Janssen Research & Development

Statistical Analysis Plan

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

The PENGUIN-2 Study

Protocol 73763989PAHPB2007; Phase 2

JNJ-73763989

Status: Approved

Date: 06 January 2022

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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

Table 1:   SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1		Not Applicable	Initial release

Status: Approved, Date: 06 January 2022

1. INTRODUCTION

The statistical analysis plan (SAP) for the 73763989PAHPB2007 phase 2 describes the statistical analyses, and definitions to assess the efficacy, safety, tolerability, and PK of the combination of JNJ-73763989 (JNJ-3989), nucleos(t)ide analogs (NAs), and pegulated interferon-alpha2a (PegIFN-α2a) in long-term (≥2 years of NA treatment) virologically suppressed, HBeAg-negative, chronic HBV-infected (CHB), adult participants.

This study is part of the platform trial PLATFORMMPAHPB2001 in participants with CHB. The protocol for 73763989PAHPB2007 constitutes the Intervention Specific Appendix 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 protocol amendment 1 finalized on 6 October 2021, 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 the efficacy in terms of HBsAg changes from baseline for the treatment regimens of 24 weeks of JNJ-3989 + 24 weeks of NA + 12 or 24 weeks of PegIFN-α2a (with immediate or delayed start of PegIFN-α2a treatment), as compared to NA standard of care treatment.	• Proportion of participants with a reduction of at least 2 $\log_{10}$ in HBsAg levels from baseline at Week 24 (EOSI).
Secondary	
• To evaluate the safety and tolerability of the study intervention.	• Safety and tolerability including but not limited to the proportion of participants with (S)AEs and abnormalities in clinical laboratory tests (including hematology, blood biochemistry, blood coagulation, urinalysis, urine chemistry, renal biomarkers), 12-lead ECGs, vital signs, and ophthalmologic and physical examinations throughout the study.
• To evaluate the efficacy of the study intervention at the end of the 24-week treatment period.	• Proportion of participants meeting the protocol-defined NA treatment completion criteria at Week 24 (EOSI) or FU Week 2 results.
• To evaluate the efficacy of the study intervention during the FU period in those participants who meet the protocol-defined NA treatment completion criteria based on the Week 24 or FU Week 2 results.	• Proportion of participants with HBsAg seroclearance at FU Week 24 and 48 (ie, 24 and 48 weeks after completion of all study interventions at Week 24) without re-starting NA treatment.

Objectives	Endpoints
	• Proportion of participants with HBV DNA <LLOQ at FU Week 24 and 48 (ie, 24 and 48 weeks after completion of all study interventions at Week 24) without re-starting NA treatment. • Frequency of virologic and/or biochemical flares. • Proportion of participants requiring NA re-treatment.
• To evaluate the efficacy of the study intervention as measured by blood markers (such as HBsAg, HBeAg, HBV DNA, and ALT) during the study intervention and follow-up (FU) period.	• Proportion of participants with HBsAg, HBeAg, HBV DNA, and ALT levels below/above different cut-offs over time. • Proportion of participants with HBsAg seroconversion. • Change from baseline over time in HBsAg. • Time to achieve HBsAg seroclearance/ seroconversion, and/or HBV DNA <LLOQ.
• To evaluate the frequency of virologic breakthrough throughout the study.	• Proportion of participants with virologic breakthrough[a].
• To evaluate the PK of JNJ-3989 (JNJ-3924 and JNJ-3976), and optionally of NA and PegIFN-α2a.	• PK parameters of JNJ-3989 (JNJ-3924 and JNJ-3976). • Optionally, PK parameters of NA and/or PegIFN-α2a.
Exploratory	
• To explore host and viral baseline and on-treatment markers associated with end of study intervention and/or off-treatment response.	• Association of baseline characteristics and baseline/on-treatment viral and host blood markers with selected on or off-treatment efficacy variables.
• To explore changes in the severity of liver disease.	• Changes in fibrosis (according to Fibroscan liver stiffness measurements) at EOSI and the end of the FU period versus baseline.
• To explore efficacy of the study intervention in terms of changes in HBV RNA and hepatitis B core-related antigen (HBcrAg) levels during the study intervention and FU period.	• Changes from baseline in HBV RNA and HBcrAg levels over time.
• To explore the relationship of PK with selected pharmacodynamic (PD) parameters of efficacy and safety.	• Relationship of various PK parameters with selected efficacy and safety endpoints.
• To explore the HBV genome sequence during the study intervention and FU period.	• Assessment of intervention-associated mutations over time.
• To explore HBV-specific T-cell responses during the study intervention and FU period.[b]	• Changes from baseline in HBV-specific peripheral blood T-cell responses over time.[b]

Objectives	Endpoints
• To explore the efficacy of NA re-treatment in participants who meet the criteria for NA re-treatment.	• Proportion of participants who reach HBV DNA <LLOQ after re-start of NA treatment during the FU period.
• To explore medical resource utilization (MRU) to manage participants during study intervention and follow-up.	• Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
	• Duration of hospitalization (total days length of stay, including duration by wards; 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 For the definition of virologic breakthrough, refer to 5.4.1.1.13.
b 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, 3-arm, multicenter study to assess efficacy, safety, tolerability, and pharmacokinetics of treatment with JNJ-3989, NA, and PegIFN-α2a in long-term (≥2 years of NA treatment) virologically suppressed, HBeAg-negative, chronic HBV-infected, adult participants.

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

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

• Screening Period (4 weeks [if necessary, 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]).

• Treatment Period (24 weeks):
   o Arm 1 (N=34): JNJ-3989 for 24 weeks + NA for 24 weeks + PegIFN-α2a for 24 weeks.
   o Arm 2 (N=34): JNJ-3989 for 24 weeks + NA for 24 weeks + PegIFN-α2a from Week 12 till Week 24.
   o Arm 3 (N=34): JNJ-3989 for 24 weeks + NA for 24 weeks + PegIFN-α2a from baseline till Week 12.

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

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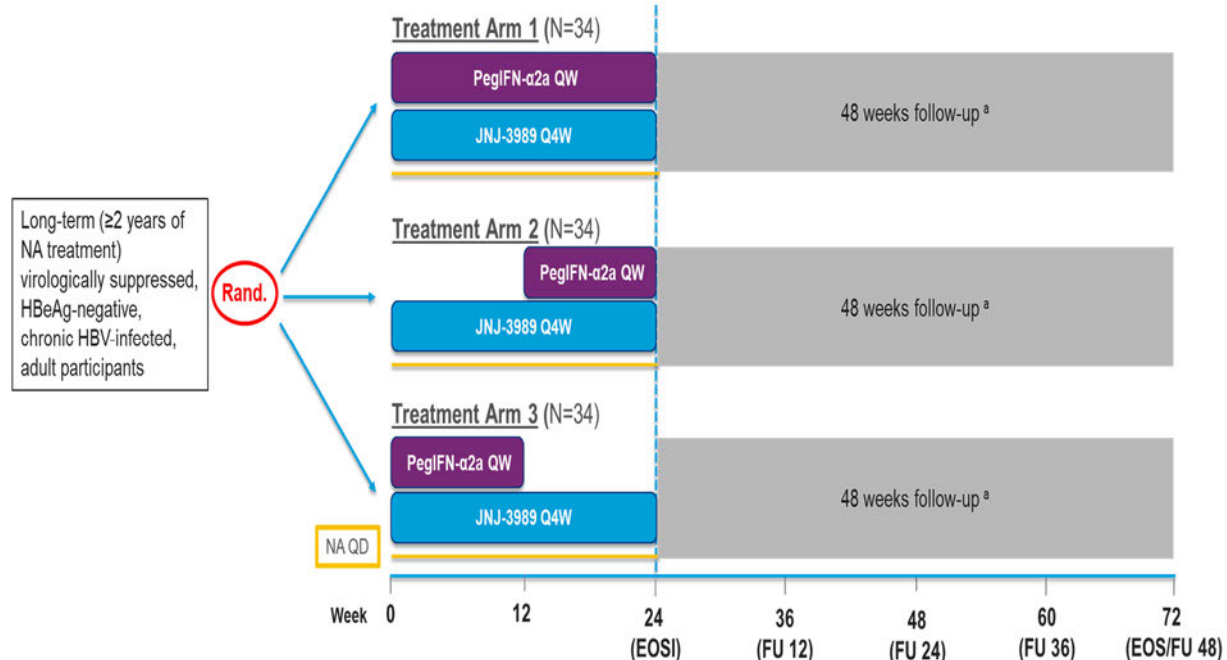
ALT: alanine aminotransferase; DNA: deoxyribonucleic acid; EOS: end of study; EOSI: end of study intervention; FU: follow-up; HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; JNJ-3989: JNJ-73763989; N: number of participants; NA: nucleos(t)ide analog; PegIFN-α2a: pegylated interferon alpha-2a; Q4W: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

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

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

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

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

All participants will receive the last dose of JNJ-3989 at Week 24 and the last dose of PegIFN-α2a at Week 23 (Arms 1 and 2) or Week 11 (Arm 3). They will start the FU period after the Week 24 visit. If the protocol-defined NA treatment completion criteria (Section 5.4.1.1.1) are met based on the Week 24 results, treatment with NA will be stopped at the next scheduled visit (ie, FU

Week 2), otherwise NA treatment will continue during the complete FU period. Note: Participants who are close to meeting the protocol-defined NA treatment completion criteria with the Week 24 results, and do meet the criteria at FU Week 2 results may be allowed to stop NA at FU Week 4, upon prior discussion with the Sponsor.

The NA treatment completion criteria which take ALT, HBV DNA, HBeAg, and HBsAg levels into consideration, have been selected to ensure that only participants with a higher chance of achieving sustained off-treatment response are allowed to stop all study intervention. Participants who meet the protocol-defined NA treatment completion criteria will be monitored closely during the 48-week FU Period and participants should re-start NA treatment if NA re-treatment criteria are met (see Clinical Protocol Section 6.5.2, NA Re-treatment Criteria During Follow-up, for more details).

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

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

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

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

2.   STATISTICAL HYPOTHESES

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

3.   SAMPLE SIZE DETERMINATION

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

assumed external control value is based on the data of the NA control arm in virologically suppressed HBeAg negative participants in study 73763989HPB2001 (REEF-1).

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

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

4.   POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Due to a potential impact of future Coronavirus Disease (COVID-19) pandemics on the study data collection, study treatment adherence and study conduct, the modified Full Analysis Set (mFAS) and modified IFN-FAS (mIFN-FAS) 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 IFN-FAS and modified FAS/IFN-FAS analysis sets will be used if there is a relevant difference from the FAS (>5% of participants in total).

Table 2:   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	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 Week 24 (EOSI), 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.

Analysis Sets	Description
IFN-FAS	All participants who were randomly assigned to an intervention arm in this ISA and received at least 1 dose of PegIFN-α2a within this ISA. Participants will be analyzed according to the study intervention they were randomly assigned to.
Modified IFN-FAS	All participants who were randomly assigned to an intervention arm in this ISA and received at least 1 dose of PegIFN-α2a within this ISA excluding those participants who, because of COVID-19 or similar pandemics related reasons, withdrew prematurely from the study prior to Week 24 (EOSI), 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 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. Participants will be analyzed according to the study intervention they were randomly assigned to.
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 treatment refers to: JNJ-3989, NA, and PegIFN-α2a

- Study agent refers to: JNJ-3989, NA, and PegIFN-α2a

- Study intervention arm refers to:

    - Arm 1: JNJ-3989 for 24 weeks + NA for 24 weeks + PegIFN-α2a for 24 weeks.

    - Arm 2: JNJ-3989 for 24 weeks + NA for 24 weeks + PegIFN-α2a from Week 12 till Week 24.

    - Arm 3: JNJ-3989 for 24 weeks + NA for 24 weeks + PegIFN-α2a from baseline till Week 12.

5.1.1.   Analysis Phase

The analyses phases are defined in Table 3 below.

Table 3:   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
Treatment period	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 – 1 day, 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 treatment period:** End of treatment period + 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. Treatment Period Relative Day

Treatment period (TP) start date (TP Day 1) is defined in Table 3. All efficacy and safety assessments during the treatment period will be assigned an analysis day relative to this date.

The study day in the treatment period phase (TP ADY) is defined as:

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

for visits on or after treatment period Day 1, and

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

for visits before TP Day 0 (Screening phase).

There is no 'TP Day 0'.

5.1.2.2. Follow Up Relative Day

Follow-up (FU) start date (FU Day 1) is defined in Table 3. 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 4. 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 treatment period 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 will include all measurements, also those multiple assessments with the same visit window/phase.

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

Table 4 provides the analysis time points and time intervals for each visit per analysis phase.

Table 4: **Visit Windows**

Analysis phase	Target Day	Analysis time point (Week)	Analysis time point (label)	Time interval (days)
Screening	-∞	-1	Screening	<0
Treatment period	1	0	Baseline	Pre-dose: 1
	15	2	Week 2	[2, 22]
	29	4	Week 4	[23, 43]
	57	8	Week 8	[44, 71]
	85	12	Week 12	[72, 92]
	99	14	Week 14	[93, 106]
	113	16	Week 16	[107, 127]
	141	20	Week 20	[128, 155]
	169	24	Week 24	[156, 183]
	Last visit in treatment period	25[a]	EOT[a]	
Follow-up	15	26	Follow-up Week 2	[1, 22]
	29	28	Follow-up Week 4	[23, 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, 183]
	197	52	Follow-up Week 28	[184, 211]
	225	56	Follow-up Week 32	[212, 239]
	253	60	Follow-up Week 36	[240, 267]
	281	64	Follow-up Week 40	[268, 295]
	309	68	Follow-up Week 44	[296, 323]
	337	72	Follow-up Week 48	[324, +∞]
	Last visit in the study	999[b]	EOS[b]	

[a] End of treatment (EOT) visit will be the last post-baseline visit in treatment 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 TP 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 (RTs) will be used for additional analyses of selected efficacy endpoints.

The PegIFN RT is defined as the last observed non-missing measurement before the first PegIFN-α2a for Arm 2. This RT will be used for additional analyses for selected efficacy endpoints after Week 12 of treatment period and FU phase.

The NA RT is defined as the last observed non-missing measurement before the start of FU phase for participants who met the NA completion criteria at the EOT. This RT will be used for additional analyses for selected efficacy endpoints for FU phase.

The JNJ-3989 RT is defined as the last observed non-missing measurement at the time of stopping JNJ-3989. This RT will be used for additional analyses for selected efficacy endpoints for 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 2% at a one-sided Type 1 error rate of 0.05 and applying the Hochberg procedure for adjusting for multiple comparisons. For the comparisons between the intervention arms (Arms 1,2,3), the Mantel-Haenszel test adjusting for the stratification factors 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 and applying the Hochberg procedure for multiple comparisons adjustment.

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 treatment date.
  - The day of the first study treatment administration, if the month/year of the AE onset date is the same as the month/year of the first study treatment administration but the month/year of the AE resolution date is different.
  - The earliest between the day of the first study treatment 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 treatment 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 (TP 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 (TP 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 treatment 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 5.

Table 5:   **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	124,925.00 IU/mL w/o dilution 249,750.00 IU/mL with dilution	0.025 IU/mL [a]	137,417.50 IU/mL w/o dilution [b] 274,725.00IU/mL [b] with dilution
HBeAg	0.11 IU/mL	1,400.00 IU/mL w/o dilution 7,000.00 IU/mL with dilution	0.055 IU/mL [a]	1,540.00 IU/mL[b] w/o dilution 7,700.00 IU/mL[b] with dilution
HBcrAg*	3.0 $\log_{10}$ U/mL	7.0 $\log_{10}$ U/mL w/o dilution 9.0 $\log_{10}$ U/mL with dilution	2.7 $\log_{10}$ U/mL	7.7 $\log_{10}$ U/mL[b][c] w/o dilution 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 (i.e. 13 cp/mL)	NAP
Anti-HBs	5 mIU/mL	10,000.0 mIU/mL	2.5 mIU/mL[a]	11,000.0 mIU/mL [b]

* As new assays become available different data handling rules may apply.
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, PegIFN-α2a, NA)

- Participants in each study analysis phase

- Participants who completed the study

- 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 unblinded during the study period

- 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 with a reduction of at least 2 $\log_{10}$ IU/mL in HBsAg levels from baseline at Week 24 (EOSI).

5.3.2.   Main Estimand for the Primary Endpoint

Study Objective: To evaluate the efficacy in terms of HBsAg changes from baseline for the treatment regimens of 24 weeks of JNJ-3989 + 24 weeks of NA + 12 or 24 weeks of PegIFN-α2a (with immediate or delayed start of PegIFN-α2a treatment), as compared to NA standard of care treatment.

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

a) Comparison vs fixed control: what is the benefit of JNJ-3989 + 24 weeks of NA + 12 or 24 weeks of PegIFN-α2a in terms of reduction of at least 2 $\log_{10}$ IU/mL in HBsAg levels from baseline at Week 24 compared with fixed proportion 2% for NA (standard of care treatment)?

b) Comparison amongst regimens: what is the benefit of JNJ-3989 + 24 weeks of NA + 12 or 24 weeks of PegIFN-α2a in terms of reduction of at least 2 $\log_{10}$ IU/mL in HBsAg levels from baseline at Week 24 compared amongst regimens (Arm 1 versus Arm 2, Arm 1 versus Arm 3, and Arm 2 versus Arm 3)?

A) Study Intervention:

- Arm 1: JNJ-3989 for 24 weeks + NA for 24 weeks + PegIFN-α2a for 24 weeks.

- Arm 2: JNJ-3989 for 24 weeks + NA for 24 weeks + PegIFN-α2a from Week 12 till Week 24.

- Arm 3: JNJ-3989 for 24 weeks + NA for 24 weeks + PegIFN-α2a from baseline till Week 12.

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

C) Variable: Response status defined as participants with reduction of at least 2 $\log_{10}$ IU/mL in HBsAg levels from baseline at Week 24 (responders) as 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 13 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 Week 24 are handled in a composite strategy as participants who die prior to Week 24 will be considered as non-responders.

E) Population-level summary:

a. **Primary (comparison vs fixed proportion):** Difference in proportion of participants with reduction of at least 2 log10 IU/mL in HBsAg levels from baseline at Week 24 using a fixed proportion of 2%.

b. **Secondary (comparison amongst regimens):** Difference in proportion of participants with reduction of at least 2 log10 IU/mL in HBsAg levels from baseline at 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. Scientific Question of Interest Part a: Comparison vs Fixed Control

The main estimator is constructed by using an exact binomial test against a fixed external control value of 2% at a one-sided Type 1 error rate of 0.05 and applying the Hochberg procedure for adjusting for multiple comparisons (Section 5.3.4).

5.3.2.1.1.2. Scientific Question of Interest Part b: Comparison Amongst Regimens

The main estimator is constructed by using the Mantel-Haenszel test (Mantel N. et al., 1959) adjusted for the randomization stratification factors (HBsAg level at baseline [<1,000 IU/mL, ≥1,000 IU/mL] and country grouping at enrollment [Poland, Russia, all other countries]) to compare the primary endpoint between the intervention arms at a one-sided alpha level of 0.05 and applying the Hochberg procedure for multiple comparisons adjustment.

5.3.2.1.2.   Data Included

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

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 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 Week 24 value, then the imputation to non-response will be applied. If the value for the endpoint at Week 24 is available, then such data will be used to determine their response status.

For the participants still in the study at 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 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 factors will be tested and, if heterogeneity is found statistically significant, a different statistical model is 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 2 randomization stratification factors and interaction terms. The model will include intervention arm, HBsAg level at baseline (<1,000 IU/mL or ≥1,000 IU/mL), and country grouping at enrollment (Poland, Russia, all other countries) 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 subject 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 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 subject 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 Week 24 is missing, the non-missing closest to Week 24 within the window of 4 weeks prior/after Week 24 visit will be used. If 2 non-missing laboratory values are equidistant, the later observation will be preferred. Participants who do not have data within the analysis window of ±4 weeks around Week 24 assessment will be defined as non-responders.

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

A) **Study Intervention:**

  o Arm 1: JNJ-3989 for 24 weeks + NA for 24 weeks + PegIFN-α2a for 24 weeks.

  o Arm 2: JNJ-3989 for 24 weeks + NA for 24 weeks + PegIFN-α2a from Week 12 till Week 24.

  o Arm 3: JNJ-3989 for 24 weeks + NA for 24 weeks + PegIFN-α2a from baseline till Week 12.

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

C) **Variable:** Response status defined as participants with reduction of at least 2 $\log_{10}$ IU/mL in HBsAg levels from baseline at Week 24 (responders) as in Section 5.3.1.

D) **Intercurrent events:**

  o 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).

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

E) **Population-level summary:**

  a. **Primary (comparison vs fixed proportion):** Difference in proportion of participants with reduction of at least 2 $\log_{10}$ IU/mL in HBsAg levels from baseline at Week 24 using a fixed proportion of 2%.

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b. **Secondary (comparison amongst regimens):** Difference in proportion of participants with reduction of at least 2 $\log_{10}$ IU/mL in HBsAg levels from baseline at 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

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 Week 24 will be considered non-responders. For the participants still in the study at Week 24 or for participants that have neither discontinued treatment early nor experienced any major protocol violations as listed at Table 13, but HBsAg values missing at 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} , $i = 1, \ldots, k$, 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 $H_{0[i]}$, $i = 1, \ldots, k$, and stop; otherwise go to Step 2.

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

. . .

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

5.3.5. Subgroup Analyses of Primary Efficacy Endpoint

The potential association between the primary endpoint and the randomization stratification factors will be assessed by a logistic regression model (Brooks ST. et al., 2004) and exploration of the interaction terms using observed case data. The model will include intervention arm, country grouping as proxy for HBV genotype at enrollment (Poland (predominantly GT-A) vs Russia (predominantly GT-D) vs all other countries (other or mixed GT prevalence)), absolute HBsAg value at baseline (<1,000 IU/mL vs ≥1,000 IU/mL), as factors, and the interaction of intervention arm-by-country grouping, and intervention arm-by-HBsAg value at baseline as interaction terms. The primary endpoint estimates for each intervention arm will be derived from this model and presented graphically with their 90% CI in a forest plot.

In addition, for assessment of internal consistency and investigation of homogeneity of the treatment effect in the primary efficacy endpoint across other subgroups (as defined in Section 5.7.7.1), similarly to what is described above, a logistic regression model (Brooks ST. et al., 2004) will be estimated for each subgroup variable at a time. The factors in the model will be intervention arm, the subgroup variable, and the two randomization stratification factors (country grouping as proxy for HBV genotype at enrollment [Poland (predominantly GT-A) vs Russia (predominantly GT-D) vs all other countries (other or mixed GT prevalence)], absolute HBsAg value at baseline [<1,000 IU/mL vs ≥1,000 IU/mL]), and the intervention arm-by-subgroup interaction term. Corresponding 90% CIs will be also calculated without multiplicity adjustment for each intervention arm. Statistical analysis of treatment heterogeneity between subgroups will be conducted by assessing the significance of the interaction term (Brooks ST. et al., 2004). The forest plot will present graphically the primary endpoint estimate, its 90% CI resulting from the model across intervention arms by the prespecified subgroups.

The primary efficacy endpoint will be summarized also descriptively using the number and percentage of participants in each intervention arm, by each subgroup of interest (Section 5.7.7.1). In addition, the tabulation of count and percentage of responders will be calculated for the combination of the 2 randomization stratification factors of country grouping-by-HBsAg at baseline categories.

5.3.6. Comparisons Between Arm 2 and Model-Based Virtual IFN-Free JNJ-3989+NA Regimen Control

As study participants were not randomized across those ISAs ongoing at the time of writing this SAP, because of the staggered ISAs initiation, any imbalance in baseline characteristics, beyond matching the key inclusion/exclusion criteria, may introduce potential bias in the treatment effect estimation. Such additional sources of variability could be driven by country effect, HBV genotype, time effect (e.g. time of the participant's enrollment into an ISA), impact of the COVID-

19 pandemic on protocol compliance, as well as by the different combination regimens and the different JNJ-3989 treatment durations across ISAs. To address these concerns another analysis of the primary efficacy endpoint will be performed constructing "virtual" IFN-free JNJ-3989 control participants for the participants in this ISA (Arm 2). Virtual control HBsAg data are defined as IFN-free regimen with JNJ-3989+NA, at the JNJ-3989 dose level used in this ISA. For each participant in Arm 2 of this ISA, the HBsAg data for "virtual" control subjects will be generated using an appropriate longitudinal model (e.g. kinetic pharmacodynamic model [KPD] or PK/PD model) developed and validated based on the data from the JNJ73763989HPB2001 (REEF-1) study. In Arm 2, the first 12 weeks of HBsAg data under treatment with JNJ-3989+NA alone will enable to estimate individual parameters (ie, Empirical Bayes Estimates) describing each participant's specific HBsAg temporal kinetics. These individual parameters will be used further to extrapolate each participant's individual HBsAg values over time, as if that participant had been treated with JNJ-3989 +NA regimen but without receiving PegIFN-α2a for the entire 24-week treatment. The observed HBsAg levels post PegIFN-α2a intake in Arm 2 will be directly compared to virtual control model-generated HBsAg data for this arm. Of Note: the model-based prediction of HBsAg between weeks 12-24 for each individual in Arm2 assumes that (i) the individual's HBsAg dynamics follow the general path of the population-level HBsAg turnover model, and (ii) assumes absence of immune-related effects.

Single-arm estimate of the primary endpoint response rate (study intervention arm and virtual control-arm): The estimated primary endpoint response rate will be calculated for the virtual control arm, and 90% CI will be estimated using Clopper-Pearson exact method for a single sample proportion. The same Clopper Pearson method will also apply to estimate the 90% CI around the response rate for the Arm 2 of this ISA.

Matched-control paired difference in the primary endpoint response rate (study intervention arm vs. virtual control-arm): The proportion of responders estimated for participants in this ISA will be compared with the proportion of responders obtained for the virtual IFN-free JNJ-3989 control participants model-generated using the McNemar test for the difference between paired matched case-control binomial proportions at 0.05 one-sided Type 1 error rate. The associated 90% CI will be estimated to accompany the point estimate of the difference in proportions.

No multiplicity adjustment will be used in this exploratory statistical comparison.

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.   NA Treatment Completion Criteria

NA treatment completion criteria are defined based on the Week 24 results as follows:

- ALT <3x ULN, and

- HBV DNA <60 IU/mL at Week 24 and HBV DNA<LLOQ at the previous visit, or HBV DNA< LLOQ at Week 24, and

- HBeAg-negative, and

- HBsAg <100 IU/mL

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

The NA completion criteria will be assessed based on clinical laboratory tests and summarized based on the Week 24 (EOSI) or FU Week 2 results, and during the FU phase.

5.4.1.1.2.   NA Re-Treatment During Follow-up

Participants who actually re-started NA treatment during the follow-up phase will be identified based on the 'Study Drug Administration for NA' CRF page.

Participants who meet the NA re-treatment criteria will be identified on the CRF page of 'NA Re-treatment Criteria Assessment'. Each sub-criteria will also be evaluated.

5.4.1.1.3.   HBsAg Cut-offs

The cut-offs for HBsAg level are as follows:

- <1000 IU/mL

- <500 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 RTs are as follow:

- decrease by $\geq 0.3 \log_{10}$ IU/mL

- decrease by $\geq 0.5 \log_{10}$ IU/mL

- decrease by $\geq 1 \log_{10}$ IU/mL

- decrease by $\geq 2 \log_{10}$ IU/mL

- decrease by $\geq 3 \log_{10}$ IU/mL

- decrease by $\geq 4 \log_{10}$ IU/mL

5.4.1.1.4. HBsAg Seroclearance

Seroclearance of HBsAg is defined as a (quantitative) HBsAg level <LLOQ (see Table 5). HBsAg seroclearance can be observed prior to the time point assessed but must be observed at the given week of interest.

5.4.1.1.4.1. On Treatment

HBsAg seroclearance will be evaluated over time during the study intervention phase.

5.4.1.1.4.2. Off Treatment

HBsAg seroclearance will be evaluated over time at each of the FU timepoints separately, with emphasis at FU Weeks 12, 24, 36 and 48 (i.e. 12, 24, 36, 48 weeks after completion of all study interventions at Week 24) and without restarting NA treatment.

For the analyses of seroclearance at the time points mentioned above, participants with HBsAg seroclearance at the respective time points (and without restarting NA treatment during the interval between the time of stopping the study intervention up to the analysis time point (FU Week 12, 24, 36 and 48)) will be considered as having achieved this endpoint.

5.4.1.1.5. Functional Cure

Functional cure will be evaluated at each of the following time points separately: FU Week 12, 24, 36 and 48. A participant will be defined as having achieved functional cure (FC) if he/she has:

- had HBsAg seroclearance at the given week of interest, and

- not required NA re-treatment between Week 24 and the given follow-up week of interest.

It can be noted that a participant may achieve HBsAg seroclearance prior to the week of interest, but the HBsAg level<LLOQ has to be shown at the given week of interest to be counted as responder.

5.4.1.1.6. Treatment Failure

A participant will be defined as on-treatment failure if he/she didn't have a reduction from baseline of at least $2 \log_{10}$ IU/mL levels at Week 24.

5.4.1.1.7.   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.

5.4.1.1.8.   HBeAg Cut-offs

The cut-offs for HBeAg level are as follows:

- ≥LLOQ
- < LLOQ (0.11 IU/mL)

5.4.1.1.9.   HBV DNA Cut-offs

The cut-offs for HBV DNA are as follows:

- < LLOQ for target detected and not detected
- < LLOQ for target not detected
- < LLOQ for target detected
- <60 IU/mL
- <100 IU/mL
- <200 IU/mL
- <1000 IU/mL
- <2000 IU/mL
- <20000 IU/mL

5.4.1.1.10.   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 FU Weeks 12, 24, 36 and 48 (i.e. 12, 24, 36, 48 weeks after completion of all study interventions at Week 24), and without restarting NA treatment.

5.4.1.1.11.   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 and off treatment but without restarting NA treatment will be evaluated over time.

Participants who were retreated with NA and who have ALT≥ULN before NA re-treatment and reach ALT normalization after NA re-treatment during follow-up will be evaluated.

Additionally, for those participants who restarted NA treatment during the follow-up, the participants who reach ALT<ULN and who have ALT less than their nadir value will be evaluated.

5.4.1.1.12. Partial Cure

Partial cure will be evaluated at each of the following time points separately: FU Week 12, 24, 36 and 48. A participant will be defined as having achieved partial cure if he/she has:

- Stopped all study interventions at any time, and

- had HBV DNA level < 2,000 IU/ml at the given follow-up week of interest, and

- had HBsAg ≥LLOQ at the given week of interest, and

- not required NA re-treatment after stopping all study interventions.

Of note, HBV DNA level < 2,000 IU/ml may be achieved prior to the week of interest but must be observed at the given week of interest.

5.4.1.1.13. 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.

5.4.1.1.14. Flares

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

1. Virologic flare is defined as follows:

Virologic flare will be assessed only for those participants who are off-treatment.

The start of a confirmed virologic flare is defined as the first date of two consecutive visits with HBV DNA >200 IU/mL. The end date of the same confirmed virologic flare is defined as the first date when HBV DNA value returns to ≤200 IU/mL or the date of NA treatment restart, whichever

comes first. Each virologic flare will be categorized based on the confirmed (i.e. two consecutive values) peak HBV DNA above any of the three thresholds within the start and end date of that flare as follows: 20,000 IU/mL 2,000 IU/mL and 200 IU/mL.

- 1 (Yes) = confirmed** HBV DNA > peak threshold.
- 0 (No) = at least one off-treatment HBV DNA measurement available and not meeting the criteria of confirmed HBV DNA > peak threshold.
- 2 (Not applicable) = no off-treatment HBV DNA quantitative measurements available.

2. **Off-treatment Biochemical flare** is defined as follows:

The start date of a confirmed off-treatment biochemical flare is defined as the first date of two consecutive visits with ALT and/or AST≥3x ULN and ≥3x off-treatment nadir (i.e. lowest value observed during off-treatment period up to the time point of meeting the biochemical flare criteria) while the participant does not receive any of the study interventions. The end date of the same off-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.

- 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

3. **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 on-treatment nadir (i.e. lowest value observed on-treatment period up to the time point of meeting the biochemical flare criteria) 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

4. **Clinical flare** is defined as follows:

A clinical flare occurs either when a virologic flare and biochemical flare overlap in time or when a biochemical flare starts within 4 weeks following the end of a virologic flare. The start date of a clinical flare is defined as the minimum start date of the virologic flare and the biochemical flare. The end date of a clinical flare is defined as the maximum end date of the virologic flare and biochemical flare, i.e., the later date of HBV DNA returns to ≤200 IU/mL and 50% reduction from the peak ALT and/or AST level.

- 1 (Yes) = confirmed** HBV DNA > peak threshold and confirmed** ALT and/or AST ≥3x ULN and confirmed** ≥3x nadir (i.e. lowest value during study participation).

- 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.

The virologic and clinical flares will be assessed only off-treatment, while biochemical flares will be identified on-treatment and off-treatment. On-treatment virologic flares are described as virologic breakthrough in Section 5.4.1.1.13. On-treatment will be defined as the time period in which the participant receives any of the study interventions. Off-treatment will be defined as the period after stopping all study interventions (including NA).

5.4.1.2. Continuous Endpoints

5.4.1.2.1. HBsAg, HBeAg, HBV DNA and ALT

Actual values (original unit and $\log_{10}$ transformed values), changes from baseline ($\log_{10}$ transformed values) and change from RTs over time in HBsAg, HBeAg, HBV DNA and ALT (actual values only) 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, HBeAg, and HBV DNA will be evaluated at 3 intervals: on-treatment nadir (first 24 weeks), during follow-up nadir, and entire study nadir.

5.4.1.3. Time to Event Endpoints

5.4.1.3.1. Time to First HBsAg Seroclearance

Time to HBsAg seroclearance is defined as the number of days between the date of first study intervention intake and the date of the first occurrence of HBsAg seroclearance (i.e. the date of the first HBsAg seroclearance – the date of first study intervention intake + 1). The participants who withdrew early from the study before achieving HBsAg seroclearance or who did not achieve HBsAg seroclearance will be censored at the last available HBsAg assessment.

Time to HBsAg seroclearance will be also analyzed considering the participants who were retreated with NA before achieving HBsAg seroclearance as censored at the date of NA retreatment.

In addition, time to the first occurrence of the following events (i.e. the date of the first occurrence of the event – the date of first study intervention intake + 1) will be analyzed:

- HBsAg <100 IU/mL

- HBsAg decline $\geq 1.0 \log_{10}$ IU/mL

- HBsAg decline $\geq 2.0 \log_{10}$ IU/mL

- HBsAg decline $\geq 3.0 \log_{10}$ IU/mL

Time to the first occurrence of the events above will be also analyzed considering the participants who were retreated with NA before achieving the event as censored at the date of NA retreatment.

5.4.1.3.2. Time to First HBsAg Seroconversion

Time to first HBsAg seroconversion is defined as the number of days between the date of first study intervention intake and the date of the first occurrence of HBsAg seroclearance and appearance of anti-HBs antibodies (i.e. the date of the first HBsAg seroclearance and anti-HBs antibodies – the date of first study intervention intake + 1). The participants who withdrew early from the study before achieving HBsAg seroclearance and anti-HBs antibodies or who did not achieve HBsAg seroclearance and anti-HBs antibodies will be censored at the last available anti-HBs antibodies assessment.

Time to first HBsAg seroconversion will be the participants who were retreated with NA before achieving HBsAg seroclearance and anti-HBs antibodies will be censored at the date of NA retreatment.

5.4.1.3.3. Time to HBV DNA < LLOQ

Time to HBV DNA < LLOQ is defined as the number of days between HBV DNA >LLOQ for participants who re-treated with NA and the date of the first occurrence of HBV DNA < LLOQ after NA re-treatment (i.e. the date of the HBV DNA < LLOQ after being re-treated with NA – the date of first occurrence of HBV DNA>LLOQ + 1). Time to first HBV DNA < LLOQ will be analyzed only for participants who met the NA treatment completion criteria and re-treated with NA during FU.

5.4.1.3.4. Time to First Virologic Breakthrough

Time to first HBV virologic breakthrough will be defined as the number of days between the date of first study intervention intake and the date of the first occurrence of virologic breakthrough (i.e. the date of the first virologic breakthrough [the first of the two confirmation visits] - the date of first study intervention intake +1). The participants who withdrew early from the study before experiencing virologic breakthrough or who did not experience virologic breakthrough will be censored at the last available HBV DNA assessment at or before EOT.

5.4.1.3.5. Time to First Flare

Time to first biochemical flare (on- and off-treatment), clinical flare off-treatment, and virologic flare off-treatment will be evaluated.

Time to first on-treatment flare will be defined as the number of days between the date of first study intervention intake and the date of the first occurrence of on-treatment flare (i.e. the date of the first on-treatment flare [the first of the two confirmation visits] of each type- the date of first study intervention intake+1). The participants who withdrew early from the study before experiencing on-treatment flare or who did not experience on-treatment flare will be censored at the last available blood markers or liver enzymes assessment at or before EOT.

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Time to the first off-treatment flare will be defined as the number of days between the date of last study intervention intake and the date of the first occurrence of off-treatment flare (i.e. the date of experiencing the first off-treatment flare [the first of the two confirmation visits] of each type- the date of last study intervention intake). The participants who withdrew early from the study before experiencing off-treatment flare or who did not experience off-treatment flare will be censored at the last available blood markers or liver enzymes assessment.

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 will 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.

5.4.2.1. Binary Endpoints

All binary endpoints defined using HBsAg values/changes from baseline (HBsAg cut-offs, HBsAg seroclearance/seroconversion, Functional Cure) will be analyzed also using the virtual control approach described in Section 5.3.6.

For single arm point and 90% CI estimates, the Clopper Pearson method will be used. For the difference between paired matched case-control binomial proportions, the McNemar test at 0.05 one-sided Type 1 error rate will be used.

Graphical displays using bar charts and/or radar plots will show the binary endpoints over time, by subgroups of interest, or combining multiple binary endpoints together.

Potential association between treatment outcome and baseline factors will be explored by multivariate logistic regression model in a similar fashion as described in Section 5.3.5.

5.4.2.1.1. LOCF Imputation Method

- 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/later than 12 weeks from the actual time point of interest (FU Week 12 and FU Week 36, respectively) will be imputed.

- If the lab value at FU Week 36 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 36 which is no earlier/later than 12 weeks from the actual time point of interest (FU Week 24 and FU Week 48, respectively) will be imputed.

- 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 36 may be carried forward.

5.4.2.1.2.   NA Treatment Completion Criteria at Week 24 and During FU

The count and proportion of participants (and associated 90% CI) who met the NA treatment completion criteria at Week 24, will be summarized by intervention arm.

Starting at the end of treatment period, the incidence of participants who did not meet the NA treatment completion criteria will be summarized at each timepoint during the study by intervention arm, accompanied by the distribution of each of the 4 criteria that is not met. The NA treatment completion criteria are based on a threshold for the laboratory tests of ALT, HBV DNA, HBeAg and HBsAg.

The count and proportion of participants (and associated 90% confidence interval) who met the NA treatment completion criteria (Section 5.4.1.1.1) at any time during the FU phase will be summarized by intervention arm. All the NA treatment completion criteria will be checked based on clinical laboratory tests in FU phase.

5.4.2.1.3.   NA Re-Treatment Criteria During FU

The count and proportion of participants (and associated 90% CI) who meet the criteria for NA re-treatment at any time during FU will be summarized descriptively by intervention arm. In addition, the count and proportion of participants (and associated 90% CI) who met the criteria according to the flag on the CRF page of 'NA Re-treatment Criteria Assessment' during the follow-up phase will be summarized over time by intervention arm. The proportion of participants who met each sub-criteria will also be summarized by intervention arm.

The count and proportion of participants (and associated 90% CI) who actually re-started NA treatment during the follow-up phase on the basis of the 'Study Drug Administration for NA' CRF page will be summarized separately over time by intervention arm.

A cross-tabulation of participants who actually re-started NA treatment (re-started/not restarted) versus participants who met the above criteria (met/not met) will be presented over time by intervention arm.

5.4.2.1.4.   HBsAg Cut-offs

The cut-offs for HBsAg values and decreases from baseline will be used in separate summaries over time by intervention arm. The count and proportion of participants who meet those HBsAg thresholds during the study will be summarized descriptively by intervention arm, and analysis phase over time and displayed in graphs like bar charts and/or radar plots.

Cross-tabulations overtime of quantitative HBsAg (<LLOQ, ≥LLOQ) versus qualitative HBsAg (positive, negative), respectively, will also be presented by intervention arm.

5.4.2.1.5. HBsAg Seroclearance

5.4.2.1.5.1. On Treatment

The count and proportion of participants (and associated 90% CI) who achieve HBsAg seroclearance over time during the study intervention phase will be summarized by intervention arm.

5.4.2.1.5.2. Off Treatment

The count and proportion of participants (and associated 90% CI) who achieve HBsAg seroclearance over time during FU will be summarized by intervention arm.

The count and proportion of participants who achieve HBsAg seroclearance will be evaluated by intervention arm at each of the following off-treatment time points: 12, 24, 36 and 48 weeks, respectively, after stopping all study interventions and without restarting NA treatment. In an additional summary, these proportions will be calculated with the denominator including only those participants who have reached the off-treatment timepoint (week 12, 24, 36 or 48), and have stopped all interventions including NA and have not restarted NA prior to the timepoint of interest.

For all time points, HBsAg seroclearance will be analyzed using the observed case data. LOCF will be used for selected time points (Section 5.4.2.1.1).

5.4.2.1.5.3. Functional Cure

The count and proportion of participants (and associated 90% CI) who achieve FC at each of the selected FU time points will be summarized descriptively by intervention arm.

The main analysis will be on observed cases data with no imputation of missing values.

Two sensitivity analyses will be performed.

1. Missing as non-response: If participants withdrew from the study prior to the selected FU time point or had missing HBsAg values at the selected FU time point, they will be considered as non-responders.

2. LOCF: If participants withdrew from the study prior to the selected FU time point, they will be considered as non-responders. The LOCF rules to handle missing data will be applied to selected time points as explained in Section 5.4.2.1.1.

5.4.2.1.6. Treatment Failure

The count and proportion of on-treatment failure participants (and associated 90% CI) will be summarized by intervention arm.

5.4.2.1.7. HBsAg Seroconversion

The count and proportion of participants (and associated 90% CI) who achieve HBsAg seroconversion will be summarized descriptively by intervention arm and analysis phase.

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.

5.4.2.1.8.   HBeAg Cut-offs

The cut-offs for HBeAg values will be used in separate summaries over time by intervention arm. The count and proportion of participants who meet those HBeAg thresholds during the study will be summarized descriptively by intervention arm and analysis phase over time and displayed in graphs like bar charts and/or radar plots.

Cross-tabulations overtime of quantitative HBeAg (<LLOQ, ≥LLOQ) versus qualitative HBeAg (positive, negative), respectively, will also be presented by intervention arm.

5.4.2.1.9.   HBV DNA Cut-offs

The cut-offs for HBV DNA values will be used in separate summaries over time by intervention arm. The count and proportion of participants who meet those HBV DNA thresholds during the study will be summarized descriptively by intervention arm and analysis phase over time.

5.4.2.1.10.   Suppressed HBV DNA

The count and proportion of participants (and associated 90% CI) with HBV DNA <LLOQ (overall and separately for HBV DNA detectable and HBV DNA TND) will be evaluated by intervention arm and analysis phase over time.

The count and proportion of participants (and associated 90% CI) with HBV DNA <LLOQ (overall and separately for HBV DNA detectable and HBV DNA TND) will be evaluated by intervention arm at each of the FU Weeks 12, 24, 36, and 48, respectively, after stopping all study interventions at Week 24 and without restarting NA treatment.

In an additional summary, these proportions will be calculated with the denominator including only those participants who have reached the off-treatment timepoint (week 12, 24, 36 or 48), and have stopped all interventions including NA and have not restarted NA prior to the timepoint of interest.

The count and proportion of participants (and associated 90% CI) with HBV DNA <LLOQ (overall and separately for HBV DNA detectable and HBV DNA TND) after restart of NA treatment during follow-up will also be presented by intervention arm.

The number of occurrences each subject 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.

For all time points, HBV DNA <LLOQ will be analyzed using the observed case data. LOCF will be used for selected time points (Section 5.4.2.1.1).

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

5.4.2.1.11.   ALT Normalization

The count and proportion of participants (and associated 90% CI) who achieve ALT normalization on treatment and off treatment but without restarting NA treatment will be summarized descriptively over time by intervention arm, only for the subjects who had ALT elevation (ALT≥ULN) at baseline.

The count and proportion of participants (and associated 90% CI) who have ALT ≥ULN before NA re-treatment and reach ALT normalization after NA re-treatment during follow-up will be summarized by intervention arm.

5.4.2.1.12.   Partial Cure

The count and proportion of participants (and associated 90% CI) who achieve partial cure during the study will be summarized descriptively by intervention arm at the selected FU time points.

The main analysis will be on observed cases data with no imputation of missing values.

Two sensitivity analyses will be performed.

1. Missing as non-response: If participants withdrew from the study prior to the selected FU time point or had missing HBsAg or HBV DNA values at the selected FU time point, they will be considered as non-responders.

2. LOCF: If participants withdrew from the study prior to the selected FU time point, they will be considered as non-responders. The LOCF rules to handle missing data for HBsAg and HBV DNA will be applied to selected time points as explained in Section 5.4.2.1.1.

5.4.2.1.13.   Virologic Breakthrough

The count and proportion of participants (and associated 90% CI) who experience a virologic breakthrough and those who experience virologic breakthrough followed by on-treatment biochemical flare will be summarized, respectively, by intervention arm and analysis phase.

5.4.2.1.14.   Flares

The incidence rate will be calculated and summarized for each type of on-treatment or off-treatment flares (virologic, biochemical and clinical) separately, as well as the overall incidence of participants experiencing at least one flare, regardless of type, 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.

For on-treatment biochemical flares, the incidence of flares causing treatment discontinuation will be summarized by intervention arm. Further, for off-treatment flares, the count and percentage of participants who experienced a flare followed by NA re-treatment will be summarized by flare type and 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.

Additional analysis for off-treatment flares will be performed for those who met the NA treatment completion criteria and stopped NA.

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 $\log_{10}$ transformed values) and changes from baseline ($\log_{10}$ transformed values) over time in HBsAg, HBeAg, HBV DNA, and ALT (original unit) will be summarized by intervention arm. Mean (+/- SE) plots of the actual values, change from baseline ($\log_{10}$ transformed) and change from RTs will be presented over time per endpoint by intervention arm and analysis phase. The change from baseline value to the nadirs (i.e. maximum decrease for each participant) in HBsAg, HBeAg and HBV DNA will be summarized descriptively by intervention arm. Box plots of the changes to nadirs in HBsAg and HBV DNA 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), their interaction, and 2 randomization stratification factors (ie, country grouping as proxy for HBV genotype (GT) at enrollment [Poland (predominantly GT-A) vs Russia (predominantly GT-D) vs all other countries (other or mixed GT prevalence)] and absolute HBsAg value at baseline [<1,000 IU/mL versus ≥1,000 IU/mL]) and baseline blood marker categorical variable 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 and the intervention arm-by-baseline interaction term. 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) and changes from baseline ($\log_{10}$ transformed values) at end of treatment in HBsAg, HBeAg and HBV DNA

will be summarized by study intervention arm by outcome response (i.e. by reduction of at least 2 $\log_{10}$ IU/mL in HBsAg levels from baseline at Week 24, by HBsAg seroclearance at Week 24, FU Week 24 and FU Week 48, and by partial cure status at Week 24, and for participants who achieved functional cure at FU Week 24 and FU Week 48).

Spaghetti plots for both absolute values and changes from baseline of HBsAg and HBV DNA will be presented over time per blood marker by intervention arm and by selected subgroups (Section 5.7.7.1).

Waterfall plots for changes from baseline and RTs of HBsAg, HBeAg, and HBV DNA will also be presented.

Descriptive statistics of the absolute values, changes from baseline and RTs 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.

5.4.2.3. Time to Event Endpoints

The Kaplan-Meier method will be used to estimate and plot the cumulative incidence by each intervention arm. The log-rank test will be performed to compare between the intervention arms. The median time with 90% CI will be estimated using Kaplan-Meier method. To explore the impact of selected baseline factors in addition of study intervention, the survival probabilities will be estimated based on a stratified Cox regression model including study intervention arm, and each baseline factor at a time with the intervention arm-by-baseline factor interaction term. The strata in the stratified Cox model are the 2 randomization stratification factors to allow for a separate baseline hazard for each level of those factors. The interaction between study intervention arm and baseline/disease characteristic will be explored graphically.

5.5. Exploratory Endpoints

5.5.1. Definitions

5.5.1.1. Binary Endpoints

5.5.1.1.1. 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. No imputation rule will be used in case of missing data.

5.5.1.1.2. HBV RNA Cut-offs

The cut-offs for HBV RNA are as follows:

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

The cut-offs for HBV RNA change from baseline and RTs are as follows:

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

5.5.1.1.3. HBcrAg Cut-offs

The cut-offs for HBcrAg are as follows:

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

The cut-offs for HBcrAg change from baseline and RTs are as follows:

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

5.5.1.1.4. Anti-HBe Antibodies

Participants who have positive and negative Anti-HBe values will be evaluated over time.

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) and changes from RTs 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.

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

5.5.1.2.3. Anti-HBs Antibodies

Actual values and change from baseline will be evaluated over time when anti-HBs antibodies are assessed.

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

5.5.1.3. Time to Event Endpoints

5.5.1.3.1. Time to First HBV RNA<LOD

Time to first HBV RNA<LOD is defined as the duration from the date of first study intervention intake to the date of the first occurrence of HBV RNA<LOD (i.e. the date of the first occurrence of HBV RNA<LOD – the date of first study intervention intake + 1). The participants who did not achieve undetectability or who early withdrew from the study before achieving HBV RNA<LOD will be censored at the last HBV RNA assessment before the date of withdrawal.

Time to first HBV RNA<LOD will be also analyzed considering the participants who were retreated with NA before achieving HBV RNA<LOD as censored at the date of NA retreatment.

Only the participants with HBV RNA values $\geq$LOD+ 0.5 $\log_{10}$ cp/mL (i.e. $\geq$1.898 $\log_{10}$ cp/mL) at baseline will be included in this analysis. Similarly, additional analyses for participants with HBV RNA values $\geq$LOD+ 1.0 $\log_{10}$ cp/mL and $\geq$LOD+ 2.0 $\log_{10}$ cp/mL, respectively, will be summarized.

5.5.1.3.2. Time to First HBcrAg Undetectability

Time to first undetectability of HBcrAg is defined as the duration from the date of first study intervention intake to the date of the first occurrence of undetectability of HBcrAg (i.e. the date of the first occurrence of HBcrAg<LLOQ – the date of first study intervention intake + 1). The participants who did not achieve undetectability or who early withdrew from the study before achieving undetectability of HBcrAg will be censored at the last HBcrAg assessment before the date of withdrawal.

Time to first undetectability of HBcrAg will be also analyzed considering the participants who were retreated with NA before achieving HBcrAg<LLOQ as censored at the date of NA retreatment.

Only the participants with HBcrAg values $\geq$LLOQ+ 0.5 $\log_{10}$ U/mL (i.e. $\geq$3.5 $\log_{10}$ U/mL) at baseline will be included in this analysis.

5.5.1.3.3. Time to Appearance of Anti-HBs Antibodies

Appearance of anti-HBs antibodies is defined as a baseline anti-HBs (quantitative) <LLOQ and a post-baseline assessment $\geq$LLOQ.

Time to appearance of anti-HBs antibodies is defined as the time (days) from the date of first study intervention intake to the date of the first occurrence of anti-HBs antibodies appearance + 1. The participants who did not experience emergence of antibodies or who early withdrew from the study before showing emergence of anti-HBs antibodies will be censored at the last anti-HBs antibodies assessment before the date of withdrawal.

Time to appearance of anti-HBs antibodies will be also analyzed considering the participants who were retreated with NA before achieving appearance of anti-HBs antibodies as censored at the date of NA retreatment.

5.5.1.3.4. Time to Appearance of Anti-HBe Antibodies

Appearance of anti-HBe antibodies is defined as a baseline anti-HBe antibodies (qualitative) with a "NEGATIVE" result and a post-baseline assessment with "POSITIVE" result.

Time to appearance of anti-HBe antibodies is defined as the time (days) from the date of first study intervention intake to the date of the first occurrence of anti-HBe antibodies appearance + 1. The participants who did not experience emergence of antibodies or who early withdrew from the study before showing emergence of anti-HBe antibodies will be censored at the last anti-HBe antibodies assessment before the date of withdrawal.

Time to appearance of anti-HBe antibodies will be also analyzed considering the participants who were retreated with NA before achieving appearance of anti-HBe antibodies as censored at the date of NA retreatment.

5.5.1.4. Endpoints for Correlation

5.5.1.4.1. Association Between Baseline Characteristics/Viral Blood Markers and Selected Efficacy Variables

Correlations between baseline characteristics and on-treatment HBV blood markers with off-treatment endpoints will be evaluated. The list of HBV blood markers, including but not limited to, are defined in Table 6.

Table 6: Pairs of off treatment endpoints and baseline characteristics/on treatment HBV markers

Off treatment HBV marker	Baseline Characteristics/On treatment HBV marker
HBsAg change from baseline at FU Week 24	- Age - HBsAg value at baseline - HBsAg change from baseline at Week 12 - HBsAg change from baseline at Week 24 - Treatment failure (Yes; No)
HBsAg change from baseline at FU Week 48	- Age - HBsAg value at baseline - HBsAg change from baseline at Week 12 - HBsAg change from baseline at Week 24 - Treatment failure (Yes; No)
HBsAg seroclearance at FU Week 24 (Yes; No)	- Age - HBsAg value at baseline - HBsAg change from baseline at Week 12

Off treatment HBV marker	Baseline Characteristics/On treatment HBV marker
	• HBsAg change from baseline at Week 24 • Treatment failure (Yes; No)
HBsAg seroclearance at FU Week 48 (Yes; No)	• Age • HBsAg value at baseline • HBsAg change from baseline at Week 12 • HBsAg change from baseline at Week 24 • Treatment failure (Yes; No)
NA re-treatment at FU Week 24 (Yes; No)	• Age • HBsAg value at baseline • HBsAg change from baseline at Week 12 • HBsAg change from baseline at Week 24 • Treatment failure (Yes; No)
NA re-treatment at FU Week 48 (Yes; No)	• Age • HBsAg value at baseline • HBsAg change from baseline at Week 12 • HBsAg change from baseline at Week 24 • Treatment failure (Yes; No)
Partial cure at FU Week 24 (Yes; No)	• Age • HBsAg value at baseline • HBsAg change from baseline at Week 12 • HBsAg change from baseline at Week 24 • Treatment failure (Yes; No)
Partial cure at FU Week 48 (Yes; No)	• Age • HBsAg value at baseline • HBsAg change from baseline at Week 12 • HBsAg change from baseline at Week 24 • Treatment failure (Yes; No)
Functional cure at FU Week 24 (Yes; No)	• Age • HBsAg value at baseline • HBsAg change from baseline at Week 12 • HBsAg change from baseline at Week 24 • Treatment failure (Yes; No)
Functional cure at FU Week 48 (Yes; No)	• Age • HBsAg value at baseline • HBsAg change from baseline at Week 12 • HBsAg change from baseline at Week 24 • Treatment failure (Yes; No)

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.

5.5.2.1. Binary Endpoints

5.5.2.1.1. Liver Stiffness Measurement

The count and proportion of participants who meet those change from baseline thresholds for LSM during the study will be summarized by intervention arm at Week 24, FU Week 24 and FU Week 48.

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

5.5.2.1.2. HBV RNA Cut-offs

The cut-offs for HBV RNA values and decreases from baseline will be used in separate summaries over time. The count and proportion of participants who meet those HBV RNA thresholds during the study will be summarized descriptively by intervention arm and analysis phase over time, and displayed in graphs like bar charts and/or radar plots.

5.5.2.1.3. HBcrAg Cut-offs

The cut-offs for HBcrAg values and decreases from baseline will be used in separate summaries over time. The count and proportion of participants who meet those HBcrAg thresholds during the study will be summarized descriptively by intervention arm and analysis phase over time, and displayed in graphs like bar charts and/or radar plots.

5.5.2.1.4. Anti-HBe Antibodies

The count and proportion of participants with positive and negative anti-HBe values will be summarized descriptively by intervention arm and analysis phase over time.

Shift tables in Anti-HBe positive/negative values from baseline will also be provided at each time point.

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.

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, SE, 90% CI, median, minimum, maximum) by intervention arm. The comparison among intervention arms will be done using ANCOVA with intervention arm, randomization stratification factors as main effects and baseline score as covariate.

Plots of mean (+/- SE) values and changes from baseline over time will be presented. In addition, a waterfall plot will be produced to display the individual changes from baseline in LSM for each participant at a given timepoint.

5.5.2.2.2.   HBV RNA and HBcrAg

The actual values, changes from baseline and changes from RTs in HBV RNA and HBcrAg, respectively, will be summarized only descriptively over time in a similar manner as for values and changes from baseline over time in HBsAg, HBeAg, and HBV DNA as described in Section 5.4.2.2.1, including the change from baseline value to nadir (i.e. maximum decrease for each participant) and the various graphical displays.

Waterfall plots for changes from baseline of HBV RNA and HBcrAg will also be presented.

5.5.2.2.3.   Anti-HBs Antibodies

The actual values of and changes from baseline in anti-HBs antibodies will be summarized only descriptively in a similar manner as described for values and changes from baseline over time in other blood disease markers in Section 5.4.2.2.1.

For all participants with positive anti-HBs antibodies at baseline who will reach HBsAg seroclearance (as defined in Section 5.4.1.1.4), descriptive statistics will be calculated for the change of anti-HBs antibodies level from baseline at the timepoint when achieving the HBsAg seroclearance. In an additional summary, the change of anti-HBs antibodies level from baseline at the specific timepoint will be summarized descriptively for the subset of the participants achieving HBsAg seroclearance at any time before or at that given timepoint.

Cross-tabulations overtime of quantitative versus qualitative anti-HBs values, respectively, will also be presented.

5.5.2.3.   Time to Event Endpoints

The time-to-event endpoints will be analyzed in a similar manner as for the time-to-event endpoints described in Section 5.4.2.3.

5.5.2.4.   Endpoints for Correlation

5.5.2.4.1.   Association Between Baseline Characteristics/Viral Blood Markers and Selected Efficacy Variables

Correlations will be evaluated graphically using scatter plots, and heat maps displaying such potential associations.

The following correlation coefficients will be calculated by intervention arm for the different correlation scenarios:

- Pearson's correlation coefficient for two continuous variables.
- Phi correlation coefficient for two binary variables.
- Point biserial correlation coefficient for one binary variable and one continuous variable.

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), physical examinations, ophthalmic examinations, vital signs measurements, clinical laboratory tests (including hematology, blood biochemistry, blood coagulation, and urinalysis), and ECGs.

For all continuous safety variables, descriptive statistics by intervention group will include the N, mean, standard deviation, 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, median, and range (minimum, maximum)) during the treatment period will be summarized. The duration of treatment with NA will be also summarized for the follow-up phase by intervention arm.

Because of the different route and frequency of treatment administration across the 3 agents (for JNJ-3989 one subcutaneous injection once every 4 weeks, for PegIFN-α2a one subcutaneous injection weekly and for NA once daily tablet) the total duration for each study treatment as follows:

- JNJ-3989: [Min ((Date of last JNJ-3989 injection in the given phase+27 days), Date of discontinuation from JNJ-3989, Date of trial disposition, cut-off date) – Date of first JNJ-3989 injection in the given phase + 1] / 7

- PegIFN-α2a: [Min (Date of the last PegIFN-α2a injection+6 days, Date of discontinuation from PegIFN-α2a, Date of trial disposition, cut-off date) – Date of first PegIFN-α2a injection + 1] /7

- NA: [Min (Date of the last NA administration in the given phase, Date of discontinuation from NA, Date of trial disposition, Date of clinical cut-off) – Date of first NA administration date in the given phase + 1] / 7

For NA treatment, the total duration of exposure will be calculated separately for treatment period and FU phases. For FU, the total duration will add up the weeks of NA treatment post-treatment period for those participants during the NA re-treatment weeks. Those participants who never restarted NA treatment after Week 24 will be counted as having zero weeks of NA exposure during the FU.

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 PegIFN-α2a or NA will be summarized separately for each study intervention by intervention arm during the

treatment period. Additionally, the number and percentage of participants who missed 2 or more JNJ-3989 injections, or who missed more than 5 doses of NA within a four-week period or who missed 2 or more PegIFN-α2a injections will be presented.

Study intervention compliance will be summarized descriptively. See Appendix 7 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 21.1 or higher). 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 including NA

- AEs by relationship to each study agent within a study intervention including NA

- AEs leading to dose interruption/dose modification of each study agent within a study intervention.

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

- Had SAEs

- Had AEs leading to discontinuation of each study agent withing a study intervention including NA

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:

- ALT/AST elevations

- Injection Site Reactions Related to JNJ-3989 and/or PegIFN-α2a

- 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 Appendix 8. Injection site reactions will be identified using the eCRF Injection Site Reaction form.

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 7.

Table 7:   **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
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) Alanine aminotransferase (ALT) Gamma-glutamyltransferase (GGT) α_1-acid glycoprotein 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 Creatine phosphokinase (CPK) Lactic acid dehydrogenase (LDH) Uric acid Calcium Phosphate Albumin Total protein Total cholesterol High-density lipoprotein cholesterol Low-density lipoprotein cholesterol Triglycerides Magnesium Lipase Amylase (reflex testing of pancreatic amylase should be done in case of amylase or lipase increase from screening onwards)	

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Laboratory Assessments	Parameters	
Routine Urinalysis	Dipstick Specific gravity pH Glucose Protein Blood Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase	Sediment (if dipstick result is abnormal) Red blood cells White blood cells Epithelial cells Crystals Casts Bacteria
	In case of a positive dipstick result, a urine sample will be set aside for additional examination of the positive parameter (e.g. quantification as applicable).	
Urine Chemistry (quantitative measurement)	Creatinine Sodium Phosphate	Glucose Protein Albumin
Renal Biomarkers	Retinol binding protein[a] Beta-2-microglobulin[a] *Note:* Other biomarkers might be measured.	

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 DAIDS Toxicity Grade Scale (see Clinical Protocol Appendix 9, DAIDS table)) 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. The incidence table of worst toxicity grade abnormality in laboratory parameters will be also presented stratified by the subgroups of interest identified in Section 5.7.7.2.

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 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, 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. Descriptive statistics will also be calculated by subgroups (eGFRcr Grade ≥3 [at least once during the treatment period] vs Grade <3, confirmed eGFRcr Grade ≥3, Type of NA at Baseline).

Plots of mean (+/- SE) values and changes from baseline over time for the renal safety parameters will be presented overall, and by subgroups (eGFRcr Grade ≥3 [at least once during the treatment period] vs Grade <3, confirmed eGFRcr Grade ≥3, Type of NA at Baseline).

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.

The analyses will be also performed using subgroups based on eGFRcys.

5.6.3.2.1.   eGFR

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. The following analyses will be done for both eGFRcr and eGFRcys

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.

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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 <u>unadjusted</u> 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 8).

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 8, 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 ($\leq$30 msec, >30- $\leq$60 msec, >60 msec) and categorized corrected QT/QTc interval values ($\leq$450 msec, >450- $\leq$480 msec, >480-$\leq$ 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 $\geq$ 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 baseline 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 either in the clinical study report or 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 PegIFN-α2a with 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. 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) will also be tabulated for PBMCs during study intervention and follow-up. The proportion (%) of chronic HBV-infected patients with detectable responses based on the magnitude of the IFN-γ T-cell response or the CD4+ or CD8+ T-cells expressing at least 1 of the cytokines amongst IL-2, TNF-α or IFN-γ for 1 of the HBV antigens as defined by ELISpot and/or ICS, respectively, will be determined. Changes from baseline (or positivity threshold) in HBV-specific peripheral blood T-cell responses will be summarized and tabulated.

Graphs showing the individual subject 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 will 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 will 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 (IFNγ and/or TNFα and/or IL-2), pie charts will 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 will be presented to reflect the mean magnitude of each combination.

5.7.4. Viral Genome Sequence Analysis

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

Viral genome sequence analysis will be performed to evaluate the presence of genetic variations (including substitutions) associated with JNJ-3989, and/or ETV or TDF/TAF treatment on both nucleotide and/or amino acid level.

Sequencing of the HBV genome will be performed to monitor HBV variants present at the time points indicated in Section 5.7.4.1.

Virology results will be presented by specified timepoints and genetic region and position of interest. Exploratory viral sequencing may be performed using HBV RNA. A separate virology report will be prepared.

5.7.4.1. Time Points and Samples

When analyzing sequencing data, the focus will be on genetic variants at

- Time Point of Sequence at Virologic Breakthrough: time point with sequence data available closest to the time point of virologic breakthrough (FTPT) (See Section 5.4.1.1.13 for virologic breakthrough definition)

- Time Point of Sequence at Virologic Flare: time point with sequence data available closest to the time point of Virologic flare (See Section 5.4.1.1.14 for virologic flare definition)

- Time Point of Sequence at Re-treatment during Post-treatment Follow-up: time point with sequence data available closest to time point where re-treatment criteria is met (See Section 5.4.1.1.1)

- Aggregated Post-Baseline Study Period (ASSEQ): entire post-baseline study period, aggregate of all available time points in the study with sequence data available

- Aggregated Post-Baseline Treatment Period (ATSEQ): entire post-baseline treatment period, aggregate of all available post-baseline time points during the treatment phase with sequence data available

Given only participants who are on stable NA treatment and who have HBV DNA <60 IU/mL at screening will be enrolled in this study, no baseline sequencing can be performed. In the exceptional case baseline HBV DNA levels are above the sensitivity limit of the sequencing assay used, the baseline sample may be sequenced.

5.7.4.2. Definitions

- The presence of genetic variations is defined as changes (on the amino acid or nucleotide level) in the subject viral sequence compared to a HBV genotype specific reference viral sequence and/or the universal HBV reference sequence (NCBI ID X02763). The reference sequence to be used is provided in the database. The reference viral sequences to be used are:

Virus	Genotype	NCBI genbank accession	NGS isolate name	Sanger genbank accession	Sanger isolate name
HBV	A	X02763	adw2	X02763	adw2
HBV	B	AB219428	PNN3	D00329	pJDW233
HBV	C	GQ924620	M38	AB014362	03D03HCC
HBV	D	AF121240	11066	V01460	ayw
HBV	E	AB106564	GA325	X75657	ayw4
HBV	F	AY090458	70H	X75658	adw4q
HBV	G	AF160501	IG29227	AB064311	USG825
HBV	H	FJ356716	CL150171	AY090460	LAS2523
HBV	I	EU833891	H4536-07		

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- Wild type: If at certain position the amino acid/nucleotide in the subject sequence matches the reference sequence, that is no genetic variation is present at that position, the virus is considered to be wild type at that position.

5.7.4.3.   Parameters to Analyze

At specified time points and for each list specified in the section below, the following parameters will be analyzed:

- Number (%) of subjects with a substitution at a specific position.

- Number (%) of subjects with a specific substitution.

- Number (%) of subjects with a specific substitution profile

- Number (%) of subjects with substitutions on amino acid level (overall and by HBV genotype (A, B, C, D, E, F, G, H, I and Unknown))

  - at positions of interest in the RT-domain of the polymerase,

  - at positions of interest in the major hydrophilic loop of HBsAg.

- Number (%) of subjects with substitutions on nucleotide level

  - at the binding site positions of JNJ-3989 (i.e. JNJ-3976 and JNJ-3924) (overall and by HBV genotype (A, B, C, D, E, F, G, H, I and Unknown)).

  - in the precore (genome position 1896) and basal core promotor (genome positions 1762/1764) region (overall, by HBV genotype (A, B, C, D, E, F, G, H, I and Unknown))

The focus will be on substitutions at a time point, and reversion to wild type state. The above summaries will be repeated for genetic variations (not needed for CSR).

In the sequence analysis, sequences will be mapped to the respective genotype specific reference sequences after which nucleotide (nt) changes and amino acid (aa) substitutions will be annotated compared to the respective genotype specific reference (see Table in Section 5.7.4.2). In addition, the X02763 (HBV genotype A), which is the master reference sequence of the HBV database (db), will be used as universal reference sequence.

All NGS data will be collected using a nt and aa read frequency cut-off of ≥ 0.01. For the analysis of nt changes and/or aa substitutions in terms of frequency of variant, a read frequency cut-off of ≥ 0.15 will be used. The persistence of nt changes and aa substitutions will be evaluated using a cut-off of ≥ 0.15 and ≥ 0.01.

The applicability of the sequencing approach described here (e.g. the 0.01 sensitivity limit) will be assessed during the development program and might be adapted if needed.

5.7.4.4. Positions & Genetic Variations of Interest

On the nucleotide level:

In the basal core promotor region:

- 1762 and 1764 (ECo numbering will be used)

In the precore region:

- 1896 (ECo numbering will be used)

In the basel core/precure region

- Combination of basal core promotor and/or precore region

In the JNJ-3989 binding pocket positions:

- JNJ-3976

    Positions of Interest in the S gene: 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280.

- JNJ-3924

    Positions of Interest in the X gene: 1781, 1782, 1783, 1784, 1785, 1786, 1787, 1788, 1789, 1790, 1791, 1792, 1793, 1794, 1795, 1796, 1797, 1798, 1799, 1800.

- In the JNJ-3976/JNJ-3924

    Combination of JNJ-3989 binding site positions JNJ-3976 and/or JNJ-3924

Amino acid level:

In the pol/RT protein:

- 169, 173, 180, 181, 184, 194, 202, 204, 236, 250

See below breakdown of relative amino acid position of the 10 POI in the RT-domain of polymerase by HBV genotype.

HBV GT-A		HBV-GT-B/C/F/H/I		HBV GT-D		HBV-GT-E/G	
POL number	RT number	POL number	RT number	POL number	RT number	POL number	RT number
517	169	515	169	504	169	514	169
521	173	519	173	508	173	518	173
528	180	526	180	515	180	525	180
529	181	527	181	516	181	526	181
532	184	530	184	519	184	529	184
542	194	540	194	529	194	539	194
550	202	548	202	537	202	547	202
552	204	550	204	539	204	549	204
584	236	582	236	571	236	581	236

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HBV GT-A		HBV-GT-B/C/F/H/I		HBV GT-D		HBV-GT-E/G	
598	250	596	250	585	250	595	250

In the major hydrophilic loop of the S-protein region (linked to vaccine escape):

- Amino acids 99 to 169

- Positions of interest: 116, 118, 120, 126, 129, 130, 131, 133, 134, 141, 142, 143, 144, 145, 164, 195, and 196.

5.7.4.5.   Analysis Methods

Frequencies and percentages will be presented at the time points specified above for the specified parameters. The denominator is the number of subjects with sequencing data at the selected time point.

A frequency output and/or figure will only be generated if number of participants with respective sequence information available (i.e. baseline sequence info for baseline outputs and paired baseline/post-baseline sequence info for post-baseline outputs) for that respective output or figure is greater or equal to 5 (N≥5).

For comparison of amino acid or nucleotide levels to universal or genotype specific HBV reference sequences descriptive summaries may be performed by subgroups.

5.7.4.5.1.   Post-Baseline

- Time of Virologic Breakthrough (if applicable)

For virologically suppressed participants who experience virologic breakthrough but who don't have baseline sequence information available, the frequency of genetic variations (with a primary focus on substitutions) at time of viral breakthrough will be tabulated in frequency outputs (n, %), based on NGS data (1% and 15% cut-off), for participants with viral sequence info available at time of viral breakthrough.

The return to wild type for subjects with virologic breakthrough and genetic variations at time of virologic breakthrough will be tabulated in frequency outputs based on NGS data, as well as the genetic variations in subjects who did not return to wild type.

- Time of Virologic /Clinical Flare (if applicable)

For virologically suppressed participants who experience virologic/clinical flare but who don't have baseline sequence information available, the frequency of genetic variations (with a primary focus on substitutions) at time of virological/clinical flare will be tabulated in frequency outputs (n, %), based on NGS data (1% and 15% cut-off), for participants with viral sequence information available at time of flare.

The return to wild type for subjects with virologic/clinical flare and genetic variations at time of virologic/clinical flare will be tabulated in frequency outputs based on NGS data, as well as the genetic variations in subjects who did not return to wild type.

- Time of Re-treatment during Post-treatment Follow-up

For virologically suppressed participants who meet NA re-treatment criteria but who don't have baseline sequence information available, the frequency of genetic variations (with a primary focus on substitutions) at time of meeting NA re-treatment criteria will be tabulated in frequency outputs (n, %), based on NGS data (1% and 15% cut-off), for participants with viral sequencing information available at time of meeting NA retreatment criteria.

The return to wild type for subjects who meet re-treatment criteria during follow-up and genetic variations at time of meeting the re-treatment criteria will be tabulated in frequency outputs based on NGS data, as well as the genetic variations in subjects who did not return to wild type.

- Other Post-Baseline

The frequency of variant of genetic variations at other time points will be tabulated in frequency outputs (n, %), based on NGS data (1% and 15% cut-off), and the genetic variations will be listed for all subjects. Time points of specific interest are end-of-treatment, time point of re-treatment, and end-of-study.

5.7.4.5.2. Over the Study Period

For all subjects, listings with relevant baseline disease and demographic characteristics, session info, all genetic variations at baseline (if available), at time of virologic breakthrough (if applicable), at end of study treatment, and at end of study will be generated.

For all subjects, listings with relevant baseline disease and demographic characteristics, session info, and aggregate post-baseline sequence data over the whole treatment period, and aggregate post-baseline sequence data over the whole study period will be generated.

5.7.5. HBV genotype

For all subjects for whom viral sequencing is performed, also an HBV genotype will be reported using the HBV full genome sequence and phylogenetic analysis. The number and percentage of subjects by HBV genotype for study analysis will be tabulated.

Exploratory HBV genotyping may be performed based on HBV RNA.

5.7.6. Health Economics

Medical resource utilization will be descriptively summarized by treatment group and analysis phase.

5.7.7. Definition of Subgroups

5.7.7.1. Subgroups for Efficacy Analyses

Table 8: Subgroups for efficacy analyses

Subgroup	Definition
Sex	Male, Female
Age	≤45 years, >45 years

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Subgroup	Definition
Race	Asian, Non-Asian
Geographical Region	Europe (Spain, UK, Poland, Russia), Asia (South Korea, Japan, Taiwan, Hong Kong, Thailand), North America (US, Canada)
Type of NA at Baseline	TeD, TAF, ETV
HBsAg level at baseline	<100 IU/mL; ≥100 IU/mL-<1,000 IU/mL; ≥1,000 IU/mL-<10,000 IU/mL; ≥10,000 IU/mL
HBV RNA level at baseline	<1,000 copies/mL; ≥1,000 copies/mL
HBcrAg level at baseline	<3 log U/mL; ≥3 log U/mL-<4 log U/mL; ≥4 log U/mL
Anti-HBs level at baseline	<10 mIU/mL; ≥10 mIU/mL
Alanine Transferase (ALT) at baseline	≤1.0 ULN; >1.0 ULN
HBV Genotype	Genotype A, B, C, D, E, F, G, H, I, J and Unknown

5.7.7.2. Subgroups for Safety Analyses

Table 9: **Subgroups for safety analyses**

Subgroup	Definition
Sex	Male, Female
Age	≤45 years, >45 years
Race	Asian, Non-Asian
BMI	- Underweight: <18.5 kg/m^2 - Normal: ≥18.5-<25 kg/m^2 - Overweight: ≥25-<30 kg/m^2 - Obese: ≥30 kg/m^2
Type of NA at Baseline	TeD, TAF, ETV

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 will be 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: approximately 50% of the randomized participants have completed Week 4 or discontinued earlier

- Thereafter, data reviews will occur approximately every 8 weeks.

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) will 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 IAs are planned when:

- Approximately 50% of the randomized participants have completed Week 12 or discontinued earlier.

- Approximately 50% of the randomized participants have completed Week 24 or discontinued earlier.

- All randomized participants have completed Week 36 (FU Week 12) or discontinued earlier.

- All randomized participants have completed Week 48 (FU Week 24) or discontinued earlier.

- All randomized participants have completed Week 60 (FU Week 36) or discontinued earlier.

The primary analysis will be conducted at the time when all participants have completed 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 10. Details on the type of summaries and analyses of both efficacy and safety variables are described in the following sections.

Table 10: **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=51)	DR approx. every 8 weeks	IA1/ Week 12 (approx. N=51)	IA2/ Week 24 (N=51)	Primary/ Week 24 (approx. N=102)	IA3/ Week 36 (N=102)	IA4/ Week 48 (N=102)	IA5/ Week 60 (N=102)	Final analysis/ Week 72 (N=102)
Subject information									
Baseline & Demographic characteristics	X	X	X	X	X	X	X	X	X
Disposition and Study Populations	X	X	X	X	X	X	X	X	X
Extend of Exposure	X	X	X	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	X	X	X
Laboratory tests	X	X	X	X	X	X	X	X	X
ECG	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X
Efficacy									
Values and Changes over time in HBsAg, HBeAg, HBV DNA and ALT		X	X	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	X	X
Other secondary efficacy endpoints			X	X	X	X	X	X	X
Exploratory endpoints			X	X	X	X	X	X	X

	DR1/ Week 4 (approx. N=51)	**DR approx. every 8 weeks**	**IA1/ Week 12 (approx. N=51)**	**IA2/ Week 24 (N=51)**	**Primary/ Week 24 (approx. N=102)**	**IA3/ Week 36 (N=102)**	**IA4/ Week 48 (N=102)**	**IA5/ Week 60 (N=102)**	**Final analysis/ Week 72 (N=102)**
Virologic breakthrough	X	X	X	X	X	X	X	X	X
Flares: Viral, Biochemical, Clinical	X	X	X	X	X	X	X	X	X
PK*			X	X	X	X	X	X	X
*If there are available data, it will be analyze.									

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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
EOT	end of treatment
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	interferon
IFN-FAS	PegIFN-α2a full analysis set
IQR	interquartile range
IRT	item response theory
ISR	injection site reaction
IU/mL	international units per milliliter
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)
PegIFN-α2a	pegylated interferon alpha-2a
PGIC	Patient Global Impression of Change
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
RGT	response-guided treatment
RR	Interval between R wave of one heartbeat and R wave of preceding heartbeat
RTs	reference timepoints
SAE	serious adverse event
SAP	statistical analysis plan
SCr	serum creatinine
SD	standard deviation
SF-36v2	Short Form 36 version 2
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
VAS	Visual Analog Scale
WBC	white blood cell

6.2.   Appendix 2 Changes to Protocol-Planned Analyses

There are no changes to the protocol-planned analyses.

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

Table 11: Demographic Variables

Continuous Variables:	Summary Type
Age (years)	
Weight at baseline (kg)	
Height at baseline (cm)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
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)	
Sex (male, female, undifferentiated)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple)	Frequency distribution with the number and percentage of participants in each category.
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 12 presents a list of the baseline characteristics variables that will be summarized by intervention group, and overall for the FAS.

Table 12: Baseline Characteristics Variables

Continuous Variables	Summary Type
HBV history	
Duration of 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	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
HBV viral activity and serology parameters	
HBeAg at screening 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	
Mode of HBV infection: Sexual transmission, intravenously injectable drug use, blood transfusion, Hemophilia-associated injection, occupational exposure, mother to child transmission, unknown and other	
Type of NA at baseline: TeD, TAF, ETV	
Duration of NA at baseline (years)	
HBV viral activity and serology parameters	
HBeAg status at least 6 months before screening (qualitative, based on historical data)	
HBsAg category at baseline (IU/mL): <100, < 1,000, < 10,000, < 100,000, $\geq$ 100,000	
HBV DNA category at baseline (IU/mL): < LLOQ Target detected (TD) or not detected (TND), < LLOQ TD, < LLOQ TND, < 60, $\geq$60	
HBV RNA category at baseline (copies/mL): TND, < LOD, < LLOQ, < 1,000, $\geq$ 1,000	
HBcrAg category at baseline (log U/mL): < 3, $\geq$ 3 - < 4, $\geq$ 4	Frequency distribution with the number and percentage of participants in each category.
HBsAg Antibody (Anti-HBs) status at baseline: Positive, Negative	
HBsAg Antibody (Anti-HBs) category at baseline (mIU/mL): < 10, $\geq$ 10	
HBeAg Antibody (Anti-HBe) status: Positive, Negative	
Baseline ALT toxicity grade according to DAIDS	
Baseline ALT categorization: $\leq$ 1.0xULN, > 1.0xULN to <2xULN, $\geq$ 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 13) 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 13. 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 13:   Selected Major Protocol Deviations for Analysis Purposes

Sequence number	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 65 years of age, inclusive	Inclusion criteria A01 (M01) not met: Participant was <specify> years old	Entered but did not satisfy criteria	Yes	No
2	Participants must be medically stable based on physical examination, medical history, vital signs, and 12-lead ECG performed at screening If there are abnormalities, they must be consistent with the underlying illness in the study population This determination must be recorded in the participant's source documents and initialed by the investigator	Inclusion criterion M02 not met: Participants must be medically stable based on physical examination, medical history, vital signs, and 12-lead ECG performed at screening If there are abnormalities, they must be consistent with the underlying illness in the study population This determination must be recorded in the participant's source documents and initialed by the investigator	Entered but did not satisfy criteria	Yes	No
3	Participants must have chronic HBV infection	Inclusion criteria A03 not met (adapted from M03a):	Entered but did not satisfy criteria	Yes	No

		Participants must have chronic HBV infection HBV infection must be documented by serum HBsAg positivity at screening In addition, chronicity must be documented by any of the following, at least 6 months prior to screening: -serum HBsAg positivity, -HBeAg positivity or HBV DNA positivity -ALT elevation above ULN without another cause than HBV infection -documented transmission event If none of the above are available, the following ways of documenting chronicity are acceptable at the time of screening: -liver biopsy with changes consistent with chronic HBV, or absence of marker for acute HBV infection such as positive immunoglobulin M (IgM) anti-hepatitis B surface (HBs) and anti-HBc antibodies - Participants should: • be HBeAg-negative, AND • be anti-HBe antibody-positive, AND • be on stable HBV treatment, defined as currently receiving NA treatment for at least 2 years prior to screening, and having been on the same NA treatment regimen (at the same dose) as used in this study for at least 3 months at the time of screening, AND • have documented serum HBV DNA <60 IU/mL on 2 sequential measurements at least 6 months apart (one of which is at screening), AND • have documented ALT values <2 0x ULN on 2 sequential measurements at least 6 months apart (one of which is at screening)			
4	Participants must have a body mass index (BMI; weight in kg divided by the square of height in meters) between 18 0 and 35 0 kg/m^2, extremes included	Inclusion criteria M04 not met Participants must have a body mass index (BMI; weight in kg divided by the square of height in meters) between 18 0 and 35 0 kg/m^2, extremes included	Entered but did not satisfy criteria	Yes	No
5	Participants must sign a Master ICF (specific for the Master Protocol PLATFORMPAHPB2001) and must sign the ICF specific for this intervention cohort, indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study	Inclusion criteria A05 (adapted from M05) not met Participants must sign a Master ICF (specific for the Master Protocol PLATFORMPAHPB2001) and must sign the ICF specific for this intervention cohort, indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study	Entered but did not satisfy criteria	Yes	No

6	Participants must sign a separate ICF if he or she agrees to provide additional optional DNA samples for research (where local regulations permit)	Inclusion criteria M06 not met Participants must sign a separate ICF if he or she agrees to provide additional optional DNA samples for research (where local regulations permit) Refusal to give consent for the optional DNA research samples does not exclude a participant from participation in the study	Entered but did not satisfy criteria	Yes	No
7	Female participants must be (as defined in Attachment 5 of the Master Protocol PLATFORMPAHPB2001): a Not of childbearing potential, OR b Of childbearing potential and practicing a highly effective, preferably user-independent method of contraception (failure rate of <1% per year when used consistently and correctly) for at least 30 days prior to screening and agrees to remain on a highly effective method while receiving study intervention and until 90 days after last dose of study intervention	Inclusion criteria A07 (adapted from M07) not met Female participants must be (as defined in Attachment 5 of the Master Protocol PLATFORMPAHPB2001): a Not of childbearing potential, OR b Of childbearing potential and practicing a highly effective, preferably user-independent method of contraception (failure rate of <1% per year when used consistently and correctly) for at least 30 days prior to screening and agrees to remain on a highly effective method while receiving study intervention and until 90 days after last dose of study intervention Examples of highly effective methods of contraception are provided in Attachment 5 of the Master Protocol PLATFORMPAHPB2001 Note: Typical use failure rates may differ from those when used consistently and correctly Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies	Entered but did not satisfy criteria	Yes	No
8	Female participants of childbearing potential must have a negative highly sensitive serum pregnancy test (β-human chorionic gonadotropin) at screening and a negative urine pregnancy test on Day 1 before the first dose of study intervention	Inclusion criteria M08 not met Female participants of childbearing potential must have a negative highly sensitive serum pregnancy test (β-human chorionic gonadotropin) at screening and a negative urine pregnancy test on Day 1 before the first dose of study intervention	Entered but did not satisfy criteria	Yes	No
9	In the investigator's opinion, the participant is able to understand and comply with protocol requirements, instructions, and study restrictions and is likely to complete the study as planned per ISA (including the procedures outlined in the Master Protocol PLATFORMPAHPB2001)	Inclusion criteria M09 not met In the investigator's opinion, the participant is able to understand and comply with protocol requirements, instructions, and study restrictions and is likely to complete the study as planned per ISA (including the procedures outlined in the Master Protocol PLATFORMPAHPB2001)	Entered but did not satisfy criteria	Yes	No
10	Male participants must agree to wear a condom when engaging in any activity that allows for passage of ejaculate to another person during the study intervention period and until 90 days after last dose of study intervention	Inclusion criteria A10(adapted from M10) not met Male participants must agree to wear a condom when engaging in any activity that allows for passage of ejaculate to another person during the study	Entered but did not satisfy criteria	Yes	No

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		intervention period and until 90 days after last dose of study intervention			
11	Female participants must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study intervention period and until 90 days after last dose of study intervention	Inclusion criteria A11 not met Female participants must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study intervention period and until 90 days after last dose of study intervention	Entered but did not satisfy criteria	Yes	No
12	Male participants must agree not to donate sperm for the purpose of reproduction during the study intervention period and until 90 days after last dose of study intervention	Inclusion criteria A12 not met Male participants must agree not to donate sperm for the purpose of reproduction during the study intervention period and until 90 days after last dose of study intervention	Entered but did not satisfy criteria	Yes	No
13	Participants must have serum HBsAg >100 IU/mL at screening, as assessed by quantitative HBsAg assay	Inclusion criteria A13 not met Participants must have serum HBsAg >100 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	Inclusion criteria A14 not met 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 (e g 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 (e g conventional liver ultrasound, computed tomography [CT] or magnetic resonance imaging [MRI]) and serum marker panels are not allowed to rule out severe fibrosis or cirrhosis	Entered but did not satisfy criteria	Yes	No
15	Participants with evidence of hepatitis A virus infection (hepatitis A antibody IgM), HCV infection (HCV antibody), hepatitis D virus (HDV) infection (HDV antibody), hepatitis E virus (HEV) infection (hepatitis E antibody IgM), or HIV-1 or HIV-2 infection (laboratory confirmed) at screening	Exclusion criterion A01 (adapted from M01) met: Subject has <history/condition> <enter details> Participants with evidence of hepatitis A virus infection (hepatitis A antibody IgM), HCV infection (HCV antibody), hepatitis D virus (HDV) infection (HDV antibody), hepatitis E virus (HEV) infection (hepatitis E antibody IgM), or HIV-1 or HIV-2 infection (laboratory confirmed) at screening	Entered but did not satisfy criteria	Yes	No

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		• Participants with a positive HCV antibody test can be enrolled if they have negative HCV RNA at screening and documented negative HCV RNA at least 6 months prior to screening • Participants with a positive HDV antibody test may be enrolled after discussion with the Sponsor if an active HDV co-infection can be ruled out by documentation of negative HDV RNA • Participants with a positive IgM antibody test for HEV infection may be enrolled after discussion with the Sponsor if an active HEV infection can be ruled out by documentation of negative anti-HEV immunoglobulin G (IgG) • Participants with a positive HIV-1 or HIV-2 antibody/antigen test at screening can be enrolled if they have a negative HIV RNA test at screening				
16	Participants with evidence of hepatic decompensation at any time point prior to or at the time of screening: a Total bilirubin >1 5x ULN, OR 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 with evidence of hepatic decompensation at any time point prior to or at the time of screening: a Total bilirubin >1 5x ULN, OR Direct bilirubin >1 2x ULN , OR b Prothrombin time >1 3x ULN (unless caused by anticoagulation therapy or vitamin K deficiency), OR c Serum albumin <3 2 g/dL	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: History or evidence of clinical signs or symptoms of hepatic decompensation, including but not limited to: -portal hypertension -ascites -hepatic encephalopathy -esophageal varices	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: 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	Entered but did not satisfy criteria		Yes	No

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		liver disease considered clinically significant by the investigator			
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 hepatocellular carcinoma (HCC) or clinically relevant renal abnormalities on an abdominal ultrasound performed within 3 months prior to screening or at the time of screening In case of suspicious findings on conventional ultrasound the participant may still be eligible if HCC or clinically relevant renal abnormalities have been ruled out by a more specific imaging procedure (contrast enhanced ultrasound, CT or MRI)	Exclusion criterion A05 (adapted from M05) met: Participants with history or signs of cirrhosis or portal hypertension (nodules, no smooth liver contour, no normal portal vein, spleen size ≥12 cm) or signs of hepatocellular carcinoma (HCC) or clinically relevant renal abnormalities on an abdominal ultrasound performed within 3 months prior to screening or at the time of screening In case of suspicious findings on conventional ultrasound the participant may still be eligible if HCC or clinically relevant renal abnormalities have been ruled out by a more specific imaging procedure (contrast enhanced ultrasound, CT or MRI)	Entered but did not satisfy criteria	Yes	No
20	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 Clinical Protocol Section 10 9, Appendix 9: DAIDS Table): a Estimated glomerular filtration rate (eGFR) ≥Grade 3 (ie, <60 mL/min/1 73 m^2) at screening, calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; b Pancreatic lipase elevation ≥Grade 3; c Pancreatic amylase elevation ≥Grade 3; d Hemoglobin ≤10 9 g/dL (males), ≤10 4 g/dL (females); e Platelet count ≤lower limit of normal (LLN); f Alpha-fetoprotein (AFP) >100 ng/mL; Note: Participants with AFP >ULN but ≤100 ng/mL may be eligible if HCC can be ruled out based on a sensitive imaging study (e g contrast-enhanced ultrasound, CT or MRI) during screening g Any other laboratory abnormality considered to be clinically significant by the investigator (also see exclusion criterion A02)	Exclusion criterion A06 (adapted from M06) met: 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 Clinical Protocol Section 10 9, Appendix 9: DAIDS Table): a Estimated glomerular filtration rate (eGFR) ≥Grade 3 (ie, <60 mL/min/1 73 m^2) at screening, calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; b Pancreatic lipase elevation ≥Grade 3; c Pancreatic amylase elevation ≥Grade 3; d Hemoglobin ≤10 9 g/dL (males), ≤10 4 g/dL (females); e Platelet count ≤lower limit of normal (LLN); f Alpha-fetoprotein (AFP) >100 ng/mL; Note: Participants with AFP >ULN but ≤100 ng/mL may be eligible if HCC can be ruled out based on a sensitive imaging study (e g contrast-enhanced ultrasound, CT or MRI) during screening g Any other laboratory abnormality considered to be clinically significant by the investigator (also see exclusion criterion A02)	Entered but did not satisfy criteria	Yes	No
21	Participants with hemoglobin A1c >8% at screening	Exclusion criterion M07 met: Participants with hemoglobin A1c >8% at screening	Entered but did not satisfy criteria	Yes	No
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	Exclusion criterion M08 met: Participants with a history of malignancy within 5 years before	Entered but did not satisfy criteria	Yes	No

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	situ of the cervix, or malignancy, which are considered cured with minimal risk of recurrence)	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)			
23	Participants with abnormal sinus rhythm (heart rate <45 or >100 beats per minute [bpm]); QT interval corrected for heart rate according to Fridericia's formula (QTcF) >450 ms for males and >470 ms for females; QRS interval ≥120 ms; PR interval >220 ms; abnormal conduction; or any other clinically significant abnormalities on a 12-lead ECG at screening

Note: Retesting of an abnormal ECG that may lead to exclusion will be allowed once without prior asking approval from the Sponsor Retesting will take place during an unscheduled visit in the screening phase Participants not meeting the above exclusion criterion at retest may be included | Exclusion criterion M09 met

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

Note: Retesting of an abnormal ECG that may lead to exclusion will be allowed once without prior asking approval from the Sponsor Retesting will take place during an unscheduled visit in the screening phase Participants not meeting the above exclusion criterion at retest may be included | Entered but did not satisfy criteria | Yes | No |
| 24 | Participants with a history of or current cardiac arrhythmias (e g extrasystole, tachycardia at rest), history of risk factors for Torsade de Pointes syndrome (e g hypokalemia, family history of long QT Syndrome) or history or other clinical evidence of significant or unstable cardiac disease (e g angina, congestive heart failure, myocardial infarction, diastolic dysfunction, significant arrhythmia and/or coronary heart disease), moderate to severe valvular disease, or uncontrolled hypertension at screening | Exclusion criterion M10 met | Entered but did not satisfy criteria | Yes | No |
| 25 | Participants with any current or previous illness for which, in the opinion of the investigator and/or Sponsor, participation would not be in the best interest of the participant (e g compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments This may include but is not limited to significant vascular, pulmonary (e g chronic obstructive pulmonary disease), gastrointestinal (e g significant diarrhea, gastric stasis, or constipation that in the investigator's opinion could influence drug absorption or bioavailability), endocrine (e g thyroid disease), neurologic, hematologic, rheumatologic, psychiatric, neoplastic, or metabolic disturbances Any condition possibly affecting drug absorption (e g gastrectomy or other significant gastrointestinal tract surgery, such as gastroenterostomy, small bowel resection, or active enterostomy) will also lead to exclusion | Exclusion criterion M11 met

Participants with any current or previous illness for which, in the opinion of the investigator and/or Sponsor, participation would not be in the best interest of the participant (e g compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments This may include but is not limited to significant vascular, pulmonary (e g chronic obstructive pulmonary disease), gastrointestinal (e g significant diarrhea, gastric stasis, or constipation that in the investigator's opinion could influence drug absorption or bioavailability), endocrine (e g thyroid disease), neurologic, hematologic, rheumatologic, psychiatric, neoplastic, or metabolic disturbances Any condition possibly affecting drug absorption (e g gastrectomy or other significant gastrointestinal tract surgery, such as gastroenterostomy, small bowel resection, or active enterostomy) will also lead to exclusion | Entered but did not satisfy criteria | Yes | No |

26	Participants who have received an organ transplant (except for skin, hair, or cornea transplants)	Exclusion criterion M12 met Participants who have received an organ transplant (except for skin, hair, or cornea transplants)	Entered but did not satisfy criteria	Yes	No
27	Participants with any history of or current clinically significant skin disease requiring regular or periodic treatment	Exclusion criterion M13 met Participants with any history of or current clinically significant skin disease requiring regular or periodic treatment	Entered but did not satisfy criteria	Yes	No
28	Participants with clinically relevant alcohol or drug abuse within 12 months of screening	Exclusion criterion M14 met Participants with clinically relevant alcohol or drug abuse within 12 months of screening	Entered but did not satisfy criteria	Yes	No
29	Participants with history of clinically relevant drug rash	Exclusion criterion M15 met Participants with history of clinically relevant drug rash	Entered but did not satisfy criteria	Yes	No
30	Participants who have taken any disallowed therapies as noted in Clinical Protocol Section 6 8, Concomitant Therapy, before screening or baseline Participants who have taken IFN within the last 3 years prior to screening Participants with lamivudine-refractory chronic hepatitis B	Exclusion criterion A16 (adapted from M16) met Participants who have taken any disallowed therapies as noted in Clinical Protocol Section 6 8, Concomitant Therapy, before screening or baseline Participants who have taken IFN within the last 3 years prior to screening Participants with lamivudine-refractory chronic hepatitis B	Entered but did not satisfy criteria	Yes (only for IFN use in last 3 years and lamivudine refractory)	No
31	Participants with known allergies, hypersensitivity, or intolerance to JNJ-3989 or its excipients (refer to the IB [IB JNJ-3989 2020]) and/or to NA and/or to PegIFN-α2a or their excipients (refer to the respective prescribing information)	Exclusion criterion A23 met Participants with known allergies, hypersensitivity, or intolerance to JNJ-3989 or its excipients (refer to the IB [IB JNJ-3989 2020]) and/or to NA and/or to PegIFN-α2a or their excipients (refer to the respective prescribing information)	Entered but did not satisfy criteria	Yes	No
32	Participants who meet any of the additional exclusion criteria for PegIFN-α2a as described in local prescribing information (e g refer to Pegasys SmPC or Pegasys USPI) per the investigator's discretion Key exclusion criteria for PegIFN-α2a include: 1 Participants with signs or symptoms compatible with autoimmune disorders 2 Participants with bone marrow suppression 3 Participants with hypoglycaemia, hyperglycaemia, and/or diabetes mellitus, who cannot be effectively controlled by medication 4 Participants with pre-existing ophthalmologic disorders 5 Participants with one or more of the following laboratory abnormalities: - Absolute neutrophil count <1,500 cells/mm3 (<1,000 cells/mm³ for black or African American participants) - Serum creatinine >1 5x ULN - Inadequately controlled thyroid function (thyroid stimulating hormone [TSH] and thyroxine [T4]) 6 Participants with pre-existing severe psychiatric conditions or a history of severe psychiatric disorders, including severe depression, suicidal ideation and attempted suicide	Exclusion criterion A24 met Participants who meet any of the additional exclusion criteria for PegIFN-α2a as described in local prescribing information (e g refer to Pegasys SmPC or Pegasys USPI) per the investigator's discretion	Entered but did not satisfy criteria	Yes	No

	Note: Contraindications to the use of PegIFN-α2a need to be checked at screening and again at Week 12 for participants in Arm 2				
33	Disallowed from 3 years prior to screening until end of follow-up: IFN, other than the PegIFN-α2a taken in the context of this study	Received protocol prohibited medication <specify medication and/or dose>	Received a disallowed concomitant treatment	If classified as major protocol deviation (reviewed case by case), excluded from PP set	Yes
34	Disallowed from 1 year prior to baseline until end of follow-up: Any oligonucleotide-based treatment (e g siRNA, nucleic acid polymers, antisense oligonucleotides), other than the study intervention taken in the context of this study	Received protocol prohibited medication <specify medication and/or dose>	Received a disallowed concomitant treatment	If classified as major protocol deviation (reviewed case by case), excluded from PP set	Yes
35	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	Received protocol prohibited medication <specify medication and/or dose>	Received a disallowed concomitant treatment	If classified as major protocol deviation (reviewed case by case), excluded from PP set	Yes
36	Disallowed from 6 months prior to baseline until end of follow-up: Any systemically (e g intravenously, intramuscularly, orally, subcutaneously) administered medication that directly or indirectly interferes with immune responses (e g cyclosporine, interleukins, systemic corticosteroids exceeding 5 mg of prednisolone equivalent/day)	Received protocol prohibited medication <specify medication and/or dose>	Received a disallowed concomitant treatment	If classified as major protocol deviation (reviewed case by case), excluded from PP set	Yes
37	Disallowed from screening until end of follow-up: Any anti-HBV drug (including vaccines) other than the study intervention taken in the context of this study Notes: • NA standard of care treatment is allowed between screening and baseline • Prior hepatic treatment with herbal or nutritional products is allowed but should be stopped at screening	Received protocol prohibited medication <specify medication and/or dose>	Received a disallowed concomitant treatment	If classified as major protocol deviation (reviewed case by case), excluded from PP set	Yes
38	Disallowed from screening until end of study intervention: Products containing Hypericum perforatum (St John's wort) -Biotin (>1 mg daily dose), either taken alone or as part of a multivitamin formulation Note: The use of other vitamins is allowed -Topical steroids (>7 days) under occlusive dressing	Received protocol prohibited medication <specify medication and/or dose>	Received a disallowed concomitant treatment	If classified as major protocol deviation (reviewed case by case), excluded from PP set	Yes
39	Approved COVID-19 vaccines or COVID-19 vaccines with conditional marketing	Subjects received approved COVID -19 Vaccine or COVID-	Received a disallowed concomitant treatment	If classified	Yes

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	authorization, emergency use authorization or special approval for emergency are allowed during the study and within 2 days prior to PegIFN-α2a administration during treatment phase 2	19 vaccine with conditional marketing authorization on the same day as PegIFN-α2a administration		as major protocol deviation (reviewed case by case), excluded from PP set	
40	Dose of study medication JNJ-3989, not administered within scheduled time window	Subject missed JNJ-3989 dose(s) If an injection of JNJ-3989 was missed, the injection should be given as soon as possible but within 3 weeks after the scheduled time Otherwise, the injection should be skipped and the next injection should be given at the next scheduled time point per the initial injection schedule	Received wrong treatment or incorrect dose	If classified as major protocol deviation (reviewed case by case), excluded from PP set	Yes
41	If a dose of NA is missed, the participant should follow the guidelines in the prescribing information	Subject missed NA doses	Received wrong treatment or incorrect dose	If classified as major protocol deviation (reviewed case by case), excluded from PP set	Yes
42	Doses of study medication PegIFN-α2a was missed	Subject missed 2 or more PegIFN-α2a doses	Received wrong treatment or incorrect dose	If classified as major protocol deviation (reviewed case by case), excluded from PP set	Yes
43	Dose modifications of JNJ-3989 and NA (increase or decrease of dose level) are not permitted	Subject received modified dose of JNJ-3989 or NA	Received wrong treatment or incorrect dose	If classified as major protocol deviation (reviewed case by case), excluded from PP set	Yes
44	For PegIFN-α2a, dose adjustment guidelines are recommended for participants who develop laboratory abnormalities during PegIFN-α2a treatment, as recommended in the locally approved prescribing information for PegIFN-α2a	Subject developed laboratory abnormalities but did not receive any PegIFN-α2a dose adjustment Recommended dose adjustments: -ANC <750 cells/mm³ Reduce to 135µg -ANC <500 cells/mm³ Discontinue treatment until ANC values return to more than 1,000 cells/mm³ Reinstitute at 90µg and monitor ANC - Platelet <50,000 cells/mm³ Reduce to 90µg - Platelet <25,000 cells/mm³ Discontinue treatment	Received wrong treatment or incorrect dose	If classified as major protocol deviation (reviewed case by case), excluded from PP set	Yes
45	Subject stopped NA treatment at week 24, although some relevant changes in participant baseline status with regards to ALT, HBV DNA levels and/or HBeAg status were observed at Week 20 or any other event that in the opinion of the investigator could prevent stopping NA, were observed	Subject stopped NA treatment at week 24, although some relevant changes in participant baseline status with regards to ALT, HBV DNA levels and/or HBeAg status were observed at Week 20 or any other event that in the opinion of the investigator could prevent stopping NA, were observed	Received wrong treatment or incorrect dose	If classified as major protocol deviation (reviewed case by case), excluded	Yes

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				from PP set	
46	Subject did not stop NA treatment at week 24, although no relevant changes in participant baseline status with regards to ALT, HBV DNA levels and/or HBeAg status or no other events that in the opinion of the investigator could prevent stopping NA treatment, were observed	Subject did not stop NA treatment at week 24, although no relevant changes in participant baseline status with regards to ALT, HBV DNA levels and/or HBeAg status or no other events that in the opinion of the investigator could prevent stopping NA treatment, were observed	Received wrong treatment or incorrect dose	If classified as major protocol deviation (reviewed case by case), excluded from PP set	Yes
	During the 48-week FU period, subject showed signs of decreasing liver function based on laboratory findings (e g International Normalized Ratio [INR], direct bilirubin) or clinical assessment (e g ascites, hepatic encephalopathy), but did not restart NA treatment	Subject has event of signs of decreasing liver function based on laboratory or clinical findings, but did not start NA treatment	Received wrong treatment or incorrect dose	If classified as major protocol deviation (reviewed case by case), excluded from PP set	Yes
47	During the 48-week FU period, subject has confirmed HBeAg seroreversion (HBeAg positive after it was negative at NA completion), but subject did not restart NA treatment	Subject has confirmed HBeAg seroreversion, but did not start NA treatment	Received wrong treatment or incorrect dose	If classified as major protocol deviation (reviewed case by case), excluded from PP set	Yes
48	During the 48-week FU period, subject has confirmed post-treatment increases in HBV DNA >2,000 IU/mL and ALT >5x ULN, over a period of at least 4 weeks, but subject did not restart NA treatment	Subject has a confirmed post-treatment increase in HBV DNA >2,000 IU/mL and ALT >5 x ULN over a period of at least 4 weeks, but did not start NA treatment	Received wrong treatment or incorrect dose	If classified as major protocol deviation (reviewed case by case), excluded from PP set	Yes
49	During the 48-week FU period, subject has confirmed post-treatment increase in HBV DNA >20,000 IU/mL over a period of at least 4 weeks, but subject did not restart NA treatment	Subject has a confirmed post-treatment increase in HBV DNA >20,000 IU/mL over a period of at least 4 weeks, but did not start NA treatment	Received wrong treatment or incorrect dose	If classified as major protocol deviation (reviewed case by case), excluded from PP set	Yes
50	Subject received incorrect injection treatment JNJ-3989	Received wrong treatment of study drug JNJ-3989: incorrect dose or placebo when randomized to active (and vice versa)	Received wrong treatment or incorrect dose	If classified as major protocol deviation (reviewed case by case), excluded from PP set	Yes
51	Subject withdrew consent but was not discontinued from the study treatment	Subject withdrew consent to the trial but was not discontinued from the study treatment	Developed withdrawal criteria but not withdrawn	Yes	No
52	The investigator believes that for safety or tolerability reasons (e g AE) it is in the best interest of the participant to discontinue investigational intervention, but the patient was not discontinued from the study treatment	Subject must discontinue the study treatment for safety reasons but subject continued study treatment	Developed withdrawal criteria but not withdrawn	Yes	No
53	The participant becomes pregnant but was not discontinued from the study treatment	Subject is pregnant but subject continued study treatment	Developed withdrawal criteria but not withdrawn	Yes	No

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54	The participant has signs of hepatic decompensation (ie, clinical evidence of ascites, bleeding varices, or hepatic encephalopathy) or an increase in direct bilirubin >1 5x ULN in combination with INR ≥1 5x ULN or albumin <3 0 g/dL, but subject did not discontinue treatment with JNJ-3989 and the study	Subject has signs of hepatic decompensation (ie, clinical evidence of ascites, bleeding varices, or hepatic encephalopathy) or an increase in direct bilirubin >1 5x ULN in combination with INR ≥1 5x ULN or albumin <3 0 g/dL, but continued treatment	Developed withdrawal criteria but not withdrawn	Yes	Yes
55	The participant has a confirmed ≥Grade 3 eGFR abnormality and a drop from baseline of >10 mL/min/1 73 m^2, considered at least possibly related to JNJ-3989 (or PegIFN-α2a, if applicable) that persists despite changing tenofovir disoproxil to ETV or TAF (if the patient was receiving tenofovir disoproxil) but was not discontinued from the study	Subjects has a confirmed ≥Grade 3 eGFR abnormality and a drop from baseline of >10mL/min/1 73 m^2, considered at least possibly related to JNJ-3989 (or PegIFN-α2a, if applicable) that persists despite changing tenofovir disoproxil to ETV or TAF (if the patient was receiving tenofovir disoproxil) but continued treatment	Developed withdrawal criteria but not withdrawn	Yes	Yes
56	The participant has a QTcF prolongation (defined as a QTcF value of >500 ms, or an increase from baseline of >60 ms) at any given time point but was not discontinued from the study	Subject has a QTcF prolongation (defined as a QTcF value of >500 ms, or an increase from baseline of >60 ms) at any given time point but continued treatment	Developed withdrawal criteria but not withdrawn	Yes	No
57	The participant requires ≥7 days of treatment with any of the disallowed medications listed in Clinical Protocol Section 6 8, Concomitant Therapy, and does not discontinue treatment with the disallowed medication	Subject received ≥7 days of treatment with any of the disallowed medications listed in Clinical Protocol Section 6 8, Concomitant Therapy, but continued treatment with the disallowed medication	Developed withdrawal criteria but not withdrawn	Yes	No
58	The participant has confirmed HBV virologic breakthrough (ie, confirmed on-treatment HBV DNA increase by >1 log$_{10}$ IU/mL from nadir or confirmed on-treatment HBV DNA level >200 IU/mL in participants who had HBV DNA level <LLOQ of the HBV DNA assay) but did not discontinue treatment	Subject has confirmed HBV virologic breakthrough (ie, confirmed on-treatment HBV DNA increase by >1 log$_{10}$ IU/mL from nadir or confirmed on-treatment HBV DNA level >200 IU/mL in participants who had HBV DNA level <LLOQ of the HBV DNA assay) but continued treatment Note: If virologic breakthrough occurs during PegIFN-α2a administration, this does not automatically lead to stop of JNJ-3989 and/or PegIFN-α2a, but should be assessed/discussed with the Sponsor In case of virologic breakthrough, a viral sequencing sample will be collected during an unscheduled visit within 7 days of the DNA increase	Developed withdrawal criteria but not withdrawn	Yes	Yes
59	The participant has ALT/AST elevations, as described in Clinical Protocol Section 8 3 6 2, Intervention-emergent ALT/AST Elevations but did not discontinue treatment	Subject has ALT/AST elevations, as described in Clinical Protocol Section 8 3 6 2, Intervention-emergent ALT/AST Elevations but discontinued treatment Note: The grades are based on the DAIDS Toxicity Grading Scale (see Clinical Protocol Section 10 9, Appendix 9: DAIDS Table) If the ALT and/or AST level is ≥3x ULN and ≥3x nadir and is associated with any of the following laboratory results or clinical symptoms: - INR ≥1 5, OR - direct bilirubin >1 5x ULN, OR - serum albumin <3 0 g/dL, OR - ascites, hepatic encephalopathy, or liver-related symptoms (e g severe fatigue, nausea, vomiting, right upper quadrant pain in the	Developed withdrawal criteria but not withdrawn	Yes	Yes

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		absence of an alternative medical explanation), OR - other indication of reduced liver function			
60	PegIFN-α2a was not discontinued but the subject developed one of the following: - evidence of hepatic decompensation during treatment, or ALT increase clinically significant or accompanied by direct bilirubin increase -thyroid disorders or diabetes during treatment and cannot be controlled with medication - new or worsening ophthalmologic disorders - any deterioration of cardiovascular status - acute hypersensitivity reaction (e g urticaria, angioedema, bronchoconstriction, anaphylaxis) - serious infection (bacterial, viral, fungal) and sepsis - persistent or unexplained pulmonary infiltrates or pulmonary function impairment - onset or worsening of psoriatic lesion - moderate or severe depression (for mild depression, treatment discontinuation may be considered) - develops colitis symptoms (such as but not limited to abdominal pain, bloody diarrhea, and fever) - symptoms or signs suggestive of pancreatitis	Subject did not discontinued PegIFN-α2a but developed one of the following: - evidence of hepatic decompensation during treatment, or ALT increase clinically significant or accompanied by direct bilirubin increase -thyroid disorders or diabetes during treatment and cannot be controlled with medication - new or worsening ophthalmologic disorders - any deterioration of cardiovascular status - acute hypersensitivity reaction (e g urticaria, angioedema, bronchoconstriction, anaphylaxis) - serious infection (bacterial, viral, fungal) and sepsis - persistent or unexplained pulmonary infiltrates or pulmonary function impairment - onset or worsening of psoriatic lesion - moderate or severe depression (for mild depression, treatment discontinuation may be considered) - develops colitis symptoms (such as but not limited to abdominal pain, bloody diarrhea, and fever) - symptoms or signs suggestive of pancreatitis	Developed withdrawal criteria but not withdrawn	Yes	Yes
61	In case of confirmed Grade 3 or Grade 4 hematologic abnormalities, discontinuation of investigational study treatment JNJ-3989 (and PegIFN-α2a if applicable) should be considered In case of discontinuation, NA treatment should be continued (see the description in Clinical Protocol Section 8 3 6 3)	Subject has confirmed Grade 3 or Grade 4 hematologic abnormalities, but discontinuation of study treatment was not considered	Developed withdrawal criteria but not withdrawn	Yes	Yes
62	Study procedure not done at scheduled visits, such as: Hematology Chemistry Blood coagulation Urine chemistry Urinalysis Pregnancy ECG Vital signs Physical Examination Liver Staging Ophthalmologic examination (including fundoscopy) Testing for hepatitis A, B, C, D, and E virus, HIV-1 and -2b Serum IgM anti-HBc antibody test AFP test Hemoglobin A1c test TSH and T4	\<enter study specific procedure(s)\> \<was/were\> not done at \<enter scheduled visit\>	Other	If classified as major protocol deviation (reviewed case by case), excluded from PP set	No
63	Efficacy evaluation not done at scheduled visits, such as: HBV Virology Qualitative and quantitative HBsAg and HBeAg HBV DNA anti-HBs anti HBe antibodies Fibroscan Ultrasound	\<enter study specific efficacy evaluation(s)\> \<was/were\> not done at \<enter scheduled visit\>	Other	If classified as major protocol deviation (reviewed case by case), excluded from PP set	No

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64	Study Visits not performed, or Visit was not performed within the allowed window as per the protocol	<enter study visit> was not performed as per protocol schedule	Other	If classified as major protocol deviation (reviewed case by case), excluded from PP set	No
65	Usage of incorrect visit material (lab kits, etc)	Incorrect <enter incorrect visit material> was used	Other	If classified as major protocol deviation (reviewed case by case), excluded from PP set	No
66	Site reported protocol deviation not specified elsewhere	<enter reported protocol deviation not specified elsewhere>	Other	If classified as major protocol deviation (reviewed case by case), excluded from PP set	No
67	Blood and urine samples were collected (e g PK Samples) erroneously when should have not been collected and have not been subsequently destroyed (sample collected in error should be destroyed)	<enter blood or urine sample> sample were collected in error however not destroyed	Other	If classified as major protocol deviation (reviewed case by case), excluded from PP set	No

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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/7) * 100%

- For PegIFN-α2a: (Total number of injections received/ Total number of injections supposed to be received [a]) * 100%

[a] For participants in Arm 1, a total of 24 injections should be administered. For participants in Arm 2 and 3, a total of 12 injections should be administered.

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6.8. Appendix 8 Adverse Events of Special Interest

Adverse events of special interest list of MedDRA preferred terms.

Table 14: **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 v23.1)	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 v23.1)	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 v23.1)	Albuminuria

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	Blood creatinine abnormal
	Blood creatinine increased
	Blood urea abnormal
	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 v23.1)	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

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		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 v23.1)	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
		Urinary casts present
		Urine phosphorus abnormal
Hematologic abnormalities	(Modified) Haematopoietic cytopenias affecting more than one type of blood cell (SMQ), (MedDRA v23.1)	Aplastic anaemia

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	Autoimmune aplastic anaemia
	Bicytopenia
	Bone marrow failure
	Cytopenia
	Febrile bone marrow aplasia
	Full blood count decreased
	Gelatinous transformation of the bone marrow
	Immune-mediated pancytopenia
	Pancytopenia
	Panmyelopathy
	Aspiration bone marrow abnormal
	Biopsy bone marrow abnormal
	Blood count abnormal
	Blood disorder
	Bone marrow disorder
	Bone marrow infiltration
	Bone marrow myelogram abnormal
	Bone marrow necrosis
	Bone marrow toxicity
	Haematotoxicity
	Myelodysplastic syndrome
	Myelodysplastic syndrome transformation
	Myelofibrosis
	Myeloid metaplasia
	Plasmablast count decreased
	Scan bone marrow abnormal
(Modified) Haematopoietic erythropenia (SMQ), (MedDRA v23.1)	Aplasia pure red cell
	Aplastic anaemia
	Erythroblast count decreased
	Erythroid maturation arrest
	Erythropenia
	Hypoplastic anaemia
	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 v23.1)	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
	Granulocytes maturation arrest
	Granulocytopenia
	Idiopathic neutropenia
	Leukopenia
	Lymphocyte count decreased
	Lymphopenia
	Metamyelocyte count decreased
	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

Leukopenia neonatal

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

White blood cell analysis abnormal

White blood cell count abnormal

White blood cell disorder

(Modified) Haematopoietic thrombocytopenia (SMQ), (MedDRA v23.1)	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

The following medications are of interest (not including disallowed medications)

1. Antimicrobial, if not already disallowed, e.g. augmentin, ciprofloxacin, nitrofurantoin, penicillin, sulfonamides, sulfamethoxazole/trimethoprim, tetracycline, rifampin, pyrazinamide, didanosine, efavirenz, flucloxacillin, minocycline, nevirapine, telithromycin

2. Anticonvulsants, if not already disallowed, e.g. valproic acid

3. Psychotropic medications, e.g. bupropion, tricyclic antidepressants, chlorpromazine, risperidone, selective serotonin reuptake inhibitors, trazodone

4. Lipid-lowering agents:

    *   HMG-CoA reductase inhibitors (statins): e.g. atorvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin

    *   nicotinic acid (niacin)

    *   inclisiran

5. Antihypertensives, e.g. labetolol, hydralazine, lisinopril, losartan, methyldopa

6. Antiarrhythmics, if not already disallowed, e.g. amiodarone, procainamide

7. Hormonal Medications, e.g. tamoxifen, testosterone, hormone replacement therapy

8. Medications used in Diabetes Mellitus, e.g. acarbose, pioglitazone, sulfonylureas

9. Antiplatelets, e.g. ticlopidine, aspirin

10. Corticosteroids: Low dose (<5 mg/day prednisone or equivalent) for ≥4 weeks, if not already disallowed

11. Analgesics: ergoloid mesylates, ergotamine tartrate, dihydroergotamine, and methylergonovine

12. Acetaminophen or paracetamol >2 g per day

13. NSAIDS, e.g. iboprufen, diclofenac, nimesulide, sulindac

14. Calcium channel blockers, if not disallowed, e.g. amlodipine, bepridil, nicardipine, nifedipine, nisoldipine

15. Phosphodiesterase-5 inhibitors, e.g. sildenafil, vardenafil, tadalafil

16. Sedatives/anxiolytics, e.g. midazolam, triazolam

17. Miscellaneous hepatotoxic medications

- halothane

- etretinate

- HIV protease inhibitors

- omeprazole

- dantrolene (muscle relaxant)

- disulfiram (substance abuse agent)

- gold salts

- propylthiouracil (antithyroid)

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 9, DAIDS Table) or in accordance with the normal ranges of the clinical laboratory if no gradings are available.

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7. REFERENCES

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