Janssen Research & Development

Statistical Analysis Plan

Phase 2 Randomized, Open-label, Parallel-group, Multicenter Study to Assess Intrahepatic and Peripheral Changes of Immunologic and Virologic Markers in Response to Combination Regimens Containing JNJ-73763989 and Nucleos(t)ide Analog With or Without JNJ-56136379 in Patients With Chronic Hepatitis B Virus Infection

Protocol 73763989HPB2003; 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

SAP Version History Summary

Document History	Date
Original SAP	14 June 2022
Amendment 1	29 March 2023

Amendment 1 (this document)

Overall rational for Amendment 1: This administrative amendment incorporates additional clarification on endpoints, data handling rules, on-treatment and off-treatment definition that have previous been documented in the Data Presentation Specification for past interim analysis.

Clarifications, Additions, Corrections		
Section Number and Name	**Description of Change**	**Rationale**
5.1.3 On-Treatment and Off-Treatment Period	Added definition for the on-treatment and off-treatment period.	Previous logic did not account for different end of the on-treatment period based on the last study agent.
5.1.5 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.
5.1.6 Analysis Specifications	Added to text to avoid time-to-event and subgroup analyses in case that there are not enough data.	Improved language for clarity.
5.3.1.2.4.2 Multiple Imputation	Reduced the number of imputed datasets to 20.	Number of imputed datasets was reduced due to limited missing data.
5.4.1.2 Intrahepatic Viral Parameters	Added the analysis of Intrahepatic HBcAg.	Added endpoint which was not included in the previous version.
5.4.2.3 HBeAg Seroclearance and Seroconversion 5.4.2.4 HBsAg, HBeAg, HBV DNA and ALT 5.4.2.4.3 HBeAg Thresholds	Updated text for HBeAg analyses which will be performed only for HBeAg positive participants at study entry.	Improved language for clarity and precision.
5.4.2.4.9 Thresholds On Multiple Markers	Added two thresholds HBsAg and HBV DNA thresholds	Additional analyses for HBsAg and HBV DNA thresholds were decided to

Clarifications, Additions, Corrections		
Section Number and Name	**Description of Change**	**Rationale**
		be performed after approval of the original SAP (dated 14 June 2022).
5.4.2.7.2. Time to Flare 5.4.2.8.2. Time to HBV Virologic Breakthrough	These sections were removed due to reduced sample size.	Time to event analyses were removed due to reduced number of events for this type of analysis.
Partial Cure	Removed the partial cure endpoint and analysis.	The initial planned analysis of this endpoint is covered by other analyses.
5.5.6 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.
5.7.3 Viral Genome Sequence Analysis	Removed subsections.	Subsections were removed to simplify the analysis.
5.7.4 Definition of Subgroups	Removed some subgroups.	Considering the small sample size, it was decided to remove some subgroups.
Medications of Special Interest	Removed the medications of special interest section.	Removal due to discontinuation of JNJ-6379.
7 References	Removed references related to Viral Genome Sequencing.	References were removed due to removal of the subsections from the Viral Genome Sequencing section.
Throughout the document	Clarification of text.	Typographical corrections or improved language for clarity and precision.

1. INTRODUCTION

This statistical analysis plan (SAP) is for study 73763989HPB2003 (INSIGHT): A Phase 2 randomized, open-label, parallel-group, multicenter study to assess intrahepatic and peripheral changes of immunologic and virologic markers in response to combination regimens containing JNJ-73763989 (JNJ-3989) and nucleos(t)ide analog (NA) with or without JNJ-56136379 (JNJ-6379) in patients with chronic hepatitis B virus (HBV) infection. Participants who provide separate consent may additionally receive optional treatment with pegylated interferon alpha-2a (PegIFN-α2a).

This SAP, which is to be interpreted in conjunction with the Clinical Protocol Amendment 6 (finalized on 25 November 2021) and country-specific Amendment 6/FRA-3 (finalized on 25 November 2021), describes the definitions of analysis sets, derived variables, and statistical methods to assess efficacy, safety, and pharmacokinetics/pharmacodynamics (PK/PD) of the study intervention arms. Details of the plasma PK/PD analyses will be described in a separate analysis and modeling plan.

INSIGHT will enroll patients in three study panels. Panel 1 will consist of participants who are HBeAg positive and not currently treated. Panel 2 will consist of participants who are HBeAg negative and virologically suppressed by entecavir (ETV), tenofovir disoproxil (TD), or tenofovir alafenamide (TAF) treatment. Panel 3 will consist of participants who are HBeAg positive or negative and are either not currently treated or virologically suppressed by ETV or TD treatment. Panels 1 and 2 will have one set of objectives and endpoints, while Panel 3 will have its own set.

As of Protocol Amendment 5, participants who were previously randomized to receive JNJ-6379 treatment had to immediately stop JNJ-6379 and will thereafter receive JNJ-3989 and NA only. New participants will enroll without randomization to receive JNJ-3989 and NA.

1.1. Objectives and Endpoints

1.1.1. For Panels 1 and 2

In Panels 1 and 2, the following objectives and endpoints will be assessed, overall and by study panel:

Objectives (Panels 1 and 2)	Endpoints (Panels 1 and 2)
Primary	
• To assess changes in intrahepatic HBsAg between baseline and on-treatment liver biopsy in response to JNJ-3989-based combination treatment	• Changes in the proportion of HBsAg positive hepatocytes between baseline and on-treatment Week 40
Secondary	
• To assess changes in intrahepatic immune response between baseline and on-treatment liver biopsy	• Changes between baseline and on-treatment liver biopsy in intrahepatic immune response (e.g., CD45+ T-cells, CD4+ T-cells, CD8+ T-cells, Natural Killer cells, and dendritic cells) in terms

Objectives (Panels 1 and 2)	Endpoints (Panels 1 and 2)
	of proportion of cells, cell types, and spatial redistribution
• To assess changes in intrahepatic viral nucleic acids and proteins between baseline and on-treatment liver biopsy	• Changes from baseline in intrahepatic viral parameters (such as cccDNA, pgRNA, intrahepatic RNA, or HBsAg in terms of copy number, or number of positive cells) • Changes from baseline in intrahepatic cccDNA levels and transcriptional activity (pgRNA/cccDNA ratio)
• To evaluate the efficacy of the study intervention as measured in the periphery	• The proportion of participants during the study intervention and follow-up phases with: – HBsAg seroclearance at Week 72 (i.e., 24 weeks after completion of all study interventions at Week 48) without restarting NA treatment. – (Sustained) Reduction, suppression, and/or seroclearance considering single and multiple markers (such as HBsAg, HBeAg, HBV DNA and ALT) – HBsAg and HBeAg seroconversion – Flares (virologic, biochemical, and clinical) • Time to first HBsAg seroclearance
• To evaluate the frequency of virologic breakthrough during study intervention	• Proportion of participants with virologic breakthrough
• To assess HBV-specific T-cell responses	• Changes from baseline in HBV-specific peripheral blood T-cell responses during the study intervention and follow-up phases
• To evaluate the safety and tolerability of the study intervention	• Proportion of participants with (S)AEs and abnormalities in clinical laboratory tests (including hematology, blood biochemistry, blood coagulation, urinalysis, urine chemistry, and renal biomarkers), 12-lead ECGs, vital signs, and physical examinations throughout the study
• To evaluate the plasma PK of JNJ-3989 (i.e., JNJ-3976 and JNJ-3924), and optionally of JNJ-6379, NA, and PegIFN-α2a, as applicable	• Plasma PK parameters of JNJ-3976, JNJ-3924, and optionally of JNJ-6379, NA, and PegIFN-α2a, as applicable

Objectives (Panels 1 and 2)	Endpoints (Panels 1 and 2)
Exploratory	
• To explore the relationship of intrahepatic markers with blood markers (immune and viral)	• Association between levels and changes in intrahepatic and blood markers
• To explore the association of baseline characteristics and intrahepatic and/or blood (immune and viral) biomarkers at baseline and on/off-treatment with selected on/off-treatment efficacy variables	• Association of baseline characteristics and baseline and on/off-treatment viral blood markers (such as baseline NA treatment duration, age, and baseline and on/off-treatment HBsAg levels) with selected off-treatment efficacy variables • Association of intrahepatic and blood biomarkers (such as cccDNA levels, T-cell frequency) with selected on/off-treatment efficacy variables
• To explore intrahepatic immune and viral changes at Week 72 and/or during off-treatment flares (only for participants with Week 72 biopsy available)	• Changes from baseline and on-treatment liver biopsy in intrahepatic immune and viral markers at Week 72 and/or during off-treatment flares (only for participants with Week 72 biopsy available)
• To explore changes in the severity of liver disease	• Changes in fibrosis (according to Fibroscan liver stiffness measurements) at the end of study intervention (EOSI) and end of follow-up versus screening/baseline*
• To explore the efficacy in terms of changes in HBV RNA and hepatitis B core-related antigen (HBcrAg) levels.	• Changes from baseline in HBV RNA and HBcrAg levels during study intervention and follow-up phases.
• To explore the relationship between plasma PK parameters (JNJ-3989 [i.e., JNJ-3976 and JNJ-3924] and/or JNJ-6379 and/or NA and/or PegIFN-α2a) and selected pharmacodynamic (PD) parameters of efficacy and/or safety, as applicable	• Relationship between various plasma PK parameters (JNJ-3976 and JNJ-3924, and/or JNJ-6379, and/or NA, and/or PegIFN-α2a) and selected efficacy and/or safety endpoints, as applicable
• To explore the HBV genome sequence	• The emergence of intervention-associated mutations during the study intervention and follow-up phases • To assess the impact of baseline HBV genome polymorphisms on selected on/off-treatment efficacy variables

* Only applicable to participants who are enrolled at a site with an on-site Fibroscan device.

1.1.2. For Panel 3

An additional single-arm Panel 3 will be enrolled to assess liver concentrations of JNJ-3989, i.e., JNJ-73763976 (JNJ-3976), JNJ-73763924 (JNJ-3924), and JNJ-87719164 (also known as M65, a deaminated metabolite of JNJ-3976) in HBV-infected participants.

The following objectives and endpoints will be assessed for Panel 3:

Objectives (Panel 3)	Endpoints (Panel 3)
Primary*	
• To assess changes in drug concentrations over time during JNJ-3989-based combination treatment	• Liver concentrations of JNJ-3989 (i.e., JNJ-3976 and JNJ-3924)* measured at treatment Weeks 12 and 40 • Assessment of drug accumulation in the liver over time • Correlation of liver and plasma PK levels
Secondary	
• To evaluate the plasma PK of JNJ-3989 (i.e., JNJ-3976 and JNJ-3924), and optionally of NA and PegIFN-α2a, as applicable	• Plasma PK parameters of JNJ-3989 (i.e., JNJ-3976 and JNJ-3924), and optionally of NA and PegIFN-α2a, as applicable
• To evaluate the efficacy of the study intervention as measured in the periphery	• The number of participants during the study intervention and follow-up phases with: – HBsAg seroclearance at Week 72 (i.e., 24 weeks after completion of all study interventions at Week 48) without restarting NA treatment. – (Sustained) Reduction, suppression, and/or seroclearance considering single and multiple markers (such as HBsAg, HBeAg, HBV DNA and ALT) – HBsAg and HBeAg seroconversion – Flares (virologic, biochemical, and clinical) • Time to first HBsAg seroclearance
• To evaluate the frequency of virologic breakthrough during study intervention	• Number of participants with virologic breakthrough
• To assess HBV-specific T-cell responses	• Changes from baseline in HBV-specific peripheral blood T-cell responses during the study intervention and follow-up phases
• To evaluate the safety and tolerability of the study intervention	• Number of participants with (S)AEs and abnormalities in clinical laboratory tests (including hematology, blood biochemistry, blood coagulation, urinalysis, urine chemistry, and renal biomarkers), 12-lead ECGs, vital signs, and physical examinations throughout the study
Exploratory	
• To assess changes in intrahepatic immune response between early and later on-treatment liver biopsy, if applicable	• Values at Weeks 12 and 40 and change at W40 from Week 12 liver biopsy in intrahepatic immune response (e.g., CD45+ T-cells, CD4+ T-cells, CD8+ T-cells, Natural Killer cells, and dendritic cells) in terms of proportion of cells and cell types

Objectives (Panel 3)	Endpoints (Panel 3)
• To assess changes in intrahepatic viral nucleic acids and proteins between early and later on-treatment liver biopsy, if applicable	• Values at Weeks 12 and 40 and change at Week 40 from Week 12 liver biopsy in intrahepatic viral parameters (such as cccDNA, pgRNA, intrahepatic RNA, or HBsAg in terms of copy number, or number of positive cells) • Values at Weeks 12 and 40 and change at Week 40 from Week 12 liver biopsy in intrahepatic cccDNA levels and transcriptional activity (pgRNA/cccDNA ratio)
• To explore the relationship between liver and plasma PK parameters (JNJ-3989 [i.e., JNJ-3976 and JNJ-3924] and/or NA and/or PegIFN-α2a) and selected pharmacodynamic (PD) parameters of efficacy and/or safety, as applicable	• Relationship between various plasma PK parameters (JNJ-3989 [i.e., JNJ-3976 and JNJ-3924], and/or NA, and/or PegIFN-α2a) and selected efficacy and/or safety endpoints, as applicable
• To explore the association of baseline characteristics and blood (immune and viral) biomarkers at baseline and on/off-treatment with selected on/off-treatment efficacy variables	• Association of baseline characteristics and baseline and on/off-treatment viral blood markers (such as baseline NA treatment duration, age, and baseline and on/off-treatment HBsAg levels) with selected off-treatment efficacy variables
• To explore changes in the severity of liver disease	• Changes in fibrosis (according to Fibroscan liver stiffness measurements) at the end of study intervention (EOSI) and end of follow-up versus screening/baseline**
• To explore the efficacy in terms of changes in HBV RNA and hepatitis B core-related antigen (HBcrAg) levels.	• Changes from baseline in HBV RNA and HBcrAg levels during study intervention and follow-up phases.
• To explore the HBV genome sequence	• The emergence of intervention-associated mutations during the study intervention and follow-up phases • To assess the impact of baseline HBV genome polymorphisms on selected on/off-treatment efficacy variables

* The focus of the primary objective for Panel 3 will be the liver concentrations of JNJ-3989 (i.e., JNJ-3976 and JNJ-3924). If there is any sample remaining after the drug concentration measurements, the applicable secondary and exploratory objectives will be assessed.
** Only applicable to participants who are enrolled at a site with an on-site Fibroscan device

1.2. Study Design

A target of 24 chronic HBV-infected male and female participants, 18-65 years (inclusive) of age will be enrolled in Panels 1 and 2, approximately 12 participants in each panel. In Panel 3, a target of 4-6 chronic HBV-infected male and female participants will be enrolled.

- Panel 1 will consist of participants who are HBeAg positive and not currently treated.
- Panel 2 will consist of participants who are HBeAg negative and virologically suppressed by ETV, TD, or TAF treatment.
- Panel 3 will consist of participants who are HBeAg positive or negative and are either not currently treated or virologically suppressed by ETV or TD treatment.

The study will be conducted in 3 phases for all participants:

- A **screening phase** (4 to 6 weeks),
- An **open-label study intervention phase** (48 weeks),
- A **follow-up phase** (48 weeks). Note that the follow-up period will be extended up to an additional 24 weeks for participants who are receiving optional treatment with PegIFN-α2a and who meet NA treatment completion criteria at the end of treatment with NA and PegIFN-α2a to ensure all participants have at least one year of follow-up after NA treatment cessation.

The duration of individual participation will be up to 102 weeks for participants who stop NA treatment at the end of the open-label phase, or up to 126 weeks for participants who stop NA treatment during the follow-up phase.

Prior to Protocol Amendment 5, in Panels 1 and 2, participants were randomized in a 1:1 ratio within each panel to receive one of the following interventions (i.e., treatments) for 48 weeks:

- **Arm 1**, combination regimen JNJ-3989+JNJ-6379+NA:
  - 200 mg JNJ-3989 (SC injection Q4W, with the last injection at Week 44), and
  - 250 mg JNJ-6379 (tablets qd), and
  - NA: ETV, TD, or TAF (tablets qd)
- **Arm 2**, combination regimen JNJ-3989+NA:
  - 200 mg JNJ-3989 (SC injection Q4W, with the last injection at Week 44), and
  - NA: ETV, TD, or TAF (tablets qd).

As of Protocol Amendment 5, in Panels 1 and 2, participants who were previously randomized to Arm 1 had to stop JNJ-6379 treatment immediately but will still receive JNJ-3989 and NA – effectively joining Arm 2. New participants will enroll without randomization to Arm 2.

No participants were enrolled in Panel 3 before Protocol Amendment 5 was in effect. Therefore, all Panel 3 participants will enroll without randomization to receive the Arm 2 regimen.

In addition, participants who provide separate consent may receive optional treatment with PegIFN-α2a starting after the Week 40 biopsy (or after the optional leukapheresis if applicable) but before the Week 48 visit. The duration (either 12 or 24 weeks) will be at the investigator's discretion. This will allow investigation of whether addition of PegIFN-α2a for 12 or 24 weeks may increase the participant's chance to achieve HBsAg loss.

All participants will complete treatment with JNJ-3989 after a fixed duration of 48 weeks. Treatment with NA will also be completed at Week 48 except for participants not meeting the NA treatment completion criteria (outlined in Protocol section 6.6.1). In participants not meeting these criteria, NA treatment will continue during the follow-up phase. Participants who are receiving optional treatment with PegIFN-α2a and who have not met NA treatment completion criteria at Week 48 may have NA treatment completion criteria assessed at the end of treatment with PegIFN-α2a and stop NA if criteria are met.

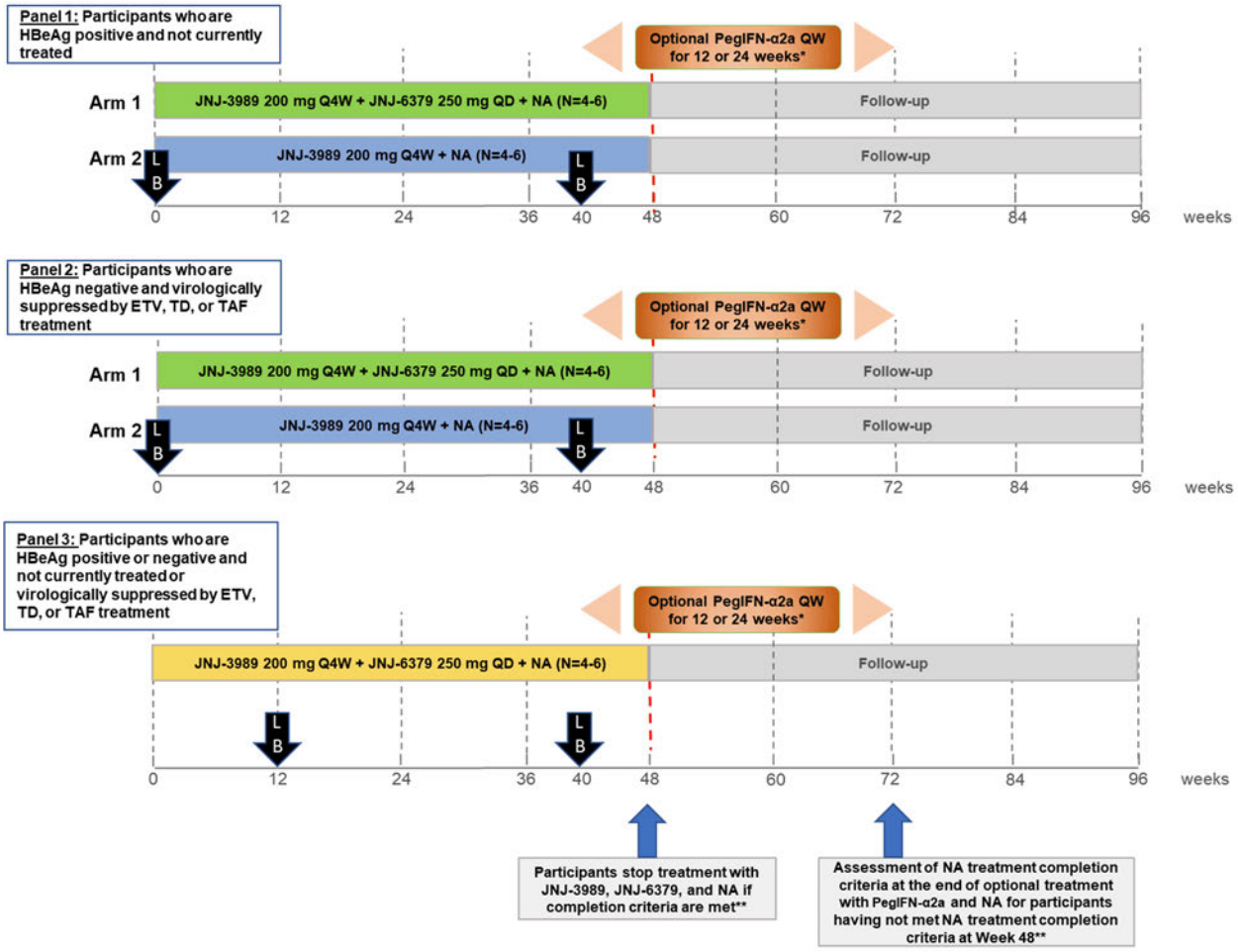
In case of premature discontinuation of study agent JNJ-3989 (before Week 48), follow-up assessments should be obtained until 48 weeks after End Of Study Intervention (EOSI) unless the participant withdraws consent. Participants who withdraw consent will be offered an optional safety follow-up visit.

The SAP will use throughout the document the following definitions:

- *Study treatment* refers to JNJ-6379, JNJ-3989, NA (either ETV, TD, or TAF), and PegIFN-α2a.
- *Study agent* refers to JNJ-6379 and JNJ-3989
  - *Arm* refers to:
    - Arm 1: JNJ-3989+JNJ-6379+NA
  - Arm 2: JNJ-3989+NA

A schematic overview of the study is presented in Figure 1 (Prior to Protocol Amendment 5) and in Figure 2 (As of Protocol Amendment 5).

Figure 1: Schematic Overview of the Study – Prior to Protocol Amendment 5

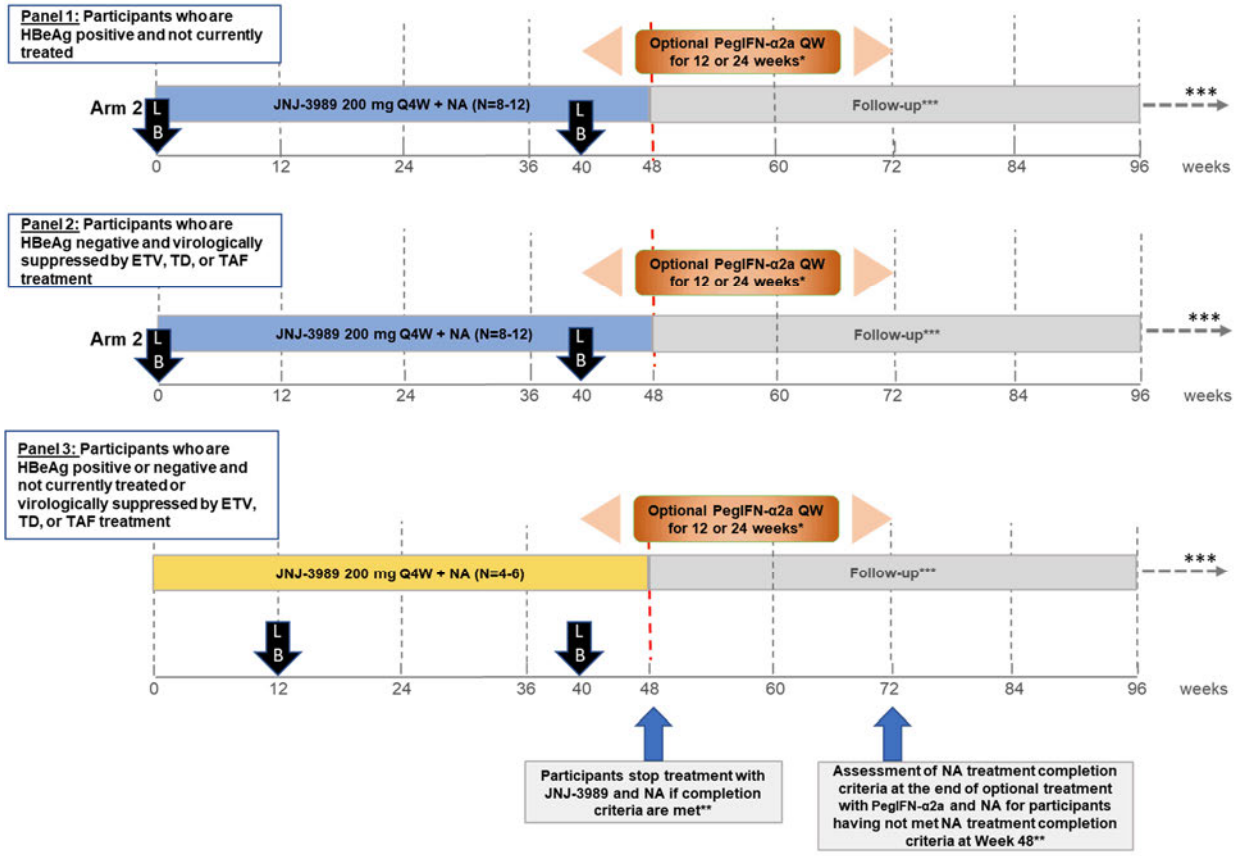


ETV: entecavir; N: number of participants; LB: (planned) liver biopsy; NA: nucleos(t)ide analog; Q4W: once every 4 weeks; qd: once daily; TAF: tenofovir alafenamide; TD: tenofovir disoproxil; QW: once weekly

* Participants who provide separate consent may receive optional treatment with PegIFN-α2a starting after the Week 40 biopsy (or after the optional leukapheresis visit if applicable) for a duration of either 12 or 24 weeks at the investigator's discretion.

** Treatment with JNJ-3989 (and JNJ-6379 if applicable) will be stopped at Week 48. Optional treatment with PegIFN-α2a will be stopped after 12 or 24 weeks (at the investigator's discretion). NA treatment may be stopped at Week 48 (or later for participants on PegIFN-α2a treatment) if NA treatment completion criteria are met.

Figure 2: Schematic Overview of the Study – As of Protocol Amendment 5



ETV: entecavir; N: number of participants; LB: (planned) liver biopsy; NA: nucleos(t)ide analog; Q4W: once every 4 weeks; qd: once daily; TAF: tenofovir alafenamide; TD: tenofovir disoproxil; QW: once weekly

* Participants who provide separate consent may receive optional treatment with PegIFN-α2a starting after the Week 40 biopsy (or after the optional leukapheresis visit if applicable) for a duration of either 12 or 24 weeks at the investigator's discretion.

** Treatment with JNJ-3989 (and JNJ-6379 if applicable) will be stopped at Week 48. Optional treatment with PegIFN-α2a will be stopped after 12 or 24 weeks (at the investigator's discretion). NA treatment may be stopped at Week 48 (or later for participants on PegIFN-α2a treatment) if NA treatment completion criteria are met.

*** The follow-up phase will be extended for participants who are receiving optional treatment with PegIFN-α2a and who meet NA treatment completion criteria at the end of treatment with NA and PegIFN-α2a to ensure all participants have at least one year of follow-up after NA treatment cessation.

Note: Former Arm 1 participants (randomized before Protocol Amendment 5) will now be joining Arm 2, both in terms of treatment assignment as well as how they will be statistically analyzed.

2. STATISTICAL HYPOTHESES

As this is an exploratory study, no hypothesis has been formulated.

3. SAMPLE SIZE DETERMINATION

This study aims to enroll 18 to 24 participants in total across Panels 1 and 2, i.e., 8 to 12 participants per study panel. In Panel 3, approximately 4-6 participants will be enrolled.

Regarding Panels 1 and 2, due to the exploratory nature of the study, the sample size was determined based on clinical and feasibility considerations related to the liver biopsy procedures performed multiple times during the study, rather than a formal statistical calculation. Nevertheless, a sample size of 8 to 12 participants each in Panel 1 and 2 is considered sufficient to provide adequate precision of the estimate of the primary endpoint (change from baseline to Week 40 in the proportion of HBsAg+ hepatocytes) as estimated by the 80% confidence interval (CI).

For the estimation of the absolute change in the proportion of HBsAg+ hepatocytes from baseline to Week 40 for the overall study population (Panels 1 and 2 combined), the following assumptions were made. Assuming an absolute reduction of 70% in Panel 1 (75% at baseline versus 5% at Week 40) and 29% in Panel 2 (30% at baseline versus to 1% at Week 40), and assuming an inter-subject variability of the change equal to 0.5 on the logit scale in both panels, a binomial model (Kassahun et al 2012) including visit as covariate with normal random effects provides an expected width of the 80% CI of 16.7% for N=24, a width of 17.9% for N=20, and a width of 20.3% for N=16. The point estimates (two-sided 80% CI) are 50.8% (42.5%; 59.1%) with N=24, 50.7% (41.8%; 59.7%) with N=20, and 50.6% (40.5%; 60.8%) with N=16.

For the between-panel difference in the absolute reduction in the proportion of HBsAg+ hepatocytes from baseline to Week 40 using the binomial model described above augmented with panel as an additional covariate and the same inter-subject variability, the estimated width of the two-sided 80% CI around the difference (Panel 1 – Panel 2) is 17.6% for N=24 (12 per panel), 19.3% for N=20 (10 per panel), and 21.2% for N=16 (8 per panel). The point estimates (80% CI) are 40.4% (31.5%; 49.2%) for N=24, 39.2% (29.6%; 48.9) for N=20, and 39.4% (28.8%; 50.0%) for N=16.

In addition, N=20 would also be sufficient to provide adequate precision for a between-panel difference in the relative change from baseline of at least 26% in case of large inter-subject variability.

Assuming a drop rate of 20%, the sample size will be therefore set to 12 participants per panel for Panels 1 and 2. See Attachment 1 for further details on the justification of the sample size.

For Panel 3, the justification of the sample size is based on clinical and feasibility considerations due to the exploratory nature of the primary endpoint (liver drug concentration).

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Analysis Sets	Description
Screened	**All participants who signed the ICF for the protocol.**
Enrolled	All participants who were enrolled in the study.
Randomized	All participants who were randomly assigned to an intervention arm before protocol amendment 5.
Intent-to-treat (ITT)[a]	All participants who were randomly assigned or enrolled to an intervention arm and received at least 1 dose of study intervention. Participants will be analyzed according to the study intervention they were randomly assigned or enrolled to.
Per Protocol (PP)	All participants in the ITT who do **not** have any of the selected major protocol deviations that may affect the assessment of efficacy. The selected major protocol deviations for efficacy analysis purposes that will be used to identify the participants included in the PP set are described in Attachment 2. Participants will be analyzed according to the study intervention they were randomly assigned or enrolled to.
Safety	All participants who received at least 1 dose of study intervention. Participants will be analyzed according to the study intervention they actually received.

[a]: defined as Full Analysis Set (FAS) as per the SAP Template v15.0

5. STATISTICAL ANALYSES

5.1. General Considerations

5.1.1. Analysis Phase

The analysis phases are defined in Table 1 below. Note that the screening, open-label, and follow-up phases are non-overlapping and cover the entire study period. The optional PegIFN-α2a treatment phase, in contrast, may overlap with both the open-label and follow-up phases.

Table 1: 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 (JNJ-3989 or JNJ-6379)
Open-label study intervention	Date of first study agent intake (JNJ-3989 or JNJ-6379)	Earliest of the following dates: • Early discontinuation date for JNJ-3989 + 5 days[a] • Study termination date • Max{ Date of last JNJ-3989 intake, Date of Week 48 visit } + 5 days[a] • Cut-off date[b]
Follow-up	End date of open-label phase + 1 day	Min (study termination date, study completion date, cut-off date[b])
Optional PegIFN-α2a treatment	Date of first PegIFN-α2a intake	Min (Date of last PegIFN-α2a intake + 5 days[a], cut-off date[b])

a : Addition of 5 days is only applicable for Adverse Events and Concomitant Medications.
b : Cut-off dates will be defined to match the prespecified timepoints for interim analyses, the primary analysis and the final analysis, respectively.

5.1.2. Visit Windows

As participants do not always adhere to the protocol visit schedule, visits will be allocated within each phase to an analysis time point based on the time intervals in Table 2.

If a participant has two or more actual visits in a visit window ("time interval" in Table 2), only one will be selected as the protocol visit according to the following rules:

1. The measurement closest to the target day will be used.
2. If the measurements fall equidistant from the target day, the last measurement in chronological order will be used.
3. 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.

Only the protocol visits will be included for calculating summary statistics across participants within a time point or for statistical models using longitudinal data. However, listings or figures

of individual participant-level data (including spaghetti plots), or analyses that identify a maximum or minimum value across time points (e.g., maximum ALT value), may include all measurements.

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

Special rule for Follow-up Week 48 (FU W48): Note that the time interval for FU W48 is open on the right, [324, +∞), while the next time interval is [352, 379]. Any visit in follow-up days [324, 351] will be assigned to FU W48. If a patient does not have a visit date in that interval but does have visits on or after follow-up day 352, then the earliest such visit will be assigned to FU W48. Any additional visits on or after follow-up day 352 will be assigned to an "Ext" follow-up visit according to Table 2.

Table 2: Visit Windows

a) **Screening and Open-Label Phases**

Analysis phase	**Target day**	**Analysis time point (Week)**	**Analysis time point (Label)**	**Open-label time interval (Days)**
Screening	-∞	-1	Screening	<0
Open-Label	1	0	Baseline	Pre-dose: 1
	15	2	Week 2	[2, 22]
	29	4	Week 4	[23, 43]
	57	8	Week 8	[44, 71]
	85	12	Week 12	[72, 99]
	113	16	Week 16	[100, 127]
	141	20	Week 20	[128, 155]
	169	24	Week 24	[156, 183]
	197	28	Week 28	[184, 211]
	225	32	Week 32	[212, 239]
	253	36	Week 36	[240, 267]
	281	40	Week 40	[268, 295]
	309	44	Week 44	[296, 323]
	337	48	Week 48	[324, 351]
	last visit in open-label phase	49 [a]	EOT [a]	

[a] End of treatment (EOT) visit will be the last post-baseline visit in open-label phase as defined in Table 1.

b) **Follow-Up Phase**

Analysis phase	Target day	Analysis time point (Week)	Analysis time point (Label)	Follow-up time interval (Days)
Follow-up	15	50	Follow-up Week 2	[1, 22]
	29	52	Follow-up Week 4	[23,43]
	57	56	Follow-up Week 8	[44, 71]
	85	60	Follow-up Week 12	[72, 99]
	113	64	Follow-up Week 16	[100, 127]
	141	68	Follow-up Week 20	[128, 155]
	169	72	Follow-up Week 24	[156, 183]
	197	76	Follow-up Week 28	[184, 211]
	225	80	Follow-up Week 32	[212, 239]
	253	84	Follow-up Week 36	[240, 267]
	281	88	Follow-up Week 40	[268, 295]
	309	92	Follow-up Week 44	[296, 323]
	337	96	Follow-up Week 48	[324, +∞)
	365	100	Follow-up Week 52 (Ext)	[352, 379]
	393	104	Follow-up Week 56 (Ext)	[380, 407]
	421	108	Follow-up Week 60 (Ext)	[408, 435]
	449	112	Follow-up Week 64 (Ext)	[436, 463]
	477	116	Follow-up Week 68 (Ext)	[464, 491]
	505	120	Follow-up Week 72 (Ext)	[492, +∞)
	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.
Note: The visits labeled with "Ext" are only for participants who completed PegIFN administration and NA treatment during the follow-up phase.

5.1.3. On-Treatment and Off-Treatment Period

The on-treatment period begins with the first drug intake 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 starts after the end of on-treatment period and stops if the NA re-treatment starts.

5.1.4. 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.

5.1.4.1. 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.

5.1.4.2. 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.

5.1.4.3. 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 dates 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 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 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.

5.1.5. 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 3.

Table 3: 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)]	274,725.00 IU/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 log_{10} cp/mL (13 cp/mL)	NAP
Anti-HBs	5 mIU/mL	10000.0 mIU/mL	2.5 mIU/mL[(a)]	11000.0 mIU/mL [(b)]

* 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 of the original result indicated in this table.

All other non-intrahepatic viral activity data not included in the data handling rules above, as well as continuous intrahepatic parameters obtained from liver biopsies (e.g., liver concentration of JNJ-3989), with values <LLOQ will be imputed by the LLOQ divided by 2. For parameters reported on the log scale, imputed values should be derived on the linear scale, not the log scale, and then converted back to the log scale. E.g., if a parameter has LLOQ = 3.0 Log_{10} U/mL (equivalent to 1,000 U/mL), the imputed value should be $\log_{10}(10^{LLOQ}/2) = LLOQ - \log_{10}(2)$ = 2.7 Log_{10} U/mL (equivalent to 500 U/mL).

5.1.6. Analysis Specifications

In general, continuous variables will be summarized using descriptive statistics including the number of participants, mean, standard deviation (SD), standard error (SE), 2-sided 80% confidence interval (CI), median, and range. Binary or categorical variables will be summarized using the number and percentage of participants in each category. For time-to-event variables, a summary table including number of participants included in the analysis, number of participants censored, 25th and 75th percentiles and median time-to event will be shown. Graphic displays will also be used to summarize the data.

Descriptive statistics on actual values (original unit and log_{10} transformed values, when appropriate) and changes from baseline (log_{10} transformed values when appropriate) will be

summarized over time. Mean (+/- SE) plots of the actual values and the change from baseline (log_{10} transformed when appropriate) will be presented over time.

As applicable, analyses will be carried out separately for each panel, for the combination of Panels 1 and 2, for the combination of all three panels, and for the pooled cohorts – across all three panels – of participants who are (1) HBeAg positive and not currently treated and (2) HBeAg negative and virologically suppressed by an NA. Additionally, some analyses will be carried out separately for participants who opt out of receiving PegIFN-α2a and those who opt to receive it for 12 or 24 weeks.

5.1.7. Level of Significance

Due to the exploratory nature of this study, no formal statistical test will be performed. Two-sided 80% CI will be provided with the summary statistics. No adjustment for multiple CIs will be made.

5.2. Participant Dispositions

The number and percentage of participants who are screened, fail screening, and reason for that screening failure will be tabulated by study panel for the Screened Analysis Set.

The number and percentage of participants enrolled, enrolled and not treated, and reason for not being treated will be tabulated by study panel for the Enrolled Analysis Set.

Study disposition and treatment disposition will be summarized for the ITT Analysis Set, as described below.

An overview of the study disposition will be provided by analysis phase, study panel, and overall. The number and percentage of participants who completed or discontinued (or are ongoing [except the final analysis]) and the number and percentage of participants for each study discontinuation reason will be summarized.

An overview of the treatment disposition will be provided. The number and percentage of participants who completed or discontinued study treatment or were ongoing at the time of the IAs or primary analysis cut-off (except the final analysis) will be presented by analysis phase, study panel, and overall. The incidences of treatment discontinuation reasons will also be summarized by analysis phase, study panel, and overall.

A listing including information (i.e., study panel, the date of last study visit, the last analysis phase and time point [phase and week], the date of discontinuation and the reason) on participants who prematurely discontinue from the study and/or study treatment will be included. Information on NA discontinuation and/or re-treatment will also be included.

5.3. Primary Endpoint Analyses

All primary endpoint analyses will be based on the ITT set, unless specified otherwise. Only selected analyses of selected endpoints will be repeated on the PP set, as will be indicated.

5.3.1. For Panels 1 and 2

5.3.1.1. Definition of Endpoint

The primary endpoint for Panels 1 and 2 is defined as the change in the proportion of HBsAg+ hepatocytes between baseline and on-treatment Week 40.

5.3.1.2. Analysis Methods

5.3.1.2.1. Missing Data Handling Rule

The primary rule to handle missing data is to use complete-case analysis, i.e., participants must have both baseline and Week 40 biopsy assessments with non-missing number of evaluated hepatocytes and HBsAg+ hepatocytes at both visits.

5.3.1.2.2. Primary Analysis of the Primary Endpoint

5.3.1.2.2.1. Overall Analysis

The change from baseline in proportion of HBsAg+ hepatocytes at Week 40 will be estimated overall – pooling Panels 1 and 2 – by modelling the proportion of HBsAg+ hepatocytes using a binomial mixed model with normal random effects to account for potential overdispersion (Kassahun et al 2012). The potential for overdispersion is supported by preliminary off-treatment results on chronic hepatitis B donors (Sources: Commercial biospecimen sources from Avaden Biospecimen and BioIVT as well as from a pilot phase of phase 0 study NOPRODHPB0012; hereafter referred to as the "donors data").

The binomial mixed model will model the number of HBsAg+ hepatocytes for each participant at each time point as follows:

$$Y_{ij} \sim \text{Binomial}\left(N_{ij}, p_{ij}\right)$$
$$\text{logit}(p_{ij}) = \underbrace{(\alpha + \xi_i)}_{\text{intercept}} + \underbrace{(\beta + \gamma_i)}_{\text{slope}} j$$
$$\text{for subject } i = 1, \ldots, n \text{ and}$$
$$\text{visit } j = 0 \text{ (for baseline) or } 1 \text{ (for Week 40)}$$
$$\xi_1, \ldots, \xi_n \overset{\text{iid}}{\sim} N(0, \text{SD}_{\text{intercept}})$$
$$\gamma_1, \ldots, \gamma_n \overset{\text{iid}}{\sim} N(0, \text{SD}_{\text{slope}})$$

with:

- Y_{ij}: number of HBsAg+ hepatocytes of subject i at visit j
- N_{ij}: total number of hepatocytes sampled from subject i at visit j
- p_{ij}: probability of a hepatocyte being HBsAg+ for subject i at visit j
- α: Fixed intercept (baseline log-odds of a hepatocyte being HBsAg+) for a "typical" subject, i.e., a subject whose random intercept and slope both equal 0
- ξ_i: Subject-specific random effect for overdispersion of the intercept
- β: Fixed slope (change in the log-odds from baseline to Week 40) for a "typical" subject

- γ_i: Subject-specific random effect for overdispersion of the slope
- n: total number of patients

The input data for this model are Y_{ij}, N_{ij}, and n. There are four parameters to estimate: α, β, $SD_{intercept}$, and SD_{slope}.

Estimates of the absolute and relative changes from baseline in the proportion of HBsAg+ hepatocytes at Week 40 and associated 80% CIs will be obtained from the model as follows. Let p_0 and p_1 be the proportion of infected hepatocytes at times 0 (baseline) and 1 (Week 40) for a "typical" subject. Based on the binomial model, $p_0 = \text{expit}(\alpha)$ and $p_1 = \text{expit}(\alpha + \beta)$, where $\text{expit}(x) = \exp(x)/[1 + \exp(x)]$ is the inverse of the logit function. The absolute and relative changes from baseline are therefore

- Absolute change: $p_1 - p_0 = \text{expit}(\alpha + \beta) - \text{expit}(\alpha)$
- Relative change: $\frac{p_1 - p_0}{p_0} = \frac{p_1}{p_0} - 1 = \frac{\text{expit}(\alpha+\beta)}{\text{expit}(\alpha)} - 1$

SAS code to fit the binomial mixed model and estimate the quantities of interest is provided in Attachment 3. We may also report estimates and CIs for p_0 and p_1.

Additional models may be evaluated depending on the distribution of data (such as Poisson, Negative-Binomial or Zero-Inflated regression models) and comparison of fit statistics would be performed to select the most adequate model. Additional covariates may be added to the model based on clinical considerations.

All biopsy data will be used for this analysis, including data collected after treatment discontinuation or occurrence of major protocol deviations potentially affecting the primary endpoint (see Attachment 2).

5.3.1.2.2.2. Comparison Between Panels 1 and 2

Study panel will be included as an additional covariate in the model described in Section 5.3.1.2.2.1. That is, the model for $\text{logit}(p_{ij})$ will become

$$\text{logit}(p_{ij}) = \underbrace{[\alpha + \delta_\alpha I(\text{panel}_i = 1) + \xi_i]}_{\text{intercept}} + \underbrace{[\beta + \delta_\beta I(\text{panel}_i = 1) + \gamma_i]}_{\text{slope}}\, j$$

with:

- α: Fixed intercept for a "typical" Panel 2 subject
- δ_α: Fixed difference in intercepts (Panel 1 minus Panel 2) for "typical" subjects
- β: Fixed slope for a "typical" Panel 2 subject
- δ_β: Fixed difference in slopes (Panel 1 minus Panel 2) for "typical" subjects
- panel_i: Panel number (1 or 2) for subject i

All other aspects of the model are unchanged from the specification in Section 5.3.1.2.2.1.

The input data for this model are Y_{ij}, N_{ij}, panel$_i$, and n. There are six parameters to estimate: α, δ_α, β, δ_β, $SD_{intercept}$, and SD_{slope}.

Estimates of the absolute and relative changes from baseline in the proportions of HBsAg+ hepatocytes at Week 40 will be provided for both Panels 1 and 2. The between-panel differences (Panel 1 minus Panel 2) in absolute and relative changes will also be estimated. Each estimate will be accompanied by an 80% CI. The estimates can be obtained from the binomial model as follows. Let p_0 and p_1 be the proportion of infected hepatocytes at times 0 (baseline) and 1 (Week 40) for a "typical" Panel 1 subject, and let q_0 and q_1 be defined analogously for a "typical" Panel 2 subject. Based on the binomial model, we have the following relations:

$$q_0 = \text{expit}(\alpha)$$
$$q_1 = \text{expit}(\alpha + \beta)$$
$$p_0 = \text{expit}(\alpha + \delta_\alpha)$$
$$p_1 = \text{expit}\big((\alpha + \delta_\alpha) + (\beta + \delta_\beta)\big)$$

From this we can obtain within-panel contrasts for the absolute change from baseline ($p_1 - p_0$ and $q_1 - q_0$) and the relative change ($\frac{p_1 - p_0}{p_0}$ and $\frac{q_1 - q_0}{q_0}$). The between-panel contrasts of interest are then

- Difference (Panel 1 minus 2) in absolute change: $(p_1 - p_0) - (q_1 - q_0)$
- Difference (Panel 1 minus 2) in relative change: $\left(\frac{p_1 - p_0}{p_0}\right) - \left(\frac{q_1 - q_0}{q_0}\right)$

SAS code to fit the binomial mixed model and estimate the quantities of interest is provided in Attachment 3. We may also report estimates and CIs for p_0, p_1, q_0, and q_1.

All biopsy data will be used and only complete cases will be considered, similarly to the approach chosen for the primary analysis.

5.3.1.2.3. Secondary Analysis of the Primary Endpoint

A secondary, descriptive analysis of the primary endpoint will be conducted. For each participant i at visit j (0 for baseline; 1 for Week 40), the observed proportion of HBsAg+ hepatocytes will be calculated as $P_{ij}^{Obs} = Y_{ij}/N_{ij}$, where Y_{ij} and N_{ij} are the number of HBsAg+ hepatocytes and the total number of evaluated hepatocytes from the biopsy sample, respectively.

The change from baseline to Week 40 will then be calculated for each participant as $\Delta_i^{Obs} = P_{i1}^{Obs} - P_{i0}^{Obs}$. The distributions of the P_{i0}^{Obs}, P_{i1}^{Obs}, and Δ_i^{Obs} across the participants will be described, both overall and by panel. Graphical displays may be used, including spaghetti plots (connecting P_{i0}^{Obs} to P_{i1}^{Obs}) and boxplots.

In addition, scatterplots displaying Y_{ij} versus N_{ij} will be provided.

5.3.1.2.4. Sensitivity Analyses

5.3.1.2.4.1. Baseline Observation Carried Forward (BOCF)

The primary and secondary analyses of the primary endpoint will be repeated by imputing any missing count of HBsAg+ hepatocytes at Week 40 (due to premature treatment discontinuation or insufficient biopsy material or missing biopsy assessment at Week 40) by the count of HBsAg+ hepatocytes at baseline. In case the number of evaluated hepatocytes at Week 40 is available but the count of HBsAg+ hepatocytes is missing, both values will be replaced by baseline data. In case of missing biopsy assessment at baseline, no imputation will be performed, and those participants will not be included in the analysis.

5.3.1.2.4.2. Multiple Imputation

The secondary analysis of the primary endpoint will be repeated by using multiple imputation (MI) to impute any missing count of HBsAg+ hepatocytes at baseline and Week 40. Participants with missing biopsy assessments at both time points will not be included in the analysis.

The MI model will be applied to the continuous, logit-transformed proportions P_{ij}^{Obs}, as defined in Section 5.3.1.2.3. The model will be used separately for each panel, and will include the available non-missing logit-transformed proportions P_{ij}^{Obs}, and may include age, gender, log-transformed peripheral HBsAg at baseline and Week 40, and type of NA (TD/TAF versus ETV).

A planned total of 20 datasets will be generated for each panel. Depending on the amount of missing data, the number of imputed datasets to be generated may be increased appropriately to ensure robustness in the MI results and relative efficiency.

From each imputed dataset we will obtain values for P_{i0}^{Obs}, P_{i1}^{Obs}, and Δ_i^{Obs}. The distributions of these three quantities across the participants and imputed datasets will be described, both overall and by panel. The means of P_{i0}^{Obs} and P_{i1}^{Obs} will be obtained for each participant across imputed datasets and displayed in a spaghetti plot.

5.3.1.2.4.3. Per-Protocol Analysis (PP)

The primary and secondary analyses of the primary endpoint will be repeated with the PP set. All biopsy data will be used and only complete cases will be considered.

5.3.1.3. Subgroup Analyses

The potential association between the primary endpoint and baseline characteristics may be explored graphically using forest and scatter plots. The baseline subgroups of interest for efficacy are defined in Section 5.7.4.

The potential association between the primary endpoint and treatment-related characteristics may be explored both by using summary tables and plots. Subgroups in this category include:

- Received at least 1 dose of JNJ-6379 (No / Yes);
- Treatment with PegIFN-α2a during study (No / Yes / Yes for 12 weeks / Yes for 24 weeks).

5.3.2. For Panel 3

5.3.2.1. Definition of Endpoints

The primary endpoints for Panel 3 are defined as the liver concentrations of JNJ-3989 (i.e., JNJ-3976, JNJ-3924, and M65), measured at treatment Weeks 12 and 40.

5.3.2.2. Primary Analysis

Individual listings and descriptive statistics (n, mean, SD, SE, median, minimum and maximum) for JNJ-3976 and JNJ-3924 liver and plasma concentrations, and M65 liver concentrations, as well as the ratio of liver to plasma concentrations at Weeks 12 and 40 will be provided. In addition, the ratio of M65 to JNJ-3976 at Weeks 12 and 40 will be calculated.

Scatterplots of individual JNJ-3976, JNJ-3924, and M65 liver concentrations by time point will be provided. Additionally, scatterplots of HBsAg change from baseline at Week 40 by JNJ-3976, JNJ-3924, and M65 liver concentrations at Week 40 will be provided.

5.4. Secondary Endpoints Analysis

All secondary endpoints will be analyzed for the ITT set.

5.4.1. Intrahepatic Secondary Endpoints

As a general consideration, no imputation rule will be applied in case of missing biopsy assessment or insufficient biopsy sample material required to obtain the individual intrahepatic markers at baseline and/or Week 12 and/or Week 40. Some imputation rule may be applied for specific endpoints and will be described in the relevant section(s).

5.4.1.1. Intrahepatic Immune Response

5.4.1.1.1. For Panels 1 and 2

The following immune cells will be evaluated:

- CD45+ T-cells,
- CD4+ T-cells,
- CD8+ T-cells,
- Natural Killer (NK) cells,
- Dendritic cells

Additional immune cells may be explored.

Estimations on change in proportions using a similar mixed model as described in Section 5.3.1.2.2 with an appropriate distribution for each type of cells will be provided. It may differ from the assumption of binomial distribution made for the primary endpoint.

In addition, similar summary statistics and graphical displays on the calculated change in proportion will be provided as defined in Section 5.3.1.2.3. Additional immune cells may be evaluated depending on data availability and clinical interest. Spatial distribution for each cell type at baseline and Week 40 will be graphically evaluated.

5.4.1.1.2. For Panel 3

The same immune cells as described in Section 5.4.1.1.1 may be analyzed for Panel 3 at Week 12 and Week 40. Descriptive analyses may be provided as defined in Section 5.3.1.2.3.

5.4.1.2. Intrahepatic Viral Parameters

5.4.1.2.1. For Panels 1 and 2

Descriptive statistics on actual values at baseline and Week 40 and changes from baseline at Week 40 will be summarized for the following parameters:

- Number and proportion of cccDNA-positive hepatocytes
- Number and proportion pgRNA-positive hepatocytes
- Number and proportion of silent hepatocytes
- cccDNA levels (copies/10^6 cells)
- pgRNA levels (copies/cell)
- pgRNA/cccDNA ratio
- Intrahepatic HBsAg (semi-quantitative: negative, low, middle, high expression)
- Intrahepatic HBcAg (semi-quantitative: negative, low, middle, high expression)
- Intrahepatic HBV RNA (semi-quantitative: negative, low, middle, high expression)

Number of cells will be expressed in original unit and proportions or ratios will be provided in both original and $\log_{10}$ transformed scales. Change from baseline will be provided in $\log_{10}$ transformed unit. In addition, same graphical displays as described in Section 5.3.1.2.3 will be provided.

5.4.1.2.2. For Panel 3

The number and proportion of HBsAg+ hepatocytes, as well as the same viral parameters described in Section 5.4.1.2.1, may be provided at Week 12 and Week 40, depending on the availability of biopsy material.

5.4.2. Blood Peripheral Secondary Endpoints

5.4.2.1. HBsAg Seroclearance

HBsAg seroclearance, defined as quantitative HBsAg <LLOQ (see Table 3), will be evaluated at all time points.

If the HBsAg value at Weeks 40 or 48 is missing, the LOCF approach will be used with the condition that no value more than 8 weeks prior to the respective time point may be carried forward. At FU Weeks 12, 24, 36 and 48, and at 24, 36, and 48 weeks after stopping all study interventions, if an HBsAg value is missing, then LOCF approach will be used with the condition that no value more than 12 weeks prior to the respective time point will be used. For all other time points, seroclearance will be analyzed as observed case without imputation.

The proportion of participants who achieve HBsAg seroclearance over time will be summarized.

5.4.2.1.1. Time to 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.

In addition, time to the first occurrence of HBsAg <10 IU/mL (i.e., the date of the first occurrence of HBsAg <10 IU/mL – the date of first study intervention intake + 1) and HBsAg <100 IU/mL (i.e., the date of the first occurrence of HBsAg <100 IU/mL – the date of first study intervention intake + 1) will also be evaluated.

The Kaplan-Meier method will be used to estimate and plot the cumulative incidence. The median time with 80% CI will be estimated using Kaplan-Meier method, if possible.

5.4.2.2. 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. If the HBsAg value is missing at that specific time point, then the non-missing lab test closest to that specific timepoint will be used. If the non-missing lab test before and after the specific timepoint fall equidistant from the target timepoint, the later one will be used to impute the missing value.

Appearance of anti-HBs antibodies is defined as a baseline anti-HBs antibodies (quantitative) <LLOQ and a post-baseline assessment ≥LLOQ. A sensitivity analysis will be conducted 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.

5.4.2.3. HBeAg Seroclearance and Seroconversion

Seroclearance of HBeAg is defined as (quantitative) HBeAg <LLOQ. The HBeAg seroclearance will be summarized only for HBeAg positive participants at study entry.

Seroclearance will be analyzed as observed case without imputation and with imputation using LOCF approach. For the imputation with LOCF approach, we impute the missing data with the following restriction. If the HBeAg value at Weeks 40 or 48 is missing, the LOCF approach will be used with the condition that no value more than 8 weeks prior to the respective time point may be carried forward. At FU Weeks, if an HBeAg value is missing, then LOCF approach will be used with the condition that no value before the FU phase or more than 12 weeks prior to the respective time point will be used. For all other time points, seroclearance will be analyzed as observed case without imputation.

The proportion of participants who achieve HBeAg seroclearance over time will be summarized.

Seroconversion of HBeAg is defined as having achieved HBeAg seroclearance together with 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. The seroconversion of HBeAg will be summarized only for HBeAg positive participants at study entry.

The seroconversion will only be assessed at the time points when the anti-HBe antibodies assessment is available. If the HBeAg value is missing at that specific time point, then the non-missing lab test closest to that specific timepoint will be used. If the non-missing lab test before and after the specific timepoint fall equidistant from the target timepoint, the later one will be used to impute the missing value.

The number and proportion of participants who achieve HBeAg seroconversion will be summarized.

5.4.2.4. HBsAg, HBeAg, HBV DNA and ALT

5.4.2.4.1. Values and Changes Over Time

5.4.2.4.1.1. Change from Baseline Over Time

Descriptive statistics on actual values [original unit and $\log_{10}$ transformed values (except for ALT)] and changes from baseline (in original unit for ALT and $\log_{10}$ transformed values otherwise) over time in HBsAg, HBeAg (for HBeAg positive participants at study entry), HBV DNA and ALT will be summarized and mean (+/- SE) plots of the values and the change from baseline over time will be presented.

Change from baseline based on $\log_{10}$ transform for quantitative HBsAg, HBeAg (for HBeAg positive participants at study entry) and HBV DNA will be analyzed using mixed effects model for repeated measures [MMRM]) including analysis time point (week), and HBV baseline status (HBeAg positive and not currently treated or HBeAg negative and virologically suppressed) as

fixed effects. In addition, the above model will be augmented with a HBV baseline status by time point interaction term. The covariance structure will include a random intercept at the level of the participant to capture between-participant variability, while within-participant variability will be captured with a Compound Symmetry (type=CS) covariance matrix. In case of convergence problems, another simpler variance-covariance structure 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), and 80% CI will be provided.

Spaghetti plots for both absolute values and changes from baseline of HBsAg, HBeAg, HBV DNA, and ALT will be presented over time.

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

5.4.2.4.1.2. Change from Baseline to Nadir

The following changes from baseline value to nadir value in HBsAg, HBeAg, and HBV DNA will be summarized descriptively and displayed graphically using boxplots.

- Change from baseline to open-label phase nadir
- Change from baseline to follow-up phase nadir
- Change from baseline to postbaseline nadir

5.4.2.4.2. HBsAg Thresholds

The number and proportion of participants who meet the following HBsAg thresholds over time will be summarized descriptively.

Thresholds for **HBsAg absolute** values:

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

Of note, seroclearance of HBsAg is defined as HBsAg <LLOQ.

Thresholds for **HBsAg reduction** from baseline:

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

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

5.4.2.4.3. HBeAg Thresholds

The number and proportion of participants who meet the following HBeAg thresholds over time will be summarized descriptively. The HBeAg thresholds will be summarized only for HBeAg positive participants at study entry.

Thresholds for **HBeAg absolute** values:

- < 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.

Thresholds for **HBeAg reduction** from baseline:

- ≥ 0.3 log_{10} IU/mL
- ≥ 0.5 log_{10} IU/mL
- ≥ 1 log_{10} IU/mL
- ≥ 2 log_{10} IU/mL
- ≥ 3 log_{10} IU/mL

5.4.2.4.4. HBV DNA Thresholds

The number and proportion of participants who meet the following HBV DNA thresholds over time will be summarized descriptively.

Thresholds for **HBV DNA absolute** values:

- < LLOQ
- < LLOQ TND
- < LLOQ TD
- <60 IU/mL
- <100 IU/mL
- <200 IU/mL
- <1000 IU/mL
- <2000 IU/mL
- <20000 IU/mL

Thresholds for **HBV DNA reduction** from baseline:

- ≥ 1 log_{10} IU/mL
- ≥ 2 log_{10} IU/mL
- ≥ 3 log_{10} IU/mL
- ≥ 4 log_{10} IU/mL
- ≥ 5 log_{10} IU/mL

5.4.2.4.5. ALT Decrease and Normalization

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

The number and proportion of participants who achieve the following ALT normalizations will be summarized descriptively over time, only for the subjects who had ALT elevation at baseline:

- On treatment ALT normalization, i.e., while being treated with JNJ-3989 and/or JNJ-6379 and/or NA and/or PegIFN-α2a).
- Off treatment ALT normalization, i.e., after stopping JNJ-3989, JNJ-6379, NA, and PegIFN-α2a.

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

5.4.2.4.6. Study Intervention Completion at Week 48 and During Follow-up

Participants will complete treatment with JNJ-3989 after a fixed duration of 48 weeks. If all of the below criteria are met based on clinical laboratory tests performed at Week 44, treatment with NA will also be completed at the next scheduled visit (ie, Week 48):

- The participant has ALT <3x ULN, AND
- The participant has HBV DNA <LLOQ, AND
- The participant is HBeAg negative, AND
- The participant has HBsAg <10 IU/mL.

Participants who do not meet the above criteria at Week 48 should continue NA treatment during the 48-week follow-up phase. Participants who are receiving optional treatment with PegIFN-α2a and who have not met NA treatment completion criteria at Week 48 may have NA treatment completion criteria assessed at the end of treatment with PegIFN-α2a and stop NA if criteria are met.

Proportion of participants who have met NA completion criteria, and reasons for not meeting, will be summarized at Week 48 and at the end of treatment with PegIFN-α2a.

5.4.2.4.7. NA Re-Treatment During Follow-up

Proportion of participants who have NA re-treatment during follow-up will be summarized.

5.4.2.4.8. ALT Normalization after NA Re-Treatment

Proportion of participants who have ALT≥ULN before NA re-treatment and reach ALT normalization after NA re-treatment during follow-up will be summarized.

5.4.2.4.9. Thresholds On Multiple Markers

The number and proportion of participants who meet the following blood marker reduction/seroclearance thresholds at 12, 24, 36 and 48 weeks, respectively, after stopping all study interventions (including NA and PegIFN-α2a) and not having NA re-treated will be summarized descriptively for each marker and each threshold listed below.

- **HBsAg<LLOQ and HBV DNA**
  - HBsAg<LLOQ and HBV DNA<LLOQ**
  - HBsAg<LLOQ and HBV DNA≥LLOQ
  - HBsAG<LLOQ and HBV<2,000 IU/ml
- **HBsAg≥LLOQ and HBV DNA<2,000 IU/ml**
  - HBsAg≥LLOQ and HBV DNA<LLOQ**
  - HBsAg≥LLOQ and HBV DNA≥LLOQ
  - HBsAg≥LLOQ and LLOQ ≤HBV DNA<2,000 IU/ml
- **HBsAg≥LLOQ and HBV DNA≥2,000 IU/ml**
  - HBsAg<100 IU/mL and HBV DNA≥2,000 IU/ml
  - HBsAg≥100 IU/mL and HBV DNA≥2,000 IU/ml
- **HBsAg<100 IU/ml and HBV DNA<2000 IU/ml**
- **HBsAg<100 IU/ml and HBV DNA<LLOQ****

** HBV DNA<LLOQ will be summarized overall. Additional analyses may assess HBV DNA<LLOQ TD versus TND.

Due to the exploratory objectives of this study, additional blood marker reduction/seroclearance thresholds may be added at a later point in time according to the clinical interest.

5.4.2.5. Functional Cure

A participant will be defined as having achieved Functional Cure (FC) at a given time point during the FU phase if he/she has HBsAg seroclearance (as defined in Section 5.4.2.1) at that time point and has stopped all study interventions (including NA and PegIFN-α2a) for at least 24 weeks without re-treatment.

Participants who discontinue treatment prior to Week 48 (except for JNJ-6379), or who withdraw from the study prior to the given time point, will be considered as non-responders for FC in this study. The CRF pages of 'Treatment Disposition of JNJ-3989', 'Treatment Disposition of NA Treatment', 'Treatment Disposition for NA Re-Treatment' and 'Treatment Disposition for PegIFN-alpha2a' will be checked to ensure all treatment actually stopped.

Subjects still in the study at a given time point but with missing HBsAg assessment at that time after implementation of LOCF (as described in Section 5.4.2.1), will be considered as non-responders.

Number and proportion of participants achieving FC will be summarized at 24, 36, and 48 weeks after stopping all study interventions (including NA and PegIFN-α2a). Subjects who never reach such time points will be considered as non-responders.

5.4.2.6. Flares

5.4.2.6.1. Definition

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:

Derivation 1. This derivation of virologic flare will be assessed only for those participants who are off-treatment and had HBV DNA<LLOQ at the last observed point on-treatment.

The start date 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.

Derivation 2. This derivation of virologic flare will be assessed only for those participants who are off-treatment and had HBV DNA ≥LLOQ at the last observed point on-treatment.

The start date of a confirmed virologic flare is defined as the first date of two consecutive visits with HBV DNA $\log_{10}$ increase > 1 $\log_{10}$ from EOT. The end date of the same confirmed virologic flare is defined as the first date when HBV DNA $\log_{10}$ increase from end of treatment returns to ≤1 $\log_{10}$ 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 increase above

any of the three thresholds within the start and end date of that flare as follows: 1 log_{10}, 2 log_{10}, 3 log_{10}.

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

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

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 and <3x ULN.

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

3. **On-treatment biochemical flare** is defined as follows:

The start date of a confirmed on-treatment biochemical flare is defined as the first date of two consecutive visits with ALT and/or AST ≥3x ULN and ≥3x 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 and <3x ULN, regardless of stopping study interventions.

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

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

A clinical flare occurs either when a virologic flare and biochemical flare overlap in time or when a biochemical flare starts within 4 weeks following the end of a virologic flare.

The start date of a clinical flare is defined as the minimum start date of the virologic flare and 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 between HBV DNA returns to ≤ 200 IU/mL (or ≤1 log10) and 50% reduction from the peak ALT and/or AST level and <3x ULN reached during the biochemical flare.

- 1 (Yes) = confirmed** HBV DNA > peak threshold (for derivation 1 of virologic flare) or HBV DNA increase from end of treatment > peak threshold (for derivation 2 of virologic flare) and confirmed**ALT and/or AST≥3x ULN and ≥3x nadir (i.e., lowest value observed up to the start of the biochemical flare).
- 0 (No) = otherwise

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

The virologic and clinical flares will be assessed only off-treatment, while biochemical flares will be identified on-treatment and off-treatment, respectively. On-treatment virologic flares are described as virologic HBV breakthrough in Section 5.4.2.7.

On-treatment will be defined as the time periods in which the participant receives any of the study interventions (JNJ-3989 or JNJ-6379 or NA or PegIFN-α2a). Off-treatment will be defined as the periods when the participants do not receive any of the study interventions (JNJ-3989, JNJ-6379, NA, and PegIFN-α2a).

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 and by study panel.

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.

5.4.2.7. HBV Virologic Breakthrough

5.4.2.7.1. Definition

HBV virologic 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 did not have on-treatment HBV DNA level < LLOQ or a confirmed on-treatment HBV DNA level >200 IU/mL in participants who had on-treatment HBV DNA level <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 (JNJ-3989 and/or JNJ-6379 and/or NA and/or PegIFN-α2a).

The number and proportion of participants who experience a virologic breakthrough will be summarized descriptively by analysis phase.

The number and proportion of participants who experience a virologic breakthrough followed by on-treatment biochemical flare will be summarized descriptively.

5.4.2.8. HBV-Specific T-Cells Response

Descriptive statistics (for example, may include n, mean, SD, CV, geometric mean, median, minimum, and maximum) will be used to describe the magnitude of the IFN-γ T cell response or the CD4+ and CD8+ T-cell responses (expressing at least 1 cytokine such as IL-2, TNF-α or IFN-γ specific to any HBV antigen) as defined by ELISpot and/or ICS, respectively. Changes from baseline (if present) will also be tabulated for PBMCs during study intervention and follow-up. The proportion (%) of CHB participants with positive responses based on the magnitude of the IFN-γ T cell response or the CD4+ or CD8+ T cells expressing at least 1 of the cytokines amongst IL-2, TNF-α or IFN-γ for 1 of the HBV antigens as defined by ELISpot and/or ICS, respectively, will be determined.

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

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

5.4.3. Subgroup Analyses

The same subgroups as described in Section 5.3.1.3 may be used to analyze key secondary endpoints.

5.5. Exploratory Endpoints Analysis

5.5.1. Relationship Between Intrahepatic and Blood Markers

Relationships between intrahepatic and blood markers and/or their change from baseline at Week 40 will be evaluated graphically with scatter plots displaying individual associations.

Means on pooled individual data by study panel and overall mean will also be plotted on the same graph.

The following correlation coefficients will be calculated by study panel and overall 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.

Potential relationship on the selected subgroups defined in Section 5.7.4 will also be explored using the same graphical approach.

The following markers will be considered, i.e., each intrahepatic marker will be plotted against each blood marker:

Table 4: List of Intrahepatic and Blood Markers of Interest

Intrahepatic Markers/Endpoints	Blood Markers/Endpoints
• Proportion of HBsAg+ hepatocytes at Week 40 • Change from Baseline at Week 40 in proportion of HBsAg+ hepatocytes • cccDNA levels at Week 40 (log_{10} copies/10^6 cells) • Change from Baseline at Week 40 in cccDNA levels (log_{10} copies/10^6 cells) • pgRNA levels at Week 40 (log_{10} copies/ cell) • Change from Baseline at Week 40 in pgRNA levels (log_{10} copies/ cell) • pgRNA/cccDNA ratio	• HBV DNA level at Week 40 (log_{10}) • HBV RNA level at Week 40 (log_{10}) • HBsAg level at Week 40 (log_{10}) • HBeAg level at Week 40 (log_{10}) • HBcrAg level at Week 40 (log_{10}) • Change from Baseline at Week 40 in HBV DNA (log_{10}) • Change from Baseline at Week 40 in HBV RNA (log_{10}) • Change from Baseline at Week 40 in HBsAg (log_{10}) • Change from Baseline at Week 40 in HBeAg (log_{10}) • Change from Baseline at Week 40 in HBcrAg (log_{10}) • Maximum on-treatment ALT decrease • HBsAg seroclearance at FU Week 24

Additional markers and endpoints may be evaluated when data will be available.

5.5.2. Association Between Baseline Characteristics or Intrahepatic/Blood Markers with Efficacy Variables

The following list of efficacy endpoints of interest will be evaluated:

- Proportion of participants with HBsAg <10 IU/mL at Week 40 (Yes/No)
- Proportion of participants with HBsAg <10 IU/ml at Off-Treatment Week 24 (Yes/No)
- Proportion of participants with HBsAg Seroconversion at Off-Treatment Week 24 (Yes/No)
- Proportion of participants with Functional Cure at Off-Treatment Week 24 (Yes/No)

For each of the endpoints listed above, the potential association with the following selection of characteristics or intrahepatic/blood markers may be assessed:

- Duration of NA (years)
- Age (years)
- Duration of infection (years)
- Baseline HBeAg level (quantitative), for panel 1 only
- Baseline HBV DNA level (log_{10})
- Baseline ALT Level (quantitative)
- Baseline Peripheral HBsAg level (log_{10})
- Baseline Number of HBsAg+ hepatocytes (log_{10})
- Proportion of HBsAg+ hepatocytes at baseline
- Baseline cccDNA levels (log_{10} copies/10^6 cells)
- Baseline pgRNA levels (log_{10} copies/ cell)
- Baseline pgRNA/cccDNA ratio
- HBeAg level (quantitative) at Week 40
- HBV DNA level (log_{10}) at Week 40
- ALT Level (quantitative) at Week 40
- Peripheral HBsAg level (log_{10}) at Week 40
- Proportion of HBsAg+ hepatocytes (log_{10}) at Week 40
- cccDNA levels (log_{10} copies/10^6 cells) at Week 40
- pgRNA levels (log_{10} copies/ cell) at Week 40
- pgRNA/cccDNA ratio at Week 40

These lists may be modified based on clinical relevance and data availability.

For Panels 1 and 2, logistic regression models will be performed for each efficacy endpoint of interest, and will include study panel and characteristics/marker of interest as factor, with and without the study panel-by-baseline variable as the interaction-terms. Covariates and/or interaction terms may be added or removed to a given model for fitting purpose.

Odd-Ratios (OR) and corresponding 80% CIs will be also calculated without multiplicity adjustment overall. Statistical analysis of treatment heterogeneity between subgroups will be conducted by assessing the significance of the interaction term. The forest plot will present graphically the on/off treatment efficacy OR estimate and its 80% CI resulting from the model by the prespecified subgroups on the overall population and by study panels.

5.5.3. Intrahepatic Immune and Viral Parameters at FU Week 24 (Week 72)

For all participants with biopsy data available at FU Week 24, the same analyses as described in Sections 5.3.1.2.3, 5.4.1.1 and 5.4.1.2 may be performed. Graphs over time will display baseline, Week 40 and FU Week 24 data.

5.5.4. Liver Stiffness Measurement (LSM)

The proportion of participants with the following LSM changes from baseline (both in terms of reductions and increases) will be evaluated over time at Week 48, FU Week 24 and FU Week 48 /EOS:

- ≥ 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.

In addition, the change from baseline in LSM will be compared between study panels at Week 48 using ANCOVA with study panel as main effect in the model and baseline score as covariate.

At each assessment time point, a frequency distribution of severity scores will be produced. A graphical display will also illustrate the findings. In addition, a waterfall plot will be produced to display the individual changes from baseline in LSM.

5.5.5. HBV RNA and HBcrAg

HBcrAg will be summarized by treatment history (not currently treated and virologically suppressed) and overall, while HBV RNA will only be summarized by treatment history.

The values of and changes from baseline in HBV RNA and HBcrAg, respectively, will be summarized only descriptively over time in a similar manner as for values and changes from baseline over time in HBsAg, HBeAg, and HBV DNA as described in Section 5.4.2.4.1, including the change from baseline value to nadir (i.e., maximum decrease for each participant) and the various graphical displays.

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

5.5.6. Sustained HBsAg Response

The definitions of sustained response are as follows:

Definition 1 (yes/no):

- For participants with data at the last scheduled follow-up visit (Follow-up Week 48 for participants who did not receive PegIFN-α2a or received PegIFN-α2a and did not meet NA

completion criteria, and last Follow-up visit for participants who received PegIFN-α2a and stopped NA during Follow-up): Participants who have a > 1 log decline in HBsAg at last scheduled follow-up visit and have an HBsAg <1000 IU/mL at the last scheduled follow-up visit.

- For participants without data at the last scheduled follow-up visit: HBsAg values have a > 2 log decline at the second most recent visit or >1.5 log decline at the latest visit (most recent value used) compared to baseline and have an HBsAg <1000 IU/mL at the last available timepoint.

Definition 2 (yes/no): For participants with a >1 log decline in HBsAg from baseline at last follow-up visit: Among the most recent three visits, the difference between log HBsAg at 2 of 3 last visit and 1 of 3 last visit is <0.2, and the difference between log HBsAg at 3 of 3 last visit and 1 of 3 last visit is <0.2.

Definition 3 (yes/no): For participants with a >1 log decline in HBsAg from baseline at last follow-up visit: Among the most recent three visits, the difference between log HBsAg at 2 of 3 last visit and 1 of 3 last visit is <0.2, and the difference between log HBsAg at 3 of 3 last visit and 1 of 3 last visit is <0.2 and have an HBsAg <1000 IU/mL at the last available timepoint.

Definition 4 (>0.2 log increase, +/-0.2 log, >0.2 log decline): Three categories regarding the difference between HBsAg level at the last Follow-up timepoint and EOT:

- >0.2 $\log_{10}$ decrease: Decreasing level
- ≤0.2 $\log_{10}$ increase or ≤0.2 log10 decrease: Stable level
- >0.2 $\log_{10}$ increase: Increasing level

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

For all definitions of the sustained HBsAg response, only participants with at least 24 weeks 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.

5.6. Safety Analyses

All safety analyses will be based on the safety analysis set based on actual study intervention received, unless otherwise specified. Summaries will be provided on the overall population and by study panel and analysis phase unless specified otherwise.

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

5.6.1. Extent of Exposure

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

Descriptive statistics for duration (N, mean, SD, median, and range [minimum, maximum]) of JNJ-3989, JNJ-6379, and NA during the open-label phase, and of PegIFN-α2a, will be summarized. Duration of treatment with NA will also be summarized for the follow up phase.

Because of the different route and frequency of treatment administration across the 3 agents (for JNJ-3989 one subcutaneous injection once every 4 weeks, for JNJ-6379 and for NA once daily tablet, and for PegIFN-α2a one subcutaneous injection every week) the total duration of exposure (weeks) will be calculated for each study treatment as follows:

- JNJ-3989: [Min ((Date of last injection+27 days), Date of trial disposition, cut-off date) – date of first injection + 1] / 7
- JNJ-6379: [Min (Date of the last JNJ-6379, Date of treatment disposition for JNJ-6379, Date of trial disposition, Date of clinical cut-off)- first drug administration date + 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) - first drug administration date in the given phase + 1] / 7
- PegIFN-α2a: [Min (Date of the last PegIFN-α2a administration +6 days, Date of discontinuation from PegIFN-α2a, Date of trial disposition, Date of clinical cut-off date) – Date of the first PegIFN-α2a administration + 1] / 7

For NA treatment, the total duration of exposure will be calculated separately for the open-label and FU phases. For FU, the total duration will add up the weeks of NA treatment in the FU phase for those participants who did not stop NA prior to/at Week 48 and the NA re-treatment weeks, if any required. Those participants who stopped NA treatment at or before Week 48 and never restarted NA treatment thereafter will be counted as having zero weeks of NA exposure during the FU.

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

The number and percentage of participants who skipped any dose of JNJ-3989 or NA during the open-label phase, or any dose of PegIFN-α2a, will be summarized separately by study panel. Additionally, the number and percentage of participants who missed 2 or more JNJ-3989 injections, or who missed more than 5 doses of NA within a four week period will be provided as well as the distribution of the total number of JNJ-3989 injections received.

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

5.6.2. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). 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 will be provided for treatment-emergent adverse events:

- AEs
- Serious AEs (SAEs)
- AEs leading to discontinuation of each study agent within a study intervention including NA
- AEs by NCI-CTAE toxicity grade
- 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:

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

Incidence of other treatment-emergent adverse events of special interest listed in Appendix 8 will be summarized.

A listing of participants who died will be provided.

5.6.3. Additional Safety Assessments

5.6.3.1. Clinical Laboratory Tests

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

Table 5: Laboratory Parameters

Laboratory Category	Parameters		
Hematology	Platelet count RBC count Hemoglobin Hematocrit Reticulocyte count Reticulocyte index	RBC Indices: Mean corpuscular volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Blood Coagulation	Activated partial thromboplastin time International normalized ratio Prothrombin time		
Clinical Chemistry	Sodium Potassium Chloride Bicarbonate Blood urea nitrogen Creatinine Cystatin C (for Panel 3 only) Glucose AST/Serum glutamic-oxaloacetic ALT/Serum glutamic-oxaloacetic Gamma-glutamyltransferase (GGT) Total, conjugated and unconjugated bilirubin Alkaline phosphatase Creatine phosphokinase	Lactic acid dehydrogenase Uric acid Calcium Phosphate Albumin Total protein Total cholesterol High-density lipoprotein cholesterol Low-density lipoprotein cholesterol Triglycerides Magnesium Lipase Amylase	
	Note: Creatinine clearance (eGFR calculated by the CKD-EPI formula, denoted as eGFRcr) will be assessed for Panels 1 and 2. For Panel 3, eGFR will be calculated based on cystatin C in serum (calculated by the CKD-EPI cystatin C equation, denoted as eGFRcys)		
Routine Urinalysis	Dipstick Specific gravity pH Glucose Protein Blood Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase	Sediment (if dipstick result is abnormal) RBCs WBCs Epithelial cells Crystals Casts Bacteria	
Urine Chemistry (quantitative measurement)	Creatinine Sodium Phosphate	Glucose Protein Albumin	
Renal Biomarkers	Retinol binding protein Beta-2-microglobulin		

Clinical laboratory tests will be displayed for the participants included in the safety analysis set by study panel and study 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 and displayed.

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

Postbaseline abnormalities will be compared with their corresponding baseline result:

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

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

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

A tabulation of percentage and number of the participants who have treatment-emergent worst toxicity grades and treatment-emergent worst abnormalities per parameter and analysis phase will be included. The incidence table of worst toxicity grade abnormality in laboratory parameters will be also presented stratified by the subgroup of interests identified in Section 5.7.4.

Plots of mean (+/- SE) values and changes from baseline over time for alanine transferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, hemoglobin, neutrophils, platelets, bilirubin (direct and indirect), lipase, amylase/pancreatic amylase, activated partial thromboplastin time, prothrombin time and phosphate will be presented by study panel. Spaghetti-plots for selected laboratory parameters will be presented by study panel 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.

5.6.3.1.1. Creatinine and Glomerular Filtration

Creatinine and glomerular filtration analyses will be analysed over time.

5.6.3.1.1.1. eGFR

Stages of eGFR (eGFRcr or eGFRcys, as described in Table 5) at baseline versus the minimum corresponding post-baseline eGFR value and the last available value will be summarized by count and percent of participants. Stage of chronic kidney disease (CKD) are defined as follows: 1 (Normal): eGFR ≥ 90; 2 (Mild): eGFR 60-89; 3 (Moderate): eGFR 30-59; 4 (Severe): eGFR <30.

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

Scatter plots of eGFR (eGFRcr or eGFRcys) 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]) will also be presented.

5.6.3.1.1.2. Proximal Renal Tubular Function

Proteinuria by Quantitative Assessment

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

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

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

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

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

Proteinuria by Urinalysis (Dipstick)

Treatment-emergent proteinuria by urinalysis (dipstick) over time will be summarized by study panel. 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 study panel and visit using descriptive statistics.

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

The number and proportion of participants with RBP 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 study panel and visit using descriptive statistics.

FEPO4 will be calculated as follows:

- Based on unadjusted serum creatinine:

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

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

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

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

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 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 any 2 out of the 4 renal parameters (serum creatinine + 1 or more of the 3 other markers of tubular dysfunction).

5.6.3.2. Vital Signs and Physical Examination Findings

The following parameters measurements will be analyzed:

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

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

An assessment is Treatment Emergent (TE) 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 phase, including unscheduled assessments. In case the same subject 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 study phase.

A cross-tabulation of the worst abnormalities versus baseline per parameter and study 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 study 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) will be provided. Additional vital signs assessments corresponding to the rash eCRF pages will be only listed as applicable.

The physical examination findings and abnormalities will be listed.

5.6.3.3. 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 following ECG parameters measurements will be analyzed:

- PR interval (ms)
- Heart Rate (bpm)
- QT interval (ms)

- QRS duration (ms)
- QTc Corrected (Fridericia's formula QTcF)

Fridericia's formula: QTcF (msec) = QT (msec) / (RR (msec)/1000)$^{1/3}$; if RR is missing, use QT (msec) * (HR(bpm)/60)$^{1/3}$;The abnormalities in ECG parameters will be determined according to the criteria specified in the Cardiovascular Safety – Abnormalities Table (see Clinical Protocol Appendix 7, Cardiovascular Safety- Abnormalities Table). Abnormalities on actual values are provided for HR, PR, QRS and QTcF. Additional abnormalities on change from baseline will be provided for QTcF. No abnormalities will be defined for actual uncorrected QT values. Uncorrected QT ≥ 500 ms will be flagged and only shown in listings.

An assessment is TE 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 TE 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 TE.

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 phase, including unscheduled assessments. In case the same subject has both abnormalities (low and high) for the same test within the same phase, the participant will be counted in the analysis for both abnormality directions (abnormally high and low).

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

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

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

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

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

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

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

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

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

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.

5.7. Other Analyses

5.7.1. Pharmacokinetics

Two types of plasma PK analyses will be conducted, including noncompartmental analysis in the PK sub-study participants (Section 5.3.2.2) and population PK analysis in all participants. Details of the plasma PK analyses will be described in a separate analysis plan and results will be reported separately.

5.7.2. Pharmacokinetic/Pharmacodynamic Relationships

Relationships of plasma PK parameters for JNJ-73763989 (JNJ-73763976 and JNJ-73763924), and optionally of JNJ-56136379, NA, and PegIFN-α2a, with selected efficacy and with selected safety endpoints will be evaluated and graphically displayed, if applicable.

Modeling of key pharmacodynamic parameters (e.g., HDV RNA, HBsAg) may be performed using population pharmacokinetics/pharmacodynamics (PK/PD). Details will be described in a population PK/PD analysis plan and results of the PK/PD analysis will be presented in a separate report.

5.7.3. 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.

5.7.4. Definition of Subgroups

Table 6: List of Subgroups of Interest for Efficacy and/or Safety Purpose

Subgroup	Purpose	Definition
Sex	Efficacy, Safety	Male, Female
Age Group	Efficacy, Safety	≤ 45 years, > 45 years
Race	Efficacy, Safety	Asian, Non-Asian
Type of NA at Baseline	Efficacy, Safety	TD, TAF, ETV
Received PegIFN-α2a	Safety	Yes, No
HBV baseline status	Safety	Not currently treated HBeAg positive, Virologically suppressed HBeAg negative*
Has never received HBV treatment (only for participants currently not treated)	Efficacy	Yes, No
Baseline cccDNA levels (log_{10} copies/10^6 cells)	Efficacy	Threshold for binary categories will be decided based on the baseline distribution
Baseline pgRNA levels (log_{10} copies/ cell)	Efficacy	Threshold for binary categories will be decided based on the baseline distribution
Baseline pgRNA/cccDNA ratio	Efficacy	Threshold for binary categories will be decided based on the baseline distribution

*The analysis by this subgroup will not be performed by panel.

This list of subgroups may be modified based on interim/final results and clinical interest.

5.8. Interim Analyses

Two Interim Analyses (IA) may be performed: when all participants have completed Week 20 in the study intervention phase (or discontinued earlier) and when they have completed Week 72 (FU Week 24) in the follow-up phase (or discontinued earlier). These IAs will be performed by the sponsor to support interactions with health authorities, as well as to support internal decisions about additional studies and/or investigation of other combination regimens.

Both primary (when all participants have completed Week 48 or discontinued earlier) and interim analyses will be based on all data available at the predefined cut-off time points and may include data at later time points for those participants who have reached subsequent visits.

The final analysis will be performed when all participants have completed the last study visit (Follow-up Week 48) or discontinued earlier.

The overview of data domains and specific endpoints that will be provided for each analysis is presented in Table 7.

Table 7: Overview of Times of Data Summaries and Analyses at Planned Interim, Primary and Final Analyses

	IA1 when all participants have completed Week 20	Primary Analysis when all participants have completed Week 48	IA2 when all participants have completed FU Week 24	Final Analysis when all participants have completed FU Week 48
DATA DOMAINS FOR ANALYSIS				
Subject Information				
Baseline & Demographic characteristics	X	X	X	X
Disposition and Study Populations	X	X	X	X
Extent of Exposure	X	X	X	X
Safety				
TEAEs, SAEs, AE of interest, fatal AEs, AEs causing treatment discontinuation	X	X	X	X
Laboratory Tests	X	X	X	X
ECG	X	X	X	X
Vital signs	X	X	X	X
Efficacy				
Primary efficacy endpoints		X	X	X
Secondary efficacy endpoints	X	X	X	X
Exploratory Endpoints	X	X	X	X
PK		X	X*	X*
Virologic breakthrough HBV	X	X	X	X
Flares: Viral, Biochemical, Clinical	X	X	X	X
Viral Genome Sequence Analysis		X	X	X

* If new data are available.

No DMC or Data Review Committee (DRC) is required for this study.

An Independent Flare Expert Panel (IFLEP) is appointed for this study to monitor ALT flares and make recommendations regarding flare management based on analysis of aggregate data. The IFLEP is composed of 3 independent medical experts with experience and expertise in hepatitis B and its treatment.

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

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATC	anatomic and therapeutic class
AUC	area under the curve
BMI	body mass index
BSA	body surface area
CHB	chronic hepatitis B
CI	confidence interval
CL	total systemic clearance
Cmax	maximum concentration
CRF	case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DMC	Data Monitoring Committee
DPS	Data Presentation Specifications
ECG	electrocardiogram
eCRF	electronic case report form
ETV	entecavir
F (%)	absolute SC bioavailability
FAS	full analysis set
FDA	Food and Drug Administration
HBcrAg	hepatitis B core-related antigen
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
ICH	International Conference on Harmonisation
ITT	intent-to-treat
IQ	interquartile
IVRS	interactive voice response system
IWRS	interactive web response system
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimum required dilution
NA	nucleos(t)ide analogs
NAb	neutralizing antibodies
PD	pharmacodynamic(s)
PegIFN-α2a	pegylated interferon alpha-2a
PI	principal investigator
PK	pharmacokinetic(s)
PP	per protocol
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SMQs	standardised MedDRA queries
TEAE	treatment-emergent adverse event
Tmax	time to maximum concentration
US NCI	United States National Cancer Institute
V	volume distribution
Vz	volume of distribution based on terminal phase
Vz/F	apparent volume of distribution based on terminal phase after extravascular administration

WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2 Changes to Protocol-Planned Analyses

No change from protocol-planned analyses.

6.3. Appendix 3 Demographics and Baseline Characteristics

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

6.3.1. Demographics

Table 8 presents a list of the demographic variables that will be summarized by study panel and overall for the ITT.

Table 8: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
Weight at baseline (kg)	
Height at baseline (cm)	
Body Mass Index (BMI) (kg/m^2)	
Number of drinks containing alcohol (weekly period)	
Type of substance (beer, wine, distilled spirits) duration in months derived as = (stop date – start date +1)/30.4375; rounded to 1 decimal	
Categorical Variables	
Age ([18 years - ≤ 30 years, > 30 years -≤ 45 years, > 45 years-≤ 60 years, > 60 years])	Frequency distribution with the number and percentage of participants in each category.
Sex (male, female, undifferentiated)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
BMI ([underweight <18.5 kg/m^2, normal 18.5-<25 kg/m^2, overweight 25-<30 kg/m2, obese >=30 kg/m^2])	
History of tobacco use (Yes, No)	
Type of substance use (beer, wine, distilled spirits) : current, former, never	

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

6.3.2. Baseline Characteristics

Table 9 presents a list of the baseline characteristics variables that will be summarized by study panel and overall for the ITT and Safety analysis set (only if ITT and Safety Analysis sets are different).

Table 9: Baseline Characteristics Variables

Continuous Variables	**Summary Type**
HBV history	
Duration of infection (years) = (treatment start date – date of HBV infection +1)/365.25; rounded to 1 decimal	
Time since HBV diagnosis (Years) = (treatment start date – date of HBV diagnosis+1)/365.25; rounded to 1 decimal	
Duration of NA at baseline (years)	

Table 9: Baseline Characteristics Variables

Continuous Variables	**Summary Type**
HBV viral activity and serology parameters	Descriptive statistics (N, mean, standard error [SE], standard deviation [SD], median and range [minimum and maximum], and IQ range).
HBeAg at baseline in IU/mL and log10 IU/mL (for HBeAg positive participants only at study entry)	
HBsAg at baseline in IU/mL and log10 IU/mL	
HBV DNA at baseline in IU/mL and log10 IU/mL	
HBV RNA at baseline: values in copies/mL and log10 copies/mL	
HBcrAg at baseline in log U/mL	
HBsAg Antibody (Anti-HBs) at baseline in mIU/mL and log10 mIU/mL	
Fibrosis score	
HBV intrahepatic viral parameters	
HBsAg (copy / cell)	
Proportion of HBsAg+ hepatocytes at baseline, derived as number of HBsAg+ hepatocytes * 100 / total number of evaluated hepatocytes	
cccDNA levels (copies/ 10^6 cells)	
Proportion of cccDNA-positive hepatocytes, derived as number of cccDNA-positive hepatocytes * 100 / total number of evaluated hepatocytes	
pgRNA levels (log10 copies / cell)	
Proportion of pgRNA-positive hepatocytes, derived as number of pgRNA-positive hepatocytes * 100 / total number of evaluated hepatocytes	
pgRNA/cccDNA ratio (transcriptional activity)	
Proportion of silent infected hepatocytes	
RNA levels (copies / cell)	
Proportion of immune cells at baseline	
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	
Treatment history: not currently treated, virologically suppressed	
History of IFN-alpha : Yes, No	
History of Lamivudine, Telbivudine, Adefovir : Yes, No	
Has never received HBV treatment (only for currently not treated participants): Yes, No	
Type of NA at study entry (only for virologically suppressed participants): TD, TAF, ETV	
HBV viral activity and serology parameters	
HBeAg status at study entry: positive, negative	
HBsAg category at baseline (IU/mL): < 500, < 1,000, < 10,000, ≥ 10,000	

Table 9: Baseline Characteristics Variables

Continuous Variables	Summary Type
HBV DNA category at baseline (IU/mL): < LLOQ Target detected (TD) or not detected (TND), < LLOQ TD, < LLOQ TND, < 60, < 2,000, < 20,000, < 100,000, ≥ 100,000	
HBV RNA category at baseline (copies/mL): TND, < Limit of Detection (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 at baseline: Positive, Negative	
Baseline ALT toxicity grade according to DAIDS	
Baseline ALT categorization: ≤ 1.0xULN, > 1.0xULN to <2.5xULN, ≥ 2.5x	
Stage of liver fibrosis: F0, F1, F2	

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 by study panel for the ITT. A listing of the major protocol deviations will be also presented.

A subset of major protocol deviations that may affect the assessment of efficacy (see list in Attachment 2) will be identified and finalized prior to database lock to define the Per-Protocol analysis set (see Section 4). The number and percentage of ITT participants who are included in the PP analysis set will be summarized by study panel, accompanied by number and percentage of ITT participants who are excluded from the PP analysis set with the incidence of the major protocol deviations.

6.5. Appendix 5 Prior and Concomitant Medications

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

Summaries of concomitant medications will be presented by ATC class 2, level 4 and preferred term, study phase, study panel, 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 study panel and overall; as well 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 by study panel and overall.

6.7. Appendix 7 Intervention Compliance

Compliance will be summarized descriptively on the Safety Set for each study treatment except NA.

Treatment compliance (%) is defined as follows:

For JNJ-3989: Total number of injections received / 12 * 100%

For JNJ-6379: Total medication intake / (4 * 7 * X) * 100%, where:

- Total medication intake = Total number of tablets dispensed – Total number of tablets returned.
- X = Number of weeks on 6379 (end date of JNJ-6379 – start date of JNJ-6379) for each participant. Note that 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), so the denominator is 4*7*X.

For PegIFN-α2a: Total number of injections received / Total number of injections supposed to receive * 100%

6.8. Appendix 8 Adverse Events of Special Interest

Adverse events of special interest are defined as follows:

AE Special Interest Category	Preferred Term
AST/ALT elevations	ALANINE AMINOTRANSFERASE ABNORMAL
	ALANINE AMINOTRANSFERASE INCREASED
	ASPARTATE AMINOTRANSFERASE ABNORMAL
	ASPARTATE AMINOTRANSFERASE INCREASED
	HEPATIC ENZYME ABNORMAL
	HEPATIC ENZYME INCREASED
	HEPATIC FUNCTION ABNORMAL
	HYPERTRANSAMINASAEMIA
	LIVER FUNCTION TEST ABNORMAL
	LIVER FUNCTION TEST INCREASED
	TRANSAMINASES ABNORMAL
	TRANSAMINASES INCREASED
Renal complications	ACUTE 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
	RENAL TUBULAR INJURY
	RENAL TUBULAR NECROSIS
	URINE OUTPUT DECREASED
	NEPHROPATHY
	NEPHROPATHY TOXIC
	GLOMERULONEPHROPATHY
	NEPHROLITHIASIS
Hematologic Abnormalities	APLASTIC ANAEMIA
	AUTOIMMUNE APLASTIC ANAEMIA
	BICYTOPENIA

AE Special Interest Category	Preferred Term
	BONE MARROW FAILURE
	CYTOPENIA
	FEBRILE BONE MARROW APLASIA
	FULL BLOOD COUNT DECREASED
	GELATINOUS TRANSFORMATION OF THE BONE MARROW
	IMMUNE-MEDIATED PANCYTOPENIA
	PANCYTOPENIA
	PANMYELOPATHY
	ASPIRATION BONE MARROW ABNORMAL
	BIOPSY BONE MARROW ABNORMAL
	BLOOD 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
	APLASIA PURE RED CELL
	APLASTIC ANAEMIA
	ERYTHROBLAST COUNT DECREASED
	ERYTHROID MATURATION ARREST
	ERYTHROPENIA
	HYPOPLASTIC ANAEMIA
	MICROCYTIC ANAEMIA
	PROERYTHROBLAST COUNT DECREASED
	RED BLOOD CELL COUNT DECREASED
	RETICULOCYTE COUNT DECREASED
	RETICULOCYTOPENIA
	ANAEMIA
	ERYTHROBLAST COUNT ABNORMAL
	ERYTHROPOIESIS ABNORMAL
	HAEMATOCRIT ABNORMAL
	HAEMATOCRIT DECREASED
	HAEMOGLOBIN ABNORMAL
	HAEMOGLOBIN DECREASED
	LEUKOERYTHROBLASTIC ANAEMIA
	NORMOCHROMIC ANAEMIA
	NORMOCHROMIC NORMOCYTIC ANAEMIA
	NORMOCYTIC ANAEMIA
	PROERYTHROBLAST COUNT ABNORMAL
	RED BLOOD CELL COUNT ABNORMAL
	RETICULOCYTE COUNT ABNORMAL

AE Special Interest Category	Preferred Term
	RETICULOCYTE PERCENTAGE DECREASED
	AGRANULOCYTOSIS
	BAND NEUTROPHIL COUNT DECREASED
	BAND NEUTROPHIL PERCENTAGE DECREASED
	BASOPHIL COUNT DECREASED
	BASOPHILOPENIA
	B-LYMPHOCYTE COUNT DECREASED
	CYCLIC NEUTROPENIA
	EOSINOPENIA
	EOSINOPHIL COUNT DECREASED
	FEBRILE NEUTROPENIA
	GRANULOCYTE COUNT DECREASED
	GRANULOCYTES MATURATION ARREST
	GRANULOCYTOPENIA
	IDIOPATHIC NEUTROPENIA
	LEUKOPENIA
	LYMPHOCYTE COUNT DECREASED
	LYMPHOPENIA
	METAMYELOCYTE COUNT DECREASED
	MONOBLAST COUNT DECREASED
	MONOCYTE COUNT DECREASED
	MONOCYTOPENIA
	MYELOBLAST COUNT DECREASED
	MYELOCYTE COUNT DECREASED
	NEUTROPENIA
	NEUTROPENIC INFECTION
	NEUTROPENIC SEPSIS
	NEUTROPHIL COUNT DECREASED
	PROMYELOCYTE COUNT DECREASED
	PURE WHITE CELL APLASIA
	T-LYMPHOCYTE COUNT DECREASED
	WHITE BLOOD CELL COUNT DECREASED
	BASOPHIL COUNT ABNORMAL
	BASOPHIL PERCENTAGE DECREASED
	B-LYMPHOCYTE ABNORMALITIES
	B-LYMPHOCYTE COUNT ABNORMAL
	DIFFERENTIAL WHITE BLOOD CELL COUNT ABNORMAL
	EOSINOPHIL COUNT ABNORMAL
	EOSINOPHIL PERCENTAGE DECREASED
	FULL BLOOD COUNT ABNORMAL
	GRANULOCYTES ABNORMAL
	LEUKOPENIA NEONATAL
	LYMPHOCYTE COUNT ABNORMAL
	LYMPHOCYTE PERCENTAGE ABNORMAL
	LYMPHOCYTE PERCENTAGE DECREASED
	MONOCYTE COUNT ABNORMAL
	MONOCYTE PERCENTAGE DECREASED

AE Special Interest Category	Preferred Term
	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
	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
Cholesterol Increase	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

AE Special Interest Category	Preferred Term
	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
	VERY LOW DENSITY LIPOPROTEIN DECREASED
	VERY LOW DENSITY LIPOPROTEIN INCREASED

6.9. Appendix 9 Laboratory Toxicity Grading

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

ATTACHMENT 1. SIMULATIONS FOR SAMPLE SIZE JUSTIFICATION

We conducted a simulation study to assess the expected precision in our estimates of the primary efficacy endpoint if we achieve the target sample size of 24 participants across Panels 1 and 2, and further how the precision would decrease with only 20 or 16 participants.

Assumptions of the Data-Generating Model

We simulated data according to the binomial mixed model as specified in Sections 5.3.1.2.2.1 and 5.3.1.2.2.2. We used the logit model specified in Section 5.3.1.2.2.2 to allow for between-panel differences in the intercept (baseline estimate) and slope (change from baseline):

$$\text{logit}(p_{ij}) = \underbrace{[\alpha + \delta_\alpha I(\text{panel}_i = 1) + \xi_i]}_{\text{intercept}} + \underbrace{[\beta + \delta_\beta I(\text{panel}_i = 1) + \gamma_i]}_{\text{slope}}\, j$$

where p_{ij} is the probability of a hepatocyte being HBsAg+ for subject i at visit j.

Datasets were simulated with either 16, 20, or 24 subjects (split between two equal-sized panels), and where we varied two aspects of the data:

1) The true proportions of HBsAg+ hepatocytes for each panel at each time point. These are specified indirectly by setting the values of α, δ_α, β, and δ_β. See Table 10 for the list of scenarios. Generally, the true proportions at baseline were assumed to be higher in Panel 1 than in Panel 2 because Panel 1 subjects are untreated at baseline.
2) The true inter-subject variability of the slope, SD_{slope}, where $\gamma_i \sim N(0, SD_{slope})$. For each scenario listed in Table 10, we examined the effect of setting SD_{slope} to 0.5, 1.0, or 2.0.

Table 10: List of scenarios for assumptions on the true proportion of HBsAg+ hepatocytes for each panel at each time point

Scenario ID	Group	% HBsAg+ hepatocytes		Reduction from baseline		Between-panel (1-2) difference in reduction from baseline	
		Baseline	Week 40	Absolute	Relative	Absolute	Relative
A	Panel 1	**75%**	**5%**	70%	93.3%	41%	-3.3%
	Panel 2	**30%**	**1%**	29%	96.7%		
	Overall	52.5%	3%	49.5%	94.3%		
B	Panel 1	**75%**	**5%**	70%	93.3%	50%	26.7%
	Panel 2	**30%**	**10%**	20%	66.7%		
	Overall	52.5%	7.5%	45%	85.7%		
C	Panel 1	**60%**	**20%**	40%	66.7%	20%	0%
	Panel 2	**30%**	**10%**	20%	66.7%		
	Overall	45%	15%	30%	66.7%		

Within each scenario, we set the percent of HBsAg+ hepatocytes at baseline and Week 40 for both Panels 1 and 2. From these four numbers (highlighted in **bold**), the remaining numbers in the table are derived. Data were simulated for each scenario using various sample sizes (assuming an equal number of subjects in each panel) and various values of SD_{slope} (standard deviation for the inter-subject random slope).

The true inter-subject variability of the intercept, $SD_{intercept}$, where $\xi_i \sim N(0, SD_{intercept})$, was set to 1.0 across all simulations based on the inter-subject differences observed from the donors data. In contrast, inter-subject differences in the slopes are unknown, so a range of values of SD_{slope} were considered.

The number of HBsAg+ hepatocytes for subject i at visit j, denoted Y_{ij}, was simulated as $Y_{ij} \sim \text{Binomial}(N_{ij}, p_{ij})$, where N_{ij} is the total number of hepatocytes sampled during a biopsy. Based on the donors data, we simulated $\log(N_{i0}) \sim N(10, 0.35)$ for the baseline biopsy, and then $\log(N_{i1}) \sim N(\log(N_{i0}), 0.1)$ for the Week 40 biopsy; values of N_{i0} and N_{i1} were then rounded to integers.

Statistical Analysis of the Simulated Data

For each simulated dataset, we fit both the overall model as specified in Section 5.3.1.2.2.1 and the between-panel model as specified in Section 5.3.1.2.2.2. From the overall model, we estimated the absolute and relative reductions from baseline in the overall proportion of HBsAg+ hepatocytes. From the between-panel model, we estimated the between-panel differences in the reductions. For each estimate we obtained an 80% confidence interval (CI). Note that, for ease of interpretation, we present the changes from baseline as "reductions" – simply the negative of changes – so that most of the reported numbers are positive. I.e., a change from 75% to 5% is reported as an absolute reduction of 70% rather than as an absolute change of -70%.

We averaged all the estimates across 1000 simulations. The primary metric of interest is the width of the 80% CIs, which tell us how precisely we can estimate the reductions of interest given the sample size and the assumptions of the data-generating model.

Simulation Results

The 80% CI widths are presented in Figure 3 and again, together with point estimates and 80% CI limits, in Table 11. Generally, we see little bias in the point estimates – the average estimated reductions and differences in reductions in Table 11 match well with the scenario assumptions in Table 10. This is as expected, as binomial mixed models were used to both simulate the data and carry out the estimation.

The precision of the estimates are of course greater – meaning narrower CIs – with 12 patients per panel than with either 8 or 10 patients. However, the loss in precision with fewer patients is not large in the simulated scenarios, as shown in Figure 3. E.g., in Scenario A with SD_{slope} = 1.0, as the sample size per panel increases from 8 to 12 the width of the 80% CI decreases from 20.3% to 16.7% for the overall absolute reduction from baseline; and from 21.8% to 18.1% for the between-panel difference in the absolute reduction.

For the overall absolute reduction (OAR) from baseline, varying the value of SD_{slope} has minimal impact on the CI widths. Across Scenarios A, B, and C, the CI widths vary from roughly 8% to 17% with 12 patients per panel and from 10% to 21% with 8 patients per panel. Generally, the CI widths appear to be larger when the true OAR is larger.

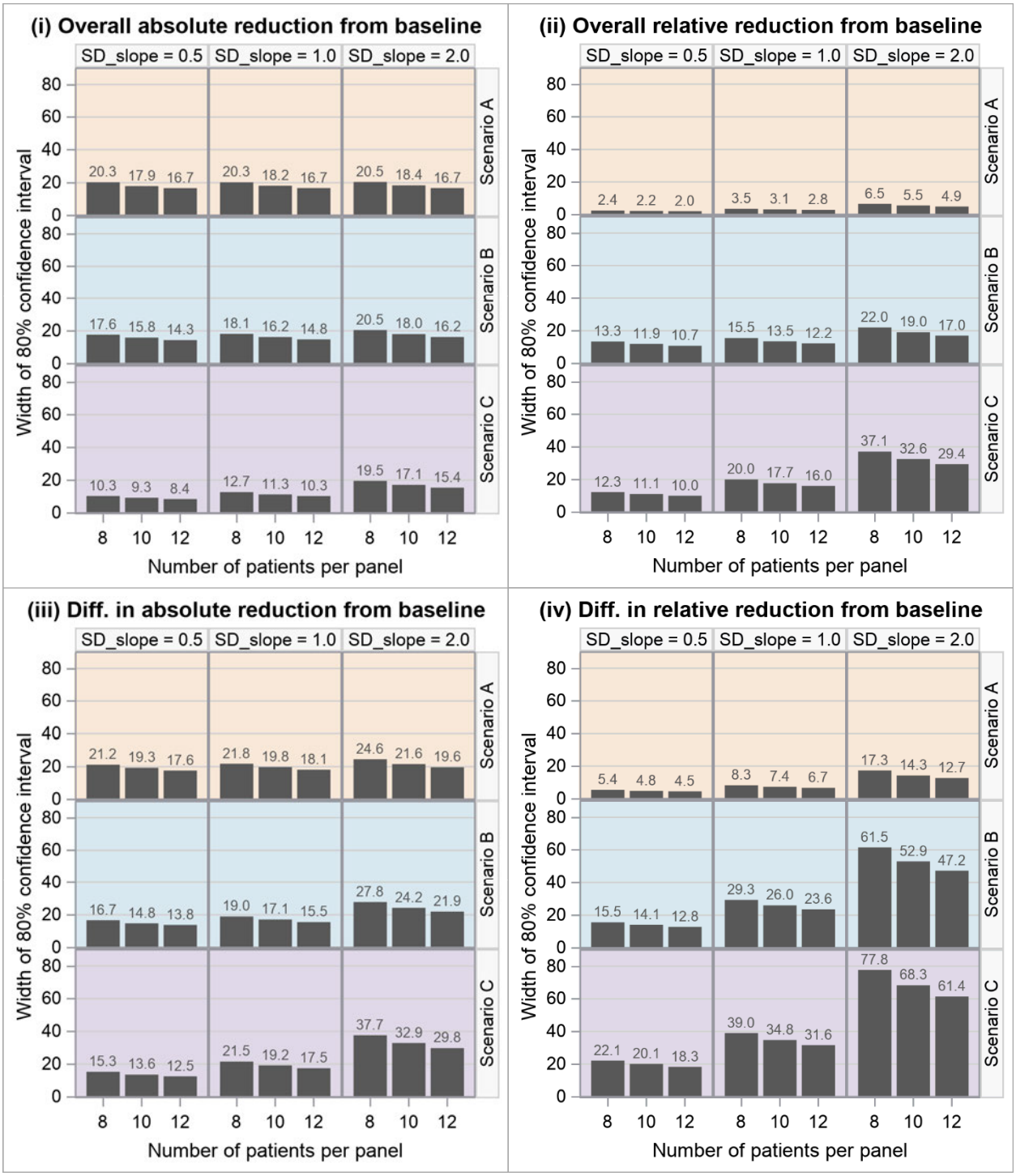
For the overall relative reduction (ORR) from baseline, both the value of SD_{slope} and the scenario assumptions (A, B, or C) have large impacts on the CI widths. In Scenario A the precision was excellent regardless of the value of SD_{slope}, but in Scenario C the precision is both worse and highly dependent on the value of SD_{slope}. In contrast with the OAR, the CI widths for the estimated ORR appear to be larger when the true ORR is smaller.

The general pattern of CI widths observed for the OAR and ORR hold as well for the between-panel difference in absolute reduction (DAR) and relative reduction (DRR). That this, the CI widths for the DAR do not vary much by SD_{slope}, but are larger when the within-panel absolute reductions (which the model must estimate for each panel in order to estimate the between-panel DAR) are larger. For the DRR, the CI widths vary both by SD_{slope} and scenario, with larger widths when the within-panel relative reductions are smaller. The CI widths for the DAR and DRR are of course larger than for the OAR and ORR – the model for between-panel differences has more parameters to estimate and, from another perspective, the DAR is essentially the difference between two OARs, and so the imprecision of the two OARs combine and propagate to the DAR (and analogously for the DRR as the difference of two ORRs).

Conclusions and Recommendations

The gains in precision as the sample size per panel increases from 8 to 12 are not large – the bigger factors are the true effect sizes and the between-patient variability, both of which are beyond our control. Yet we recommend maintaining the current target of 12 patients per panel (for Panels 1 and 2) both to gain as much precision as is feasible and to allow for the likelihood of incomplete data due to patient dropout. Assuming 20% dropout, we would have only 9-10 patients per panel with usable data for the primary analysis. With this sample size, we may still achieve adequate precision for the overall reduction from baseline, whether absolute or relative. For the between-panel differences, however, we have less confidence in achieving adequate precision regardless of the sample size we choose.

Figure 3: Simulation-based estimated widths of 80% confidence intervals for the (i and ii) overall and (iii and iv) between-panel analyses of the reduction in proportion of positive hepatocytes



The widths of the 80% CIs were obtained by averaging the estimates across 1000 simulations. The true proportions of HBsAg+ hepatocytes at baseline → Week 40 in each scenario were:

Scenario A: 75% → 5% for Panel 1 and 30%→ 1% for Panel 2
Scenario B: 75% → 5% for Panel 1 and 30%→10% for Panel 2
Scenario C: 60% → 20% for Panel 1 and 30%→10% for Panel 2

Table 11: Simulation-based estimates for the overall and between-panel analyses of the reduction in proportion of positive hepatocytes

Scenario ID	SD_{slope}	Sample size per panel	Overall reduction from baseline (80% CI) [width of 80% CI]		Between-panel (1-2) difference in reduction from baseline (80% CI) [width of 80% CI]	
			Absolute (%)	Relative (%)	Absolute (%)	Relative (%)
A	0.5	8	50.6 (40.5,60.8) [20.3]	95.7 (94.5,97.0) [2.4]	39.4 (28.8,50.0) [21.2]	-3.5 (-6.2,-0.8) [5.4]
		10	50.7 (41.8,59.7) [17.9]	95.7 (94.6,96.8) [2.2]	39.2 (29.6,48.9) [19.3]	-3.4 (-5.8,-1.0) [4.8]
		12	50.8 (42.5,59.1) [16.7]	95.7 (94.7,96.7) [2.0]	40.4 (31.5,49.2) [17.6]	-3.5 (-5.8,-1.3) [4.5]
	1.0	8	50.7 (40.6,60.8) [20.3]	95.6 (93.8,97.3) [3.5]	39.1 (28.2,50.0) [21.8]	-3.6 (-7.7,0.5) [8.3]
		10	50.4 (41.3,59.5) [18.2]	95.6 (94.1,97.2) [3.1]	39.3 (29.4,49.2) [19.8]	-3.5 (-7.1,0.2) [7.4]
		12	50.9 (42.5,59.3) [16.7]	95.7 (94.3,97.1) [2.8]	40.2 (31.1,49.2) [18.1]	-3.6 (-6.9,-0.3) [6.7]
	2.0	8	50.4 (40.2,60.6) [20.5]	95.1 (91.9,98.4) [6.5]	38.4 (26.1,50.7) [24.6]	-4.2 (-12.9,4.4) [17.3]
		10	50.3 (41.2,59.5) [18.4]	95.4 (92.6,98.1) [5.5]	39.6 (28.8,50.4) [21.6]	-3.7 (-10.8,3.5) [14.3]
		12	50.8 (42.5,59.2) [16.7]	95.5 (93.0,98.0) [4.9]	39.7 (29.9,49.6) [19.6]	-3.8 (-10.1,2.6) [12.7]
B	0.5	8	45.7 (36.9,54.5) [17.6]	86.4 (79.8,93.1) [13.3]	49.1 (40.7,57.4) [16.7]	27.0 (19.2,34.8) [15.5]
		10	45.7 (37.8,53.6) [15.8]	86.5 (80.5,92.4) [11.9]	49.8 (42.5,57.2) [14.8]	26.9 (19.9,34.0) [14.1]
		12	45.8 (38.6,52.9) [14.3]	86.5 (81.2,91.9) [10.7]	49.4 (42.5,56.3) [13.8]	27.0 (20.6,33.4) [12.8]
	1.0	8	45.6 (36.5,54.7) [18.1]	86.0 (78.3,93.7) [15.5]	49.4 (39.9,58.9) [19.0]	28.0 (13.3,42.7) [29.3]
		10	45.6 (37.5,53.7) [16.2]	86.3 (79.6,93.1) [13.5]	49.3 (40.8,57.9) [17.1]	27.6 (14.6,40.6) [26.0]
		12	45.7 (38.3,53.1) [14.8]	86.4 (80.3,92.5) [12.2]	49.6 (41.9,57.4) [15.5]	27.3 (15.6,39.1) [23.6]
	2.0	8	44.7 (34.5,55.0) [20.5]	85.1 (74.1,96.1) [22.0]	50.0 (36.1,63.9) [27.8]	31.7 (1.0,62.5) [61.5]
		10	45.2 (36.2,54.2) [18.0]	85.5 (76.0,95.0) [19.0]	49.5 (37.4,61.6) [24.2]	29.6 (3.1,56.1) [52.9]
		12	45.8 (37.6,53.9) [16.2]	85.9 (77.4,94.4) [17.0]	49.4 (38.4,60.4) [21.9]	28.9 (5.3,52.5) [47.2]
C	0.5	8	29.9 (24.8,35.1) [10.3]	67.6 (61.5,73.8) [12.3]	19.0 (11.4,26.7) [15.3]	0.1 (-11.0,11.1) [22.1]
		10	29.9 (25.3,34.6) [9.3]	67.6 (62.1,73.1) [11.1]	19.7 (12.9,26.5) [13.6]	-0.2 (-10.2,9.9) [20.1]
		12	30.0 (25.8,34.2) [8.4]	67.7 (62.7,72.8) [10.0]	19.5 (13.3,25.8) [12.5]	0.1 (-9.0,9.3) [18.3]
	1.0	8	29.7 (23.3,36.0) [12.7]	66.8 (56.8,76.8) [20.0]	19.0 (8.2,29.7) [21.5]	0.4 (-19.1,19.9) [39.0]
		10	29.9 (24.2,35.5) [11.3]	67.4 (58.5,76.2) [17.7]	19.1 (9.5,28.7) [19.2]	0.6 (-16.8,18.0) [34.8]
		12	29.9 (24.7,35.0) [10.3]	67.5 (59.4,75.5) [16.0]	19.4 (10.7,28.2) [17.5]	-0.3 (-16.1,15.5) [31.6]
	2.0	8	28.8 (19.1,38.6) [19.5]	65.3 (46.7,83.8) [37.1]	18.2 (-0.6,37.1) [37.7]	1.5 (-37.3,40.4) [77.8]
		10	29.4 (20.8,37.9) [17.1]	66.2 (49.9,82.5) [32.6]	19.1 (2.6,35.5) [32.9]	1.4 (-32.8,35.5) [68.3]
		12	29.7 (22.0,37.4) [15.4]	67.0 (52.3,81.7) [29.4]	19.3 (4.4,34.2) [29.8]	1.6 (-29.1,32.3) [61.4]

Each point estimate, along with the width of its 80% CI, was obtained by averaging the estimates across 1000 simulations. The true proportions of HBsAg+ hepatocytes at baseline → Week 40 in each scenario were:
Scenario A: 75% → 5% for Panel 1 and 30%→ 1% for Panel 2
Scenario B: 75% → 5% for Panel 1 and 30%→10% for Panel 2
Scenario C: 60% → 20% for Panel 1 and 30%→10% for Panel 2

ATTACHMENT 2. SELECTED MAJOR PROTOCOL DEVIATIONS FOR ANALYSIS PURPOSES

The major protocol deviations that may affect the assessment of efficacy will be finalized prior to the primary analysis database lock. The major deviations that are selected to exclude participants from the PP set are listed below.

Sequence No.	Protocol Deviation Description (DVTERM)	Protocol Deviation Coded Term (DVDECOD)	Exclude from PP
1	Inclusion criterion 3 not met: Participant had not confirmed chronic HBV infection. In addition, chronicity was not documented at least 6 months prior to screening.	Entered but did not satisfy criteria	Yes
2	Inclusion criterion 4 not met: For Panel 1 Participant not currently treated including treatment naïve participants was not: a. HBeAg positive, AND b. with serum HBV DNA at screening ≥20,000 IU/mL, AND c. with ALT levels at screening <10x ULN, AND d. with indication for NA treatment according to local standard practice	Entered but did not satisfy criteria	Yes
3	Inclusion criterion 4.1 not met: For Panel 3 Participant not currently treated was not: a. HBeAg positive AND with serum HBV DNA at screening ≥20,000 IU/mL OR HBeAg negative AND with serum HBV DNA at screening ≥2,000 IU/mL, AND b. with ALT levels at screening <10x ULN, AND c. with indication for NA treatment according to local standard practice	Entered but did not satisfy criteria	Yes
4	Inclusion criterion 5 not met: For Panel 2 Virologically suppressed participant was not: a. HBeAg negative b. on stable HBV treatment, defined as currently receiving NA treatment (ETV, tenofovir disoproxil, or TAF) for at least 6 months prior to screening and have been on the same NA treatment regimen (at the same dose) for at least 3 months at the time of screening, AND c. with serum HBV DNA <60 IU/mL on 2 measurements at least 3 months apart (one of which is at screening), AND d. with documented ALT values <2.0x ULN on 2 measurements at least 3 months apart (one of which is at screening).	Entered but did not satisfy criteria	Yes
5	Inclusion criterion 5.1 not met: For Panel 3 Patients HBeAg negative or HBeAg positive Virologically suppressed participant not a. on stable HBV treatment, defined as currently receiving NA treatment (ETV, tenofovir disoproxil, or TAF) for at least 6 months prior to screening and have been on the same NA treatment regimen (at the same dose) for at least 3 months at the time of screening, AND b. with serum HBV DNA <60 IU/mL on 2 measurements at least 3 months apart (one of which is at screening), AND c. with documented ALT values <2.0x ULN on 2 measurements at least 3 months apart (one of which is at screening).	Entered but did not satisfy criteria	Yes
6	Inclusion Criterion 6 not met: Participant has HBsAg ≤100 IU/mL at screening.	Entered but did not satisfy criteria	Yes
7	Inclusion Criterion 8 not met: Participant did not have fibroscan liver stiffness measurement ≤9.0 kPa within 6 months prior to screening or at the time of screening. Note: Other radiologic liver staging modalities (eg, acoustic radiation force impulse) might be used if standard practice at the site or if otherwise validated and agreed with the sponsor. Results should be equivalent to Metavir F0-F2 with absence of signs of portal hypertension.	Entered but did not satisfy criteria	Yes
8	Exclusion Criterion 1.2 met: Participant had evidence of hepatitis A virus (hepatitis A antibody IgM), HCV infection (HCV antibody), hepatitis D virus (HDV) infection (HDV antibody),	Entered but did not satisfy criteria	Yes

Sequence No.	Protocol Deviation Description (DVTERM)	Protocol Deviation Coded Term (DVDECOD)	Exclude from PP
	or hepatitis E virus (HEV) infection (HEV antibody IgM), or HIV-1 or HIV-2 infection (confirmed by antibodies) at screening. Note: Participants with a positive HCV antibody test can be enrolled if they have negative HCV RNA at screening and documented negative HCV RNA at least 6 months prior to screening. Note: Participants with a positive HDV antibody test may be enrolled after discussion with the sponsor if an active HDV co-infection can be ruled out by documentation of negative HDV RNA. Note: Participants with a positive IgM antibody test for HEV infection may be enrolled after discussion with the sponsor if an active HEV infection can be ruled out by documentation of negative anti-HEV IgG. Note: Participants with a positive HIV-1 or HIV-2 antibody/antigen test at screening should have a confirmatory HIV RNA test, to rule out false positive results. They can be enrolled if they have a negative HIV RNA test at screening. Participants with evidence of HIV-1 or HIV-2 infection who are on antiretroviral treatment are excluded.		
9	Exclusion Criterion 2 met: Participant had any of the following laboratory abnormalities within 12 months prior to screening or at the time of screening: a. Total bilirubin >1.5x ULN, OR b. Direct bilirubin >1.2x ULN, OR c. Serum albumin <3 2 g/dL	Entered but did not satisfy criteria	Yes
10	Exclusion Criterion 3 met: Participant had history or evidence of clinical signs/symptoms of hepatic decompensation manifested through <enter signs/symptoms>	Entered but did not satisfy criteria	Yes
11	Exclusion Criterion 4 met: Participant had evidence of liver disease of non-HBV etiology: <enter liver disease etiology>	Entered but did not satisfy criteria	Yes
12	Subject used disallowed medication as specified in the concomitant medication protocol Section:<*specify treatment, dose, unit, frequency, reason administered*>.	Received a disallowed concomitant treatment	Yes if classified as major protocol deviation
13	Received wrong treatment of study drug JNJ-3989/JNJ6379: *incorrect dose when randomized to active (and vice versa)*	Received wrong treatment or incorrect dose	Yes if classified as major protocol deviation
14	Subject did not receive dose of study drug JNJ-3989 within window: Within three weeks of the planned administration JNJ-3989 should be administered, if realized later than three weeks the dose should be skipped and administration of the next planned dose as per visit schedule should be awaited.	Received wrong treatment or incorrect dose	Yes if classified as major protocol deviation
15	Subject missed NA treatment for more than 5 doses within a four week period.	Received wrong treatment or incorrect dose	Yes if classified as major protocol deviation
16	Subject received expired study medication <*JNJ-3989, JNJ-6379, NA, PegIFN-a2a or placebo*>.	Received wrong treatment or incorrect dose	Yes if classified as major protocol deviation
17	Subject has confirmed signs of hepatic decompensation <*specify*> but subject continued study treatment.	Developed withdrawal criteria but not withdrawn	Yes
18	The subject has confirmed HBV virological breakthrough but continued study treatment.	Developed withdrawal criteria but not withdrawn	Yes
19	Study procedure not done at scheduled Visits.	Other	Yes if classified as major protocol deviation
20	Efficacy evaluation not done at scheduled Visits	Other	Yes if classified as major protocol deviation
21	Study Visits not performed per protocol.	Other	Yes if classified as major protocol deviation

ATTACHMENT 3. SAS CODE TO FIT BINOMIAL MIXED MODELS

SAS (version 9.4) PROC NLMIXED may be used to fit the binomial mixed models specified in Sections 5.3.1.2.2.1 and 5.3.1.2.2.2. The advantage of NLMIXED over PROC GLIMMIX – which can also fit binomial mixed models – lies in the power of NLMIXED's ESTIMATE statement, which can conveniently estimate non-linear functions of model parameters. In particular, this allows for convenient estimation of both point estimates and confidence intervals for the absolute and relative changes from baseline and the between-panel differences in the changes.

For the overall analysis in Section 5.3.1.2.2.1, code similar to the following may be used, where the input dataset `insight` should have variables named `id`, `time`, `y`, and `N`.

```
%macro expit(x);
      (exp(&x) / (1 + exp(&x)))
%mend;

ods output AdditionalEstimates=estimates; * save ESTIMATE statement output;
proc nlmixed data=insight alpha=0.2;
  parms a b 0 SD_int SD_slope 0.5; * initialize parameters;

  * specify binomial model with random effects;
  intercept = a + RE_int;
  slope = b + RE_slope;
  logit p = intercept + slope*time;
  p = %expit(logit p);
  random RE_int RE_slope ~ normal([0,0],[SD_int**2,0,SD_slope**2]) subject=id;
  model y ~ binomial(N,p);

  * estimate proportions and the change in proportions;
  p0 = %expit(a);
  p1 = %expit(a+b);
  estimate "(1) p0" 100*p0;
  estimate "(2) p1" 100*p1;
  estimate "(3) Abs. change (p1-p0)" 100*(p1 - p0);
  estimate "(4) Rel. change (p1-p0)/p0" 100*(p1/p0 - 1);
run;
```

For the between-panel analysis in Section 5.3.1.2.2.2, code similar to the following may be used, where the input dataset `insight` should have variables named `id`, `time`, `panel`, `y`, and `N`.

```
ods output AdditionalEstimates=estimates; * save ESTIMATE statement output;
proc nlmixed data=insight alpha=0.2;
  parms a delta_a b delta_b 0 SD_int SD_slope 0.5; * initialize parameters;

  * specify binomial model with random effects;
  intercept = a + delta_a*(panel = 1) + RE_int;
  slope = b + delta b*(panel = 1) + RE_slope;
  logit_p = intercept + slope*time;
  p = %expit(logit_p);
  random RE int RE slope ~ normal([0,0],[SD_int**2,0,SD_slope**2]) subject=id;
  model y ~ binomial(N,p);

  * estimate proportions, changes in proportions, and differences in changes;
  q0 = %expit(a);
  q1 = %expit(a+b);
```

```
  p0 = %expit(a+delta a);
  p1 = %expit(a+delta_a + b+delta_b);

  estimate "(A1) Panel 1: p0" 100*p0;
  estimate "(A2) Panel 1: p1" 100*p1;
  estimate "(A3) Panel 1: Abs. change (p1-p0)" 100*(p1 - p0);
  estimate "(A4) Panel 1: Rel. change (p1-p0)/p0" 100*(p1/p0 - 1);

  estimate "(B1) Panel 2: q0" 100*q0;
  estimate "(B2) Panel 2: q1" 100*q1;
  estimate "(B3) Panel 2: Abs. change (q1-q0)" 100*(q1 - q0);
  estimate "(B4) Panel 2: Rel. change (q1-q0)/q0" 100*(q1/q0 - 1);

  estimate "(C1) Panel 1 minus 2: Diff in abs. change (A3-B3)"
      100*(p1 - p0) - 100*(q1 - q0);
  estimate "(C2) Panel 1 minus 2: Diff in rel. change (A4-B4)"
      100*(p1/p0 - 1) - 100*(q1/q0 - 1);
run;
```

7. REFERENCES

1. Kassahun W. Neysens T., Molenbergh G., Faes C., Verbeke G. (2012). Modeling overdispersed longitudinal binary data using a combined beta and normal random-effects model. Archives of Public Health, 70:7.