Janssen Research & Development

Statistical Analysis Plan

A Phase 2, Open-label, Single-arm, Multicenter Study to Assess Efficacy, Safety, Tolerability, and Pharmacokinetics of Treatment With JNJ-73763989, JNJ-56136379, Nucleos(t)ide Analogs, and Pegylated Interferon Alpha-2a in Virologically Suppressed Patients With Chronic Hepatitis B Virus Infection

The PENGUIN Study

Protocol 73763989PAHPB2006; Phase 2

JNJ-73763989 and JNJ-56136379

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

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VERSION HISTORY

Document History	
Document	**Date**
Original SAP	30 June 2021
Amendment 1	15 October 2021
Amendment 2	18 May 2023

Amendment 2 (this document)

Overall rationale of this Amendment:

This is an administrative amendment that incorporates additional clarifications on endpoints, data handling rules, and updates to descriptive analyses that were previously documented in the Data Presentation Specifications.

Clarifications, Additions, Corrections		
Section Number and Name	**Description of Change**	**Rationale**
Section 5.1.9. Data Handling Rules	Revised ULOQ and Imputed Values data cutpoints for HBsAg, HBeAg and HBcrAg. Updated guidelines for the imputation of HBV DNA.	Improved language for clarity and precision.
Section 5.1.10. Main Groups for Analysis Section 5.3.2. Analysis Methods Section 5.4.2. Analysis Methods Section 5.5.2. Analysis Methods Section 5.6. Safety Analyses	Analyses will be focused on all subjects, and some analyses will be performed by group.	Change in the scope of the analysis.
Section 5.4.1.1.2 NA Re-Treatment Criteria During FU Section 5.4.2.1.2.1. NA Re-Treatment Criteria During FU	Removed NA re-treatment sub-criteria analysis.	NA re-treatment sub-criteria was not collected in CRF.

Clarifications, Additions, Corrections		
Section Number and Name	**Description of Change**	**Rationale**
Section 5.4.1.1.12. ALT Normalization Section 5.4.2.1.8. HBeAg Seroconversion Section 5.5.2.2.3. Anti-HBs Antibodies	Removed an analysis.	Majority of participants had ALT values within normal range at baseline. HBeAg seroclearance is defined only for participants who were HBeAg positive at baseline. Qualitative anti-HBs results are not collected.
Section 5.4.1.1.15. Flares	For on and off treatment biochemical flare definitions, nadir definition is updated to the lowest value observed up to the start of the flare.	The nadir definition was updated to include screening visit.
Section 5.4.2.1.10. Suppressed HBV DNA	Added two thresholds HBsAg and HBV DNA thresholds.	Additional analyses for HBsAg and HBV DNA thresholds were decided to be performed
Section 5.4.2.1.10. Suppressed HBV DNA Section 5.4.2.2.1. HBsAg, HBeAg, HBV DNA and ALT Section 5.5.1.4.1. Association Between Baseline Characteristics/Viral Blood Markers and Selected Efficacy Variables Section 5.5.2.2.3. Anti-HBs Antibodies	Added to text to avoid analyses in case of insufficient data.	Improved language for clarity.
Section 5.4.2.2.1. HBsAg, HBeAg, HBV DNA and ALT	Clarification of text.	Typographical corrections.
Section 5.4.2.2.1. HBsAg, HBeAg, HBV DNA and ALT Section 5.5.2.2.1. Liver Stiffness Measurement	Specified time points for the analysis and removed HBV DNA from the scope.	Clarification of text.

Clarifications, Additions, Corrections		
Section Number and Name	**Description of Change**	**Rationale**
Section 5.5.2.2.2. HBV RNA and HBcrAg		
Section 5.5.1.3.4. Time to Appearance of Anti-HBe Antibodies	Updated text for time to appearance of anti-HBe antibodies analysis which will be performed only for anti-HBe negative participants at study entry.	Improved language for clarity and precision.
Section 5.5.1.5. Sustained HBsAg Response Section 5.5.2.5. Sustained HBsAg Response	Added section with definitions of HBsAg sustained response and their analyses.	Additional analysis for HBsAg was included to better characterize off-treatment HBsAg response.
Section 5.5.2.2.3. Anti-HBs Antibodies	Removed cross-tabulation evaluation for anti-HBs.	Qualitative results for anti-HBs antibodies were not collected.
Section 5.7.3. Immune Analyses	Removed some analyses.	Change in the scope of the analysis.
Section 5.7.4. Viral Genome Sequence Analysis	Removed subsections.	Subsections were removed to simplify the analysis.
Section 5.7.5.1. Subgroups for Efficacy Analyses	Removed some subgroups.	Remaining subgroups are sufficient for the scope.
Appendix 8 Adverse Events of Special Interest	Updated preferred terms.	MedDRA was updated from v23.0 to v25.1.
Appendix 9 Medications of Interest	Removed the medications of special interest section.	Removal due to discontinuation of JNJ-6379.

Amendment 1

Overall rationale for the Amendment:

Based on emerging data from recent interim analyses of the REEF-1 (73763989HPB2001) and REEF-2 (73763989PAHPB2002) studies, the benefit-risk profile of JNJ-56136379 (JNJ-6379) in combination with JNJ-73763989 (JNJ-3989)+NA is unfavorable compared to JNJ-3989+NA. Therefore, the primary reason for this amendment is to align with Protocol Amendment 3 which removed JNJ-56136379 as study intervention, added a new nucleos(t)ide analog (NA) re-treatment criterion for participants who discontinued NA treatment during follow-up, and included more frequent monitoring for participants who discontinued NA treatment during follow-up.

Furthermore, clarifications, additions and corrections were made throughout the SAP detailed below.

Main Changes		
Section Number and Name	**Description of Change**	**Rationale**
Throughout the document	JNJ-6379 has been removed as study intervention. Participants enrolled before Protocol Amendment 3 (issued on 04 October 2021) had to stop JNJ-6379 treatment immediately. They will continue with JNJ-3989+NA treatment up to the end of Treatment Period 1 (12 weeks) and will then enter Treatment Period 2 (12 weeks) during which they will have PegIFN-α2a added to their treatment regimen. Patients that were already in Treatment Period 2 prior to Protocol Amendment 3, will stop JNJ-6379 immediately and continue with JNJ-3989+NA+PegIFN-α2a. Throughout the protocol, elements specific for JNJ-6379 have been modified.	Based on emerging data from recent interim analyses of the REEF-1 and REEF-2 studies, showing that the benefit-risk profile of JNJ-6379 in combination with JNJ-3989+NA is unfavorable compared to JNJ-3989+NA.

Clarifications, Additions, Corrections		
Section Number and Name	**Description of Change**	**Rationale**
Section 1.1 Objectives and Endpoints	Updated objectives and endpoints table and footnote regarding JNJ-6379	To be in line with Protocol Amendment 3
Section 1.2 Study Design	Updated the study design using the Protocol Amendment 3 Added Figure 2 Schematic Overview of the Study – As of Protocol Amendment 3	To be in line with Protocol Amendment 3
Section 5.1 General Considerations	Updated study intervention based on Protocol Amendment 3	To be in line with Protocol Amendment 3
Section 5.1.3 Visit Windows	Updated Table 4	To account for additional follow-up visits for participants who continue NA treatment and for participants who have restarted NA treatment during the follow-up period, provided that their HBV DNA and ALT values are stable.

Clarifications, Additions, Corrections		
Section Number and Name	**Description of Change**	**Rationale**
Section 5.1.10 Main Groups for Analysis	Added to state the main groups for analysis	To refer to it in later sections
Section 5.6.1 Extent of Exposure	Modified the formula for the calculation of total duration of exposure to JNJ-6379	To reflect the change in Protocol Amendment 3
Section 6.7 Intervention Compliance	Treatment compliance for JNJ-6379 was updated.	Due to change in study design regarding JNJ-6379
Throughout the document	Clarification of text	Typographical corrections or improved language for clarity and precision

1. INTRODUCTION

The statistical analysis plan (SAP) for the 7376763989PAHPB2006 phase 2 trial describes the statistical analyses and definitions to assess the efficacy, and safety of the study intervention including JNJ-73763989, JNJ-56136379, Nucleos(t)ide analogs (NA), and pegylated interferon alpha-2a (PegIFN-α2a) in virologically suppressed participants with chronic hepatitis B (CHB) virus infection. In the rest of the document the abbreviations JNJ-3989 and JNJ-6379 are used to refer to the treatments JNJ-73763989 and JNJ-56136379, respectively. Prior to Protocol Amendment 3, the study intervention also included JNJ-6379. Note that as of Protocol Amendment 3, JNJ-6379 has been removed as study intervention and the study will continue with JNJ-3989, NA and PegIFN-α2a only. Participants had to stop JNJ-6379 treatment immediately after the implementation of Urgent Safety Measure (USM) and approval of the protocol amendment 3.

This study is part of the platform trial PLATFORMPAHPB2001 in participants with CHB. The protocol for 73763989PAHPB2006 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-3 finalized on 04 October 2021, and with the Master Protocol Amendment-3 for PLATFORMPAHPB2001 finalized on 21 January 2021.

Details of the pharmacokinetic (PK) and pharmacokinetic/pharmacodynamics (PK/PD) analyses will be described in a separate analysis and modeling plan.

1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy in terms of HBsAg levels of the study intervention (i.e. JNJ-3989 + JNJ-6379[d] + NA and PegIFN-α2a).	• Proportion of participants with a reduction of at least 2 $\log_{10}$ IU/mL in HBsAg levels from baseline to Week 24 (end of study intervention [EOSI]).
Secondary	
• To evaluate the safety and tolerability of the study intervention.	• Safety and tolerability including but not limited to the proportion of participants with (serious) adverse events (S)AEs and abnormalities in clinical laboratory tests (including hematology, blood biochemistry, blood coagulation, urinalysis, urine chemistry, and renal biomarkers), 12-lead electrocardiograms (ECGs), vital signs, and ophthalmic 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 EOSI.
• To evaluate the efficacy of the study intervention as measured by blood markers (such as HBsAg, HBeAg[a], HBV DNA, and alanine aminotransferase [ALT]) during the study intervention and follow-up (FU) period.	• Proportion of participants with HBeAg[a], HBsAg, HBV DNA, and ALT levels below/above different cut-offs. • Proportion of participants with HBsAg and/or HBeAg[a] seroconversion.

Objectives	Endpoints
	• Change from baseline over time in HBsAg, HBeAg[a], and/or HBV DNA. • Time to achieve HBsAg and/or HBeAg[a] seroclearance/seroconversion, and/or HBV DNA< lower limit of quantification (LLOQ).
• To evaluate the frequency of virologic breakthrough[b] during the 24-week treatment period, as well as during the FU period for participants who continue treatment with NA.	• Proportion of participants with virologic breakthrough[b].
• To evaluate the efficacy of the study intervention during the FU period.	• Proportion of participants with HBsAg seroclearance at Week 48 (ie, 24 weeks after completion of all study interventions at Week 24) without re-starting NA treatment. • Proportion of participants with HBV DNA <LLOQ at Week 48 (ie, 24 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 pharmacokinetics (PK) of JNJ-3989 (JNJ-3924 and JNJ-3976), and optionally of JNJ-6379, NA and PegIFN-α2a.	• PK parameters of JNJ-3989 (JNJ-3924 and JNJ-3976). • Optionally, PK parameters of JNJ-6379, NA and/or PegIFN-α2a compared to historical data.
Exploratory	
• To explore host and viral baseline and on-treatment markers associated with end of treatment and/or off-treatment response.	• Association of baseline characteristics and baseline/on-treatment host and viral blood markers (such as age and HBsAg levels) with selected on or off-treatment efficacy variables.
• To explore changes in the severity of liver disease.	• Changes in fibrosis (accounting 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 effect of PegIFN-α2a coadministration on the PK of JNJ-3989 (JNJ-3924 and JNJ-3976) and JNJ-6379[e], as applicable (PK substudy).	• Effect of PegIFN-α2a coadministration on the PK of JNJ-3989 (JNJ-3924 and JNJ-3976) and JNJ-6379, as applicable.
• 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.[c]	• Changes from baseline in HBV-specific peripheral blood T-cell responses over time.[c]

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.

a. In HBeAg-positive participants only.

b. 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.

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

d. As per Protocol Amendment 3, JNJ-6379 has been removed as study intervention and the study will continue with JNJ-3989, NA and PegIFN-α2a only. Participants had to stop JNJ-6379 treatment immediately.

e. Not all participants completed treatment with JNJ-6379, as JNJ-6379 has been removed as study intervention with the implementation of Protocol Amendment 3.

1.2. Study Design

This is a Phase 2a, open-label, single-arm, multicenter study to assess efficacy, safety, tolerability and pharmacokinetics of treatment with JNJ-3989, JNJ-6379 (as applicable), NA, and PegIFN-α2a in virologically suppressed patients with chronic hepatitis B virus infection. Prior to Protocol Amendment 3, the study intervention also included JNJ-6379. Note that as of Protocol Amendment 3, JNJ-6379 has been removed as study intervention and the study will continue with JNJ-3989, NA and PegIFN-α2a only. Participants had to stop JNJ-6379 treatment immediately after the implementation of Urgent Safety Measure (USM) and approval of the protocol amendment 3.

Approximately 50 virologically suppressed CHB-infected participants, 18-65 years (inclusive) of age, will be enrolled in this study. Approximately 40% HBeAg-positive participants will be enrolled.

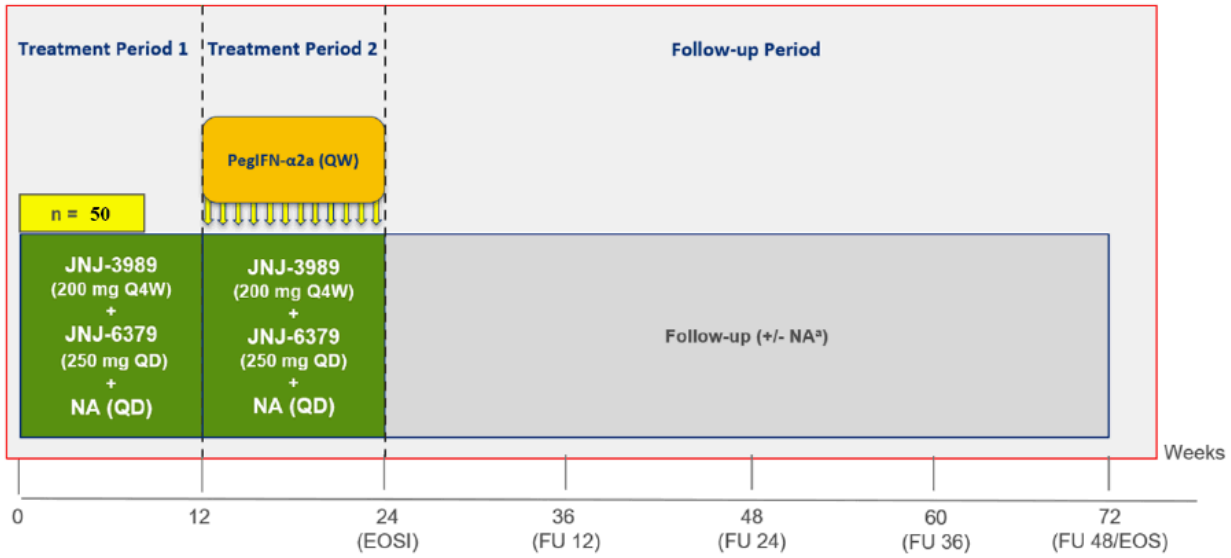
The study will be conducted in 4 periods:

- Screening period (4 weeks [if necessary, can be extended to a maximum of 8 weeks decided on a case-by-case basis and in agreement with the sponsor]).
- Treatment Period 1 (12 weeks) consisting of combination treatment with JNJ-3989 + NA.
- Treatment Period 2 (12 weeks) adding PegIFN-α2a to the combination treatment regimen of Treatment Period 1.
- Follow-up (FU) Period (48 weeks).

The total duration of individual participation will be up to 76 weeks (including 4 weeks of screening).

A schematic of the trial prior to Protocol Amendment 3 is presented in Figure 1.

Figure 1: Schematic Overview of the Study – Prior to Protocol Amendment 3

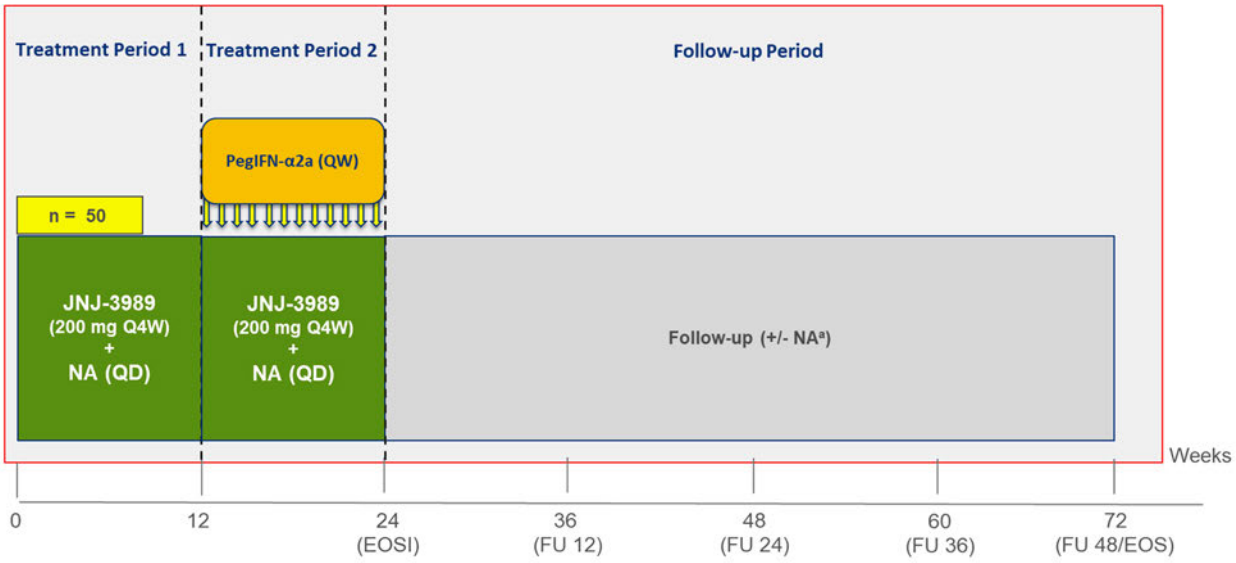


ALT: alanine aminotransferase; DNA: deoxyribonucleic acid; EOS: end of study; EOSI: end of study intervention; FU: follow-up; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; JNJ-3989: JNJ-73763989; JNJ-6379: JNJ-56136379; LLOQ: lower limit of quantification; n: number of participants; NA: nucleos(t)ide analog; PegIFN-α2a: pegylated interferon alpha-2a; ULN: upper limit of normal; Q4W: every 4 weeks; QD: once daily; QW: once weekly.

a. If NA treatment completion criteria (HBsAg <10 IU/mL, and HBeAg-negative, and HBV DNA <LLOQ, and ALT <3x ULN) have been met at Week 24, NA will be stopped at the next scheduled visit (ie, FU Week 2), otherwise NA treatment will continue during the complete FU period.

A schematic of the trial as of Protocol Amendment 3 is presented in Figure 2.

Figure 2: Schematic Overview of the Study – As of Protocol Amendment 3



ALT: alanine aminotransferase ; DNA: deoxyribonucleic acid; EOS: end of study; EOSI: end of study intervention; FU: follow-up; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; JNJ-3989: JNJ-73763989; LLOQ: lower limit of quantification; n: number of participants; NA: nucleos(t)ide analog;

PegIFN-α2a: pegylated interferon alpha-2a; ULN: upper limit of normal; Q4W: every 4 weeks; QD: once daily; QW: once weekly.

[a] If NA treatment completion criteria (HBsAg <10 IU/mL, and HBeAg-negative, and HBV DNA <LLOQ, and ALT <3x ULN) have been met at Week 24, NA will be stopped at the next scheduled visit (ie, FU Week 2), otherwise NA treatment will continue during the complete FU period.

Prior to Protocol Amendment 3:

Enrolled participants (approximately n=50) will start Treatment Period 1 with triple combination treatment (JNJ-3989 [200 mg once every 4 weeks (Q4W)] + JNJ-6379 [250 mg once daily (QD)] + NA [tenofovir disoproxil (TeD; 245 mg), or tenofovir alafenamide (TAF; 25 mg), or entecavir (ETV; 0.5 mg) (QD)]) for a duration of 12 weeks.

At Week 12, participants who still meet the eligibility criteria for PegIFN-α2a will start Treatment Period 2 with quadruple combination treatment (JNJ-3989 [200 mg once every 4 weeks (Q4W)] + JNJ-6379 [250 mg once daily (QD)] + NA [tenofovir disoproxil (TeD; 245 mg), or tenofovir alafenamide (TAF; 25 mg), or entecavir (ETV; 0.5 mg) (QD)] + PegIFN-α2a [180 µg once weekly]) for a duration of 12 weeks.

Participants no longer meeting the PegIFN-α2a eligibility criteria at Week 12 will continue with the Period 1 treatment until Week 24.

At Week 24, all participants will stop treatment with JNJ-3989 + JNJ-6379 + PegIFN-α2a and start the FU Period. NA treatment will be continued during the FU phase in patients not meeting the NA completion criteria.

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

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

As of Protocol Amendment 3:

Enrolled participants will start Treatment Period 1 with the following combination treatment regimen (JNJ-3989 [200 mg once every 4 weeks (Q4W)] + NA [tenofovir disoproxil (TeD; 245 mg), or tenofovir alafenamide (TAF; 25 mg), or entecavir (ETV; 0.5 mg) (QD)]) for a duration of 12 weeks.

At Week 12, participants who still meet the eligibility criteria for PegIFN-α2a will start Treatment Period 2 with triple combination treatment (JNJ-3989 [200 mg once every 4 weeks (Q4W)] + NA [tenofovir disoproxil (TeD; 245 mg), or tenofovir alafenamide (TAF; 25 mg), or entecavir (ETV; 0.5 mg) (QD)] + PegIFN-α2a [180 µg once weekly]) for a duration of 12 weeks.

Participants no longer meeting the PegIFN α2a eligibility criteria at Week 12 will continue with the Period 1 treatment until Week 24.

At Week 24, all participants will stop treatment with JNJ-3989 + PegIFN-α2a and start the FU Period. NA treatment will be continued during the FU phase in patients not meeting the NA completion criteria.

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

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

2. STATISTICAL HYPOTHESES

As this is an exploratory proof of concept (PoC), single-arm study, no formal hypothesis has been formulated.

3. SAMPLE SIZE DETERMINATION

No formal sample size calculation was performed, as this is a single-arm study for exploratory and PoC purposes. However, with a sample size of 50 participants having data for the primary efficacy endpoint at Week 24, if at least 25 (50%) participants are responders, it can be concluded with 90% confidence that the true response rate is at least 0.38, with a confidence interval (CI) width of 0.248 (90% CI: 0.376-0.624). With a sample size of 20 participants (for one of the interim analyses [IAs]) the precision of the estimate of the primary efficacy endpoint decreases, as the two-sided 90% CI width increases. For the same assumed proportion of responders of 50% (10 out of 20 participants), the 90% CI width becomes 0.396. Table 1 shows the 90% CI and the corresponding width for proportion of responders of 0.30, 0.50, 0.70, and 0.90.

Table 1: Confidence intervals for a range of proportions

	N=20		N=50	
Proportion of responders	**90% CI***	**Width of CI**	**90% CI***	**Width of CI**
0.30	0.140-0.508	0.368	0.195-0.424	0.229
0.50	0.302-0.698	0.396	0.376-0.624	0.248
0.70	0.492-0.860	0.368	0.576-0.805	0.229
0.90	0.717-0.982	0.265	0.801-0.960	0.159

CI: confidence interval.
* Clopper-Pearson exact method is used.

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 the efficacy analyses will be the FAS set, 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 difference of at least 2 participants between analysis sets.

Table 2: Analysis Sets for Analysis

Analysis Sets	Description
Screened	All participants who signed the ICF for the Master Protocol and an ICF specific for the ISA.
Enrolled	All participants who were enrolled in this ISA.
Full Analysis Set (FAS)	All participants who were enrolled and who received at least 1 dose of study intervention within this ISA.
Modified FAS	All participants who were enrolled and who received at least 1 dose of study intervention excluding those participants who, because of COVID-19 or similar pandemics related reasons, withdrew prematurely from the study prior to Week 24 (end of study intervention [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.
IFN-FAS	All participants who were enrolled and who received at least 1 dose of PegIFN-α2a within this ISA.
Modified IFN-FAS	All participants who were enrolled and who received at least 1 dose of PegIFN-α2a 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.
Safety	All participants who received at least 1 dose of study intervention. Participants will be analyzed according to the study intervention they actually received.
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, JNJ-6379, NA, and PegIFN-α2a
- *Study agent* refers to: JNJ-3989, JNJ-6379, and PegIFN-α2a
- *Study intervention refers to:*
  - Treatment Period 1:
    - JNJ-3989 + JNJ-6379 + NA
    - JNJ-3989 + NA
  - Treatment Period 2:

- JNJ-3989 + JNJ-6379 + NA + PegIFN-α2a
- JNJ-3989 + NA + PegIFN-α2a

NA can be either ETV, TeD or TAF.

5.1.1. Analysis Phase

The analysis 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 (excluding PegIFN-α2a)
Treatment Period 1	Date of first study agent intake (excluding PegIFN-α2a)	**For participants who receive PegIFN-α2a:** Min [Date of first PegIFN-α2a intake - 1 day, cut-off date[b]]
		For participants who do not receive PegIFN-α2a: Date of Week 12 study agent intake - 1 day
		For participants who discontinue treatment before Week 12: Max [last intake date of any study agent, study agent discontinuation date, early study withdrawal visit date] + 5 days[a] or cut-off date[b], whichever occurs first
Treatment Period 2	**For participants who receive PegIFN-α2a:** Date of first PegIFN-α2a intake	**For participants who did not withdraw from the study prior to the projected/actual Week 24 visit date:** Max [last intake date of any study agent, study agent discontinuation date, projected/actual Week 24 visit date] + 5 days[a] or cut-off date[b], whichever occurs first **Participants who withdrew from the study prior to the projected/actual Week 24 visit date:** Max [last intake date of any study agent, study agent discontinuation date, early study withdrawal visit date] + 5 days[a] or cut-off date[b], whichever occurs first
	For participants who do not receive PegIFN-α2a: Date of Week 12 study agent intake Otherwise: missing	
Follow-up	**Participants who did not withdraw informed consent during treatment period 1 or 2:** Max [End date of Treatment Period 1, End date of the Treatment Period 2] + 1 day Otherwise: missing	Max [study discontinuation date, study completion date] or cut-off date[b], whichever occurs first Otherwise: missing

[a] Addition of 5 days is only applicable for Adverse Events and Concomitant Medications.
[b] Cutoff dates will be defined to match the prespecified timepoints for DRC safety monitoring, interim analyses, the primary and 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.

5.1.2.1. Treatment Period 1 Relative Day

The treatment period 1 start date (TP Day 1) is defined as the date of the first study agent intake (excluding PegIFN-α2a). All efficacy and safety assessments during the treatment period 1 will be assigned an analysis study day relative to this date.

The study day in the treatment period 1 phase (TP1 ADY) is defined as:

$$TP1\ ADY = visit\ date - TP1\ start\ date + 1$$

for visits on or after treatment period 1 Day 1, and

$$TP1\ ADY = visit\ date - TP1\ start\ date$$

for visits before TP1 Day 1 (Screening phase).

There is no 'TP1 Day 0'.

5.1.2.2. Treatment Period 2 Relative Day

The treatment period 2 start date (TP2 Day 1) is defined as the date of first PegIFN-α2a injection for those who receive PegIFN-α2a in treatment period 2, and the date of Week 12 agent intake for those who don't receive PegIFN-α2a. Efficacy and safety assessments during the TP2 will be assigned an analysis study day relative to this date, unless otherwise specified.

The study day in the TP2 phase (TP2 ADY) is defined as:

$$TP2\ ADY = visit\ date - TP2\ start\ date + 1$$

for visits on or after TP2 Day 1.

5.1.2.3. 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 1 (EOT1), end of treatment period 2 (EOT2), and end of study (EOS) visits. If a participant has 2 or more actual visits in one 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. Spaghetti plots will also display all measurements.

End of treatment period 1 (i.e. EOT1), end of treatment period 2 (i.e. EOT2) and end of study (i.e. EOS) time points will be included in all analyses over time unless stated otherwise.

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

Table 4: Visit Windows

a) Screening, Treatment Period 1, and Treatment Period 2

Analysis phase	Target day	Analysis time point (Week)	Analysis time point (label)	Time interval (days)
Screening	-∞	-1	Screening	<0
Treatment period 1	1	0	Baseline	Pre-dose: 1
	15	2	Week 2	[2,22]
	29	4	Week 4	[23,43]
	57	8	Week 8	[44,81]
	85[a]	12.1	Week 12 period 1	[82, 92][a]
	Last visit in treatment period 1	12.15[b]	EOT1[b]	
Treatment period 2	85[a]	12.2	Week 12 period 2	[82, 92][a]
	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 2	25[c]	EOT2[c]	

[a] Day 85 is the target day for the first administration of PegIFN-α2a. Time interval [82-92] was selected to align the visit window with the protocol Schedule of Activities for Week 12. Any assessments performed before the administration of PegIFN-α2a (date/time) at week 12 will be considered under treatment period 1 (Week 12 period 1) and assessments after the administration of PegIFN-α2a (date/time) will be considered as treatment period 2 (Week 12 period 2).
[b] End of treatment period 1 (EOT1) visit will be the last visit of treatment period 1.
[c] End of treatment period 2 (EOT2) visit will be the last visit of treatment period 2.

b) Follow-up

Analysis phase	FU Target day	Analysis time point (Week)	Analysis time point (label)	Time interval (FU days)
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 [a]	EOS [a]	

[a] End of study (EOS) visit (last available data during the follow-up phase) 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 TP1 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. Additional Reference Timepoint

An additional reference timepoint (RT) will be used for an additional analysis of selected efficacy endpoints for treatment period 2 and FU phase.

The RT for those analyses is defined as the last observed non-missing measurement before the first PegIFN-α2a intake.

5.1.6. Analysis Specifications

In general, continuous variables will be summarized using descriptive statistics including the number of participants, mean, 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 single sample proportion (Newcombe 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.

5.1.7. Level of Significance

Due to exploratory nature of this study, no formal test will be performed. Only two-sided 90% CIs will be provided with no adjustment for multiplicity.

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 (TP1 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 (TP1 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 baseline visit 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	249,750.00 IU/mL with dilution	0.025 IU/mL [(a)]	274,725.00IU/mL [(b)] with dilution
HBeAg	0.11 IU/mL	7,000.00 IU/mL with dilution	0.055 IU/mL [(a)]	7,700.00 IU/mL[(b)] with dilution
HBcrAg*	3.0 log_{10} U/mL	9.0 log_{10} U/mL with dilution	2.7 log_{10} U/mL	9.9 log_{10} U/mL [(b)] with dilution
HBV DNA	20 IU/mL	170,000,000 IU/mL w/o dilution	If target detected: 15 IU/mL If target not detected: 5 IU/mL**	187,000,000[(b)(c)] IU/mL w/o dilution
HBV RNA*	LLOQ = 2.939 log_{10} cp/mL (i.e. 869 cp/mL) LOD = 1.398 log_{10} cp/mL (i.e. 25 cp/mL)	NAP	If <LOD or target not detected then 1.114 log10 cp/mL (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.
** For HBV DNA <LLOQ: Spaghetti plots showing absolute values, the imputed value will be 15 IU/mL for both target detected, and target not detected. All other tables, listings, and figures will be produced using 15 IU/mL as an imputed value if target is detected and 5 IU/mL if target is not detected.

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.

5.1.10. Main Groups for Analysis

While most analyses will be focused on all subjects without separating by study intervention, some analysis will be performed in three different groups:

1. Group 1: Participants who received at least one tablet of JNJ-6379 during treatment period 2:
    - Treatment Period 1: JNJ-3989 + JNJ-6379 + NA
    - Treatment Period 2: JNJ-3989 + JNJ-6379 + NA + PegIFN-α2a
2. Group 2: Participants who did not receive JNJ-6379 at treatment period 2:
    - Treatment Period 1:
        - JNJ-3989 + JNJ-6379 + NA
        - JNJ-3989 + NA
    - Treatment Period 2: JNJ-3989 + NA + PegIFN-α2a

   Some analysis will be performed separately by the study intervention of treatment period 1 and overall.
3. Group 3: all participants who were enrolled in the trial

Post-hoc analyses may be performed based on duration of exposure to JNJ-6379.

5.1.11. On-treatment and off-treatment periods

The on-treatment period begins with the first drug intake date and finishes with the maximum between:

- Last dose of NA + 2 days
- Last dose of PegIFN α2a + 10 days,
- Last dose of JnJ-3989 + 28 days.

The off-treatment period stops if the NA re-treatment starts.

5.2. Participant Dispositions

All the summaries will be done on the FAS analysis set. The IFN-FAS and modified FAS/IFN-FAS analysis sets will be used if there is a difference of at least 2 participants between analysis sets.

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

The number of participants in the following disposition categories will be summarized by analysis phase.

- Participants who received any study intervention (JNJ-3989, JNJ-6379, PegIFN-α2a or NA)
- Participants in each study analysis phase
- Participants who completed the study

- Participants who discontinued study interventions
  - Reasons for discontinuation of study interventions
- Participants who terminated study prematurely
  - Reasons for termination of study

A listing of participants will be provided for the following categories

- Participants who discontinued study interventions
- Participants who terminated study prematurely

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 to Week 24.

5.3.2. Analysis Methods

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 difference of at least 2 participants between analysis sets.

Some analysis will be performed by group, as defined in Section 5.1.10 above.

The count and proportion of participants with a reduction of at least 2 $\log_{10}$ IU/mL in HBsAg levels from baseline to Week 24 and the associated 90% CI using the Clopper-Pearson method will be calculated.

5.3.2.1. Missing Data Handling Rule

The missing as non-responder is the primary rule to handle missing data. Two sensitivity analyses will be conducted using the observed case data and LOCF approach, respectively.

5.3.2.1.1. Missing as Non-Responder

Participants who do not have HBsAg data in the analysis window of Week 24 will be defined as non-responders.

5.3.2.1.2. Observed Case Analysis

Only participants who have HBsAg data at Week 24 will be used for the analysis.

5.3.2.1.3. Last Observation Carried Forward (LOCF)

If the HBsAg value at Week 24 is missing, the non-missing value 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 the Week 24 assessment will be defined as non-responders.

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 at Week 24 and During FU

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

- HBsAg <10 IU/mL, and
- HBeAg-negative, and
- HBV DNA <LLOQ, and
- ALT <3x ULN

The NA completion criteria will be assessed based on clinical laboratory tests and summarized at Week 24 (EOSI) and during FU phase.

5.4.1.1.2. NA Re-Treatment Criteria During FU

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'.

5.4.1.1.3. HBsAg Cut-offs

The cut-offs for HBsAg level are as follow:

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

The cut-offs for HBsAg change from baseline and RT are as follow:

- decrease by ≥ 0.3 $\log_{10}$ IU/mL
- decrease by ≥ 0.5 $\log_{10}$ IU/mL
- decrease by ≥ 1 $\log_{10}$ IU/mL
- decrease by ≥ 2 $\log_{10}$ IU/mL

- decrease by ≥ 3 log_{10} IU/mL
- decrease by ≥ 4 log_{10} IU/mL

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 12, 24, 36 and 48 weeks after stopping all study interventions at the end of treatment period 2 and without restarting NA treatment.

HBsAg seroclearance will be also evaluated when assessed at 12, 24, 36 and 48 weeks after stopping all study interventions (regardless when intervention was stopped) 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:

- met the criteria for stopping NA treatment at Week 24, and
- had HBsAg seroclearance at the given week of interest, and
- not required NA re-treatment between FU Week 2 and the given 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 in HBsAg 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:

- < 100 IU/mL
- < 10 IU/mL
- < 1 IU/mL
- < LLOQ (0.11 IU/mL)

Of note, seroclearance of HBeAg is defined as (quantitative) HBeAg<LLOQ.

The cut-offs for HBeAg change from baseline and RT are as follows:

- decrease by ≥ 0.3 $\log_{10}$ IU/mL
- decrease by ≥ 0.5 $\log_{10}$ IU/mL
- decrease by ≥ 1 $\log_{10}$ IU/mL
- decrease by ≥ 2 $\log_{10}$ IU/mL
- decrease by ≥ 3 $\log_{10}$ IU/mL

Only HBeAg positive participants will be used for the analysis of the HBeAg cut-offs.

5.4.1.1.9. HBeAg Seroconversion

Seroconversion of HBeAg is defined as having achieved HBeAg seroclearance together with appearance of anti-HBe antibodies.

Seroclearance of HBeAg is defined as (quantitative) HBeAg <LLOQ. 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.

5.4.1.1.10. 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

5.4.1.1.11. Suppressed HBV DNA

HBV DNA < LLOQ (HBV DNA detectable or HBV DNA TND) will be evaluated over all time points when assessed with emphasis at FU Weeks 12, 24, 34 and 48, after stopping all study interventions at the end of treatment period 2 and without restarting NA treatment.

HBV DNA < LLOQ (HBV DNA detectable or HBV DNA TND) will also be evaluated at 12, 24, 36 and 48 weeks after stopping all study interventions (regardless when intervention was stopped) and without restarting NA treatment.

5.4.1.1.12. Thresholds on HBV DNA and HBsAg

The count and proportion of participants who meet HBsAg and HBV DNA thresholds will be assessed using the last available measurement.

5.4.1.1.13. 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.

5.4.1.1.14. 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 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.

5.4.1.1.15. 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 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.

5.4.1.1.16. 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 and had HBV DNA<LLOQ at the last observed point on all study treatments.

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

   - 1 (Yes) = confirmed** ALT and/or AST ≥3x ULN and ≥3x nadir (i.e. lowest value observed up to the start of 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 5.4.1.1.15. 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 changes from RT ($\log_{10}$ transformed values) 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 five intervals: treatment period 1 nadir (first 12 weeks of treatment), treatment period 2 nadir (second 12 weeks of treatment), on-treatment nadir (first 24 weeks), during follow-up nadir, and entire study nadir.

Only HBeAg positive participants will be used for the analysis of HBeAg values and changes from baseline.

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 ≥ 1.0 $\log_{10}$ IU/mL
- HBsAg decline ≥ 2.0 $\log_{10}$ IU/mL
- HBsAg decline ≥ 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 sereoconversion 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 First HBeAg Seroclearance

Seroclearance of HBeAg is defined as (quantitative) HBeAg level < LLOQ.

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

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

Time to first HBeAg seroclearance will be calculated only for HBeAg positive participants.

5.4.1.3.4. Time to First HBeAg Seroconversion

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

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

Time to first HBeAg seroconversion will be calculated only for HBeAg positive participants.

5.4.1.3.5. Time to First HBV DNA < LLOQ

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

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

5.4.1.3.6. 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.

5.4.1.3.7. 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.

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

All secondary endpoints will be analyzed using the FAS. The analysis may be repeated in the IFN-FAS and modified FAS/IFN-FAS analysis sets if there is a difference of at least 2 participants between analysis sets.

Some analysis will be performed by group, as defined in Section 5.1.10.Summaries and graphs will be provided for each analysis phase, unless specified otherwise.

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.

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 will show the binary endpoints over time, by subgroups of interest, or combining multiple binary endpoints together.

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 the end of treatment period 2, will be summarized.

Starting at end of treatment period 2, the incidence of participants who did not meet the NA treatment completion criteria will be summarized at each timepoint during the study, 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. All the NA treatment completion criteria will be checked based on clinical laboratory tests in FU phase.

5.4.2.1.2.1. 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. 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.

The count and proportion of participants (and associated 90% CI) who 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.

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.

5.4.2.1.2.2. HBsAg Cut-offs

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

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

5.4.2.1.3. HBsAg Seroclearance

5.4.2.1.3.1. 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.

5.4.2.1.3.2. Off Treatment

The count and proportion of participants (and associated 90% CI) who achieve HBsAg seroclearance over time during FU will be summarized. Separate analyses will be performed for participants who completed treatment as planned (at the end of treatment period 2), and regardless when treatment was stopped.

The count and proportion of participants who achieve HBsAg seroclearance will be evaluated 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).

5.4.2.1.4. 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.

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.

5.4.2.1.5. Treatment Failure

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

5.4.2.1.6. HBsAg Seroconversion

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

5.4.2.1.7. HBeAg Cut-offs

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

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

5.4.2.1.8. HBeAg Seroconversion

The count and proportion of participants (and associated 90% CI) who achieve HBeAg seroconversion will be summarized by analysis phase. Separate tabulations will be made for the subset of participants who were HBeAg positive at baseline and for the subset of participants who were anti-HBe negative at baseline, respectively. The seroconversion will only be assessed at the time points when the anti-HBe antibodies assessment is available.

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

5.4.2.1.9. HBV DNA Cut-offs

The cut-offs for HBV DNA values will be used in separate summaries over time. The count and proportion of participants who meet those HBV DNA thresholds during the study will be summarized descriptively by 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 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 at each of the FU Weeks 12, 24, 36, and 48, respectively, after stopping all study interventions at the end of treatment period 2 and without restarting NA treatment.

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 at each of the following off-treatment timepoints: 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.

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.

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 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), if there is at least 10% of the participants with missing HBV DNA results for the selected time points.

5.4.2.1.11. Thresholds on HBV DNA and HBsAg

The number and proportion of participants who meet the following HBV DNA reduction and seroclearance thresholds at last available timepoint will be summarized descriptively. Only participants who stopped all study treatments without restarting NA will be assessed.

Thresholds based on HBV DNA and HBsAg

- HBV DNA < 2000 IU/mL
- HBV DNA < LLOQ
- HBsAg<LLOQ and HBV DNA<LLOQ

- HBsAg<100 IU/mL and HBV DNA<LLOQ
- HBsAg<100 IU/mL and HBV DNA<2,000 IU/mL

5.4.2.1.12. 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, 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.

5.4.2.1.13. Partial Cure

The count and proportion of participants (and associated 90% CI) who achieve partial cure during the study will be summarized descriptively 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.

5.4.2.1.14. 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 analysis phase.

5.4.2.1.15. 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. 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.

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

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 (except for ALT)], changes from baseline and changes from RT over time in HBsAg, HBeAg, HBV DNA and ALT will be summarized. Mean (+/- SE) plots of the values, change from baseline and change from RT over time will be presented by analysis phase. The change from baseline value to nadir (i.e. maximum decrease for each participant) in HBsAg, HBeAg and HBV DNA will be summarized descriptively. Box plots of the changes to nadir in HBsAg, HBeAg, and HBV DNA will display the distribution.

Change from baseline based on log_{10} transform for quantitative HBsAg and HBeAg will be analyzed using mixed effects model for repeated measures [MMRM]) including analysis time point (week), baseline blood marker variable, and their interaction. 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) will be provided.

Descriptive statistics on actual values (original unit and log_{10} transformed values) and changes from baseline (log_{10} transformed values) at the end of treatment in HBsAg, HBeAg, HBV DNA and ALT (original unit) will be summarized by outcome response (i.e. by achieving a reduction of at least 2 log_{10} IU/mL in HBsAg levels from baseline to Week 24, by NA treatment completion criteria status), by HBsAg seroclearance at the end of treatment period 2, FU Week 24 and FU Week 48, and by partial cure status at FU Week 24 and FU Week 48, and for participants who achieved functional cure at FU Week 24 and FU Week 48 if there is at least 10% response for each by-group.

Spaghetti plots for both absolute values and changes from baseline of HBsAg and HBV DNA will be presented over time per blood marker by selected subgroups (Section 5.7.5.1).

Waterfall plots for changes from baseline of HBsAg and HBeAg will be presented over time.

Descriptive statistics of the absolute values and changes from baseline over time in ALT will be summarized by analysis phase for those participants who had ALT elevation at baseline.

5.4.2.3. Time to Event Endpoints

The Kaplan-Meier method will be used to estimate and plot the cumulative incidence and estimate the median time with 90% CI. In addition, the number and percentage of participants who had an event or were censored will be reported.

5.5. Exploratory Endpoints

See Section 1.1 for a list of the exploratory endpoints. All exploratory endpoints will be analyzed using observed case data.

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:

- ≥ 1 kPa
- ≥ 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 RT 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 RT 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 RT 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 five intervals: treatment period 1 nadir (first 12 weeks of treatment), treatment period 2 nadir (second 12 weeks of treatment), 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 ≥LOD+ 0.5 $\log_{10}$ cp/mL (i.e. ≥1.898 $\log_{10}$ cp/mL) at baseline will be included in this analysis. Similarly, additional analyses for participants with HBV

RNA values ≥LOD+ 1.0 log_{10} cp/mL and ≥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 ≥LOD+ 0.5 log_{10} cp/mL (i.e. ≥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 ≥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.

Time to appearance of anti-HBe antibodies will be calculated only for anti-HBe negative participants.

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.

A categorical off-treatment HBV marker will be evaluated if there is at least 10% response.

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 • NA treatment completion at Week 24 (Yes; No) • 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 • NA treatment completion at Week 24 (Yes; No) • Treatment failure (Yes; No)
HBsAg seroclearance 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 • NA treatment completion at Week 24 (Yes; No) • 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 • NA treatment completion at Week 24 (Yes; No) • 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

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 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 • NA treatment completion at Week 24 (Yes; No) • 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 • NA treatment completion at Week 24 (Yes; No) • Treatment failure (Yes; No)

5.5.1.5. Sustained HBsAg Response

The definitions of sustained HBsAg response are as follows:

- Definition #1:
  - For participants with Follow-up Week 48 data: participants who had a >1 $\log_{10}$ decline from baseline in HBsAg at Follow-up Week 48 and HBsAg < 1,000 IU/mL at Follow-up Week 48.
  - For participants without Follow-up Week 48 data: participants who had a >2 $\log_{10}$ decline from baseline in HBsAg at Follow-up Week 24 or a >1.5 $\log_{10}$ decline in HBsAg at Follow-up Week 36 (most recent value used) and had HBsAg <1,000 IU/mL at the last available timepoint.
- Definition #2:
  - For participants with a >1 $\log_{10}$ decline from baseline in HBsAg at the last Follow-up visit: among the 3 most recent visits, the difference between $\log_{10}$ HBsAg at 2 of the 3 last visits and 1 of the 3 last visits is <0.2 $\log_{10}$ IU/mL and the difference between $\log_{10}$ HBsAg at 3 of the 3 last visits and 1 of the 3 last visits is <0.2 $\log_{10}$ IU/mL.
- Definition #3:
  - For participants with a >1 $\log_{10}$ decline from baseline in HBsAg at the last Follow-up visit: among the 3 most recent visits, the difference between $\log_{10}$ HBsAg at 2 of the 3 last visits and 1 of the 3 last visits is <0.2 $\log_{10}$ IU/mL and the difference between $\log_{10}$ HBsAg at 3 of the 3 last visits and 1 of the 3 last visits is <0.2 $\log_{10}$ IU/mL and had HBsAg <1,000 IU/mL at the last available timepoint.
- Definition #4:

- Three categories regarding the difference between HBsAg level at the last Follow-up timepoint and Week 24 (EOT):
  - >0.2 $\log_{10}$ decrease: Decreasing level
  - ≤0.2 $\log_{10}$ increase or ≤0.2 $\log_{10}$ decrease: Stable level
  - ≤0.2 $\log_{10}$ increase or ≥0.2 $\log_{10}$ decrease: Stable or Decreasing level
  - >0.2 $\log_{10}$ increase: Increasing level

For all definitions of the sustained HBsAg response, only participants with at least 24 weeks of follow-up data after JNJ-3989 stop will be used for the analysis.

The count and proportion (%) of participants achieving sustained HBsAg response will be summarized.

Spaghetti plots for HBsAg actual values and change from baseline will be presented by study panel over time using color coding by category.

5.5.2. Analysis Methods

All exploratory endpoints will be analyzed using the FAS. The analysis may be repeated in the IFN-FAS and modified FAS/IFN-FAS analysis sets if there is a difference of at least 2 participants between analysis sets.

Some analysis will be performed by group, as defined in Section 5.1.10.

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

All exploratory endpoints will be analyzed based on the observed case data. No imputation for missing data will be used.

5.5.2.1. Binary Endpoints

The methods of analysis of the binary exploratory endpoints will be the same as those described in Section 5.4.2.1.

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 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, decreases from baseline, and RT will be used in separate summaries over time. The number and proportion of participants who meet those HBV RNA thresholds during the study will be summarized descriptively by analysis phase over time and displayed in graphs like bar charts.

5.5.2.1.3. HBcrAg Cut-offs

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

5.5.2.1.4. Anti-HBe Antibodies

The number and proportion of participants with positive and negative anti-HBe values will be summarized descriptively by 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).

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 over time.

5.5.2.2.2. HBV RNA and HBcrAg

The actual values, changes from baseline and changes from RT in HBV RNA and HBcrAg, respectively, will be summarized only descriptively over time in a similar manner as for values, changes from baseline and changes from RT 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 over time.

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 if there is at least 10% of the participants for the subset.

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 study 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.

5.5.2.5. Sustained HBsAg Response

Summary tables with counts and percentages of participants who meet each of the definition will be presented if there is at least 1 participant who meet the criteria.

Spaghetti plots for both absolute values and changes from baseline of HBsAg will be presented over time for each of the definition.

5.6. Safety Analyses

All safety analyses will be performed using the safety analysis set. All assessments will be presented by analysis phase (for treatment period 1, for treatment period 2 and FU phase) and overall. All summaries will be descriptive.

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.

Continuous parameters will be summarized using the following statistics: number of observations, mean, standard deviation (SD), standard error (SE), minimum, median and maximum, unless specified otherwise. Frequencies and percentages will be used for summarizing categorical data.

Some analysis will be performed by group, as defined in Section 5.1.10.

5.6.1. Extent of Exposure

Because of the different route and frequency of treatment administration across the 4 agents (for JNJ-3989 one subcutaneous injection every 4 weeks (Q4W), for JNJ-6379 once daily tablets (QD), for NA once daily tablet (QD), and for PegIFN-α2a one subcutaneous injection weekly (QW)) the total duration of exposure (weeks) will be calculated for each agent as follows:

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

The total duration of exposure (weeks) to JNJ-6379 will be calculated for participants who received JNJ-6379 as follows:

- JNJ-6379: [Min (Date of the last JNJ-6379 administration in the given phase, Date of treatment disposition for JNJ-6379, Date of trial disposition, Date of clinical cut-off)- Date of first JNJ-6379 administration in the given phase+ 1] / 7

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

Descriptive statistics for duration of each study treatment within a study intervention (N, mean, SD, median, and range (minimum, maximum)) during the 24 weeks of treatment (treatment period 1 and 2) will be summarized. The duration of treatment with NA will be summarized also for the FU phase. Those participants who stopped NA treatment at or before Week 24 and never restarted NA treatment thereafter will be counted as having zero weeks of NA exposure during the FU phase.

The number and percentage of participants who skipped any dose of JNJ-3989 or JNJ-6379 or NA or PegIFN-α2a will be summarized separately for each study intervention. Additionally, the number and percentage of participants who missed 2 or more JNJ-3989 injections, or who missed more than 5 JNJ-6379 doses within a four-week period, 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.

Summary tables and listings 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

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

- SAEs
- AEs leading to discontinuation of each study agent within 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
- Renal Complications
- Cholesterol increase
- Hematologic abnormalities (platelet count, hemoglobin, reticulocytes, neutrophil count)

The list of all preferred terms belonging to ALT/AST elevation, renal complication, cholesterol increase, 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
	Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. An RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.		
Hematology Coagulation	Activated partial thromboplastin time Prothrombin Intl. normalized ratio Prothrombin time		
Clinical Chemistry	Sodium Potassium Chloride Bicarbonate Blood urea nitrogen (BUN) Creatinine Glucose Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Gamma-glutamyltransferase (GGT) α_1-acid glycoprotein Calculated creatinine clearance (by CKD-EPI formula) (i.e. eGFR calculation based on Creatinine) Fibrinogen (on blood) Cystatin C eGFR calculation based on Cystatin C	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)	
Routine Urinalysis	Dipstick Specific gravity pH Glucose Protein Blood Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase	Sediment (if dipstick result is abnormal) Red blood cells White blood cells Epithelial cells Crystals Casts Bacteria	
	In case of a positive dipstick result, a urine sample will be set aside for additional examination of the positive parameter (eg, quantification as applicable).		
Urine Chemistry (quantitative measurement)	Creatinine Sodium Phosphate	Glucose Protein Albumin	

Table 7: Laboratory Parameters

Laboratory Assessments	Parameters
Renal Biomarkers	Retinol binding protein Beta-2-microglobulin ***Note:*** Other biomarkers might be measured.
Thyroid Function Tests	Thyroid Stimulating Hormone (TSH) Thyroxine (T4)

Clinical laboratory tests will be summarized using safety analysis set for chemistry, hematology, urinalysis and renal biomarkers panels.

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

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.

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.

Abnormality criteria (based on the criteria specified in the DAIDS Toxicity Grading 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 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 (eg, 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 (eg, 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 within 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).

Imputation rules:

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 also including 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 5.7.5.2.

Plots of mean (+/- SE) values and changes from baseline over time for selected laboratory parameters will be presented. Spaghetti-plots for selected laboratory parameters will be presented over time (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 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). The same analysis will be performed by eGFRcys subgroups.

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.

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. This 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.

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 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.

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. 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 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 visit using descriptive statistics.

FEPO4 will be calculated as follows:

- Based on unadjusted serum creatinine:

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

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

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

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

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. 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).

Only data from the vendor ERT will be analyzed. All other ECG data will be listed.

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.

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 analysis phase.

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

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

5.6.3.4. Vital Signs and Body Temperature

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.

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

Descriptive statistics (n, mean, standard deviation [SD], coefficient of variation [CV], geometric mean, median, minimum, and maximum) will be calculated for the plasma concentrations of JNJ-3989 (JNJ-3976, and JNJ-3924), and, optionally, of NA, PegIFN-α2a and/or JNJ-6379, and for the derived plasma PK parameters for noncompartmental PK analyses.

For each participant with intensive PK sampling, plasma concentration-time data of JNJ-3976, and JNJ-3924, and, optionally, of NA, PegIFN-α2a and/or JNJ-6379, will be graphically presented. Similarly, graphs of the mean plasma concentration-time profiles and overlay graphs with combined individual plasma concentration-time profiles will be produced. Plasma PK parameters in participants undergoing intensive PK sampling will be calculated via noncompartmental methods for JNJ-3976, and JNJ-3924, and, optionally, NA, PegIFN-α2a and/or JNJ-6379. The PK parameters will be C_{max}, C_{24h}, and AUC_{24h}; other PK parameters may also be calculated. The PK parameters will be subjected to an exploratory graphical analysis, including various transformations, to get a general overview.

To assess the effect of PegIFN-α2a on JNJ-6379 (as applicable) and JNJ-3989, the PK parameters of JNJ-6379 (as applicable) and JNJ-3989 coadministered with PegIFN-α2a at Week 20 (or 16) will be compared to those of JNJ-6379 (as applicable) and JNJ-3989 at Week 4 (or 8) as reference. The primary PK parameters are Cmax and AUC_{24h} on the logarithmic scale. A mixed effects model

will be fitted to log-transformed PK parameters with treatment period as a fixed effect and participant as a random effect.

Special attention will be paid to the plasma concentrations and PK parameters of those participants who discontinued the study for an AE, or who experienced an AE ≥grade 3, or an SAE.

Population PK analysis of plasma concentration-time data of JNJ-6379 (as applicable), JNJ-3976, and 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 (eg, 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, of NA, PegIFN-α2a and/or JNJ-6379 with selected efficacy and/or safety endpoints may be evaluated and graphically displayed.

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

5.7.3. Immune Analyses

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

Changes from baseline (or positivity threshold) in HBV-specific peripheral blood T-cell responses may 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 may be presented. The spaghetti plots may be used to show the patient profiles per time point for each assay. A graph showing the median and IQR over time may be presented. A bar chart may be used to show the breadth of response (i.e. HBV-specific immune response rate for combinations of peptide pools).

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

5.7.4. Viral Genome Sequence Analysis

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

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

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

5.7.5. Definition of Subgroups

5.7.5.1. Subgroups for Efficacy Analyses

Table 8: Subgroups for efficacy analyses

Subgroup	Definition
Sex	Male, Female
Age Group	≤45 years, > 45 years
Race	Asian, Non-Asian
Geographical region	Asia, Europe, Oceania
Type of NA at baseline	TeD, TAF, ETV
HBsAg level at baseline	<1,000 IU/mL; ≥1,000 IU/mL-<10,000 IU/mL; ≥10,000 IU/mL
HBeAg at baseline	Positive, Negative

5.7.5.2. Subgroups for Safety Analyses

Table 9: Subgroups for safety analyses

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

5.8. Interim Analyses and Data Review Committee

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: 20 participants have reached the Week 12 (end of treatment period 1) time point or discontinued earlier.
- DR2: 20 participants have reached the Week 16 time point or discontinued earlier.
- DR3: 20 participants have reached the FU Week 12 time point or discontinued earlier.
- DR4: 20 participants have reached the FU Week 48 time point or discontinued earlier.

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 internal decisions about additional studies and/or investigation of other treatment combinations. The IAs are planned when all:

- Approximately 20 participants have completed Week 24 (EOSI) or discontinued earlier.

- All participants have completed Week 36 (FU Week 12) or discontinued earlier.
- All participants have completed Week 48 (FU Week 24) or discontinued earlier.
- An optional IA may be conducted when all 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 performed when all participants have completed the last study visit (FU Week 48) or discontinued earlier.

5.8.3.3. Analysis 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 12 (N=20)	DR2/ Week 16 (N=20)	IA1/ Week 24 (N=20)	DR3 / FU Week 12 (N=20)	Primary Analysis/ Week 24 (N=50)	IA2/ FU Week 12 (N=50)	IA3 / FU Week 24 (N=50)		DR4 / FU Week 48 (N=20)	IA4 / FU Week 36 (N=50) (optional)	Final Analysis/ FU Week 48 (N=50)
Subject Information											
Baseline & Demographic characteristics	X	X	X	X	X	X	X		X	X	X
Disposition and Study Populations	X	X	X	X	X	X	X		X	X	X
Extent of Exposure	X	X	X	X	X	X	X		X	X	X
Safety											
TEAEs, SAEs, AE of interest, fatal AEs, AEs causing treatment discontinuation	X	X	X	X	X	X	X		X	X	X
Laboratory Tests	X	X	X	X	X	X	X		X	X	X
ECG	X	X	X	X	X	X	X		X	X	X
Vital signs	X	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	X	X
Proportion of participants with a reduction of at least 2 $\log_{10}$ IU/mL in HBsAg levels from baseline over time	X	X	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	X	X
Other secondary efficacy endpoints			X	X	X	X	X		X	X	X
Exploratory endpoints			X	X	X	X	X		X	X	X
Virologic breakthrough	X	X	X	X	X	X	X		X	X	X
Flares: Viral, Biochemical, Clinical	X	X	X	X	X	X	X		X	X	X
PK*	X	X	X	X	X	X	X		X	X	X

*If there are available data, it will be analyzed.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomic and therapeutic class
AUC	area under the curve
BMI	body mass index
BUN	blood urea nitrogen
CHB	chronic hepatitis B
CI	confidence interval
Cmax	maximum concentration
CPK	creatine phosphokinase
CRF	case report form
CSR	Clinical Study Report
CV	coefficient of variation
DAIDS	division of acquired immunodeficiency syndrome
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
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
HBe	hepatitis B envelope
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
ICH	International Conference on Harmonisation
ICS	intracellular cytokine staining
IFLEP	Independent Flare Expert Panel
IFN-FAS	Interferon-Full Analysis Set
IQR	Interquartile range
ISR	injection site reaction
IU/mL	international units per milliliter
KPD	kinetic pharmacodynamic model
LDh	lactic acid dehydrogenase
LOQ	lower limit of quantification
LOCF	last observation carried forward
LOD	limit of detection
LSM	liver stiffness measurements
MedDRA	Medical Dictionary for Regulatory Activities

mFAS	modified full analysis set
MH	Mantel Haenszel
NA	nucleos(t)ide analogs
NGS	next generation sequencing
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PegIFN-α2a	pegylated interferon alpha-2a
PI	principal investigator
PK	pharmacokinetic(s)
PoC	Proof of Concept
QTc	corrected QC interval
QTcF	QT interval corrected for heart rate according to Fridericia
RBP	retinol binding protein
RR	Interval between R wave of one heartbeat and R wave of preceding heartbeat
RT	Reference Timepoint
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCr	serum creatinine
SD	standard deviation
SMQs	standardised MedDRA queries
SPO4	serum phosphate
TAF	tenofovir alafenamide
TEAE	treatment-emergent adverse event
TD	Target detected
TeD	tenofovir disoproxil
Tmax	time to maximum concentration
TND	target not detected
TNF	tumor necrosis factor
TSH	thyroid stimulating hormone
T4	thyroxine
UACR	urine albumin to creatinine ratio
UCr	urine creatinine
ULN	Upper limit of normal
UPCR	urine protein to creatinine ratio
WBC	white blood cell
WHO-DD	World Health Organization Drug Dictionary

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 overall. In addition, the distribution of participants by 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 overall for the FAS.

Table 11: Demographic Variables

Continuous Variables:	Summary Type
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
Weight at baseline (kg)	
Height at screening (cm)	
Body Mass Index at baseline (BMI) (kg/m^2)	
Number of drinks containing alcohol (weekly period)	
Period of time using substances (beer, wine, distilled spirits) in months derived as = (stop date – start date +1)/30.4375; rounded to 1 decimal point	
Categorical Variables	
Age (≤ 45 years, > 45 years)	Frequency distribution with the number and percentage of participants in each category.
Sex (male, female, undifferentiated)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
Country (Poland, Taiwan, Japan, New Zealand)	
BMI at baseline (underweight <18.5 kg/m2, normal ≥18.5-<25 kg/m2, overweight ≥25-<30 kg/m2, obese ≥30 kg/m2)	
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 overall for the FAS.

Table 12: Baseline Characteristics Variables

Continuous Variables	Summary Type
HBV history	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
Duration of infection (years) = (treatment start date – date of HBV infection +1)/365.25; rounded to 1 decimal point	
Time since HBV diagnosis (Years) = (treatment start date – date of HBV diagnosis+1)/365.25; rounded to 1 decimal point	
HBV viral activity and serology parameters	
HBeAg at baseline in IU/mL and $\log_{10}$ IU/mL (for HBeAg positive participants only)	
HBsAg at baseline in IU/mL and $\log_{10}$ IU/mL	
HBV DNA at baseline in IU/mL and $\log_{10}$ IU/mL	

Table 12: Baseline Characteristics Variables

Continuous Variables	Summary Type
HBV RNA at baseline: values in copies/mL and log_{10} copies/mL	
HBcrAg at baseline in log_{10} U/mL	
HBsAg Antibody (Anti-HBs) at baseline in mIU/mL and log_{10} mIU/mL	
Liver Stiffness Measurement at baseline (kPa)	
Categorical Variables	**Summary Type**
HBV history	Frequency distribution with the number and percentage of participants in each category.
Mode of HBV infection: Sexual 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 screening: positive, negative	
HBeAg status at least 6 months before screening (qualitative, based on historical data)	
HBsAg category at baseline (IU/mL): < 1,000, < 10,000, < 100,000, ≥ 10,000	
HBV DNA category at baseline (IU/mL): < LLOQ Target detected (TD) or not detected (TND), < LLOQ TD, < LLOQ TND, < 60, ≥60	
HBV RNA category at baseline (copies/mL): TND, < LOD, < LLOQ, < 1,000, ≥ 1,000	
HBcrAg category at baseline (log U/mL): < 3, ≥ 3 - < 4, ≥ 4	
HBsAg Antibody (Anti-HBs) status at baseline: Positive, Negative	
HBsAg Antibody (Anti-HBs) category at baseline (mIU/mL): < 10, ≥ 10	
HBeAg Antibody (Anti-HBe) status: Positive, Negative	
Baseline ALT toxicity grade according to DAIDS	
Baseline ALT categorization: ≤ 1.0xULN, > 1.0xULN to <2xULN, ≥ 2xULN	

6.4. Appendix 4 Protocol Deviations

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

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

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

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, 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 overall and ATC class 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 and overall.

6.7. Appendix 7 Intervention Compliance

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

Treatment compliance for treatment period 1 and treatment period 2 is defined as follows.

Treatment period 1

- For JNJ-3989: (Total number of injections received/3) * 100%
- For JNJ-6379: (Total medication intake / 4 *a) * 100%

  As the 250 mg daily dose of JNJ-6379 consists of 4 tablets (2 tablets of 100 mg strength and 2 tablets of 25 mg strength). The numerator representing the total medication intake for JNJ-6379 is calculated as:

  Total medication intake=(Total number of tablets dispensed–Total number of tablets returned).

  a: for each participant, the individual period (days) of receiving JNJ-6379 (end date of JNJ-6379 – start date of JNJ-6379)

Treatment period 2

For JNJ-3989 : (Total number of injections received/ 3) * 100%

For PegIFN-α2a: (Total number of injections received/ 12) * 100%

For JNJ-6379: (Total medication intake/ 4 *a) * 100%

As the 250 mg daily dose of JNJ-6379 consists of 4 tablets (2 tablets of 100 mg strength and 2 tablets of 25 mg strength). The numerator representing the total medication intake for JNJ-6379 is calculated as:

Total medication intake=(Total number of tablets dispensed–Total number of tablets returned).

a: for each participant, the individual period (days) of receiving JNJ-6379 (end date of JNJ-6379 – start date of JNJ-6379)

Compliance to JNJ-6379 will be calculated only for participants who received JNJ-6379.

6.8. Appendix 8 Adverse Events of Special Interest

Adverse events of special interest list of MedDRA preferred terms.

Adverse Event of Special Interest	Source	Preferred Term
ALT/AST elevation	(Modified) Liver related investigations, signs and symptoms (SMQ) narrow, (MedDRA v25.1)	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	(Modified) Acute renal failure (SMQ) broad (MedDRAv25.1)	Acute kidney injury
		Anuria
		Nephropathy toxic
		Oliguria
		Renal failure
		Renal impairment
		Subacute kidney injury
		Blood creatinine abnormal
		Blood creatinine increased
		Creatinine renal clearance abnormal
		Creatinine renal clearance decreased
		Creatinine urine abnormal
		Creatinine urine decreased
		Crystal nephropathy
		Glomerular filtration rate abnormal
		Glomerular filtration rate decreased
		Nephritis
		Proteinuria
		Renal function test abnormal
		Renal tubular disorder
		Renal tubular dysfunction

Adverse Event of Special Interest	Source	Preferred Term
		Renal tubular injury
		Renal tubular necrosis
		Urine output decreased
		Nephropathy
		Nephropathy toxic
		Glomerulonephropathy
		Nephrolithiasis
Cholesterol increase	Dyslipidaemia (SMQ), (MedDRA v25.1)	
		Blood cholesterol abnormal
		Blood cholesterol esterase increased
		Blood cholesterol increased
		Dyslipidaemia
		High density lipoprotein abnormal
		High density lipoprotein decreased
		High density lipoprotein increased
		Hypercholesterolaemia
		Hyperlipidaemia
		Hypo HDL cholesterolaemia
		Intermediate density lipoprotein decreased
		Intermediate density lipoprotein increased
		LDL/HDL ratio decreased
		LDL/HDL ratio increased
		Lipid metabolism disorder
		Lipids abnormal
		Lipids increased
		Lipoprotein abnormal
		Lipoprotein increased
		Low density lipoprotein abnormal
		Low density lipoprotein decreased
		Low density lipoprotein increased
		Non-high-density lipoprotein cholesterol decreased
		Non-high-density lipoprotein cholesterol increased
		Primary hypercholesterolaemia
		Remnant hyperlipidaemia
		Remnant-like lipoprotein particles increased
		Total cholesterol/HDL ratio abnormal
		Total cholesterol/HDL ratio decreased
		Total cholesterol/HDL ratio increased
		Very low density lipoprotein abnormal

Adverse Event of Special Interest	Source	Preferred Term
		Very low density lipoprotein decreased
		Very low density lipoprotein increased
Hematologic abnormalities	(Modified) Haematopoietic cytopenias affecting more than one type of blood cell (SMQ), (MedDRA v25.1)	
		Aplastic anaemia
		Autoimmune aplastic anaemia
		Bicytopenia
		Bone marrow failure
		Cytopenia
		Febrile bone marrow aplasia
		Full blood count decreased
		Gelatinous transformation of the bone marrow
		Immune-mediated pancytopenia
		Pancytopenia
		Panmyelopathy
		Aspiration bone marrow abnormal
		Biopsy bone marrow abnormal
		Full blood count abnormal
		Blood disorder
		Bone marrow disorder
		Bone marrow infiltration
		Bone marrow myelogram abnormal
		Bone marrow necrosis
		Haematotoxicity
		Myelodysplastic syndrome
		Myelodysplastic syndrome transformation
		Myelofibrosis
		Myeloid metaplasia
		Plasmablast count decreased
		Scan bone marrow abnormal
	(Modified) Haematopoietic erythropenia (SMQ), (MedDRA v25.1)	
		Aplasia pure red cell
		Aplastic anaemia
		Erythroblast count decreased
		Erythroid maturation arrest
		Erythropenia
		Hypoplastic anaemia
		Microcytic anaemia

Adverse Event of Special Interest	Source	Preferred Term
		Proerythroblast count decreased
		Red blood cell count decreased
		Reticulocyte count decreased
		Reticulocytopenia
		Anaemia
		Erythroblast count abnormal
		Erythropoiesis abnormal
		Haematocrit abnormal
		Haematocrit decreased
		Haemoglobin abnormal
		Haemoglobin decreased
		Leukoerythroblastic anaemia
		Normochromic anaemia
		Normochromic normocytic anaemia
		Normocytic anaemia
		Proerythroblast count abnormal
		Red blood cell count abnormal
		Reticulocyte count abnormal
		Reticulocyte percentage decreased
	(Modified) Haematopoietic leukopenia (SMQ), (MedDRA v25.1)	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

Adverse Event of Special Interest	Source	Preferred Term
		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

Adverse Event of Special Interest	Source	Preferred Term
	(Modified) Haematopoietic thrombocytopenia (SMQ), (MedDRA v25.1)	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 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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