Janssen Research & Development

Statistical Analysis Plan

Intervention-specific Appendix 7 to Clinical Protocol PLATFORMHPB2001

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

JNJ-73763989

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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VERSION HISTORY

Document History	
Document	Date
Original SAP	20 September 2022
Amendment 1	23 August 2023
Amendment 2	10 June 2024

Amendment 2 (10 June 2024)

The main purpose of this SAP amendment is to document changes in the scope of the final analyses, based on results of the primary analysis.

Section number and Name	Description of Change	Brief Rationale
5.3.6. Comparisons Between Arm 1, 2 and Model-Based Virtual Nivolumab-Free JNJ-3989+NA Regimen Control	Section Removed.	Virtual Control analysis is no longer of interest.
5.4.1.2. Continuous Endpoints	Section Updated.	Change from baseline value to the nadir is of interest only in HBsAg.
5.4.2.1.1. HBsAg Cut-offs and 5.4.2.1.4. HBeAg Cut-offs	Section Removed.	Cross-Tabulation for Quantitative Result vs. Qualitative Result Over Time for HBsAg and HBeAg removed as according to the protocol, qualitative HBsAg and HBeAg are only collected at screening and baseline.
5.4.2.2.1. HBsAg, HBeAg, HBV DNA and ALT	Section Updated.	• Waterfall plots of changes from Reference Timepoints in HBsAg removed • Descriptive statistics of changes from RTs in ALT removed • Changes from baseline analyses are removed for HBV DNA • Changes from baseline outputs are only displayed in the log 10 scale for all viral parameters • Change from Nivolumab RT and Follow-up Week 4 RT are of interest only for HBsAg

Section number and Name	Description of Change	Brief Rationale
5.5.1.3. and 5.5.2.3. Endpoints for Correlation	Section Removed.	Endpoints for Correlation is no longer of interest.
5.5.2.2.2. HBV RNA and HBcrAg	Section Removed.	Change from baseline value to the nadir is of interest only in HBsAg.
5.3.5. Subgroup Analyses of Primary Efficacy Endpoint and 5.7.6. Definition of Subgroups	Section Removed.	Subgroup Analysis is removed due to low number of observed events of interest.

Amendment 1

Overall rationale of this SAP Amendment: The main reason for this SAP amendment was to align with the protocol amendment 2 that was performed due to difficult recruitment. Therefore, a strategic decision was taken to not extend further enrollment beyond the planned enrollment period and continue the study with a reduced sample size. In the meantime, there has been a new amendment (amendment 3 – 30 June 2023) of the protocol filed. The main reason for the protocol amendment 3 was 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. Treatment with JNJ-3989 and/or nucleos(t)ide analog was continued as planned. The impact of this amendment 3 has been discussed and it has been agreed that this does not affect the Statistical Analysis Plan.

Section number and Name	Description of Change	Brief Rationale
1.2. Study Design 3. Sample Size Determination	Reduction of sample size.	Due to difficult recruitment.
5.1.9. Data Handling Rules	Revised ULOQ and Imputed Values data cutpoints for HBsAg, HBeAg and HBcrAg. Updated guidelines for the imputation of HBV DNA.	Improved for clarity and precision.
5.5.1.1.5. Anti-HBe Antibodies 5.5.1.2.3. Anti-HBs Antibodies	Analysis removed.	Qualitative anti-HBs results are not collected.

Section number and Name	Description of Change	Brief Rationale
5.8.3.1. Data Reviews	Change in frequency and timing of Data Reviews.	Change in the scope of the study.
5.8.3.2. Interim Analysis	Reduction of number of planned interim analyses. They may be done instead of will be done.	Change in the scope of the study.
5.5.1.3.1. Association between Baseline Characteristics/ Viral Blood Markers and Selected Efficacy Variables	Analysis of Correlations between baseline characteristics and HBV blood markers may be done instead of will be done and at a later time point in a post hoc nature.	Clarification.
5.4.1.1.1. HBsAg Cut-offs	Number of categories reduced	Clarification.
5.4.2. Analysis Methods	Analysis of Secondary Endpoints may be done instead of will be done.	Clarification.
5.7.3. Receptor Occupancy	Section Added.	Added for completeness.
5.4.1.3. Time to Event Endpoints 5.4.2.3. Time to Event Endpoints 5.5.1.3. Time to Event Endpoints 5.5.2.3. Time to Event Endpoints	Time to event endpoints have been removed.	Time to event endpoints are no longer of interest.
5.7.4. Immune Analysis	Immune Analysis may be done instead of will be done.	Clarification.
5.7.4. Viral Genome Sequence Analysis	Removed subsections. This analysis may be done instead of will be done.	Subsections were removed to simplify the analysis.
Health Economics	Section Removed.	Clarification.
HBV genotype	Section Removed.	Clarification.
Throughout the SAP	Minor grammatical, formatting, or spelling changes were made.	Typographical corrections or improved language for clarity and precision.
5.7.6. Definition of Subgroups	Removed some subgroups.	Considering the small sample size, it was

Section number and Name	Description of Change	Brief Rationale
		decided to remove some subgroups.
6.4. Appendix 4 Protocol Deviations	List was updated to incorporate the updated list as per protocol amendment #3.	For completeness

1. INTRODUCTION

The statistical analysis plan (SAP) for the 73763989PAHPB2008 phase 2 trial describes the statistical analyses, and definitions to assess the efficacy, safety, tolerability, and pharmacodynamics of the combination of JNJ-73763989 (JNJ-3989), nucleos(t)ide analogs (NAs), and nivolumab in virologically suppressed, HBeAg-negative, chronic HBV-infected (CHB), adult participants < 56 years of age.

This study is part of the platform trial PLATFORMPAHPB2001 in participants with CHB. The protocol for 73763989PAHPB2008 constitutes the Intervention Specific Appendix 7 that describes all the specific and/or additional features of this study complementing the common design elements of the platform trial described in the Master Protocol.

This SAP is to be interpreted in conjunction with the clinical trial protocol amendment 1 finalized on 30 June 2022, and with the Master Protocol Amendment-3 for PLATFORMPAHPB2001 finalized on 21 January 2021.

Details on pharmacokinetic (PK) and pharmacokinetic/pharmacodynamic (PK/PD) analyses will be described in a separate analysis and modelling plan.

1.1. Objectives and Endpoints

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.	• 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 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, e.g. intensive care unit). • Number and character of diagnostic and therapeutic tests and procedures. • Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications).

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

1.2. Study Design

This is a Phase 2, open-label, 2-arm, multicenter study to assess efficacy, safety, tolerability, PK and PD of a combination of JNJ-3989, nivolumab, and NAs in virologically suppressed, HBeAg-negative, chronic HBV-infected, adult participants.

Initially a target of approximately 44 virologically suppressed, HBeAg-negative chronic HBV-infected adult participants ≥18 (or the legal age of consent in the jurisdiction in which the study is taking place) to <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).

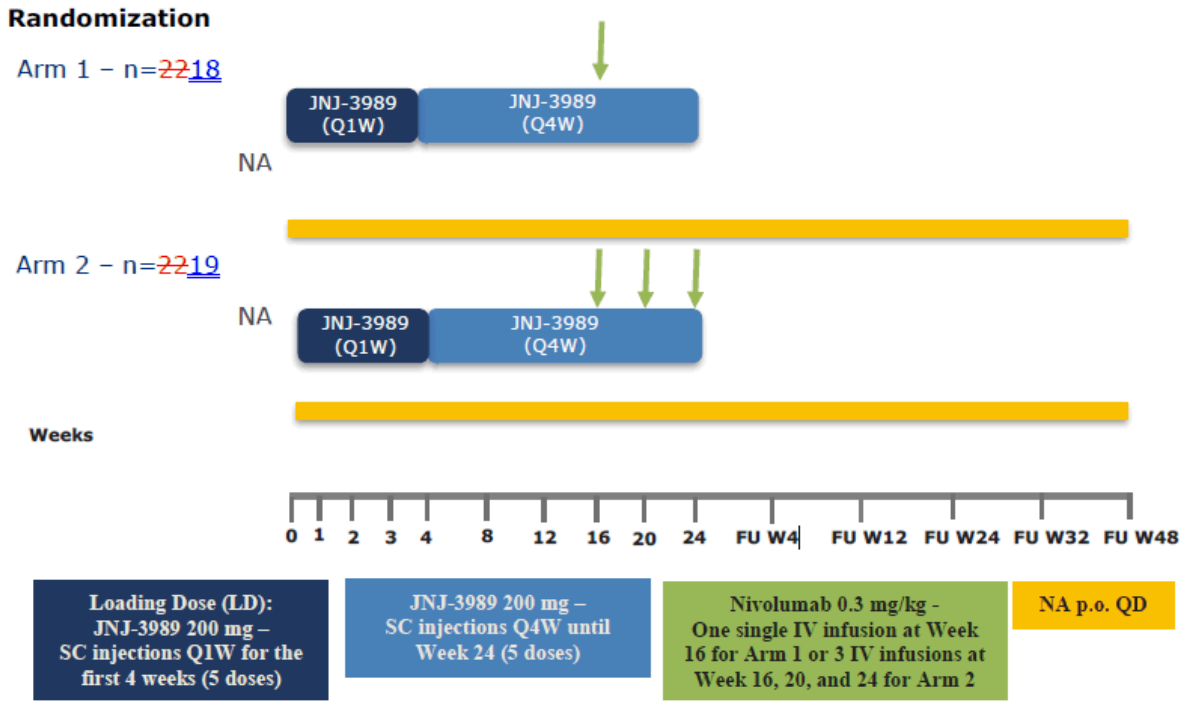
This open-label study will be conducted in 3 periods:

- Screening Period (6 weeks [if necessary, e.g. for operational reasons, can be extended to a maximum of 8 weeks decided on a case-by-case basis and in agreement with the Sponsor]).
- Study intervention (24 weeks):
  - 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
- Follow-up (FU) Period (48 weeks), during which NA treatment will be continued.

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

A schematic overview of the trial is presented in Figure 1.

Figure 1: Schematic Overview of the Study



FU: follow-up; JNJ-3989: JNJ-73763989; n: number of participants; NA: nucleos(t)ide analog; Q1W: once weekly; Q4W: every 4 weeks; QD: once daily.

Note: In red: number of participants per arm according to the initial design. In blue: the actual sample size.

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.

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 (see Clinical Protocol Section 1.3) 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.

2. 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).

3. SAMPLE SIZE DETERMINATION

According to the initial protocol, 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.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Due to a potential impact of Coronavirus Disease (COVID-19) pandemics on the study data collection, study intervention adherence and study conduct, the modified Full Analysis Set (mFAS) and modified FAS-N (mFAS-N) are defined to target the estimation of effects without the pandemic-related influences.

The primary set for efficacy analyses will be the FAS, and for the safety analyses the safety set. The FAS-N and modified FAS/FAS-N analysis sets will be used if there is a relevant difference from the FAS (>5% of participants in total). Analysis sets for analysis are described in Table 1

Table 1: Analysis Sets for Analysis

Analysis Sets	Description
Screened	All participants who signed the ICF for the Master Protocol and the ICF specific for this ISA.
Enrolled	All participants who were enrolled in this ISA.
Randomized	The randomized analysis set includes all participants who were randomized in the study.
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.
Modified FAS (mFAS)	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 excluding those participants who, because of COVID-19 or similar pandemics related reasons, withdrew prematurely from the study prior to FU Week 24, or had no efficacy assessment for the primary endpoint. COVID-19 or similar pandemics related reasons may include for example missed visits due to travel restriction, shortage of lab kits at the planned visit, missed collection of blood sample at key time points for the primary efficacy endpoint etc. Participants will be analyzed according to the study intervention they were randomly assigned to.
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.
Modified FAS-N (mFAS-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 excluding those participants who, because of COVID-19 or similar pandemics related reasons, withdrew prematurely from the study prior to FU Week 24, or had no efficacy assessment for the primary endpoint. COVID-19 or similar pandemics related reasons may include for example missed visits due to travel restriction, shortage of lab kits at the planned visit, missed collection of blood sample at key time points for the primary efficacy endpoint etc. Participants will be analyzed according to the study intervention they were randomly assigned to.
Safety	All participants who received at least 1 dose of study intervention within this ISA. Participants will be analyzed according to the study intervention they actually received.
Per Protocol Analysis Set (PP)	All participants in the FAS who do not have any of the selected major protocol deviations that may affect the assessment of efficacy in terms of the primary endpoint at FU Week 24. The selected major protocol deviations for efficacy analysis purposes that will be used to identify the participants included in the PP set are described in Section 6.4.
Pharmacokinetics Analysis Set	All participants who received at least 1 dose of study intervention and have at least 1 valid blood sample drawn for PK analysis.

5. STATISTICAL ANALYSES

5.1. General Considerations

The SAP will use throughout the document the following definitions:

- Study agent refers to: JNJ-3989, and nivolumab
- Study intervention arm refers to:
  - Arm 1: JNJ-3989 + nivolumab (1 infusion) + NA
  - Arm 2: JNJ-3989 + nivolumab (3 infusions) + NA

5.1.1. Analysis Phase

The analyses phases are defined in Table 2 below.

Table 2: Analysis Phases Start and End Dates

Analysis Phase	Start Date	End Date
Screening	The date of signing the informed consent	1 day before the first study agent intake
Study Intervention	Date of first study agent intake	**If participant did not withdraw from the study and did not discontinue treatment early prior to the projected/actual Week 24 Visit date:** Min [Date of Week 24 study agent intake + 5 days[a], cut-off date[b]] **Otherwise:** Max [Early study withdrawal visit date, study agent discontinuation date] + 5 days[a] or cut-off date[b], whichever occurs first
Follow-up	**Participants who did not withdraw informed consent during study intervention phase:** End of study intervention phase + 1 day **Otherwise:** missing	Max [study discontinuation date, study completion date] or cut-off date[b], whichever occurs first

[a] Addition of 5 days is only applicable for Adverse Events and Concomitant Medications.

[b] Cut-off dates will be defined to match the prespecified timepoints for DRC safety monitoring, interim analyses, the primary and the final analyses, respectively.

5.1.2. Relative Day by Study Phase

An analysis relative day (ADY) will be calculated for all assessments at all visits for each participant by study phase.

5.1.2.1. Study Intervention Relative Day

Study Intervention (SI) start date (SI Day 1) is defined in Table 2. All efficacy and safety assessments during the study intervention period will be assigned an analysis day relative to this date.

The study day in the study intervention period (SI ADY) is defined as:

$$SI\ ADY = visit\ date - SI\ start\ date + 1$$

for visits on or after study intervention period Day 1, and

$$SI\ ADY = visit\ date - SI\ start\ date$$

for visits before SI Day 1 (Screening phase).

There is no 'SI Day 0'.

5.1.2.2. Nivolumab Relative Day

Nivolumab start date (NV Day 1) is defined as the date of the first Nivolumab administration. Efficacy and safety assessments during the study intervention (after receiving Nivolumab) and FU phase will be assigned a day relative to this date. The study day is defined as:

$$NV\ ADY = visit\ date - NV\ start\ date + 1$$

for visits on or after NV Day 1.

5.1.2.3. Follow Up Relative Day

Follow-up (FU) start date (FU Day 1) is defined in Table 2. Efficacy and safety assessments during the FU phase will be assigned a day relative to this date. The FU study day in the FU phase (ADY) is defined as:

$$FU\ ADY = visit\ date - FU\ start\ date + 1$$

for visits on or after FU Day 1.

5.1.3. Visit Windows

As participants do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits. All visits for all assessments (safety, efficacy or PK) will be uniquely allocated within each phase to an analysis time point based on the analysis relative day (ADY) compared with the target day based on Table 3. All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be used for a

later time point except for the end of study intervention period (EOSI) and end of study (EOS) visits. If a participant has 2 or more actual visits in 1 visit window, the visit closest to the target day will be used as the protocol visit for that visit window. The other additional visit(s) will not be used in the summaries or analyses, but they can be used for determination of clinically important endpoints. If 2 actual visits are equidistant from the target day within a visit window, the later visit is used. If there are two or more measurements on the same day, then the last measurement in chronological order will be used. If the time of the assessment is not available, the highest record/sequence number will be selected.

The listings and spaghetti plots will include all measurements, also those multiple assessments with the same visit window/phase.

End of study intervention (EOSI) and end of study (EOS) time points will be included in all analyses over time unless otherwise stated.

Table 3 provides the analysis time points and time intervals for each visit per analysis phase.

Table 3: Visit Windows

Analysis phase	Target Day	Analysis time point (Week)	Analysis time point (label)	Time interval (days)
Screening	-∞	-1	Screening	<0
Study Intervention period	1	0	Baseline	Pre-dose: 1
	8	1	Week 1	[2, 11]
	15	2	Week 2	[12, 18]
	22	3	Week 3	[19, 25]
	29	4	Week 4	[26, 43]
	57	8	Week 8	[44, 71]
	85	12	Week 12	[72, 99]
	113	16	Week 16	[100, 127]
	141	20	Week 20	[128, 155]
	169	24	Week 24	[156, 183]
	Last visit in study intervention period	25[a]	EOSI[a]	
Follow-up	29	28	Follow-up Week 4	[1, 43]
	57	32	Follow-up Week 8	[44, 71]
	85	36	Follow-up Week 12	[72, 99]
	113	40	Follow-up Week 16	[100, 127]
	141	44	Follow-up Week 20	[128, 155]
	169	48	Follow-up Week 24	[156, 197]
	225	56	Follow-up Week 32	[198, 253]
	281	64	Follow-up Week 40	[254, 309]
	337	72	Follow-up Week 48	[310, +∞]
	Last visit in the study	999[b]	EOS[b]	

[a] End of study intervention (EOSI) visit will be the last post-baseline visit in study intervention period.
[b] End of study (EOS) visit (last available data during the follow-up visit) will be the last visit in the study.

5.1.4. Baseline

In general, the baseline assessment is defined as the last observed non-missing measurement before the date and time of the first administration of any of study agents.

In case the first administration measurement time is missing, the first observed measurement on SI Day 1 will be used as the baseline measurement. If no observed measurement on Day 1, the last observed measurement before Day 1 will be used as the baseline assessment.

5.1.5. Analysis Specifications

In general, continuous variables will be summarized using descriptive statistics including the number of participants, mean, standard error (SE), standard deviation (SD), two-sided 90% confidence interval (CI), median, and range. The 90% CI for continuous endpoints is constructed using the t-distribution. Binary or categorical variables will be summarized using the number and percentage of participants in each category and 90% CI using Clopper-Pearson exact method for the simple sample proportion (Newcombe RG,1998). For time-to-event variables, using the Kaplan-Meier approach, a summary table including number of participants included in the analysis, number of participants censored, 25th and 75th percentiles, median time-to-event and 90% CI will be shown. Graphic displays will also be used to summarize the data.

5.1.6. Additional Reference Timepoints

Three additional Reference Timepoints (RT) will be used for additional analyses of selected efficacy endpoints.

5.1.6.1. Nivo RT

The Nivo RT is defined as the last observed non-missing measurement before the date and time of the first Nivolumab administration. In case the first administration measurement time is missing, the first observed measurement on NV Day 1 (Nivolumab relative day 1) will be used as the nivolumab reference measurement. If no observed measurement on NV Day 1, the last observed measurement before NV Day 1 will be used as the nivolumab reference assessment.

The Nivo RT will be used for additional analyses for selected efficacy endpoints after Week 16 of study intervention period and FU phase.

5.1.6.2. W24 RT

The W24 RT is defined as the last observed non-missing measurement at the time of stopping JNJ-3989 administration at Week 24. This RT will be used for additional analyses for selected efficacy endpoints for FU phase.

5.1.6.3. FUW4 RT

The Follow up Week 4 RT (FUW4 RT) is defined as the last observed non-missing measurement at the FU Week 4 visit (4 weeks after the last JNJ-3989 administration). In case the measurement is missing at FU Week 4, the first non-missing measurement after FU Week 4 will be used as FU Week 4 reference assessment.

The FUW4 RT will be used for additional analyses for selected efficacy endpoints during FU phase.

5.1.7. Level of Significance

For the primary efficacy endpoint analysis, 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 (see Section 5.3.4).

For the comparisons between the intervention arms (Arms 1,2), the Mantel-Haenszel test adjusting for the stratification factor will be used in a secondary analysis to compare the primary endpoint between the intervention arms at a one-sided alpha level of 0.05.

For all other efficacy analyses, only two-sided 90% CIs will be provided with no adjustment for multiplicity, unless otherwise specified.

5.1.8. Missing and Partial Dates Imputation Rules

For analysis and reporting purposes, missing or partial dates in adverse event (AE onset date; AE end date), HBV diagnosis and infection dates, concomitant therapies (start date; end date) will be imputed according to the rules in the following subsections. The original, non-imputed, dates will be used only in listings.

5.1.8.1. Adverse Event Onset Date and Resolution Date

Partial AE onset dates will be imputed as follows:

- If the AE onset date is missing the day only, it will be set to:
  - The first day of the month when the AE occurred, if month/year of the AE onset date is different than the month/year of the first administration of study agent date.
  - The day of the first study agent administration, if the month/year of the AE onset date is the same as the month/year of the first study agent administration but the month/year of the AE resolution date is different.
  - The earliest between the day of the first study agent administration date and day of AE resolution date, if month/year of the AE onset are the same as both the month/year of the first study drug administration and the AE resolution date.
- If the AE onset date is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, as long as this date is on or after the first study drug administration.
  - Month and day of the first study agent administration, if this date is in the same year of AE onset date.
  - December 31 if the AE onset date year is prior to the year of the first study drug administration.
  - The AE resolution date.

- Completely missing onset dates will not be imputed.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- If the resolution date of an AE is missing the day only, it will be set to the earliest of the last day of that month or the day of the date of death, if the participant died in that month.
- If the resolution date of an AE is missing both day and month, it will be set to the earliest of December 31 of that year or the day and month of the date of death, if the participant died in that year.
- Completely missing resolution dates will not be imputed.

5.1.8.2. HBV Diagnosis and Infection Dates

If the reported date is partially missing, the following imputation rules will be applied:

- the 15th of the month, if only the day is missing.
- the 30th of June, if only the year is available.
- No imputation if completely missing.

5.1.8.3. Concomitant Medication Dates

In case of partially missing concomitant medication start/end dates, the following imputation rules will be applied:

- the 15th of the month, if only the day is missing.
- the 30th of June, if only the year is available.
- If the imputed start date is after the concomitant medication end date, further adjustment of the imputed start date is required. It will be imputed as the concomitant medication end date.
  - No imputation if completely missing.

If the medication was taken prior to study start (SI Day 1) based on eCRF question, and the imputed start date is after first treatment date, further adjustment of the imputed start date is required. It will be imputed as the day prior to first dosing date.

If the medication was taken after study start (SI Day 1) based on eCRF question, and the imputed start date is prior to first dosing date, the imputed start date will be further adjusted to be the first study agent dosing date. The partially missing medication end date will be imputed following the rule described at the beginning of this section to ensure it is on or after first dosing date, and after its start date.

- In case of a completely missing start date, the concomitant therapy will be considered as having started before the trial, unless the eCRF indicating that the medication was taken after study start.
- In case of a completely missing end date, the concomitant therapy will be considered as ongoing at the end of the trial, unless the eCRF indicating not ongoing.

5.1.8.4. Dates of Alcohol Consumptions

In case of partially missing start/end dates, the following imputation rules will be applied:

- the 15th of the month, if only the day is missing.
- the 30th of June, if only the year is available.
- If the imputed start date is after the end date, further adjustment of the imputed start date is required. It will be imputed as the end date.
- If end date is completely missing and marked as Ongoing then impute with randomization date. Otherwise, no imputation if completely missing.

5.1.9. Data Handling Rules

Those measurements collected from screening visit to the end of study will be handled according to the following rules summarized in Table 4.

Table 4: Data Handling Rules for HBV Virology and Serology Assessments

HBV parameter	LLOQ	ULOQ	Imputed Values	
			If value< LLOQ	**If value> ULOQ**
HBsAg	0.05 IU/mL	249,750.00 IU/mL with dilution	0.025 IU/mL [(a)]	274,725.00IU/mL [(b)] with dilution
HBeAg	0.11 IU/mL	7,000.00 IU/mL with dilution	0.055 IU/mL [(a)]	7,700.00 IU/mL[(b)] with dilution
HBcrAg*	3.0 $\log_{10}$ U/mL	9.0 $\log_{10}$ U/mL with dilution	2.7 $\log_{10}$ U/mL	9.9 $\log_{10}$ U/mL [(b)] with dilution
HBV DNA	20 IU/mL	170,000,000 IU/mL w/o dilution	If target detected: 15 IU/mL** If target not detected: 5 IU/mL**	187,000,000[(b)(c)] IU/mL w/o dilution
HBV RNA*	LLOQ = 2.939 $\log_{10}$ cp/mL (i.e. 869 cp/mL) LOD = 1.398 $\log_{10}$ cp/mL (i.e. 25 cp/mL)	NAP	If <LOD or target not detected then 1.114 log10 cp/mL (13 cp/mL)	NAP
Anti-HBs	5 mIU/mL	10000.0 mIU/mL	2.5 mIU/mL(a)	11000.0 mIU/mL (b)

Table 4: Data Handling Rules for HBV Virology and Serology Assessments

HBV parameter	LLOQ	ULOQ	Imputed Values	
			If value< LLOQ	If value> ULOQ

* As new assays become available different data handling rules may apply.
** For HBV DNA spaghetti plots showing absolute values, the imputed value will be 15 IU/mL. For all other tables, listings and figures, the main analysis will be performed using 15 IU/mL to impute HBV DNA<LLOQ and the two methods of imputation may be used as exploratory analysis.
Key: NAP=Not applicable
(a) LLOQ/2
(b) ULOQ+(ULOQ/10)
(c) If the original result > ULOQ, then take the re-test value (i.e., diluted result). If the diluted result is not available, use the imputed value indicated in this table.

All other viral activity data with values <LLOQ which are not included in the data handling rules above will be imputed by the absolute value divided by 2.

5.2. Participant Dispositions

All the summaries will be done on the FAS analysis set unless specified otherwise.

Screened participants and reason for screen failures will be summarized overall.

The number of participants in the following disposition categories will be summarized throughout the study by intervention group and overall:

- Participants randomized
- Participants who received any study intervention (JNJ-3989, Nivolumab)
- Participants in each study analysis phase
- Participants who completed the study
- Participants who completed study intervention but dropped off during follow-up
- Participants who discontinued any study intervention
- Reasons for discontinuation of any study intervention
- Participants who terminated study prematurely
- Reasons for termination of study

A listing of participants will be provided for the following categories:

- Participants who discontinued any study intervention
- Participants who terminated study prematurely
- Participants who were randomized yet did not receive study intervention.

5.3. Primary Efficacy Endpoint

5.3.1. Definition

The primary endpoint is the proportion of participants who achieved HBsAg seroclearance (HBsAg<LLOQ) at FU Week 24.

5.3.2. Main Estimand for the Primary Endpoint

Study Objective: To evaluate the efficacy in terms of HBsAg seroclearance for the treatment regimens of JNJ-3989 + nivolumab at Week 16 + NA (Arm 1), and JNJ-3989 + nivolumab at Weeks 16, 20, 24 + NA (Arm 2), as compared to JNJ-3989 + NA.

Scientific Question of Interest: in HBeAg negative virologically suppressed adult population with chronic HBV infection

a) Comparison vs fixed external control: what is the benefit of JNJ-3989 + nivolumab (1 or 3 infusions) + NA compared with a fixed external proportion of 1% for JNJ-3989 + NA, measured by proportion of participants achieving HBsAg seroclearance at FU Week 24?

b) Comparison amongst regimens: what is the difference between JNJ-3989 + nivolumab (1 infusion) + NA and JNJ-3989 + nivolumab (3 infusions) + NA, measured by proportion of participants achieving HBsAg seroclearance at FU Week 24?

The attributes for the main estimand for the primary endpoint are:

A) Study Intervention Arms:

- Arm 1: JNJ-3989 + nivolumab (1 infusion) + NA
- Arm 2: JNJ-3989 + nivolumab (3 infusions) + NA

B) Study Population: HBeAg-negative chronic HBV-infected adult patients who are virologically suppressed by being treated with NA.

C) Variable: Individual participant response status defined as whether an individual participant achieved HBsAg seroclearance at FU Week 24 (responders) as detailed in Section 5.3.1.

D) Intercurrent events:

- Treatment discontinuation prior to Week 24: if the participant discontinued treatment prior to Week 24 then s/he will be considered non-responder (composite strategy).
- Major protocol deviations affecting efficacy: Table 9 identifies the deviations considered intercurrent event. Participants with such deviations and who have missing data for the endpoint will be considered as non-responders (composite strategy). For all other deviations not considered intercurrent events, the data are used regardless of the occurrence of major protocol deviations (treatment policy strategy).

– Deaths prior to FU Week 24 are handled in a composite strategy as participants who die prior to FU Week 24 will be considered as non-responders.

E) Population-level summary:

a. Primary (comparison vs fixed external proportion): Difference in proportion of participants with HBsAg seroclearance at FU Week 24 using a fixed external proportion of 1%.

b. Secondary (comparison amongst regimens): Difference in proportion of participants with HBsAg seroclearance at FU Week 24 between study intervention arms.

5.3.2.1. Main Estimator

5.3.2.1.1. Analysis Methods

5.3.2.1.1.1. Comparison vs Fixed External Control

The main estimator is constructed by 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 (Section 5.3.4).

5.3.2.1.1.2. Comparison Amongst Regimens

The main estimator is constructed by using the Mantel-Haenszel test (Mantel N. et al., 1959) adjusted for the randomization stratification factor (HBsAg level at screening [<100 IU/mL, 100 to <1,000 IU/mL, and ≥1,000 IU/mL]) to compare the primary endpoint between the intervention arms at a one-sided alpha level of 0.05.

5.3.2.1.2. Data Included

The main analysis of the primary endpoint will be conducted using the FAS. The FAS-N and modified FAS/FAS-N analysis sets will be used if there is a relevant difference from the FAS (>5% of participants in total).

FU Week 24 response status data from the selected population analysis set, after taking into account all the intercurrent events and applying the intercurrent event strategies in Section 5.3.2, will be included.

5.3.2.1.3. Assumptions

- Missing Data for HBsAg are Missing Not at Random (MNAR)
- The treatment effect is homogeneous across strata

5.3.2.1.4. Missing Data Handling Rule

Participants who withdraw from the study prior to FU Week 24 will be considered as non-responders.

If a participant remains in the study after experiencing a major protocol deviation (defined for the purpose of efficacy analyses and is an intercurrent event) and has missing FU Week 24 value, then the imputation to non-response will be applied. If the value for the endpoint at FU Week 24 is available, then such data will be used to determine their response status.

For the participants still in the study at FU Week 24 or for participants that have neither discontinued treatment early nor experienced any major protocol violations (defined for the purpose of efficacy analyses and is an intercurrent event), and HBsAg values missing at FU Week 24, then the primary method to handle missing data will be the missing as non-responder (MANR).

5.3.2.2. Sensitivity Estimators of the Main Estimand

Sensitivity analyses will be conducted by constructing three sensitivity estimators for the main estimand as defined in Section 5.3.2.

5.3.2.2.1. Sensitivity Estimator 1 of the Main Estimand (Homogeneity Assumption)

Homogeneity will be assessed for scientific question of interest part b, comparison amongst regimens. For this sensitivity estimator 1, the same included data, missing data assumption, and missing data handling rule (MANR) as well as the same approach to control the Type I error rate (Section 5.3.2.1) will be applied. The assumption for homogeneity of treatment effect across the stratification factor will be tested and, if heterogeneity is found statistically significant, a different statistical model will be used to define the sensitivity estimator.

5.3.2.2.1.1. Assumptions

- Missing Data for HBsAg are Missing Not at Random (MNAR)
- The treatment effect is non-homogeneous across strata

5.3.2.2.1.2. Analysis Methods

Homogeneity of treatment effect for each stratification factor separately will be tested using the weighted least squares chi-squared statistic (Lui K. J. et al., 2000) for one-way homogeneity. Tests of homogeneity will be assessed at the one-sided 10% level of significance.

Any heterogeneity found to be statistically significant will be explored using the following statistical model.

Statistical model: A logistic regression model on the primary efficacy endpoint using the randomization stratification factor and interaction terms. The model will include intervention arm, HBsAg level at screening (<100 IU/mL, 100 to <1,000 IU/mL or ≥1,000 IU/mL), as factors, and the intervention arm-by-factor interaction terms.

5.3.2.2.2. Sensitivity Estimator 2 of the Main Estimand (Observed Case Analysis)

For this sensitivity estimator 2, the same statistical model, and data included will be used as for the main estimator (Section 5.3.2.1). The assumption for missing data and the rule to handle missing data have changed.

5.3.2.2.2.1. Assumptions

- Missing Data for HBsAg are Missing Completely at Random (MCAR) (Barnes A. et al., 2008)
- The treatment effect is homogeneous across strata

5.3.2.2.2.2. Missing Data Handling Rule

For sensitivity estimator 2, participants who withdrew from the study prior to Week 24 will not be included in the analysis. After taking into account all the intercurrent events and applying the intercurrent event strategies specified in Section 5.3.2, if a participant who did not experience any ICEs has missing response status for the primary endpoint then this participant will not be used for the analysis.

5.3.2.2.3. Sensitivity Estimator 3 of the Main Estimand (LOCF)

For this sensitivity estimator 3, the same statistical model, and data included will be used as for the main estimator (Section 5.3.2.1). The assumption for missing data and the rule to handle missing data have changed.

5.3.2.2.3.1. Assumptions

- Missing Data for HBsAg are MCAR (Barnes A. et al., 2008)
- The treatment effect is homogeneous across strata

5.3.2.2.3.2. Missing Data Handling Rule

For sensitivity estimator 3, participants who withdraw from the study prior to FU Week 24 will be considered as non-responders. After taking into account all the intercurrent events and applying the intercurrent event strategies specified in Section 5.3.2, if a participant who did not experience any ICEs has missing response status for the primary endpoint then the LOCF approach will be used as follows.

If the HBsAg value at FU Week 24 is missing, the LOCF in conjunction with the next available observation imputation approach will be used. The non-missing value closest to FU Week 24 will be selected among the non-missing values which are no earlier than 12 weeks prior to FU Week 24 or no later than 12 weeks after FU Week 24. If 2 non-missing laboratory values are equidistant, the later observation will be preferred. If a participant who did not experience any ICE and does not have HBsAg data within the analysis window of ±12 weeks around FU Week 24 assessment will be considered as non-responder.

5.3.3. Supplementary Estimand for the Primary Endpoint (Per-Protocol Analysis Set)

The attributes for the supplementary estimand for the primary endpoint are:

A) Study Intervention Arms:

- Arm 1: JNJ-3989 + nivolumab (1 infusion) + NA
- Arm 2: JNJ-3989 + nivolumab (3 infusions) + NA

B) Study Population: HBeAg-negative chronic HBV-infected adult patients who are virologically suppressed by being treated with NA.

C) Variable: Individual participant response status defined as whether an individual participant achieved HBsAg seroclearance at FU Week 24 (responders) as defined in Section 5.3.1.

D) Intercurrent events:

- Treatment discontinuation prior to Week 24: if the participant discontinued treatment prior to Week 24 then s/he will be considered non-responder (composite strategy).
- Deaths prior to FU Week 24 are handled in a composite strategy as participants who die prior to FU Week 24 will be considered as non-responders.

E) Population-level summary:

a. **Primary (comparison vs fixed external proportion):** Difference in proportion of participants with HBsAg seroclearance at FU Week 24 using a fixed external proportion of 1%.

b. **Secondary (comparison amongst regimens):** Difference in proportion of participants with HBsAg seroclearance at FU Week 24 between study intervention arms.

5.3.3.1. Main Estimator of the Supplementary Estimand

5.3.3.1.1. Analysis Methods

Similar methods as described for the main estimator of the main estimand will be used (Section 5.3.2.1.1).

5.3.3.1.2. Data Included

FU Week 24 response status data from randomized participants that are included in the PP analysis set will be used, after taking into account the intercurrent events and applying the intercurrent event strategies specified in Section 5.3.3.

To complement this analysis because of its inherent bias and allow a better interpretation of the results, the proportions of participants excluded from the PP analysis set will be summarized by intervention arm and by type of major protocol deviation.

5.3.3.1.3. Assumptions

- Missing Data for HBsAg are MANR
- The treatment effect is homogeneous across strata.

5.3.3.1.4. Missing Data Handling Rule

Participants who withdraw from the study prior to FU Week 24 will be considered non-responders. For the participants still in the study at FU Week 24 or for participants that have neither discontinued treatment early nor experienced any major protocol violations as listed in Table 9, but HBsAg values missing at FU Week 24, then the primary method to handle missing data will be the imputation to non-responder.

5.3.4. Hochberg Procedure

Consider testing the family of hypotheses H_{0i}, i = 1, . . . , k.

Let p_i , i = 1, . . . , k, denote the sample p-values of tests for H_{0i} , $i = 1, \ldots\ldots, k$, computed without multiplicity adjustment. Let [1], . . . , [k] denote the random indices such that

$p_{[1]} \leq \cdots \leq p_{[k]}$.

That is, $[i]$ is the anti-rank of p_i among $p_1, \ldots, p_k$.

Hochberg's step-up method proceeds as follows.

Step 1. If $p_{[k]} < a$, reject $H_{0[i]}$, $i = 1, \ldots\ldots, k$, and stop; otherwise go to Step 2.

Step 2. If $p_{[k-1]} < a/2$, reject $H_{0[i]}$, $i = 1, \ldots\ldots, k-1$, and stop; otherwise go to Step 3.

. . .

Step k. If $p_{[1]} < a/k$, reject $H_{0[i]}$, $i = 1$, and stop.

5.4. Secondary Efficacy Endpoints

See Section 1.1 for a list of the secondary endpoints. All secondary endpoints will be analyzed using observed case data. Additional analyses with specific imputation methods for missing data are added for selected endpoints.

5.4.1. Definitions

5.4.1.1. Binary Endpoints

5.4.1.1.1. HBsAg Cut-offs

The cut-offs for HBsAg level are as follows (yes vs no):

- <1000 IU/mL
- <100 IU/mL
- <10 IU/mL
- <1 IU/mL
- <LLOQ (0.05 IU/mL)

The cut-offs for HBsAg change from baseline and Nivo RT are as follows (yes vs no):

- decrease by ≥ 0.5 $\log_{10}$ IU/mL
- decrease by ≥ 1 $\log_{10}$ IU/mL
- decrease by ≥ 2 $\log_{10}$ IU/mL
- decrease by ≥ 3 $\log_{10}$ IU/mL
- decrease by ≥ 4 $\log_{10}$ IU/mL

The cut-offs for HBsAg change from FUW4 RT are as follows (yes vs no):

- increase by ≤ 0.2 $\log_{10}$ IU/mL
- increase by ≤ 0.5 $\log_{10}$ IU/mL
- increase by ≤ 1 $\log_{10}$ IU/mL
- decrease by > 0.2 $\log_{10}$ IU/mL
- within +/- 0.2 $\log_{10}$ IU/mL

5.4.1.1.2. HBsAg Seroclearance

Seroclearance of HBsAg is defined as a (quantitative) HBsAg level <LLOQ (see Table 4). HBsAg seroclearance can be observed prior to the time point assessed but must be observed at the given week of interest.

HBsAg seroclearance will be evaluated over all time points when assessed, with emphasis at Week 24, FU Week 12, FU Week 32 and FU Week 48.

For the analyses of seroclearance at the time points mentioned above, participants with HBsAg seroclearance at the respective time points will be considered as having achieved this endpoint.

5.4.1.1.3. HBsAg Seroconversion

Seroconversion of HBsAg is defined as having achieved HBsAg seroclearance and appearance of anti-HBs antibodies.

The seroconversion will only be assessed at the time points when the anti-HBs antibodies assessment is available.

Appearance of anti-HBs antibodies is defined as a baseline anti-HBs antibodies (quantitative) <LLOQ and a post-baseline assessment ≥LLOQ. An additional seroconversion will be applied using the threshold of 10 mIU/mL, i.e. appearance of anti-HBs antibodies is defined as a baseline anti-HBs antibodies (quantitative) <10 mIU/mL and a post-baseline assessment ≥10 mIU/mL.

5.4.1.1.4. HBeAg Cut-offs

The cut-offs for HBeAg level are as follows (yes vs no):

- < LLOQ
- <1 IU/mL
- <10 IU/mL

5.4.1.1.5. HBV DNA Cut-offs

The cut-offs for HBV DNA are as follows (yes vs no):

- < LLOQ for target detected or not detected
  - < LLOQ for target not detected
  - < LLOQ for target detected
- <60 IU/mL
- <200 IU/mL
- <2000 IU/mL
- <20000 IU/mL

5.4.1.1.6. Suppressed HBV DNA

HBV DNA < LLOQ (HBV DNA detectable or HBV DNA TND) and HBV DNA < 60 IU/mL will be evaluated over all time points when assessed, with emphasis at Week 24, FU Week 12, FU Week 24, FU Week 32 and FU Week 48.

5.4.1.1.7. ALT Normalization

ALT elevation at baseline is defined as ALT≥ULN. A participant with ALT elevation at baseline achieves ALT normalization if his/her ALT value post-baseline is <ULN at any given time point.

Participants who achieve ALT normalization on treatment will be evaluated over time.

5.4.1.1.8. Virologic Breakthrough

HBV virological breakthrough is defined as having a confirmed on-treatment HBV DNA increase by >1 log_{10} from nadir level (lowest level reached during treatment) in participants who didn't have on-treatment HBV DNA level below the lower limit of quantification (LLOQ) or a confirmed on-treatment HBV DNA level >200 IU/mL in participants who had on-treatment HBV DNA level below the lower limit of quantification (LLOQ). Confirmed HBV DNA increase/level means that the criterion should be fulfilled at 2 or more consecutive time points or at the last observed time points or at the last observed on-treatment time point. On-treatment will be defined as the time period in which the participant receives any of the study interventions (including NA).

In addition, participants who experience a virologic breakthrough followed by on-treatment biochemical flare will be evaluated.

5.4.1.1.9. Flares

The criteria based on blood markers/lab tests for each of the flare types are defined below.

On-treatment Biochemical flare is defined as follows:

The start date of a confirmed on-treatment biochemical flare is defined as the first date of two consecutive visits with ALT and/or AST≥3x ULN and ≥3x nadir (i.e. lowest value observed up to the start of the flare) while the participant receives any of the study interventions. The end date of the same on-treatment biochemical flare is defined as the first date when there is a 50% reduction from the peak ALT and/or AST level & <3x ULN, regardless of stopping the study interventions.

- 1 (Yes) = confirmed** ALT and/or AST ≥3x ULN and ≥3x nadir (i.e. lowest value observed up to the start of the flare)
- 0 (No) = otherwise

** Confirmed means that the criterion should be fulfilled at 2 or more consecutive time points or at the last observed time point.

5.4.1.2. Continuous Endpoints

5.4.1.2.1. HBsAg, HBeAg, HBV DNA and ALT

Actual values (original unit and/or log_{10} transformed values), changes from baseline (log_{10} transformed values) and change from RTs over time in HBsAg will be evaluated, and actual values (original unit and/or log10 transformed values), over time in HBeAg, HBV DNA and ALT will be evaluated.

Change from baseline is defined as the value at a given time point minus baseline value.

The change from baseline value to the nadir (i.e. maximum decrease for each participant) in HBsAg will be evaluated at 3 intervals: during study intervention nadir (first 24 weeks), during follow-up nadir, and entire study nadir.

5.4.2. Analysis Methods

Summaries and graphs will be provided for each intervention arm and analysis phase, unless specified otherwise.

Statistical comparisons of the secondary endpoints among intervention arms may be done with no adjustment for multiplicity.

All secondary endpoints will be analyzed based on the observed case data. Additional analyses with specific imputation methods for missing data are added for selected endpoints.

Inferential and descriptive subgroup analyses may not be performed if there are not enough data to perform the analyses.

5.4.2.1. Binary Endpoints

The count and proportion (%) of participants achieving the endpoints defined in Section 5.4.1.1 will be summarized. The associated 90% CI will be included for the following endpoints:

- HBsAg seroclearance
- HBsAg seroconversion
- Suppressed HBV DNA
- ALT Normalization
- Virologic Breakthrough
- Flares

For all time points, binary endpoints will be analyzed using the observed case data. LOCF (Section 5.4.2.1.1) will be used for HBsAg seroclearance and Suppressed HBV DNA analyses at Week 24, FU Week 12, FU Week 24, FU Week 32 and FU Week 48.

The HBsAg seroclearance analyses at Week 24, FU Week 12, FU Week 24, FU Week 32 and FU Week 48 will be compared between treatment arms using a 2-sided 90% CI of the difference in proportions between the treatment groups (Arm 1 minus Arm 2) that will be constructed using a Mantel-Haenszel test controlling for stratification factor.

For single arm, point and 90% CI estimates, the Clopper Pearson method will be used.

Subsections below describe the additional analyses planned for only those specific other secondary binary endpoints that require further evaluations.

5.4.2.1.1. LOCF Imputation Method

- If the lab value at Week 24 is missing, the LOCF approach will be used with the condition that no value earlier than Week 20 may be carried forward.
- If the lab value at FU Week 12 is missing, the LOCF in conjunction with the next available observation imputation approach will be used. The available non-missing lab test closest to

FU Week 12 which is no earlier than FU Week 4 and no later than FU Week 24 will be imputed. If the non-missing lab value before and after the specific timepoint fall equidistant from the target timepoint, the later one will be used to impute the missing value.

- If the lab value at FU Week 24 is missing, the LOCF in conjunction with the next available observation imputation approach will be used. The available non-missing lab test closest to FU Week 24 which is no earlier than FU Week 12 and no later than FU Week 32 will be imputed. If the non-missing lab value before and after the specific timepoint fall equidistant from the target timepoint, the later one will be used to impute the missing value.
- If the lab value at FU Week 32 is missing, the LOCF in conjunction with the next available observation imputation approach will be used. The available non-missing lab test closest to FU Week 32 which is no earlier than FU Week 24 and no later than FU Week 48 will be imputed. If the non-missing lab value before and after the specific timepoint fall equidistant from the target timepoint, the later one will be used to impute the missing value.
- If the lab value at FU Week 48 is missing, the LOCF approach will be used with the condition that no value earlier than FU Week 32 may be carried forward.

5.4.2.1.2. HBsAg Seroconversion

For participants achieving HBsAg seroconversion, descriptive statistics will be calculated for the level of anti-HBs antibodies at the timepoint when achieving the HBsAg seroconversion. In an additional summary, the level of anti-HBs antibodies at the specific timepoint will be summarized for the subset of the participants achieving HBsAg seroconversion at any time before or at that given timepoint.

In addition, the count and proportion of participants (and associated 90% CI) with appearance of anti-HBs antibodies but without seroclearance of HBsAg will also be summarized by intervention arm and analysis phase.

5.4.2.1.3. Suppressed HBV DNA

The number of occurrences each participant has HBV DNA <LLOQ (overall and separately for HBV DNA detectable and HBV DNA TND) will be determined and summarized by intervention arm using frequency distributions and descriptive statistics. Additionally, the number of occurrences will be displayed graphically.

The same analyses will also be performed for HBV DNA < 60 IU/mL.

5.4.2.1.4. Flares

The incidence rate will be calculated and summarized for on-treatment biochemical flares by intervention arm. Additionally, for each participant the total number of flares the participant experienced will be counted by type. Such counts will be used to summarize the distribution of the total number of flares by type and intervention arm.

The number and percentage of participants with ALT flares will be calculated by the peak ALT value during the flare using the following cut-offs:

- <3 x ULN
- ≥3-<5 x ULN
- ≥5-<10 x ULN
- ≥10 x ULN.

The incidence rate of flares will also be calculated before and after week 12.

For on-treatment biochemical flares, the incidence of flares causing treatment discontinuation will be summarized by intervention arm. Similarly, the incidence of flares followed by the achievement of HBsAg seroclearance (at any time) will be summarized by flare type and intervention arm.

Flares that are associated with signs of liver decompensation will be provided in a listing.

5.4.2.2. Continuous Endpoints

5.4.2.2.1. HBsAg, HBeAg, HBV DNA and ALT

Descriptive statistics on actual values (original unit and/or $\log_{10}$ transformed values) over time in HBsAg, HBeAg, HBV DNA, and ALT (original unit) will be summarized by intervention arm. Changes from baseline ($\log_{10}$ transformed values) over time in HBsAg, HBeAg, and ALT (original unit) and changes from RTs ($\log_{10}$ transformed) over time in HBsAg will be summarized by intervention arm. Mean (+/- SE) plots of the actual values in HBsAg, HBV DNA and ALT (original unit) and change from baseline ($\log_{10}$ transformed)) will be presented over time in HBsAg and ALT (original unit) - by intervention arm and analysis phase. Change from RTs ($\log_{10}$ transformed) will be presented over time in HBsAg by intervention arm and analysis phase The change from baseline value to the nadirs (i.e. maximum decrease for each participant) in HBsAg will be summarized descriptively by intervention arm. Box plots of the changes to nadirs in HBsAg will display the distribution by intervention arm.

Change from baseline based on $\log_{10}$ transform for quantitative HBsAg, HBeAg and HBV DNA will be analyzed using mixed effects model for repeated measures [MMRM]) including intervention arm, analysis time point (week), and the randomization stratification factor (ie, absolute HBsAg value at screening [<100 IU/mL, 100 to <1,000 IU/mL versus ≥1,000 IU/mL]) as fixed effects. In addition, the above model will be augmented with an intervention arm-by-analysis week interaction term (i.e. treatment-by-time interaction term) to evaluate the change of treatment effect over time. The covariance structure will include a random intercept at the level of the participant to capture between-participant variability, while within-participant variability will be captured with an unstructured (type=UN) covariance matrix. In case of convergence problems, simpler variance-covariance structures such as Toeplitz or AR (1) will be considered. The selection of any of these structures will be determined after exploration of the observed correlation structure. The LS mean of change from baseline, standard error (SE), 90% confidence interval (CI) and p-values will be provided.

Descriptive statistics on actual values (original unit and $\log_{10}$ transformed values) in HBsAg, HBeAg and HBV DNA and changes from baseline ($\log_{10}$ transformed values) at end of treatment

in HBsAg, HBeAg and will be summarized by study intervention arm by outcome response (i.e. by HBsAg seroclearance at FU Week 24 and FU Week 48).

Waterfall plots for actual values, changes from baseline of HBsAg will also be presented.

Descriptive statistics of the absolute values, changes from baseline over time in ALT will be summarized by intervention arm and analysis phase for those participants who had ALT elevation at baseline. An additional summary of descriptive statistics of the ALT absolute values and changes from baseline over time will be summarized by intervention arm and analysis phase for those participants who had ALT values within the normal range at baseline.

5.5. Exploratory Endpoints

5.5.1. Definitions

5.5.1.1. Binary Endpoints

5.5.1.1.1. Sustained HBsAg Response

The definitions of sustained response are as follows (yes/no):

Definition 1:

- For participants with follow-up week 48 data: Participants who have a > 1 log decline in HBsAg at follow-up week 48 and have an HBsAg <1000 IU/mL at follow-up week 48.
- For participants without follow-up week 48 data: HBsAg values have a > 2 log decline at follow-up week 24 or >1.5 log decline at follow-up week 40 (most recent value used) compared to baseline and have an HBsAg <1000 IU/mL at the last available timepoint.

Definition 2: For participants with a >1 log decline in HBsAg from baseline at last follow-up visit: Among the most recent three visits, the difference between log HBsAg at 2 of 3 last visit and 1 of 3 last visit is <0.2, and the difference between log HBsAg at 3 of 3 last visit and 1 of 3 last visit is <0.2.

Definition 3: For participants with a >1 log decline in HBsAg from baseline at last follow-up visit: Among the most recent three visits, the difference between log HBsAg at 2 of 3 last visit and 1 of 3 last visit is <0.2, and the difference between log HBsAg at 3 of 3 last visit and 1 of 3 last visit is <0.2 and have an HBsAg <1000 IU/mL at the last available timepoint.

Due to the exploratory objectives of this Phase 2 study, additional sustained HBsAg response definitions may be explored according to the clinical interest.

5.5.1.1.2. Liver Stiffness Measurement

The following liver stiffness measurements (LSM) changes from baseline (in terms of reductions) will be evaluated over time at Week 24, FU Week 24 and FU Week 48:

- ≥ 2 kPa
- ≥ 4 kPa

- ≥ 6 kPa

Only participants from sites with available VCTE (Fibroscan) will be included in the analysis. Within these participants, missing LSM (in kPa) at a specific timepoint will be considered as non-responders for that timepoint.

5.5.1.1.3. HBV RNA Cut-offs

The cut-offs for HBV RNA are as follows (yes vs no):

- TND
- < LOD
- < LLOQ
- <1000 copies/mL

The cut-offs for HBV RNA change from baseline are as follows (yes vs no):

- decrease by ≥ 1.0 log copies/mL
- decrease by ≥ 2.0 log copies/mL
- decrease by ≥ 3.0 log copies/mL

5.5.1.1.4. HBcrAg Cut-offs

The cut-offs for HBcrAg are as follows (yes vs no):

- < 3.0 log U/mL
- < 4.0 log U/mL

The cut-offs for HBcrAg change from baseline are as follows (yes vs no):

- decrease by ≥ 1.0 log U/mL
- decrease by ≥ 2.0 log U/mL
- decrease by ≥ 3.0 log U/mL
- decrease by ≥ 4.0 log U/mL

5.5.1.2. Continuous Endpoints

5.5.1.2.1. Liver Stiffness Measurement

Severity of liver disease at the end of study intervention and follow-up versus baseline will be evaluated by the changes in fibrosis over time according to Fibroscan LSM.

Change from baseline is defined as the value at a given time point minus baseline value.

5.5.1.2.2. HBV RNA and HBcrAg

Actual values, changes from baseline (log transformed value) over time in HBV RNA and HBcrAg will be evaluated.

Change from baseline is defined as the value at a given time point minus baseline value.

5.5.2. Analysis Methods

Summaries and graphs will be provided for each intervention arm and analysis phase, unless specified otherwise.

Statistical comparisons of all exploratory endpoints among intervention arms will be done with no adjustment for multiplicity.

All exploratory endpoints will be analyzed based on the observed case data.

Inferential and descriptive subgroup analyses may not be performed if there are not enough data to perform the analyses.

5.5.2.1. Binary Endpoints

The count and proportion (%) of participants achieving the endpoints defined in Section 5.4.2.1 will be summarized. The associated 90% CI may also be included.

5.5.2.2. Continuous Endpoints

The methods of analysis of the continuous exploratory endpoints will be the same as those described in Section 5.4.2.2.

Waterfall plots for changes from baseline HBcrAg and fibrosis will also be presented.

Subsections below describe the additional analyses planned for only those specific exploratory endpoints that require further evaluations.

5.5.2.2.1. Liver Stiffness Measurement

The changes from baseline at Week 24, FU Week 24, and FU Week 48 will be summarized using descriptive statistics (n, mean, SD, SE, 90% CI, median, minimum, maximum) by intervention arm. The comparison among intervention arms will be done using ANCOVA with intervention arm, randomization stratification factor as main effects and baseline score as covariate.

At each assessment time point, a frequency distribution of severity scores will be produced.

5.5.2.2.2. Anti-HBs Antibodies

For all participants with positive anti-HBs antibodies at baseline who will reach HBsAg seroclearance (as defined in Section 5.4.1.1.2), descriptive statistics will be calculated for the change of anti-HBs antibodies level from baseline at the timepoint and subsequent timepoints when achieving the HBsAg seroclearance. In an additional summary, the change of anti-HBs antibodies level from baseline at the specific timepoint and subsequent timepoints will be summarized descriptively for the subset of the participants achieving HBsAg seroclearance at any time before or at that given timepoint.

5.6. Safety Analyses

Summaries will be provided on the overall population and by intervention arm and analysis phase unless specified otherwise.

Safety and tolerability will be assessed by evaluating treatment emergent-adverse events (TEAEs), immune related AEs, physical examinations, vital signs measurements, clinical laboratory tests (including hematology, blood biochemistry, blood coagulation, and urinalysis), renal biomarkers and ECGs.

For all continuous safety variables, descriptive statistics by intervention group will include the N, mean, standard deviation, standard error, median, minimum, and maximum. Categorical variables will be summarized by intervention group using frequency counts and percentages.

5.6.1. Extent of Exposure

The number and percentage of participants who receive each study agent within a study intervention will be summarized.

Descriptive statistics for duration of each study agent within a study intervention (N, mean, SD, SE, median, and range (minimum, maximum)) during the study intervention period will be summarized.

Because of the different route and frequency of treatment administration across the 3 agents (for JNJ-3989 one subcutaneous injection every week for the first 4 weeks and then once every 4 weeks, for nivolumab one intravenous infusion at Week 16 in Arm 1 and Week 16, 20 and 24 in Arm 2, and for NA once daily tablet) the total duration for each study agent as follows:

- JNJ-3989:
  - Discontinuation of JNJ-3989 before Week 4:
    - [Min ((Date of last JNJ-3989 (loading dose) injection +6 days), Date of trial disposition, cut-off date) – Date of first JNJ-3989 injection+ 1] / 7
    - Otherwise: [Min ((Date of last JNJ-3989 injection + 27 days), Date of trial disposition, cut-off date) – Date of first JNJ-3989 injection + 1] / 7
- Nivolumab: [Min (Date of the last nivolumab infusion + 27 days, Date of trial disposition, cut-off date) – Date of first nivolumab infusion + 1] /7

Cutoff dates will be defined to match the prespecified timepoints for interim analyses and the primary analysis, respectively (Section 5.8).

The number and percentage of participants who skipped any dose of JNJ-3989 or nivolumab will be summarized separately for each study intervention by intervention arm during the study intervention period. Additionally, the number and percentage of participants who missed 2 or more JNJ-3989 injections, or who missed 1 or more nivolumab infusion will be presented.

Study intervention compliance will be summarized descriptively. See Appendix 7 Intervention Compliance for further details.

5.6.2. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 25.0). Any AE occurring at or after the initial administration of study intervention is considered to be treatment emergent. If the event occurs on the day of the initial administration of study intervention, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study intervention based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention arm.

Summary tables will be provided for treatment-emergent adverse events:

- AEs
- Serious AEs (SAEs)
- AEs leading to discontinuation of any study agent within a study intervention
- AEs by relationship to each study agent within a study intervention
- AEs leading to dose interruption/dose modification of each study agent within a study intervention.
- AEs leading to systemic corticosteroid administration.

In addition to the summary tables, listings will be provided for participants who:

- Had SAEs
- Had AEs leading to discontinuation of each study agent within a study intervention

For participants reporting rash, a listing with specific grade will be provided.

Incidence of treatment-emergent adverse events of special interest will be summarized by analysis phase and overall

The adverse events of special interest include:

- Immune related AEs
- ALT/AST elevations
- Injection Site Reactions Related to JNJ-3989
- Infusion Reactions Related to nivolumab
- Renal Complications
- Hematologic Abnormalities (platelet count, hemoglobin, reticulocytes, neutrophil count)

The list of all preferred terms belonging to ALT/AST elevation, renal complications, and hematologic abnormalities is provided in Table 10 Appendix 8. Injection and infusion site reactions will be identified using the eCRF Injection Site Reaction Assessment form for JNJ-3989 and Infusion-related reactions for Nivolumab. Immune related AEs will be also identified using the eCRF Adverse events/Serious AEs form based on the related question.

A listing of participants who died will be provided.

5.6.3. Additional Safety Assessments

5.6.3.1. Clinical Laboratory Tests

Laboratory data will be summarized by category of laboratory test. The different categories and laboratory tests used in the analysis are listed in Table 5.

Table 5: Laboratory Parameters

Laboratory Assessments	**Parameters**		
Hematology	Platelet count Red blood cell count Hemoglobin Hematocrit	RBC Indices: MCV MCH % Reticulocytes	White Blood Cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	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.		
Hematology Coagulation	Activated partial thromboplastin time Prothrombin Intl. normalized ratio Prothrombin time		
Clinical Chemistry	Sodium Potassium Chloride Bicarbonate Blood urea nitrogen (BUN) Creatinine Cystatin C 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)	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	

Table 5: Laboratory Parameters

Laboratory Assessments	Parameters	
		amylase or lipase increase from screening onwards)
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 (e.g. quantification as applicable).	
Urine Chemistry (quantitative measurement)	Creatinine Sodium Phosphate	Glucose Protein Albumin
Renal Biomarkers	Retinol binding protein Beta-2-microglobulin ***Note:*** Other biomarkers might be measured.	
Other Tests	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 Thyroid function tests: TSH, T3 and T4	

Clinical laboratory tests will be displayed for the participants included in the safety analysis set.

Descriptive statistics and graphical displays will be presented for all chemistry, hematology, and urinalysis laboratory tests at scheduled time points.

Change from baseline over time will be summarized for chemistry, hematology, urinalysis tests and renal biomarkers and displayed.

Abnormality criteria (based on the criteria specified in the Modified DAIDS Toxicity Grade Scale (see Clinical Protocol Appendix 8, DAIDS Table with Modifications (DAIDS [Modified]))) will be applied to baseline and postbaseline values or in accordance with the normal ranges of the clinical laboratory if no gradings are available.

Postbaseline abnormalities will be compared with their corresponding baseline result:

- For toxicity grades, treatment emergent (TE) will be concluded if the postbaseline grade is worse than the baseline grade.

- For abnormalities based on normal range and/or criteria: If the postbaseline value is above the upper limit and the baseline value is below the upper limit (e.g. Normal or Low), then the postbaseline abnormality will be considered TE. The same applies to the postbaseline value being below the lower limit with the baseline value being above the lower limit (e.g. Normal or High).
- If the baseline value is missing, a postbaseline abnormality will always be considered as TE.

For each lab parameter, a worst-case analysis will be performed by using the worst abnormality and/or worst toxicity grade lab value and time point per participant. The worst toxicity case is the value associated to the highest toxicity grade and is derived per parameter and toxicity direction (hypo/hyper). Worst-case will be derived withing each analysis phase, including unscheduled assessments. For abnormalities, in case the same participant has both abnormalities (low and high) for the same lab test within the same phase, the participant will be counted in the analysis for both toxicity directions (abnormally high and low).

In case continuous laboratory results are not numerically expressed, but as a character (e.g. 'less than 2', '>25'), these results will be numerically imputed as follows:

- If the analysis result contains '<' then the result will be multiplied by 0.999 (e.g. <6.1 becomes 6.0939).
- If analysis result contains '>' then the result will be multiplied by 1.001 (e.g. >6.1 becomes 6.1061).
- If analysis result contains '≤' or '≥' then only the numeric portion of the result will be used.

This also applies to normal limits expressed as such.

Shift tables will be provided summarizing the shift in laboratory values from baseline over time with respect to abnormality criteria (low, normal, high) for each laboratory parameter by analysis phase.

The cross-tabulations of the worst toxicity grades over time versus baseline grade and the worst abnormalities versus baseline grade per parameter and per analysis phase will be presented including also the number of participants per worst grade and the number of participants per abnormality.

A tabulation of percentage and number of the participants who have treatment-emergent worst toxicity grades and treatment-emergent worst abnormalities per parameter and analysis phase will be included.

Plots of mean (+/- SE) values and changes from baseline over time for selected laboratory parameters will be presented by intervention arm. Spaghetti-plots for selected laboratory parameters will be presented over time by intervention arm (with Week shown on x-axis).

A listing including all parameters with at least one treatment-emergent toxicity or abnormality per participant (exclusion of urinalysis) will be generated.

5.6.3.2. Renal Safety

Renal safety parameters include the urine creatinine, serum creatinine, urine glucose, total urine protein, total urine albumin, urine protein to creatinine ratio (UPCR), urine albumin to creatinine ratio (UACR), retinol binding protein (RBP), beta-2-microglobulin, RBP to creatinine ratio, beta-2-microglobulin to creatinine ratio, urine fractional excretion of phosphate (FEPO4), Cystatin C, eGFR based on Creatinine (eGFRcr), eGFR based on Cystatin C (eGFRcys).

Descriptive statistics (n, mean, SD, SE, minimum, median, and maximum) will be calculated for each parameter for observed values and changes from baseline at each scheduled time point by intervention arm and analysis phase.

Plots of mean (+/- SE) values and changes from baseline over time for the renal safety parameters will be presented.

A confirmed eGFRcr Grade ≥3 is defined as a Grade 3 or higher at 2 consecutive post-baseline measurements or an abnormality observed at 1 measurement followed by study drug discontinuation.

A listing including all renal safety parameters for participants with at least one treatment-emergent eGFRcr Grade 3 or higher will be generated. Another listing will be generated with renal safety parameters for participants who had a confirmed eGFRcr Grade 3 or higher.

5.6.3.2.1. eGFR Creatinine and eGFR Cystatin C

The following analyses will be done for both eGFRcr and eGFRcys

Stages of eGFR at baseline versus the minimum post-baseline eGFR value and the last available value will be summarized by count and percent of participants. Kidney disease stages are defined as follows: 1 (Normal): eGFR ≥ 90; 2 (Mild): eGFR 60-89; 3 (Moderate): eGFR 30-59; 4 (Severe): eGFR <30.

In addition to the above, the number and proportion of participants with a 10-<30%, 30-<50% and ≥50% decrease from baseline will be tabulated.

Scatter plots of eGFR versus other renal biomarkers (total urine protein, total urine albumin, urine protein to creatinine ratio [UPCR], urine albumin to creatinine ratio [UACR], retinol binding protein (RBP) and beta-2-microglobulin, RBP to creatinine ratio and beta-2-microglobulin to creatinine ratio, and urine fractional excretion of phosphate [FEPO4]) as well as spaghetti plots will be presented.

In addition, cystatin C assessment is being performed as part of this study. eGFRcys will also be calculated by using the CKD-EPI cystatin C equation.

Differences between the two types of GFR calculation will be assessed. Cross-tabulation of eGFRcr (<10%, 10-<30%, 30-<50% and ≥50% decrease from baseline) versus eGFRcys (<10%, 10-<30%, 30-<50% and ≥50% decrease from baseline) will be presented over time.

5.6.3.2.2. Proximal Renal Tubular Function

Proteinuria by Quantitative Assessment

Total urine protein, total urine albumin, UPCR and UACR will be summarized by intervention arm and visit using descriptive statistics.

The number and proportion of participants with UACR and UPCR results in the following categories over time will be tabulated:

- UACR: < 30, ≥ 30 to 300, >300 mg/g
- UPCR: < 200 mg/g versus ≥ 200 mg/g

Median (Q1, Q3) percent change from baseline over time will be plotted by intervention arm.

The evolution over time of total urine protein and total urine albumin will also be presented.

Proteinuria by Urinalysis (Dipstick)

Treatment-emergent proteinuria by urinalysis (dipstick) over time will be summarized by intervention arm. Cross-tabulation of grades overtime versus baseline will also be presented.

Other Renal Biomarkers

Selected renal biomarkers RBP and beta-2-microglobulin, RBP to creatinine ratio and beta-2-microglobulin to creatinine ratio will be summarized by intervention arm and visit using descriptive statistics.

The number and proportion of participants with beta-2-microglobulin to creatinine ratio ≤343.5 µg/g and >343.5 µg/g will be tabulated over time.

The number and proportion of participants with retinal binding protein to creatinine ratio results in the following categories overtime will be tabulated:

- < 50 years of age: < 130 mcg/g creatinine, ≥ 130 mcg/g creatinine
- ≥ 50 years of age: < 172 mcg/g creatinine, ≥ 172 mcg/g creatinine

Phosphate excretion

Other renal biomarkers include FEPO4 that will be summarized by intervention arm and visit using descriptive statistics.

FEPO4 will be calculated as follows:

- Based on unadjusted serum creatinine:

  $FEPO4\ (\%) = (SCr \times UPO4) / (SPO4 \times UCr) \times 100\ (\%)$

Where SCr is serum creatinine concentration, UPO4 is urine phosphate concentration, SPO4 is serum phosphate concentration, and UCr is urine creatinine concentration.

The proportions of participants with FEPO4 ≤10% and >10% will be tabulated.

The baseline, post-baseline, and change from baseline in FEPO4 will be summarized by intervention arm and visit using descriptive statistics. Median (Q1, Q3) change from baseline in FEPO4 over time will be plotted by intervention arm.

Subclinical renal proximal tubulopathy

Potential Markers of Renal Proximal Tubulopathy are:

1. Confirmed increase in serum creatinine ≥ 0.40 mg/dL from baseline.
2. Confirmed ≥ 2 grade level increase from baseline in graded proteinuria
3. Confirmed ≥ 1 grade level increase from baseline in graded hypophosphatemia
4. Confirmed ≥ 1 grade level increase from baseline in graded glycosuria concurrent with serum glucose ≤100 mg/dL (normoglycemic glycosuria)

A confirmed laboratory abnormality is defined as an abnormality observed at 2 consecutive post-baseline measurements or an abnormality observed at 1 post-baseline measurement followed by study drug discontinuation.

A subclinical renal proximal tubulopathy will be defined as confirmed abnormalities in any 2 out of the 4 renal parameters (serum creatinine and one or more of the 3 other markers of tubular dysfunction).

Baseline Subclinical renal proximal tubulopathy

Potential Markers of Renal Proximal Tubulopathy at Baseline

1. Grade ≥ 1 serum creatinine
2. Grade ≥ 2 proteinuria
3. Grade ≥ 1 hypophosphatemia
4. Grade ≥ 1 glycosuria concurrent with serum glucose ≤100 mg/dL (normoglycemic glycosuria)

A baseline subclinical renal proximal tubulopathy will be defined as abnormalities in 2 out of the 4 renal parameters (serum creatinine + 1 or more of the 3 other markers of tubular dysfunction).

5.6.3.3. Vital Signs

The following parameters measurements will be analyzed:

- Supine pulse rate (bpm)

- Supine systolic blood pressure (mmHg)
- Supine diastolic blood pressure (mmHg)
- Body temperature (°C)

The abnormalities in vital signs will be determined according to the criteria specified in the Cardiovascular Safety – Abnormalities Table (see Clinical Protocol Appendix 7).

An assessment is treatment-emergent if abnormality worsened as compared to the abnormality at baseline; this also includes the shift from abnormally high to abnormally low and vice-versa. Post-baseline abnormalities are always treatment-emergent with regard to missing abnormalities at baseline. The abnormally high values (i.e. abnormally high, grade 1 or mild, grade 2 or moderate, grade 3 or severe) versus the abnormally low values are considered equally important.

For each parameter, a "worst-case" analysis will be performed by using the worst abnormality and time point per participant. Worst-case will be derived within each analysis phase, including unscheduled assessments. In case the same participant has both abnormalities (low and high) for the same test within the same phase, the participant will be counted in the analysis for both abnormality directions (abnormally high and low).

Vital signs records with partial dates (any of day/month/year is missing) will not be used in the analysis but will be listed.

Descriptive statistics of continuous vital sign parameters and body temperature will be calculated for observed values and changes from baseline at each scheduled time point.

Shift tables will be provided summarizing the shift in vital sign and body temperature values from baseline over time with respect to abnormality criteria (low, normal, high) for each parameter by analysis phase.

A cross-tabulation of the worst abnormalities versus baseline per parameter and analysis phase will be presented including also the number of participants per abnormality, the number of participants with treatment emergent abnormalities per abnormality.

A tabulation of percentage and number of the participants who have treatment-emergent worst abnormalities per parameter and analysis phase will be included.

A listing including all parameters for participants with at least one treatment-emergent abnormality (on actual values or change from baseline) is provided. Additional vital signs assessments corresponding to the rash eCRF pages will be only listed as applicable.

The physical examination findings and abnormalities will be listed.

5.6.3.4. Electrocardiogram

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

The ECG parameters that will be analyzed are heart rate (bpm), PR interval (ms), RR interval (ms), QRS interval (ms), QT interval (ms), and corrected QT (QTc) interval using the following correction methods:

Fridericia's formula: QTcF (msec) = QT (msec) / (RR (msec)/1000)$^{1/3}$; if RR is missing, use QT (msec) * (HR(bpm)/60)$^{1/3}$;

The abnormalities in ECG parameters will be determined according to the criteria specified in the Cardiovascular Safety – Abnormalities Table (see Clinical Protocol Appendix 7, Cardiovascular Safety- Abnormalities Table). Abnormalities on actual values are provided for HR, PR, QRS and QTcF. Additional abnormalities on change from baseline will be provided for QTcF. No abnormalities will be defined for actual uncorrected QT values. Uncorrected QT ≥ 500 ms will be flagged and only shown in listings.

An assessment is treatment-emergent if abnormality worsened as compared to the abnormality at baseline; this also includes the shift from abnormally high to abnormally low and vice-versa. Post-reference abnormalities are always treatment-emergent with regard to missing abnormalities at baseline. The abnormally high values (i.e. abnormally high, borderline prolonged, prolonged, pathologically prolonged) versus the abnormally low values are considered equally important. Abnormalities defined on changes from baseline are always treatment-emergent.

For each parameter, a "worst-case" analysis will be performed by using the worst abnormality and time point per participant. Worst-case will be derived within each analysis phase, including unscheduled assessments. In case the same participant has both abnormalities (low and high) for the same test within the same phase, the participant will be counted in the analysis for both abnormality directions (abnormally high and low).

For the time points on which triplicate ECGs apply, a rounded mean value to the next integer per triplet will be calculated per time point before any further handling. This rounded mean value will be used through the entire analysis also in case of 1 or 2 missing values.

ECG records with partial dates (any of day/month/year is missing) will not be used in analysis, except in the listings. The following imputation rules will be applied.

If heart rate (HR) is missing, it will be calculated using RR (if available) and rounded to the integer value (see formula below) before any further handling if applicable.

$$\frac{1000}{RR(ms)} = \frac{HR(bpm)}{60}$$

HR from the vital signs section (i.e. pulse) will not be used in this ECG analysis section. RR values (if available) will only be listed. Recalculated HR values will be flagged.

Descriptive statistics will be calculated for observed values and changes from baseline per parameter (all parameters except for RR) at each scheduled time point by intervention arm and analysis phase.

Shift tables will be provided summarizing the shift in ECG values from baseline over time with respect to abnormality category (low, normal, high) for each parameter by analysis phase.

A cross-tabulation of the worst abnormalities (on actual values) versus baseline per parameter by analysis phase will be presented including also the number of participants per abnormality. A tabulation of number and percentage of the participants who have treatment-emergent worst abnormalities per parameter (i.e. for HR, PR, QRS and QTcF) and analysis phase will also be presented.

A cross-tabulation of the worst change from baseline abnormalities (i.e. for QTcF) versus the baseline category per parameter will be presented by intervention arm and analysis phase.

Frequency tabulations of categorized corrected QT/QTc change from baseline (≤30 msec, >30-≤60 msec, >60 msec) and categorized corrected QT/QTc interval values (≤450 msec, >450- ≤480 msec, >480-≤ 500 msec, >500 msec) per timepoint will be presented by intervention arm.

Listings including all parameters for participants with at least one treatment-emergent abnormality (on actual values or change from baseline), including all findings (e.g. interpretation, rhythm, or technical findings) for participants with uncorrected QT values ≥ 500 ms will be provided separately.

5.6.3.5. Physical and Ophthalmic Examinations

The physical and ophthalmic examination findings and abnormalities will be listed. A listing of participants who experienced a decrease or loss of vision at any timepoint during study will be provided.

5.7. Other Analyses

5.7.1. Pharmacokinetics

Population PK analysis of plasma concentration-time data of JNJ-73763976 (JNJ-3976), and JNJ-73763924 (JNJ-3924) may be performed using non-linear mixed effects modeling. Data from the current study may be combined with prior information available from Phase 1 and/or 2 studies to support a relevant structural model. Available participant characteristics (e.g. demographics, laboratory variables, genotypes) may be included in the model as necessary. If a population PK analysis is conducted, the results will be presented in a separate report.

5.7.2. Pharmacokinetic/Pharmacodynamic Relationships

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

Modeling of key PD parameters (e.g. 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.

5.7.3. Receptor Occupancy

Individual Receptor Occupancy values may be provided in a listing and summarized by descriptive statistics (n, mean, SD, geometric mean, median, minimum, and maximum and IQ range). Individual and summarized RO results may be graphically presented by intervention arm and selected time points.

5.7.4. Immune Analyses

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

Graphs showing the individual participant values as dots, together with horizontal lines indicating the corresponding median and interquartile range (IQR) per time point for each assay will be presented. The spaghetti plots may be used to show the patient profiles per time point for each assay. A graph showing the median and IQR over time by intervention arm will be presented. A bar chart may be used to show the breadth of response (i.e. HBV-specific immune response rate for combinations of peptide pools).

For intracellular cytokine staining (ICS), for all cytokine combinations (IFN-γ and/or TNF-α and/or IL-2), pie charts may be presented to reflect the distribution of each of the cytokine combinations (i.e. the proportion of a specific cytokine combination of the CD4 or CD8 T-cells secreting at least one cytokine), and bar charts may be presented to reflect the mean magnitude of each combination.

5.7.5. Viral Genome Sequence Analysis

Viral genome sequence analysis may be performed to identify pre-existing baseline polymorphisms and to evaluate emergence of genetic variations (including substitutions) associated with JNJ-56136379, JNJ-3989, and/or ETV or TD treatment on both nucleotide and/or amino acid level.

The sequencing of samples may be triggered by the sponsor virologist based on changes in HBV DNA levels observed in each individual participant and the limits of the sequencing assay.

Virology results may be presented by specified timepoints and genetic region and position of interest. A separate virology report may be prepared.

5.8. Data Review Committee and Interim Analyses

5.8.1. Data Review Committee

The internal DRC will conduct periodic data review to ensure the continuing safety of the study participants during the entire course of the study. The DRC will also review the results of the primary and interim analyses (IAs) comprising cumulative safety and selected efficacy endpoints for providing the sponsor with further insight and interpretation of the data. Details on the roles and responsibilities of the DRC, as well as data reviews and the flows of communication, are documented in the DRC charter. Description of the DRC is provided in Section 9.6 of the Master Protocol PLATFORMPAHPB2001.

5.8.2. Independent Flare Expert Panel

An IFLEP is 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 is included in the IFLEP charter.

5.8.3. Data Reviews and Interim Analyses

The DRC will conduct periodic safety data reviews (DRs) to ensure the continuing safety of the study participants during the entire course of the study.

5.8.3.1. Data Reviews

The DRC will periodically review unblinded cumulative safety and efficacy data at the following timepoints:

- DR1: All randomized participants have completed Week 4 or discontinued earlier.
- Additional data reviews will occur quarterly after the first review for 2023 and then every 6 months. If the timing of a data review is close to the cutoff point for any of the interim analyses, then only the closest IA will take place.

Safety data comprising AEs, SAEs, AEs of special interest, laboratory data, electrocardiogram (ECG) data and any other data applicable for the study, will be summarized, plotted and provided as appropriate.

Besides the safety variables listed above, selected efficacy parameters for review may include values and changes from baseline over time in HBV disease blood markers (such as HBsAg, HBeAg, HBV DNA and ALT), proportion of participants with virologic breakthrough and flares.

5.8.3.2. Interim Analyses

Interim analyses (IAs) may be conducted to assess safety and efficacy to support the sponsor's interactions with health authorities, as well as to inform decisions about additional studies and/or investigation of other treatment combinations. The 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 primary analysis will be conducted at the time when all participants have completed FU Week 24 or discontinued earlier.

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

The final analysis will be conducted at the time when all participants have completed the last study visit (FU Week 48) or discontinued earlier.

5.8.3.3. Overview of Data Reviews, Interim, Primary and Final Analyses

The overview of data domains and specific endpoints that will be provided to the DRC for review is presented in Table 6. Details on the type of summaries and analyses of both efficacy and safety variables are described in the following sections.

Table 6: Overview of Data Summaries and Analyses to be Provided to the DRC at Data Reviews, Interim, Primary and Final Analyses

	DR1/ Week 4 (approx. N=37)	DR approx. every 8 weeks	IA1/ Week 24 (N=37)	IA2/ FU Week 12 (approx. N=37)	Primary analysis/ FU Week 24 (N=37)	Final analysis/ Week 72 (N=37)
Participant information						
Baseline & Demographic characteristics	X	X	X	X	X	X
Disposition and Study Populations	X	X	X	X	X	X
Extent of Exposure	X	X	X	X	X	X
Safety						
TEAEs, SAEs, AE of special interest, fatal AEs, AEs causing treatment discontinuation	X	X	X	X	X	X
Laboratory tests	X	X	X	X	X	X
ECG	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X
Efficacy						
Proportion of participants with HBsAg seroclearance		X	X	X	X	X
Values and Changes over time in HBsAg, HBeAg, HBV DNA and ALT	X**	X**	X	X	X	X
Proportion of participants with HBsAg, HBeAg, HBV DNA and ALT below/above different cutoffs	X**	X**	X	X	X	X
Other secondary efficacy endpoints		X	X	X	X	X
Exploratory endpoints		X	X	X	X	X
Virologic breakthrough	X	X	X	X	X	X
Flares	X	X	X	X	X	X
PK*			X	X	X	X
Immune response*					X	X
RO*			X	X	X	X

* If there are available data to analyze.
**Only HBsAg will be analyzed for Data Reviews.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

aa	amino acid
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATC	anatomic and therapeutic class
AUC	area under the curve
BMI	body mass index
BUN	blood urea nitrogen
CI	confidence interval
Cmax	maximum concentration
CPK	creatinine phosphokinase
CRF	case report form
CSR	Clinical Study Report
CV	coefficient of variation
DAIDS	division of acquired immunodeficiency syndrome
db	database
DR	data review
DRC	Data Review Committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
eGFRcr	estimated glomerular filtration rate calculated based on Creatinine
eGFRcys	estimated glomerular filtration rate calculated based on Cystatin C
EOS	end of study
EOSI	end of study intervention
ETV	entecavir
FAS	full analysis set
FC	functional cure
FEPO4	urine fractional excretion of phosphate
FU	follow-up
GGT	Gamma-glutamyltransferase
HBcrAg	hepatitis B core-related antigen
HBs	hepatitis B surface
HbeAg	hepatitis B envelope antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HBV DNA	hepatitis B virus deoxyribonucleic acid
HBV RNA	hepatitis B virus ribonucleic acid
IA	interim analysis
ICS	intracellular cytokine staining
iFLEP	independent flares expert panel
IFN-N	Nivolumab full analysis set
IQR	interquartile range
IRT	item response theory
ISR	injection site reaction
IU/mL	international units per milliliter
IV	intravenous
IWRS	interactive website response system
LiPA	line probe assay
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LSM	liver stiffness measurement
MCS	mental component summary

MedDRA	medical dictionary for regulatory activities
MANR	missing as non-responder
MCAR	missing completely at random
mFAS	modified full analysis set
MH	Mantel-Haenszel
MI	multiple imputation
mIFN-FAS	modified PegIFN-α2a full analysis set
MNAR	missing not at random
MRU	medical resource utilization
NA	nucleos(t)ide analog
NCBI	National Center for Biotechnology Information
NGS	next generation sequencing
nt	nucleotide
PBMC	peripheral blood mononuclear cell
PC	precore
PCS	physical component summary
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	per protocol
Q4W	every 4 weeks
qd	once daily
QTc	corrected QC interval
QTcF	QT interval corrected for heart rate according to Fridericia
QW	once weekly
RR	Interval between R wave of one heartbeat and R wave of preceding heartbeat
RT	reference timepoint
RO	receptor occupancy
SAE	serious adverse event
SAP	statistical analysis plan
SCr	serum creatinine
SD	standard deviation
SEB	staphylococcal enterotoxin assay
SPO4	serum phosphate
T4	thyroxine
TAF	tenofovir alafenamide
TD	target detected
TEAE	treatment-emergent adverse event
TeD	tenofovir disoproxil
Tmax	time to maximum concentration
TND	target not detected
TNF	tumor necrosis factor
TSH	thyroid stimulating hormone
ULN	upper limit of normal
ULOQ	upper limit of quantification
UPCR	urine protein to creatinine ratio
USM	Urgent Safety Issue
VAS	Visual Analog Scale
WBC	white blood cell

6.2. Appendix 2 Changes to Protocol-Planned Analyses

Changes to protocol-planned analyses are documented in this SAP.

6.3. Appendix 3 Demographics and Baseline Characteristics

The number of participants in each analysis set will be summarized and listed by intervention group, and overall. In addition, the distribution of participants by region, country, and site ID will be presented unless otherwise noted.

6.3.1. Demographics

Table 7 presents a list of the demographic variables that will be summarized by intervention group, and overall for the FAS.

Table 7: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
Weight at baseline (kg)	
Height at baseline (cm)	
Body Mass Index (BMI) at baseline (kg/m^2)	
Number of drinks containing alcohol (weekly period)	
Period of time using substances (beer, wine, distilled spirits) in months derived as = (stop date – start date+1)/30.4375; rounded to 1 decimal point	
Categorical Variables	
Age (≤45 years, >45 years)	Frequency distribution with the number and percentage of participants in each category.
Sex (male, female, undifferentiated)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
BMI at baseline (underweight <18.5 kg/m^2, normal ≥18.5-<25 kg/m^2, overweight ≥25-<30 kg/m^2, obese ≥30 kg/m^2)	
History of tobacco use (Yes, No)	
Type of substance use (beer, wine, distilled spirits): current, former, never	

[a] If multiple race categories are indicated, the Race is recorded as 'Multiple'

6.3.2. Baseline Characteristics

Table 8 presents a list of the baseline characteristics variables that will be summarized by intervention group, and overall for the FAS.

Table 8: Baseline Characteristics Variables

Continuous Variables	**Summary Type**
HBV history	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
Duration of HBV infection (years) = (date of randomization – date of HBV infection +1)/365.25; rounded to 1 decimal point	
Time since HBV diagnosis (Years) = (date of randomization – date of HBV diagnosis+1)/365.25; rounded to 1 decimal point	
Duration of NA at baseline (years)= (Sum of all NA treatment duration [prior and current])/365.25; rounded to 1 decimal; calculated as: end date – start date +1. If the end date is missing for latest NA treatment, then the randomization date is used.	

Table 8: Baseline Characteristics Variables

Continuous Variables	**Summary Type**
HBV viral activity and serology parameters	
HBeAg at baseline in IU/mL and log_{10} IU/mL	
HBsAg at baseline in IU/mL and log_{10} IU/mL	
HBV DNA at baseline in IU/mL and log_{10} IU/mL	
HBV RNA at baseline: values in copies/mL and log_{10} copies/mL	
HBcrAg at baseline in log_{10} U/mL	
HBsAg Antibody (Anti-HBs) at baseline in mIU/mL and log_{10} mIU/mL	
Liver Stiffness Measurement at baseline (kPa)	
Categorical Variables	**Summary Type**
HBV history	Frequency distribution with the number and percentage of participants in each category.
Mode of HBV infection: Sexual contact, injection needle reuse, blood transfusion, occupational exposure, vertical transmission, unknown and other	
Type of NA at baseline: TeD, TAF, ETV	
HBV viral activity and serology parameters	
HBsAg category at baseline (IU/mL): <100, ≥ 100 - < 1,000, ≥ 1000 - < 10,000, ≥ 10,000 - < 100,000, ≥ 100,000	
HBV DNA category at baseline (IU/mL): < LLOQ Target detected (TD) or not detected (TND), < LLOQ TD, < LLOQ TND, ≥ LLOQ - < 60, ≥60	
HBV RNA category at baseline (copies/mL): TND, < LOD, < LLOQ, ≥ LLOQ - < 1,000, ≥ 1,000	
HBcrAg category at baseline (log U/mL): < 3, ≥ 3 - < 4, ≥ 4	
HBsAg Antibody (Anti-HBs) status at baseline: Positive, Negative	
HBsAg Antibody (Anti-HBs) category at baseline (mIU/mL): < 10, ≥ 10	
HBeAg Antibody (Anti-HBe) status: Positive, Negative	
Baseline ALT toxicity grade according to DAIDS	
Baseline ALT categorization: ≤ 1.0xULN, > 1.0xULN to <2xULN, ≥ 2xULN	

6.4. Appendix 4 Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to database lock and the participants with major protocol deviations will be summarized by category.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other

All major protocol deviations will be tabulated by coded term for the FAS. A listing of the major protocol deviations will be also presented.

A subset of major protocol deviations that may affect the assessment of efficacy (Table 9) will be identified and finalized prior to database lock. The major deviations that are selected to exclude participants for the PP set are listed at Table 9. The flag for Intercurrent Event is added to each deviation for facilitating the implementation of the estimands for the primary endpoint.

The count and proportion of FAS participants without any major protocol deviations will be summarized by intervention arm, accompanied by count and proportion of FAS participants who had a major protocol deviation with the incidence of the major protocol deviations.

Table 9: Selected Major Protocol Deviations for Analysis Purposes

Sequence number (as reported in MPD)	Description	Protocol Deviation Description (DVTERM) as entered in Study Specific Issue System	Protocol Deviation Coded Term (DVDECOD)	Exclude from PP	Intercurrent Event
1	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.	Inclusion criteria A01 (adapted from M01) not met: Participant was <specify age> years old.	Entered but did not satisfy criteria	Yes	No
3	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,	Inclusion criteria A03 (adapted from M03a) not met: Participant does not have chronic HBV infection documented as required by protocol criteria: HBsAg positivity at screening with evidence of chronicity at least 6 months prior to screening: serum HBsAg	Entered but did not satisfy criteria	Yes	No

Table 9: Selected Major Protocol Deviations for Analysis Purposes

Sequence number (as reported in MPD)	Description	Protocol Deviation Description (DVTERM) as entered in Study Specific Issue System	Protocol Deviation Coded Term (DVDECOD)	Exclude from PP	Intercurrent Event
	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).	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. Participant was not: • HBeAg negative at screening, OR • 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, OR • having serum HBV DNA <60 IU/mL on 2 sequential			

Table 9: Selected Major Protocol Deviations for Analysis Purposes

Sequence number (as reported in MPD)	Description	Protocol Deviation Description (DVTERM) as entered in Study Specific Issue System	Protocol Deviation Coded Term (DVDECOD)	Exclude from PP	Intercurrent Event
		measurements at least 6 months apart (one of which is at screening), OR • having documented ALT values <2.0x ULN on 2 sequential measurements at least 6 months apart (one of which is at screening).			
13	Participants must have serum HBsAg from ≥5 to ≤10,000 IU/mL at screening, as assessed by quantitative HBsAg assay.	Inclusion criteria A13 not met Participant has serum HBsAg <5 or >10,000 IU/mL at screening, as assessed by quantitative HBsAg assay.	Entered but did not satisfy criteria	Yes	No
14	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	Inclusion criteria A14 not met Participant does not have Fibroscan liver stiffness measurement ≤9.0 kPawithin 6 months prior to screening or at the time of screening or a liver biopsy result classified as Metavir F0-F2 within 1 year prior to screening	Entered but did not satisfy criteria	Yes	No

Table 9: Selected Major Protocol Deviations for Analysis Purposes

Sequence number (as reported in MPD)	Description	Protocol Deviation Description (DVTERM) as entered in Study Specific Issue System	Protocol Deviation Coded Term (DVDECOD)	Exclude from PP	Intercurrent Event
	allowed to rule out severe fibrosis or cirrhosis.				
	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. • 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	Exclusion criterion A01 (adapted from M01) met: Participants has evidence of hepatitis A virus infection, HCV infection, HDV infection, hepatitis E virus (HEV) infection, or HIV-1 or HIV-2 infection at screening.	Entered but did not satisfy criteria	Yes	No

Table 9: Selected Major Protocol Deviations for Analysis Purposes

Sequence number (as reported in MPD)	Description	Protocol Deviation Description (DVTERM) as entered in Study Specific Issue System	Protocol Deviation Coded Term (DVDECOD)	Exclude from PP	Intercurrent Event
	HIV-2 infection who are on antiretroviral treatment are excluded				
16	Participants with evidence of hepatic decompensation at any time point prior to or at the time of screening (Unless explained by a clinical setting that is not hepatic decompensation): a. Total bilirubin >1.5x ULN, OR b. Direct bilirubin >1.2x ULN, OR c. Prothrombin time >1.3x ULN (unless caused by anticoagulation therapy or vitamin K deficiency), OR d. Serum albumin <3.2 g/dL.	Exclusion criterion A02 (adapted from M02) met: Participants had Total bilirubin >1.5x ULN or Direct bilirubin >1.2x ULN or Prothrombin time >1.3x ULN (unless caused by anticoagulation therapy or vitamin K deficiency) or Serum albumin <3.2 g/dL at any time point prior to or at the time of screening	Entered but did not satisfy criteria	Yes	No
17	History or evidence of clinical signs or symptoms of hepatic decompensation, including but not limited to: portal hypertension, ascites, hepatic encephalopathy, esophageal varices.	Exclusion criterion M03 met: Participant has a history or evidence of hepatic decompensation <Specify>.	Entered but did not satisfy criteria	Yes	No
18	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.	Exclusion criterion M04 met: Participant has evidence of <specify liver disease of non-HBV etiology>.	Entered but did not satisfy criteria	Yes	No
19	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	Exclusion criterion A05 (adapted from M05) met: Participant has history or signs of cirrhosis or portal hypertension	Entered but did not satisfy criteria	Yes	No

Table 9: Selected Major Protocol Deviations for Analysis Purposes

Sequence number (as reported in MPD)	Description	Protocol Deviation Description (DVTERM) as entered in Study Specific Issue System	Protocol Deviation Coded Term (DVDECOD)	Exclude from PP	Intercurrent Event
	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).	(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.			
20.1	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 m2) 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/mm3 for participants of African ancestry);	Exclusion criterion A06.1 (adapted from M06) met: 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 m2) 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;	Entered but did not satisfy criteria	Yes, for platelets; Otherwise, no.	No

Table 9: Selected Major Protocol Deviations for Analysis Purposes

Sequence number (as reported in MPD)	Description	Protocol Deviation Description (DVTERM) as entered in Study Specific Issue System	Protocol Deviation Coded Term (DVDECOD)	Exclude from PP	Intercurrent Event
	g. Alpha-fetoprotein (AFP) >100 ng/mL; Note: Participants with AFP >ULN but ⩽100 ng/mL may be eligible if HCC can be ruled out based on a sensitive imaging study (eg, contrast-enhanced ultrasound, CT or MRI) during screening. h. Abnormal thyroid function (including thyroid-stimulating hormone [TSH], free triiodothyronine [T3] and free thyroxine [T4]) i. Positive autoantibody test results for at least one of the following: o Anti-nuclear antibodies (ANA) titer ⩾1:80; o Anti-smooth muscle antibodies (ASMA) titer ⩾1:80; o Anti-mitochondrial antibodies (AMA) titer ⩾1:80; o Anti-thyroid peroxidase antibodies ⩾35 IU/mL; o Anti-Neutrophil Cytoplasmic Antibody (ANCA) titer ⩾1:20; o Rheumatoid factor ⩾ 14 IU/mL. Note: In case of ⩾2 positive tests but below the exclusionary cut-off, subject may be enrolled if approved by the sponsor before randomization. j. Any other laboratory abnormality considered to be clinically significant by	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/mm3 for participants of African ancestry); g. Alpha-fetoprotein (AFP) >100 ng/mL; Note: Participants with AFP >ULN but ≤100 ng/mL may be eligible if HCC can be ruled out based on a sensitive imaging study (eg, contrast-enhanced ultrasound, CT or MRI) during screening. h. Abnormal thyroid function (including thyroid-stimulating hormone [TSH], free triiodothyronine [T3] and free thyroxine [T4]) i. Positive autoantibody test results for at least one of the following: o Anti-nuclear antibodies (ANA) titer ≥1:80; o Anti-smooth muscle antibodies (ASMA) titer ≥1:80; o Anti-mitochondrial antibodies			

Table 9: Selected Major Protocol Deviations for Analysis Purposes

Sequence number (as reported in MPD)	Description	Protocol Deviation Description (DVTERM) as entered in Study Specific Issue System	Protocol Deviation Coded Term (DVDECOD)	Exclude from PP	Intercurrent Event
	the investigator (also see exclusion criterion A02).	(AMA) titer ≥1:80; o Anti-thyroid peroxidase antibodies ≥35 IU/mL; o Anti-Neutrophil Cytoplasmic Antibody (ANCA) titer ≥1:20; o Rheumatoid factor ≥14 IU/mL. Note: In case of ≥2 positive tests but below the exclusionary cut-off, subject 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).			
22	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)	Exclusion criterion M08 met: Participant has 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)	Entered but did not satisfy criteria	Yes	No

Table 9: Selected Major Protocol Deviations for Analysis Purposes

Sequence number (as reported in MPD)	Description	Protocol Deviation Description (DVTERM) as entered in Study Specific Issue System	Protocol Deviation Coded Term (DVDECOD)	Exclude from PP	Intercurrent Event
26	Participants who have received an organ transplant (except for skin, hair, or cornea transplants).	Exclusion criterion M12 met: Participant has received an organ transplant (except for skin, hair, or cornea transplants).	Entered but did not satisfy criteria	Yes	No
30	Participants who have taken any disallowed therapies as noted in Section 6.5, Concomitant Therapy before screening.	Exclusion criterion M16 met: Participant has taken a disallowed therapy before Screening: <specify disallowed therapy>.	Entered but did not satisfy criteria	Yes	No
31	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.	Exclusion criterion A17 (adapted from M17) met: Participant 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.	Entered but did not satisfy criteria	Yes	No
42	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.	Exclusion criterion A28 met: Participant 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.	Entered but did not satisfy criteria	Yes	No

Table 9: Selected Major Protocol Deviations for Analysis Purposes

Sequence number (as reported in MPD)	Description	Protocol Deviation Description (DVTERM) as entered in Study Specific Issue System	Protocol Deviation Coded Term (DVDECOD)	Exclude from PP	Intercurrent Event
44	**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.	Received disallowed medication from 12 months prior to screening until end of follow-up < specify treatment, dose, unit, frequency, reason administered >.	Received a disallowed concomitant treatment	Yes	Yes
45	**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	Received disallowed medication from 6 months prior to screening until end of follow-up < specify treatment, dose, unit, frequency, reason administered >.	Received a disallowed concomitant treatment	Yes	Yes

Table 9: Selected Major Protocol Deviations for Analysis Purposes

Sequence number (as reported in MPD)	Description	Protocol Deviation Description (DVTERM) as entered in Study Specific Issue System	Protocol Deviation Coded Term (DVDECOD)	Exclude from PP	Intercurrent Event
	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 Clinical Protocol Sections 7.1.1 and 7.1.2 are met. In addition, use of inhaled, topical, local, and intranasal corticosteroids is permitted.				
46	**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: 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	Received disallowed medication from screening until end of follow-up < specify treatment, dose, unit, frequency, reason administered >.	Received a disallowed concomitant treatment	Yes	Yes

Table 9: Selected Major Protocol Deviations for Analysis Purposes

Sequence number (as reported in MPD)	Description	Protocol Deviation Description (DVTERM) as entered in Study Specific Issue System	Protocol Deviation Coded Term (DVDECOD)	Exclude from PP	Intercurrent Event
	part of a multivitamin formulation. Note: The use of other vitamins is allowed. • Topical steroids (>7 days) under occlusive dressing.				
47	Dose of study medication JNJ-3989 missed or not administered within scheduled time window.	Subject did not receive dose of study drug JNJ-3989 within window. <specify visit number, if the dose was administered before/after the projected window and number of days out of window>	Received wrong treatment or incorrect dose	If classified as major protocol deviation (reviewed case by case), excluded from PP set.	Yes
48	Dose of study medication Nivolumab missed or not administered within scheduled time window.	Subject did not receive dose of study drug Nivolumab within window. <specify visit number, if the dose was administered before/after the projected window and number of days out of window>	Received wrong treatment or incorrect dose	If classified as major protocol deviation (reviewed case by case), excluded from PP set.	Yes
52	Volume of JNJ-3989 was not totally injected.	Volume of JNJ-3989 was not totally injected. <Specify visit number, the prescribed volume and the administered value >	Received wrong treatment or incorrect dose	If classified as major protocol deviation (reviewed case by case), excluded from PP set.	Yes
53	Participant received a wrong dose of study intervention (JNJ-3989 or nivolumab)	Dose error for <insert Nivolumab or JNJ-3989, specify visit number, the prescribed volume and the administered value >	Received wrong treatment or incorrect dose	If classified as major protocol deviation (reviewed case by case), excluded from PP set.	Yes
54	Volume of Nivolumab was not totally infused.	Volume of Nivolumab was not totally infused. <Specify visit number, the prescribed volume and the administered value >	Received wrong treatment or incorrect dose	If classified as major protocol	Yes

Table 9: Selected Major Protocol Deviations for Analysis Purposes

Sequence number (as reported in MPD)	Description	Protocol Deviation Description (DVTERM) as entered in Study Specific Issue System	Protocol Deviation Coded Term (DVDECOD)	Exclude from PP	Intercurrent Event
				deviation (reviewed case by case), excluded from PP set.	
64	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 but the subject was not discontinued from the study intervention.	Subject received <specify day> days of treatment with disallowed medications <specify disallowed medications>, but subject continued study intervention. <Specify dates when the subject initiated and ended treatment with disallowed medications and number of visits completed and doses administered after>	Developed withdrawal criteria but not withdrawn	Yes	No

6.5. Appendix 5 Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study intervention. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study intervention, including those that started before and continue on after the first dose of study intervention.

Summaries of concomitant medications will be presented by ATC class level 2, level 4 and preferred term, intervention arm, analysis phase and overall. The proportion of participants who receive each concomitant medication will be summarized as well as the proportion of participants who receive at least 1 concomitant medication.

Prior medications will be summarized by intervention arm and overall, and ATC class level 2, level 4 and preferred term.

6.6. Appendix 6 Medical History

A tabulation of the general medical history coded terms will be provided by body system class, intervention arm and overall.

6.7. Appendix 7 Intervention Compliance

Compliance will be summarized for the safety analysis set by intervention arm for each study agent (i.e. excluding NA).

Treatment compliance is defined as follows.

- For JNJ-3989: (Total number of injections received/10) * 100%
- For nivolumab: (Total number of infusions received/ Total number of infusions supposed to be received [a]) * 100%

[a] For participants in Arm 1, 1 infusion should be administered. For participants in Arm 2, a total of 3 infusions should be administered.

6.8. Appendix 8 Adverse Events of Special Interest

Adverse events of special interest list of MedDRA preferred terms.

Table 10: Adverse Events of Special Interest and Preferred Terms

Adverse Event of Special Interest	Source	Preferred Term
ALT/AST elevation	(Modified) Liver related investigations, signs and symptoms (SMQ) narrow, (MedDRA v25.0)	Alanine aminotransferase abnormal
		Alanine aminotransferase increased
		Aspartate aminotransferase abnormal
		Aspartate aminotransferase increased
		Hepatic enzyme abnormal
		Hepatic enzyme increased
		Hepatic function abnormal
		Hypertransaminasaemia
		Liver function test abnormal
		Liver function test increased
		Transaminases abnormal
		Transaminases increased
Renal Complications	Acute renal failure (SMQ) narrow (MedDRA v25.0)	Acute kidney injury
		Acute phosphate nephropathy
		Anuria
		Azotaemia
		Continuous haemodiafiltration
		Dialysis
		Foetal renal impairment
		Haemodialysis
		Haemofiltration
		Neonatal anuria
		Nephropathy toxic
		Oliguria
		Peritoneal dialysis
		Prerenal failure
		Renal failure
		Renal failure neonatal
		Renal impairment
		Renal impairment neonatal
		Subacute kidney injury
	Acute renal failure (SMQ) broad (MedDRA v25.0)	Albuminuria
		Blood creatinine abnormal
		Blood creatinine increased
		Blood urea abnormal

Table 10: Adverse Events of Special Interest and Preferred Terms

Adverse Event of Special Interest	Source	Preferred Term
		Blood urea increased
		Blood urea nitrogen/creatinine ratio increased
		Creatinine renal clearance abnormal
		Creatinine renal clearance decreased
		Creatinine urine abnormal
		Creatinine urine decreased
		Crystal nephropathy
		Fractional excretion of sodium
		Glomerular filtration rate abnormal
		Glomerular filtration rate decreased
		Hypercreatininaemia
		Hyponatriuria
		Intradialytic parenteral nutrition
		Kidney injury molecule-1
		Nephritis
		Neutrophil gelatinase-associated lipocalin increased
		Oedema due to renal disease
		Protein urine present
		Proteinuria
		Renal function test abnormal
		Renal transplant
		Renal tubular disorder
		Renal tubular dysfunction
		Renal tubular injury
		Renal tubular necrosis
		Tubulointerstitial nephritis
		Urea renal clearance decreased
		Urine output decreased
	Tubulointerstitial diseases narrow (MedDRA v25.0)	Acidosis hyperchloraemic
		Acquired aminoaciduria
		Acute phosphate nephropathy
		Aminoaciduria
		Beta-N-acetyl-D-glucosaminidase increased
		Crystal nephropathy
		Eosinophils urine present
		Fanconi syndrome acquired
		Hyperphosphaturia
		Isosthenuria
		Metabolic nephropathy
		Nephritis allergic

Table 10: Adverse Events of Special Interest and Preferred Terms

Adverse Event of Special Interest	Source	Preferred Term
		Nephrogenic diabetes insipidus
		Nephropathy toxic
		Renal glycosuria
		Renal papillary necrosis
		Renal phospholipidosis
		Renal tubular acidosis
		Renal tubular atrophy
		Renal tubular disorder
		Renal tubular dysfunction
		Tubulointerstitial nephritis
		Tubulointerstitial nephritis and uveitis syndrome
		Urine phosphorus increased
		Urine retinol binding protein increased
	Tubulointerstitial diseases broad (MedDRA v25.0)	Albumin urine present
		Albuminuria
		Blood chloride increased
		Blood uric acid decreased
		Crystal urine present
		Crystalluria
		Cylindruria
		Haematuria
		Haemoglobin urine present
		Haemoglobinuria
		Hypercalcaemic nephropathy
		Hyperchloraemia
		Kidney fibrosis
		Kidney small
		Microalbuminuria
		pH urine abnormal
		pH urine increased
		Polyuria
		Potassium wasting nephropathy
		Protein urine present
		Proteinuria
		Red blood cells urine positive
		Renal atrophy
		Renal tubular injury
		Renal tubular necrosis
		Sterile pyuria

Table 10: Adverse Events of Special Interest and Preferred Terms

Adverse Event of Special Interest	Source	Preferred Term
		Urinary casts present
		Urine phosphorus abnormal
Hematologic abnormalities	(Modified) Haematopoietic cytopenias affecting more than one type of blood cell (SMQ), (MedDRA v25.0)	Aplastic anaemia
		Autoimmune aplastic anaemia
		Bicytopenia
		Bone marrow failure
		Cytopenia
		Febrile bone marrow aplasia
		Full blood count decreased
		Gelatinous transformation of the bone marrow
		Immune-mediated cytopenia
		Myelosuppression
		Pancytopenia
		Panmyelopathy
		Aspiration bone marrow abnormal
		Biopsy bone marrow abnormal
		Blood disorder
		Bone marrow disorder
		Bone marrow infiltration
		Bone marrow myelogram abnormal
		Bone marrow necrosis
		Congenital aplastic anaemia
		Haematotoxicity
		Myelodysplastic syndrome
		Myelodysplastic syndrome transformation
		Myelofibrosis
		Myeloid metaplasia
		Plasmablast count decreased
		Primary myelofibrosis
		Scan bone marrow abnormal
	(Modified) Haematopoietic erythropenia (SMQ), (MedDRA v25.0)	Anaemia macrocytic
		Aplasia pure red cell
		Aplastic anaemia
		Erythroblast count decreased
		Erythroid maturation arrest
		Erythropenia
		Hypoplastic anaemia

Table 10: Adverse Events of Special Interest and Preferred Terms

Adverse Event of Special Interest	Source	Preferred Term
		Microcytic anaemia
		Proerythroblast count decreased
		Red blood cell count decreased
		Reticulocyte count decreased
		Reticulocytopenia
		Anaemia
		Erythroblast count abnormal
		Erythropoiesis abnormal
		Haematocrit abnormal
		Haematocrit decreased
		Haemoglobin abnormal
		Haemoglobin decreased
		Leukoerythroblastic anaemia
		Normochromic anaemia
		Normochromic normocytic anaemia
		Normocytic anaemia
		Proerythroblast count abnormal
		Red blood cell count abnormal
		Reticulocyte count abnormal
		Reticulocyte percentage decreased
	(Modified) Haematopoietic leukopenia (SMQ), (MedDRA v25.0)	Agranulocytosis
		Band neutrophil count decreased
		Band neutrophil percentage decreased
		Basophil count decreased
		Basophilopenia
		B-lymphocyte count decreased
		Cyclic neutropenia
		Eosinopenia
		Eosinophil count decreased
		Febrile neutropenia
		Granulocyte count decreased
		Granulocyte percentage decreased
		Granulocytes maturation arrest
		Granulocytopenia
		Idiopathic neutropenia
		Leukopenia
		Lymphocyte count decreased
		Lymphopenia
		Metamyelocyte count decreased

Table 10: Adverse Events of Special Interest and Preferred Terms

Adverse Event of Special Interest	Source	Preferred Term
		Monoblast count decreased
		Monocyte count decreased
		Monocytopenia
		Myeloblast count decreased
		Myelocyte count decreased
		Neutropenia
		Neutropenic infection
		Neutropenic sepsis
		Neutrophil count decreased
		Promyelocyte count decreased
		Pure white cell aplasia
		T-lymphocyte count decreased
		White blood cell count decreased
		Basophil count abnormal
		Basophil percentage decreased
		B-lymphocyte abnormalities
		B-lymphocyte count abnormal
		Differential white blood cell count abnormal
		Eosinophil count abnormal
		Eosinophil percentage decreased
		Full blood count abnormal
		Granulocytes abnormal
		Lymphocyte count abnormal
		Lymphocyte percentage abnormal
		Lymphocyte percentage decreased
		Monocyte count abnormal
		Monocyte percentage decreased
		Mononuclear cell count decreased
		Myeloblast percentage decreased
		Myelocyte percentage decreased
		Myeloid maturation arrest
		Neutrophil count abnormal
		Neutrophil percentage decreased
		Plasma cell disorder
		Plasma cells absent
		T-lymphocyte count abnormal
		White blood cell analysis abnormal
		White blood cell count abnormal
		White blood cell disorder

Table 10: Adverse Events of Special Interest and Preferred Terms

Adverse Event of Special Interest	Source	Preferred Term
	(Modified) Haematopoietic thrombocytopenia (SMQ), (MedDRA v25.0)	Acquired amegakaryocytic thrombocytopenia
		Megakaryocytes decreased
		Platelet count decreased
		Platelet maturation arrest
		Platelet production decreased
		Platelet toxicity
		Thrombocytopenia
		Megakaryocytes abnormal
		Platelet count abnormal
		Platelet disorder
		Plateletcrit abnormal
		Plateletcrit decreased

6.9. Appendix 9 Medications of Special Interest

Table 11: Medications of Special Interest

Concomitant Medication Special Interest Category	Concomitant Medication Special Interest ATC level 1	Standard ATC Name (level 2)	Standard Medication Name/group (ATC level 3, 4 or 5)
Systemic corticosteroids	Systemic hormonal preparations, excl. Sex hormones and insulins (H)	Corticosteroids for systemic use (H02)	H02A: Corticosteroids for systemic use, Plain H02B: Corticosteroids for systemic use, Combinations
Miscellaneous hepatotoxic medications	Nervous system (N)	Anesthetics, general (N01)	Halothane (N01AB01)
	Dermatology (D)	Antipsoriatics (D05)	Etretinate (D05BB01)
	Antiinfectives for systemic use (J)	Antivirals for systemic use (J05)	Protease inhibitors (J05AE) Lopinavir and ritonavir: J05AR10 Darunavir and cobicistat: J05AR14 Atazanavir and cobicistat: J05AR15 emtricitabine, tenofovir alafenamide, darunavir and cobicistat :J05AR22 Atazanavir and ritonavir: J05AR23 Darunavir and ritonavir: J05AR26
	Alimentary tract and metabolism (A)	Drugs for acid related disorders (A02)	Omeprazole: A02BC01
	Musculo-skeletal system (M)	Muscle relaxant (M03)	Dantrolene (M03CA01)
	Antiparasitic products, insecticides and repellents (P)	Ectoparasiticides, incl. scabicides, insecticides and repellents (P03)	Disulfiram, combinations (P03AA54)
	Musculo-skeletal system (M)	Antiinflammatory and antirheumatic products (M01)	Gold preparations (M01CB)
	Systemic hormonal preparations, excl. Sex hormones and insulins (H)	Thyroid therapy (H03)	Propylthiouracil (H03BA02)
Immunosuppressive medications for the management of immune-related	Systemic hormonal preparations, excl. Sex hormones and insulins (H)	Corticosteroids for systemic use (H02)	H02A: Corticosteroids for systemic use, Plain H02B: Corticosteroids for systemic use, Combinations

Table 11: Medications of Special Interest

Concomitant Medication Special Interest Category	**Concomitant Medication Special Interest ATC level 1**	**Standard ATC Name (level 2)**	**Standard Medication Name/group (ATC level 3, 4 or 5)**
AEs, injection site reactions or infusion-related reactions	Antineoplastic and immunomodulating agents (L)	Immunosuppressants (L04)	L04AB Tumor necrosis factor alpha (TNF-α) inhibitors
	Antineoplastic and immunomodulating agents (L)	Immunosuppressants (L04)	L04AA06: mycophenolic acid

The method of analysis of the medications of special interest will be the same as the analysis described in Section 6.5.

6.10. Appendix 10 Laboratory Toxicity Grading

The laboratory abnormalities will be determined according to the criteria specified in the DAIDS Toxicity Grading Scale (see Clinical Protocol Appendix 8, DAIDS Table with Modifications (DAIDS [Modified]) or in accordance with the normal ranges of the clinical laboratory if no gradings are available.

7. REFERENCES

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