed following treatment with anti-PD-1 therapies. The events have typically been identified through either routine periodic monitoring of specific laboratory tests (eg, TSH) or as part of a work-up for associated symptoms (eg, fatigue). Events may occur within weeks of beginning treatment, but also have been noted to occur after many months (while still on treatment). More than 1 endocrine organ may be involved (eg, hypophysitis [pituitary inflammation] may need to be evaluated at the time adrenal insufficiency or thyroid disorder is suspected). Participants should be advised to seek medical evaluation if they notice new-onset fatigue, lightheadedness, or difficulty with vision or if baseline fatigue worsens. Refer to Table 10 for the management of immune-related endocrinopathies.

Table 10: Management of Immune-Related Endocrinopathies

Grade	Recommended Actions
Asymptomatic TSH elevation	**TSH <0.5xLLN** or **TSH >2xULN** or **TSH >ULN in 2 subsequent measurements:** include free T4 assessment prior/after subsequent cycles of study treatment; consider endocrinology consultation
Symptomatic endocrinopathy	Assess endocrine function with appropriate laboratory testing; consider pituitary MRI scan **With abnormal lab and pituitary scan:** 1.0–2.0 mg/kg/d methylprednisolone IV or oral equivalent; initiate appropriate hormone therapy; consider prophylactic antibiotics; discontinue nivolumab • In hyperthyroidism, non-selective beta-blockers (eg, propranolol) are suggested as initial therapy. • In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care. **Clinical and laboratory improvement:** taper steroids over at least 4 weeks; patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component **Without abnormal lab and pituitary scan but symptoms persist:** repeat laboratory assessments in ≤3 weeks and MRI in 4 weeks

Grade	Recommended Actions
Suspicion of adrenal crisis (eg, severe dehydration, hypotension, shock out of proportion to current illness)	Rule out sepsis **Immediately:** initiate/stress dose of IV corticosteroids; fluids IV; consult endocrinologist; discontinue nivolumab **Adrenal crisis ruled out:** treat as symptomatic endocrinopathy
Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)	For T1DM or Grade 3-4 Hyperglycemia: Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria. Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
General	Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. The lower bioavailability of oral corticosteroids needs to be considered.

8.3.6.2.6. Rash

Nivolumab can cause immune-mediated rash or dermatitis, defined as requiring the use of steroids and no clear alternate etiology. Exfoliative dermatitis, including Stevens-Johnson Syndrome, toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/L-1 blocking antibodies.

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 and management of rash events will be performed as described in Table 14 in Section 10.6, Appendix 6: Rash Management.

Digital pictures may be taken when considered appropriate at the discretion of the investigator and in accordance with local regulations; it is recommended to collect images in case of Grade 3 and 4 rash or other skin reactions. Digital pictures will only be taken and collected from participants who consent separately to this component of the study. If digital pictures are taken, they should be anonymized and provided to the sponsor.

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

The participant may be treated symptomatically until the rash resolves. Oral antihistamines (eg, cetirizine, levocetirizine) and/or topical corticosteroids may provide symptomatic relief, but effectiveness of these measures has not been established. JNJ-3989 and nivolumab should be discontinued in case of ≥Grade 3 rash. If systemic corticosteroids are required for treatment of rash, nivolumab must be permanently discontinued. If systemic corticosteroids exceeding 5 mg of prednisolone equivalent/day for ≥7 days are required for treatment of rash (and the participant does not intend to stop corticosteroids), JNJ-3989 needs to be permanently discontinued. NAs can be continued. If the rash is considered to be most likely due to concomitant illness or non-study interventions, standard management, including discontinuation of the likely causative agent, should be undertaken.

8.3.6.2.7. Uveitis and Visual Complaints

Immune therapies have been uncommonly associated with visual complaints. Inflammation of components within the eye (eg, uveitis) is an uncommon, but clinically important, event. An ophthalmologist should evaluate visual complaints with examination of the conjunctiva, anterior and posterior chambers, and retina. Complaints of double vision should also prompt medical evaluation. In addition to ocular inflammatory events, a work-up should also consider pituitary inflammation as a cause. Refer to Table 11 for the management of uveitis and visual complaints.

If systemic corticosteroids are required for treatment of rash uveitis and visual complaints, nivolumab need to be permanently discontinued.

Table 11: Management of Uveitis and Visual Complaints

Grade	Recommended Actions
Grade 1-2	Thorough eye examination Topical corticosteroids should be considered Persisting despite topical steroids, treat as Grade 3-4
Grade 3-4	Thorough eye examination Systemic corticosteroids Discontinue nivolumab

8.3.6.2.8. Lipase/Amylase Elevations

Asymptomatic elevations in lipase and amylase have been reported in anti-PD-1 therapy studies in which systemic monitoring was used. Very few participants reported associated symptoms (eg, abdominal pain) or radiographic findings (eg, stranding) consistent with pancreatitis. Thus, there does not seem to be clinical significance to the elevated laboratory values. The recommended management of anti-PD-1 therapy-related elevated lipase/amylase values centers around close observation. Investigators should ensure that participants have no associated symptoms consistent with pancreatitis, such as abdominal pain. Serum lipase levels are evaluated at the timepoints listed in the Schedule of Activities. If pancreatitis is suspected based on serum lipase level, amylase should be checked. Corticosteroids do not seem to alter the natural history of lipase/amylase elevations. Laboratory values tend to fluctuate on a day-to-day basis and eventually return to baseline or low-grade levels over the course of weeks, whether or not participants receive corticosteroids. Asymptomatic elevations should be monitored approximately weekly.

8.3.6.2.9. Infusion-related Reactions

Hypersensitivity reactions can occur with nivolumab treatment. Since nivolumab contains only human immunoglobulin protein sequences, it is less likely to induce a hypersensitivity reaction. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. Management of IRRs is provided in Table 12. Investigators should follow their institutional treatment guidelines if acute allergic reaction or anaphylaxis occurs. For management of acute systemic allergic reactions during JNJ-3989 administration, refer to Table 13.

All Grade 3 or 4 IRRs (refer to Appendix 8: DAIDS Table with Modifications) should be reported within 24 hours to the sponsor's Medical Monitor and reported as an SAE if criteria are met.

Table 12: Management of Infusion-related Reactions

Grade	Recommended Actions
Grade 1	No intervention indicated; remain at bedside and monitor participant until recovery from symptoms. Consider diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes.
Grade 2	**Stop infusion**; start IV saline infusion; give diphenhydramine 50 mg (or equivalent) IV and/or paracetamol 325 to 1000 mg (acetaminophen); consider corticosteroids and bronchodilator therapy; remain at bedside and monitor participant until recovery from symptoms. If systemic corticosteroids are used for treatment of Grade 2 IRRs, nivolumab needs to be permanently discontinued. **Restart infusion at 50% of initial rate (only if no systemic corticosteroids were administered):** if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate; monitor participant closely. **Symptoms recur:** stop and discontinue further treatment at that visit; administer diphenhydramine 50 mg IV, and remain at bedside and monitor the participant until resolution of symptoms. The amount of study drug infused must be recorded in the CRF.
Grade 3-4	**Stop infusion**; start IV saline infusion; recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

8.3.6.2.10. Infections

Participants with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

8.3.6.3. Other Adverse Events of Special Interest Related to JNJ-3989

8.3.6.3.1. Hematologic Abnormalities

Hematological abnormalities including Grade 3 and Grade 4 neutropenia, thrombocytopenia, anemia, and autoimmune hemolytic anemia were reported with nivolumab used in the oncology setting.

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 SC injections of JNJ-3989 alone over a period of up to 12 weeks with background of NAs. The transient thrombocytopenia was not considered clinically significant. No thrombocytopenia or pancytopenia was observed in 12 participants when JNJ-3989 was given in combination with JNJ-6379 over a 12-week period in the same study.

Based on the nonclinical 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 2 consecutive visits.

In case of confirmed Grade 3 or Grade 4 hematologic abnormalities (platelet count, hemoglobin, and neutrophil count), discontinuation of JNJ-3989 (and nivolumab if applicable) should be considered. In case of discontinuation, NA treatment should be continued.

8.3.6.3.2. Injection Site Reactions

At the time points specified in the Schedule of Activities or at an unscheduled visit if needed, an evaluation of the injection site will be performed based on participant's description and/or physical examination. Evaluations will be recorded in the source documents and will include at a minimum the time of occurrence, time of resolution and a description of the abnormality including its maximal diameter.

For each ISR, information on pain, erythema, induration and pruritus should be obtained as specified in Section 10.8, Appendix 8: DAIDS Table with Modifications.

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 made anonymous and provided to the sponsor.

8.3.6.4. Other Adverse Events

8.3.6.4.1. Acute Systemic Allergic Reactions

Table 13: Management of Acute Systemic Allergic Reactions

Grade	Recommended Actions
Grade 1 (Localized Urticaria [Wheals] With no Medical Intervention Indicated)	Participants may continue study intervention. 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 study intervention. 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 JNJ-3989 (and nivolumab if applicable). Rechallenge is not allowed.
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 JNJ-3989 (and nivolumab if applicable). Rechallenge is not allowed. 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, NA, and nivolumab. Serum collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

8.4.1. Evaluations

All participants will have sparse PK sampling during the study intervention period.

Blood samples will be collected for measurement of plasma concentrations of JNJ-3989 and NA, and serum concentrations of nivolumab at time points specified in the Schedule of Activities in Section 1.3.1. Bioanalysis of NA and nivolumab 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 and optionally NA and/or nivolumab 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 and optionally NA and/or nivolumab will be derived using population PK modeling. Baseline covariates (eg, body weight, age, sex, creatinine clearance [CrCL], race) may be included in the model, if relevant.

Pharmacokinetic/Pharmacodynamic Evaluations

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

8.5. Pharmacodynamics

Whole blood samples will be collected for assessment of nivolumab RO on circulating T-cells by flow cytometry analysis.

Pharmacodynamic biomarkers will be evaluated in all participants pretreatment, on-treatment, and posttreatment with study intervention as shown in Schedule of Activities in Section 1.3.1 and Section 1.3.2.

Refer to laboratory manuals for sample collection requirements.

8.6. 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 in participants who consent. These samples could for example be used to assess changes in frequencies of immune cells.

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.

8.7. 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.

A FNA biopsy sample may be collected from participants who consent separately to this component of the study (as permitted by local regulations). If participants agree to undergo an optional FNA biopsy of the liver, following local standard practice, the biopsy location will be identified and/or guided with ultrasound and the FNA biopsy samples will be collected after application of local anesthesia to allow for exploratory biomarker research.

The FNA biopsy procedure should be preceded and followed by standard medical monitoring according to local medical practice. This may include an overnight stay at the investigator's discretion. Prior to each to FNA biopsy, a recent (≤2 weeks) coagulation and hematology panel are required to ensure normal platelet count and normal coagulation parameters. The use of local laboratories may be allowed at the investigator's discretion. Optional FNA biopsy will only be completed at selected sites that have expertise and capacity to perform FNA biopsy. Intrahepatic immune response to treatment will be assessed in FNA biopsy samples.

Infiltrating immune cells will be used for the evaluation of immune responses, which can be compared to responses in PBMCs.

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.

8.8. 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 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. Leftover PBMC samples may be used at the sponsor's discretion for additional exploratory research 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/or nivolumab. Antidrug antibodies may be analyzed using assays such as an enzyme-linked immunosorbent assay or functional assays.

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

8.9. Medical Resource Utilization and Health Economics

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+nivolumab+NA is more efficacious than JNJ-3989+NA treatment, as measured by the primary efficacy endpoint (ie, the proportion of participants with HBsAg seroclearance at FU Week 24). Because the study does not include a regimen arm without nivolumab, the hypothesis is formulated assuming a fixed response rate for JNJ-3989+NA of 1% based on previous Study 73763989HPB2001 (REEF-1).

9.2. Sample Size Determination

According to the initial protocol, the study aimed to have a sample size of 20 participants per intervention arm which yielded ≥85% statistical power to detect a ≥15% and ≥20% difference for the proportions of participants with HBsAg seroclearance at FU Week 24 in the 2 intervention arms, respectively, vs a fixed proportion of ≤1%. Statistical power to test the primary hypothesis was assessed for each of the intervention arms, 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 fixed rate assumed for the external active control (JNJ-3989 [200 mg]+NA treatment) is based on the data of Study 73763989HPB2001 (REEF-1).

The total study sample size was adjusted to 44 participants (22 per arm), with 1:1 randomization ratio to each of the intervention arms, to account for an approximate 10% attrition rate.

Due to the decision to not extend further enrollment beyond the planned enrollment period and proceed with a reduced sample size, the final sample size is 37 (18 in Arm 1 and 19 in Arm 2). Under the same assumptions and methods of the initial protocol, an approximate sample size of 16 participants per intervention arm (assuming 10% attrition) yields ≥75% statistical power to detect the same differences in HBsAg seroclearance at FU Week 24.

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

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.
Full Analysis Set for nivolumab (FAS-N)	All participants who were randomly assigned to an intervention arm in this ISA and received at least 1 dose of nivolumab 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 SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

Refer to Section 9.4.1 of the Master Protocol PLATFORMPAHPB2001.

9.4.2. Efficacy Analyses

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

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

All efficacy summaries will be presented with descriptive statistics and 90% CIs 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 factor (ie, absolute HBsAg value at baseline [<100 IU/mL, 100 to <1,000 IU/mL, and ≥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 Endpoints

The proportion of participants who achieved HBsAg seroclearance at FU Week 24 will be summarized for each intervention arm paired together with a two-sided, single arm 90% 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 1% 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 may be explored using logistic regression analyses and classification and regression tree analysis (CART).

The Mantel-Haenszel test adjusted for the randomization stratification factors will be used in a secondary analysis comparing the primary endpoint between the 2 study intervention arms at a one-sided alpha level of 0.05.

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 may 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, and waterfall 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 may 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.

More details on this approach and its application to secondary endpoints will be provided, if applicable, in a separate 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 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 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 Analyses

Population PK analysis of concentration-time data of JNJ-3976 and JNJ-3924, and, optionally, of NA and/or nivolumab 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/or nivolumab, with RO, selected efficacy and/or 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.

Pharmacodynamic Analyses

Descriptive statistics by treatment will be used to summarize PD parameters at each applicable time point. Statistics include sample size (n), mean, SD, coefficient of variation (CV), geometric mean, median, minimum, and maximum. Additional PD analyses may be performed, as deemed necessary.

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 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.

Immune Analyses

Descriptive statistics (n, mean, SD, CV, geometric mean, median, minimum, and maximum) may be used to describe the magnitude of the IFN-γ T-cell response or the CD4+ and CD8+ T-cell responses (expressing at least 1 cytokine such as IL-2, TNF-α or IFN-γ specific to any HBV antigen) as defined by ELISpot and/or ICS, respectively. Changes from baseline (or positivity threshold) 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 over time.

9.5. Interim Analysis

Interim analyses (IAs) 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.

Optional IAs are planned when:

- All randomized participants have completed Week 24 or discontinued earlier.
- All randomized participants have completed FU Week 12 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 cut-offs 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 the 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

Differences with the Master Protocol PLATFORMPAHPB2001 are highlighted (colored fill).

10.1. Appendix 1: Abbreviations and Definitions

AE	adverse event
AFP	alpha-fetoprotein
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMA	anti-mitochondrial antibodies
ANA	anti-nuclear antibodies
ANC	absolute neutrophil count
ANCA	anti-neutrophil cytoplasmic antibody
ASMA	anti-smooth muscle antibodies
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BMI	body mass index
cccDNA	covalently closed circular deoxyribonucleic acid
CFB	change from baseline
CHB	chronic hepatitis B
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum plasma concentration
CMV	cytomegalovirus
CRF	case report form
CRP	C-reactive protein
CV	coefficient of variation
DAIDS	Division of Acquired Immunodeficiency Syndrome
DILI	drug induced liver-injuries
DNA	deoxyribonucleic acid
DRC	Data Review Committee
DRESS	drug rash with eosinophilia and systemic symptoms
ECG	electrocardiogram
EFD	embryofetal development
eGFR	estimated glomerular filtration rate
eGFRcr	estimated glomerular filtration rate based on serum creatinine
eGFRcys	estimated glomerular filtration rate based on cystatin C
ELISpot	enzyme-linked immunospot
EOSI	end of study intervention
ETV	entecavir
FAS	full analysis set
FCA	foci of cellular alteration
FNA	fine needle aspiration
FOIA	Freedom of Information Act
FSH	follicle-stimulating hormone
FU	follow-up
GLP	Good Laboratory Practice
HBc	hepatitis B core protein
HBcrAg	hepatitis B core-related antigen
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBs	hepatitis B surface 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
HRT	hormonal replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICI	immune checkpoint inhibitors
ICS	intracellular cytokine staining
IFLEP	Independent Flare Expert Panel
IFN(-α/γ)	interferon (alpha/gamma)
IgG	immunoglobulin G
IgM	immunoglobulin M
IL	interleukin
IMP	investigational medicinal product
INR	International Normalized Ratio
irAE	immune-related AE
IRM	indirect response model
IRR	Infusion-related reaction
ISR	injection site reaction
LLN	lower limit of normal
LLOQ	lower limit of quantification
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NA	nucleos(t)ide analog
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHP	non-human primate
NIMP	non-investigational medicinal product
NOAEL	no observed adverse effect level
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PD-1	programmed cell death protein receptor-1
pgRNA	pre-genomic ribonucleic acid
PK	pharmacokinetic(s)
PoC	proof of concept
Q1W	every week
Q4W	every 4 weeks
QD	once daily
QTcF	QT interval corrected for heart rate according to Fridericia's formula
QW	weekly
RBC	red blood cell
rcDNA	relaxed circular deoxyribonucleic acid
RNAi	ribonucleic acid interference
RO	receptor occupancy
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCN	single-cell necrosis
SD	standard deviation
SE	standard error
siRNA	small interfering ribonucleic acid
T3	triiodothyronine
T4	thyroxine
TAF	tenofovir alafenamide
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
t_{max}	time to reach C_{max}
TMDD	transporter-mediated drug disposition

TNF	tumor necrosis factor
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
USM	urgent safety measure
WBC	white blood cell
WD	withdrawal
YU	yeast units

Definitions of Terms

ALT/AST nadir	Lowest ALT/AST value during study participation
End of study intervention	Time of the last administration of study intervention
Functional cure	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) and nivolumab
Background treatment	NA (either ETV, tenofovir disoproxil, or TAF)
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).

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

Protocol-Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="3">Parameters</th></tr>
<tr><td rowspan="2">Hematology</td><td>Platelet count
Red blood cell count
Hemoglobin
Hematocrit</td><td><u>RBC Indices:</u>
MCV
MCH
% Reticulocytes</td><td><u>White Blood Cell (WBC) count with Differential:</u>
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td colspan="3">Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. A RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.</td></tr>
<tr><td>Clinical Chemistry</td><td colspan="2">Sodium
Potassium
Chloride
Bicarbonate
Blood urea nitrogen (BUN)
Creatinine
Glucose
Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic
Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic
Gamma-glutamyltransferase (GGT)
Fibrinogen (on blood)
eGFR calculation based on creatinine (by CKD-EPI formula, eGFRcr)
eGFR calculation based on cystatin C (by CKD-EPI formula, eGFRcys)</td><td>Total, direct, indirect bilirubin
Alkaline phosphatase (ALP)
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, Appendix10.5). • 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, autoantibodies (anti-nuclear antibodies [ANA], anti-smooth muscle antibodies [ASMA], anti-mitochondrial antibodies [AMA], anti-Neutrophil Cytoplasmic antibodies [ANCA], anti-thyroid peroxidase antibodies and rheumatoid factor) will be measured. • At screening and time points as indicated in the Schedule of Activities, C-reactive protein (CRP) 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, T3, and T4) will be performed at screening and time points indicated in the Schedule of Activities. • Tests in response to ALT flare (refer to Section 8.3.6.1)	

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.

Each participant must give consent according to local requirements after the nature of the study has been fully explained.

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

10.3.4. Data Protection

Refer to Attachment 3 of the Master Protocol PLATFORMPAHPB2001.

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

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

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

10.3.5. Long-Term Retention of Samples for Additional Future

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.

The first participant screened is considered the first act of recruitment and it becomes the study start date.

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.

A participant pregnancy or participant partner(s) pregnancy is also considered a special reporting situation in this ISA.

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, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

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

Woman Not of Childbearing Potential

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

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

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

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

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

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED 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 must be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT[b] **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 must be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. b. User-dependent, highly effective forms of contraception are not acceptable as the sole method of contraception for female study participants of childbearing potential. They are acceptable as the sole method of contraception only for female partners of male study participants.

10.6. Appendix 6: Rash Management

Table 14: Management of Rash Events by Severity Grade

	Activities by Day[a]	In case of suspicion of immune-related rash events
Grade 1 rash (with or without pruritus)[b]	**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. **Day 1 and thereafter:** Appropriate follow-up visits at the investigator's discretion until resolution of rash. Safety laboratory assessments and digital pictures[c] of skin lesions may be performed at the investigator's discretion. **Study intervention may be continued at the investigator's discretion**	Treat with topical emollients and/or mild-moderate potency topical corticosteroids. Counsel patients to avoid skin irritants and sun exposure
Grade 2 rash (with or without pruritus)[b]	**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). The participant may be referred to a dermatologist at the investigator's discretion[d], who may perform a biopsy. 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. **Day 1 and thereafter:** Appropriate follow-up visits at the investigator's discretion until resolution of rash or until clinical stability is reached. Safety laboratory assessments are required on Day 1 and are required thereafter only if the previous values were abnormal (but may be performed at the investigator's discretion). If the rash progresses to a higher grade, safety laboratory assessments of the higher grade should be followed. Digital pictures[c] of skin lesions may be taken at the investigator's discretion. **Study intervention may be continued at the investigator's discretion**	**Immediately:** Symptomatic therapy (eg, antihistamines, topical steroids) **Persistence ≥2 weeks or recurrence:** consider skin biopsy; consider 0.5-1.0 mg/kg/d methylprednisolone IV or oral equivalent; consider prophylactic antibiotics **Improvement to ≤Grade 1:** taper steroids over at least 4 weeks **Worsening to >Grade 2:** treat as Grade 3-4 In case of treatment with systemic corticosteroids initiated, nivolumab must be discontinued.

Table 14: Management of Rash Events by Severity Grade

	Activities by Day[a]	In case of suspicion of immune-related rash events
Grade 3 rash[b]	**Day 0:** Required on-site visit. Safety laboratory assessments required to be performed. Referral to a dermatologist required[d], who may perform a biopsy. Digital pictures[c] of skin lesions may be taken at the investigator's discretion (recommended). **Day 1 and thereafter:** 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. **Must permanently discontinue study intervention; no rechallenge allowed**	**Immediately:** consult dermatologist; consider skin biopsy; start 0.5-1.0 mg/kg methylprednisolone IV or IV equivalent; add prophylactic antibiotics **Improvement to ≤Grade 1:** taper steroids over at least 4 weeks
Grade 4 rash	Day 0: required on-site visit. Safety laboratory assessments required to be performed. Referral to a dermatologist required[d] and biopsy to be performed as soon as possible after onset of rash. Digital pictures[c] of skin lesions may be taken at the investigator's discretion (recommended). Day 1 and thereafter: 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. **Must permanently discontinue study intervention; no rechallenge allowed**	**Immediately:** referral to a dermatologist required[d]; biopsy to be performed as soon as possible after onset of rash; start 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; add prophylactic antibiotics **Improvement to ≤Grade 1:** taper steroids over at least 4 weeks

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.*
- *The grades are based on the DAIDS Toxicity Grading Scale and NCI-CTCAE (see Section 10.8, Appendix 8: DAIDS Table with Modifications).*

10.7. Appendix 7: Cardiovascular Safety – Abnormalities

ECG

All important abnormalities from the ECG readings will be listed.

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

ECG: electrocardiogram; NAP = not applicable

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

10.8. Appendix 8: DAIDS Table with Modifications (DAIDS [Modified])

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.

DAIDS Table with Modifications

DAIDS table (version 2.1) does not include specific severity grading for irAEs. In order to capture severity grading for irAEs properly, the severity grading for irAEs from the NCI-CTCAE (version 5.0) is adopted for the study (refer to the last table in Appendix 8). The redundant severity grading for rash in DAIDS table (version 2.1) is removed. In addition, the DAIDS severity grading of Grade 1 and 2 for ALT and AST have been adjusted, in view of the CHB population to align with toxicity management guidelines for immune-related hepatic AEs (refer to the Laboratory Values table below).

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

IV: intravenous; NAP: not applicable

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

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

NAP: not applicable

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

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

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

IV: intravenous; NAP: not applicable

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

IV: intravenous; NAP: not applicable

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

BMD: bone mineral density; NAP: not applicable

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

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

CNS: central nervous system; NAP: not applicable

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

NAP: not applicable

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

ID: identity, NAP: not applicable

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

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

NAP: not applicable

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

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

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

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

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

IV: intravenous; NAP: not applicable

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

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

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

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

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

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

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

NAP: not applicable

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

NAP: not applicable

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

LABORATORY VALUES[m]				
CHEMISTRIES				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Acidosis	NAP	pH ≥7.3 to <LLN	pH <7.3 without life-threatening consequences	pH <7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to <LLN *30 to <LLN*	≥2.0 to <3.0 *≥20 to <30*	<2.0 *<20*	NAP
ALP, High	1.25 to <2.5×ULN	2.5 to <5.0×ULN	5.0 to <10.0×ULN	≥10.0×ULN
Alkalosis	NAP	pH >ULN to ≤7.5	pH >7.5 without life-threatening consequences	pH >7.5 with life-threatening consequences
ALT or SGPT, High *Report only 1*	>1.0 to <3.0×ULN	3.0 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*	>1.0 to <3.0×ULN	3.0 to <5.0×ULN	5.0 to <10.0×ULN	≥10.0×ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to <LLN *16.0 to <LLN*	11.0 to <16.0 *11.0 to <16.0*	8.0 to <11.0 *8.0 to <11.0*	<8.0 *<8.0*
Bilirubin ***Direct Bilirubin,[n] High*** *aged >28 days*	NAP	NAP	>ULN with other signs and symptoms of hepatotoxicity	>ULN with life-threatening consequences (eg, signs and symptoms of liver failure)
aged ≤28 days	ULN to ≤1 mg/dL	>1 to ≤1.5 mg/dL	>1.5 to ≤2 mg/dL	>2 mg/dL
Total Bilirubin, High *aged >28 days*	1.1 to <1.6×ULN	1.6 to <2.6×ULN	2.6 to <5.0×ULN	≥5.0×ULN
aged ≤28 days	Refer to Appendix A[o]	Refer to Appendix A[o]	Refer to Appendix A[o]	Refer to Appendix A[o]

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

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

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

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

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

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

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

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

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

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

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

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

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

[s] Revised by the sponsor.

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

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

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

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

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

NAP: not applicable; RBC: red blood cell

CTCAE Severity Grading for irAEs						
CTCAE Term	**CTCAE Definition**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Bullous dermatitis	A disorder characterized by inflammation of the skin characterized by the presence of bullae which are filled with fluid.	Asymptomatic; blisters covering <10% body surface area (BSA)	Blisters covering 10 - 30% BSA; painful blisters; limiting instrumental activities of daily living (ADL)	Blisters covering >30% BSA; limiting self-care ADL	Blisters covering >30% BSA; associated with fluid or electrolyte abnormalities; Intensive Care Unit (ICU) care or burn unit indicated	Death
Colitis	A disorder characterized by inflammation of the colon.	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Dry skin	A disorder characterized by flaky and dull skin; the pores are generally fine, the texture is a papery thin texture.	Covering <10% BSA and no associated erythema or pruritus	Covering 10 - 30% BSA and associated with erythema or pruritus; limiting instrumental ADL	Covering >30% BSA and associated with pruritus; limiting self-care ADL	-	-
Eczema	A disorder characterized by skin which becomes itchy, red, inflamed, crusty, thick, scaly, and/or forms blisters.	Asymptomatic or mild symptoms; additional medical intervention over baseline not indicated	Moderate; topical or oral intervention indicated; additional medical intervention over baseline indicated	Severe or medically significant but not immediately life-threatening; IV intervention indicated	-	-
Erythema multiforme	A disorder characterized by target lesions (a pink-red ring around a pale center).	Target lesions covering <10% BSA and not associated with skin tenderness	Target lesions covering 10 - 30% BSA and associated with skin tenderness	Target lesions covering >30% BSA and associated with oral or genital erosions	Target lesions covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Erythroderma	A disorder characterized by generalized inflammatory erythema and exfoliation. The inflammatory process involves > 90% of the body surface area.	-	Erythema covering >90% BSA without associated symptoms; limiting instrumental ADL	Erythema covering >90% BSA with associated symptoms (eg, pruritus or tenderness); limiting self-care ADL	Erythema covering >90% BSA with associated fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Myocarditis	A disorder characterized by inflammation of the muscle tissue of the heart.	-	Symptoms with moderate activity or exertion	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated; new onset of symptoms	Life-threatening consequences; urgent intervention indicated (eg, continuous IV therapy or mechanical hemodynamic support)	Death
Pneumonitis	A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma.	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated	Death

CTCAE Severity Grading for irAEs						
CTCAE Term	**CTCAE Definition**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
					(eg, tracheotomy or intubation)	
Papulopustular rash	A disorder characterized by an eruption consisting of papules (a small, raised pimple) and pustules (a small pus filled blister), typically appearing in face, scalp, and upper chest and back. Unlike acne, this rash does not present with whiteheads or blackheads, and can be symptomatic, with itchy or tender lesions.	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL; papules and/or pustules covering > 30% BSA with or without mild symptoms	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; IV antibiotics indicated	Life-threatening consequences	Death
Rash acneiform	A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back.	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL; papules and/or pustules covering > 30% BSA with or without mild symptoms	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Life-threatening consequences; papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated	Death
Rash maculo-papular	A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbillform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritis.	Macules/papules covering <10% BSA with or without symptoms (eg, pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental ADL; rash covering > 30% BSA with or without mild symptoms	Macules/papules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL	-	-
Stevens-Johnson syndrome	A disorder characterized by less than 10% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex	-	-	Skin sloughing covering <10% BSA with associated signs (eg, erythema, purpura, epidermal detachment,	Skin sloughing covering 10 - 30% BSA with associated signs (eg, erythema, purpura, epidermal detachment	Death

CTCAE Severity Grading for irAEs						
CTCAE Term	**CTCAE Definition**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
	affecting the skin and the mucous membranes.			and mucous membrane detachment)	and mucous membrane detachment)	
Toxic epidermal necrolysis	A disorder characterized by greater than 30% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.	-	-	-	Skin sloughing covering >=30% BSA with associated symptoms (eg, erythema, purpura, or epidermal detachment)	Death
Urticaria	A disorder characterized by an itchy skin eruption characterized by wheals with pale interiors and well-defined red margins.	Urticarial lesions covering <10% BSA; topical intervention indicated	Urticarial lesions covering 10 - 30% BSA; oral intervention indicated	Urticarial lesions covering >30% BSA; IV intervention indicated	-	-

10.9. Appendix 9: Study Conduct During a Natural Disaster

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, isolation or quarantine of participants and study site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being unavailable, isolated, or 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 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 intervention 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. Modifications made to the study conduct as a result of the COVID-19 should be summarized in the clinical study report.

If the participant has tested positive for the COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for administration of study intervention, performing. study assessments, and follow-up. Modifications made to the study conduct as a result of the COVID-19 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 and NA Background Regimen:

- 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 NA background treatment, where allowed per local regulations, can be provided.
- For participants unable to visit the study site, shipment or handover to a caregiver or delegate of NA background treatment, may be implemented, where allowed per local regulations and if requested by the treating study physician. Where shipments or handover to delegates are deemed necessary, the process must be coordinated between the site and participant for arranging shipment and adhering to associated approvals and documentation requirements.
- JNJ-3989 and nivolumab 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 and nivolumab) or NA background treatment is missed.

Continuation of Study Intervention and/or NA Background Treatment:

- Any issue with continuation and/or provision of study intervention and/or NA background treatment should be discussed with the sponsor and should be well documented.
- Study intervention should be continued if, in the assessment of the investigator, it does not result in risk to the participant. If at any time the participant's safety is considered at risk due to study intervention, study intervention will be temporarily or permanently discontinued, while every effort should be made to maintain follow-up on study. The benefit of continuing study intervention should be assessed by the investigator for each individual participant, considering the potential impact of reduced direct clinical supervision on participant safety.

- If a participant develops a SARS-CoV-2 infection, the investigator should contact the sponsor to discuss plans for study intervention and follow-up. A decision to continue study intervention should be made by the investigator depending on symptoms and concomitant medication(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 AEs related to SARS-CoV-2 infection improve to Grade ≤1, the investigator should discuss with the sponsor about resuming study intervention.

COVID-19 Vaccination During the Study:

Locally approved COVID-19 vaccines (including those that received emergency use authorization or conditional marketing authorization) are allowed throughout the study with the exception of the second dose of Sputnik V.

During nivolumab treatment, the following recommendations should be applied to accommodate COVID-19 vaccination:

- COVID-19 vaccine and nivolumab should not be administered on the same day. If required, nivolumab administration can be delayed by 2-5 days.
- The next nivolumab administration should be performed at the scheduled time.
- If required, skipping a nivolumab administration may be considered after consultation with the sponsor.

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

Study Visits and Assessments:

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

- 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 ISRs), 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.

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.

10.10. Appendix 10: Protocol Amendment History

Amendment 2 (28 March 2023)

Overall Rationale for the Amendment: The main reason for the protocol amendment is that due to difficult recruitment a strategic decision was taken to not extend further enrollment beyond the planned enrollment period and continue the study with a reduced sample size. There is no change in the benefit/risk for the participants.

Section number and Name	Description of Change	Brief Rationale
1.1. Synopsis 1.2. Schema 4.1. Overall Design 9.2. Sample Size Determination	Reduction of sample size.	Due to difficult recruitment.
1.1. Synopsis 9.5. Interim Analysis	Reduction of number of planned interim analyses.	The remaining optional interim analyses at Week 24 and FU Week 12, in addition to the final analysis (at FU Week 48), provide sufficient information to assess safety and evaluate the time course of different safety and efficacy markers during study conduct.
1.3.1. Schedule of Activities – Screening Phase and Study Intervention Phase 1.3.2. Schedule of Activities – Follow-up Phase 8.7. Exploratory Host Biomarkers	Removed the sentence: 'For participants' convenience, the coagulation test may be collected at the visit preceding the scheduled FNA biopsy.'	Correction.
1.3.2. Schedule of Activities – Follow-up Phase 8. STUDY ASSESSMENTS AND PROCEDURES	Reduction of samples collection and analyses during the follow-up period. Therefore, the total blood volume was updated accordingly.	Protocol simplification without impacting participant's safety and maintaining scientific value.
1.1. Synopsis 6.1. Study Intervention(s) Administered 6.8. Treatment of Overdose	Added flexibility for nivolumab dosing and updated the overdose definition.	To consider the necessary rounding and standard practice for the preparation and intravenous administration of drugs dosed by weight.
2.3.2.1. Known Risks	Added: 'Treatment with anti-PD-1 medications is associated with a risk of HBV reactivation in CHB patients. This risk is reduced with concurrent NA treatment or continuation of ongoing NA treatment.'	Clarification.
2.3.3. Benefit-Risk Assessment for Study Participation	Added: 'Participants will be regularly monitored for HBV reactivation and virologic breakthroughs throughout the study.'	Clarification.
5.2. Exclusion Criteria	Exclusion criteria M09 and M10 were further clarified.	Clarification.
7.1.1. Discontinuation of JNJ-3989	Added: 'based on creatinine (calculated by the CKD-EPI formula)'.	Clarification.
8.2.1. Physical Examinations	Added thyroid check to physical examination.	Clarification.

Section number and Name	Description of Change	Brief Rationale
8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting	Added coding conventions for the AEs reported by investigators.	Clarification.
8.3.6.3.1. Hematologic Abnormalities	Added hematological abnormalities for nivolumab when used in the oncology setting.	Clarification.
10.8. Appendix 8: DAIDS Table with Modifications (DAIDS [Modified])	Updated the CTCAE Severity Grading for irAEs table by adding severity grading for myocarditis.	For investigator convenience.
11. REFERENCES	Update of IB version.	Update of IB version
INVESTIGATOR AGREEMENT	Update of Sponsor's Responsible Medical Officer.	Update of Sponsor's Responsible Medical Officer.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 1 (30 June 2022)

Overall Rationale for the Amendment: The rationale of this amendment is to allow inclusion of participants with low titers of autoantibodies, to remove certain procedures, to implement changes regarding immune-related gastro-intestinal adverse event management based on Health Authority feedback and clarifications of sampling collection.

Section number and Name	Description of Change	Brief Rationale
1.1. Synopsis 1.3.1. Schedule of Activities – Screening Phase and Study Intervention Phase 4.1. Overall Design 5. STUDY POPULATION	Text added to indicate the screening duration extension to 6 weeks (42 days)	To take into account the turnaround time for certain screening tests
1.3.1. Schedule of Activities – Screening Phase and Study Intervention Phase 1.3.2. Schedule of Activities – Follow-up Phase 5.2. Exclusion Criteria 10.2. Appendix 2: Clinical Laboratory Tests	Text was added to provide a full list of autoantibodies to be tested and their respective exclusionary cut-off	To allow inclusion of participants with low titers of autoantibodies. Autoantibodies may be found in otherwise healthy participants
1.1. Synopsis 1.3.1. Schedule of Activities – Screening Phase and Study Intervention Phase 1.3.2. Schedule of Activities – Follow-up Phase 3. OBJECTIVES AND ENDPOINTS 8.5. Pharmacodynamics	Functional receptor occupancy (RO) assay was removed Time points for RO assay for Arm 1 and Arm 2, previously provided in Table 14 (removed), were added to the Schedule of Activities	Comparative functional RO data is not available for nivolumab For clarification
1.3.1. Schedule of Activities – Screening Phase and Study Intervention Phase 8.4.1. Evaluations	Text was added to clarify blood sampling for sparse PK	For clarification

Section number and Name	Description of Change	Brief Rationale
1.3.2. Schedule of Activities – Follow-up Phase	Text was added in the footnote of Schedule of Activities to clarify that participants who discontinued study prematurely will have an early withdrawal visit	For clarification
1.3.1. Schedule of Activities – Screening Phase and Study Intervention Phase 1.3.2. Schedule of Activities – Follow-up Phase 8.7. Exploratory Host Biomarkers	Removal of the platelet aggregation test	Platelet aggregation test is not part of the recommended pre fine needle aspiration (FNA) work-up
5.2. Exclusion Criteria	Text was added to exclude participants with absolute neutrophil count <1,500/mm^3 (<1,000/mm^3 for participants of African ancestry)	Nivolumab may induce neutropenia
7.2.1. Withdrawal From the Use of Research Samples	Text was added to align with guidance regarding management of optional research samples	To not destroy samples already collected in case of participant withdrawal if the participant agrees to have his/her samples further stored and analyzed
8. STUDY ASSESSMENTS AND PROCEDURES	Text was added to reflect adjustment of total blood, peripheral blood mononuclear cell (PBMC) and pharmacogenomic sample volumes	Blood volumes were adjusted to reflect total volumes collected during the study
8.3.6.1. Intervention-emergent ALT/AST Elevations Including Immune-related Hepatic AEs Table 5	Text was updated to clarify mandatory histologic assessment in case of potential immune-related hepatic AE	The histologic assessment as a prerequisite to initiate corticosteroids and stop nivolumab was made not mandatory to avoid delay in potential irAE management
8.3.6.2.1. Gastrointestinal Adverse Events	Text was added to specify medical assessment for treatment-emergent colitis ≥Grade 2	To align with American society of clinical oncology (ASCO) guidelines for the management of immune-related Adverse Events in patients treated with Immune Checkpoint Inhibitor therapy
1.1. Synopsis 9.5. Interim Analysis	Text was added to indicate an additional interim analysis when all randomized participants have completed Week 24 or discontinued earlier	Optimization of the interim analysis schedule
10.2. Appendix 2: Clinical Laboratory Tests	Table updated to add C-reactive protein (CRP)	For clarification
10.9. Appendix 9: Study Conduct During a Natural Disaster	Text was revised to clarify nucleos(t)ide analog (NA) background treatment and remove reference to direct-to-patients process.	Clarification of NA background treatment

Section number and Name	Description of Change	Brief Rationale
7.1.2. Discontinuation of Nivolumab	Text was added to include discontinuation of nivolumab by the investigator for safety reasons	For completeness
10.1. Appendix 1: Abbreviations and Definitions	Abbreviation and definition list updated	For completeness
Throughout the protocol	Minor grammatical, spelling changes or formatting changes were made	Minor errors were noted

11. REFERENCES

Clinical Protocol Amendment 2: 73763989HPB2001 (REEF-1). Janssen Research & Development (January 2020).

Clinical Protocol Amendment 2: 73763989PAHPB2002 (REEF-2). Intervention-specific Appendix 2 to Master Protocol PLATFORMPAHPB2001. Janssen Research & Development (January 2020).

Clinical Protocol Amendment 2: 73763989PAHPB2006 (PENGUIN). Intervention-specific Appendix 4 to Master Protocol PLATFORMPAHPB2001. Janssen Research & Development (May 2021).

Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol 2010;28(19):3167-3175.

Cattley RC and Cullen JM. Chapter 45: Liver and Gall Bladder. Haschek and Rousseaux's. Handbook of Toxicologic Pathology, Third Ed., 2013.

Ebeling M, Kung E, See A, et al. Genome-based analysis of the nonhuman primate Macaca fascicularis as a model for drug safety assessment. Genome Res. 2011; 21:1746-1756.

El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non- comparative, phase 1/2 dose escalation and expansion trial. Lancet. 2017; 389(10088):2492-2502.

Fang Z, Li J, Yu X, et al. Polarization of monocytic myeloid-derived suppressor cells by hepatitis B surface antigen is mediated via ERK/IL-6/STAT3 signaling feedback and restrains the activation of T cells in chronic hepatitis B virus infection. J Immunol. 2015;195(10):4873-4483.

Gane E, Daniel JV, Anna EB, et al. Anti-PD-1 blockade with nivolumab with and without therapeutic vaccination for virally suppressed chronic hepatitis B: A pilot study. J Hepatol 2019;71:900-907-

Givlaari (givosiran; NDA212194) NDA/BLA Multi-Disciplinary Review and Evaluation, Center for Drug Evaluation and Research. 20 November 2019.

Greaves P. Chapter 2: Integumentary system- skin and subcutaneous tissue (pages 39-42). Histopathology of preclinical toxicity studies: Interpretation and relevance in drug safety studies, Fourth editioned., 2012.

Henry SP, Johnson M, Zanardi TA, et al. Renal uptake and tolerability of a 2'-O-methoxyethyl modified antisense oligonucleotide (ISIS 113715) in monkey. Toxicology. 2012;301(1-3):13-20.

Holsapple MP, Pitot HC, Cohen SM, et al. Mode of action in relevance of rodent liver tumors to human cancer risk. Toxicol Sci, 2006; 89(1):51-56.

Investigator's Brochure: JNJ-73763989 (IB JNJ-3989) Edition 6 Janssen Research & Development (8 April 2022).

Janas MM, Harbison CE, Perry VK, et al. The nonclinical safety profile of GalNac-conjugated RNAi therapeutics in subacute studies. Toxicol Pathol. 2018a;46(7):735-745.

Janas MM, Schlegel MK, Harbison CE, et al. Selection of GalNAc-conjugated siRNAs with limited off-target-driven rat hepatotoxicity. Nat Commun, 2018b;9(1):723.

Lautenschlager I, Höckerstedt K, Häyry P. Fine-needle aspiration biopsy in the monitoring of liver allografts. Transpl Int. 1991;4(1):54-61.

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

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

Memorandum to the file for BLA 125554 OPDIVO (nivolumab). Approvability of Pharmacology and Toxicology. Bristol-Myers Squibb Company; 04 December 2014.

Nivolumab Summary of Product Characteristics (NSPC). Uxbridge, United Kingdom: Bristol-Myers Squibb Pharma EEIG. https://www.ema.europa.eu/en/documents/product-information/nivolumab-bms-epar-product-information_en.pdf. Accessed 23 March 2023.

Nivolumab US Package Insert (NUSPI). Princeton, NJ: Bristol-Myers Squibb Company. https://packageinserts.bms.com/pi/pi_opdivo.pdf. Accessed 23 March 2023.

Setten RL, Rossi JJ and Han S-P. The current state and future directions of RNAi-based therapeutics. Nat Rev Drug Discov. 2019;18(6):421-446.

Shah NJ, Al-Shbool G, BlackburnM, et al. Safety and efficacy of immune checkpoint inhibitors (ICIs) in cancer patients with HIV, hepatitis B, or hepatitis C viral infection. J Immunother Cancer. 2019;7(1):353.

Tang TJ, Janssen HLA, Kusters JG, et al. The intrahepatic immune response during chronic hepatitis B infection can be monitored by the fine-needle aspiration biopsy technique. FEMS Immunol Med Microbiol. 2003;39(1):69-72.

Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366(26):2443-2454.

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

Wooddell CI, Yuen M-F, Chan HKL, et al. RNAi-Based Treatment of Chronically Infected Patients and Chimpanzees Implicates Integrated Hepatitis B Virus DNA as a Source of HBsAg. Sci. Transl. Med. 2017; 9(409).

Yang S, Zeng W, Zhang J, et al. Restoration of a functional antiviral immune response to chronic HBV infection by reducing viral antigen load: if not sufficient, is it necessary? Emerg Microbes Infect. 2021;10(1):1545-1554.

Yuen M-F, Gane JE, Kim DJ, et al. Antiviral Activity, Safety, and Pharmacokinetics of Capsid Assembly Modulator NVR 3-778 in Patients with Chronic HBV Infection. Gastroenterology 2019; 156(5):1392-1403.e7.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that in conjunction with the accompanying Master Protocol, 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 [redacted]	30-Jun-2023 16:06:26 (GMT)	Document Approval