Janssen Research & Development

Statistical Analysis Plan

Intervention-specific Appendix 3 to Master Protocol PLATFORMPAHPB2001

A Phase 2, randomized, open-label, multicenter study to evaluate efficacy, pharmacokinetics, safety, and tolerability of treatment with JNJ-73763989, pegylated interferon alpha-2a, nucleos(t)ide analog with or without JNJ-56136379 in treatment-naïve patients with HBeAg positive chronic hepatitis B virus infection

The REEF-IT Study

Protocol 73763989PAHPB2005; Phase 2

JNJ-73763989 and JNJ-56136379

Status: Approved
Date: 27 March 2024
Prepared by: Janssen Research & Development, a division of Janssen Pharmaceutica NV
Document No.: EDMS-RIM-152699, 5.0

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

AMENDMENT HISTORY

Document History	
Document	**Date**
Amendment 4	01 April 2024
Amendment 3	06 April 2023
Amendment 2	29 March 2023
Amendment 1	3 December 2021
Original SAP	26 February 2021

Amendment 4:

Overall rationale of this Amendment:

This administrative amendment incorporates additional clarifications on subgroups and analyses which have been documented in the Data Presentation Specification.

Clarifications, Additions, Corrections		
Section Number and Name	**Description of Change**	**Rationale**
2.5.1 Subgroup for Efficacy Analyses	Addition of the following subgroups: - Immune tolerant - Peg-responder definition #1 - Peg-responder definition #2 Removal of the following subgroups: - NA treatment history - Fibrosis stage - Sex - Geographical region - Duration of exposure to antigens Regrouping of the age categories: >30 years - ⩽45 years, >45 years - ⩽55 years in one category: >30 years	To allow for a more focused assessment of factors impacting efficacy outcomes and reduce the overall number of outputs
5.4.1.3.1. Association Between Baseline Characteristics/Viral Blood Markers and Selected Efficacy Variables	Removal of the correlation analyses between off-treatment HBV markers and other endpoints	Insufficient data for correlation analysis since there is only one patient who has met the NA treatment completion criteria and stopped NA (i.e. off-treatment) at CW12.
5.4.1.3.1. Association between several endpoints	The title has been changed to reflect the analyses detailed in this subsection.	To characterize association between changes in viral and safety markers during PegIFN administration.

Clarifications, Additions, Corrections		
Section Number and Name	**Description of Change**	**Rationale**
after the beginning of the consolidation phase	Addition of the correlations between the following endpoints will be evaluated: - Maximum ALT increase (U/L) vs Maximum HBV DNA increase (log10 IU/mL) between Consolidation Baseline and FU Week 4 - Maximum ALT increase (U/L) vs Maximum Neutrophils (10^9/L) decrease between Consolidation Baseline and FU Week 4 - Maximum ALT increase (U/L) vs Maximum HBsAg decrease (log10 IU/mL) between Consolidation Baseline and FU Week 4 - Additional HBsAg decline (log10 IU/mL) at CW12 vs Maximum Neutrophils decrease between Consolidation Baseline and FU Week 4 - Additional HBsAg decline (log10 IU/mL) at CW12 vs Maximum ALT increase (U/L) between Consolidation Baseline and FU Week 4	

Amendment 3:

Two hyperlinks were not working correctly. Updates have been made to have the SAP submission ready.

Amendment 2:

Overall rationale of this Amendment:

This administrative amendment incorporates additional clarifications on endpoints, on analysis population, on sample size, which have been documented in the Data Presentation Specification.

Clarifications, Additions, Corrections		
Section Number and Name	**Description of Change**	**Rationale**
2.3 Analysis set	The PegIFN α2a ITT and mPegIFN α2a ITT analysis sets have been removed	These two analysis sets are not part of the protocol and not so different from the ITT population. They are no longer of interest.
2.4. On-treatment and off-treatment periods	A section to define the on-treatment and off-treatment periods has been added	Clarification
2.5.1 Subgroup for Efficacy Analyses	Removal of the following subgroups: - NA treatment history - Fibrosis stage Subcategories have been regrouped/removed for the following factors: - For HBsAg level at baseline: the subcategories <1,000 IU/mL and ≥1,000 IU/mL-<10,000 IU/mL are replaced by <10,000 IU/mL - For HBcrAg level at baseline: all patients are in the category >4 log10 IU/mL and ≤9 log10 IU/mL, this subgroup has been removed - For HBeAg level at baseline: the subcategories >ULOQ and >5 log10 IU/mL have no patient so new subcategories have been set: ≥3 log10 IU/mL and <3 log10 IU/mL	Subcategories have been regrouped/removed to have enough patients (at least 6 patients, which corresponds to 10% of the targeted sample size) or because they are no longer of interest.
Section 5.3.1.1.2.2 NA Re-Treatment criteria	The proportion of participants who met each sub-criterion will not be calculated	This information is not available in the CRF
Section 5.3.1.1.7. Thresholds Based on HBsAg, HBeAg, HBV DNA and Multiple Markers	Subcategories have been added based on multiple markers threshold (HBsAg and HBV DNA)	New subcategories of interest have been added to be consistent with REEF-1
Section 5.3.1.3 Time to Event Endpoints	The following time to event endpoints have been removed: - Time to first HBsAg <10 IU/mL - Time to first HBsAg <100 IU/mL	The only time to event of interest are the following: - Time to first HBsAg seroclearance - Time to first HBV DNA<LLOQ

Clarifications, Additions, Corrections		
Section Number and Name	**Description of Change**	**Rationale**
	- Time to first HBsAg decline >1 log10 IU/mL - Time to first HBsAg decline >2 log10 IU/mL - Time to first HBsAg decline >3 log10 IU/mL - Time to first flare - Time to first HBeAg seroclearance - Time to first virologic breakthrough	The remaining time to event endpoints are no longer of interest.
Section 5.4.1.1.1 Partial cure	The section has been removed	The Partial cure is no longer of interest
Section 5.4.1.3, Time to event endpoints	This section has been removed	The following time to event endpoints are no longer of interest: - Time to first HBV RNA<LOD - Time to first HBcrAg undetectability - Time to Appearance of Anti-HBs antibodies - Time to Appearance of Anti-HBe antibodies
Section 5.4.2.1.1 Partial cure	The section has been removed	The definition for partial cure is outdated and thus no need to perform the analyses.
Section 5.4.2.3,Time to event endpoints	This section has been removed	The following time to event endpoints are no longer of interest: - Time to first HBV RNA<LOD - Time to first HBcrAg undetectability - Time to Appearance of Anti-HBs antibodies - Time to Appearance of Anti-HBe antibodies
Section 7.4 Positions & Genetic Variations of Interest	Added lists of genetic variations for JNJ-3976 and JNJ-3924	List of positions and variants has been updated to reduce analyses, to focus on the essential lists and to capture that other lists have been removed.
Section 8.3 Immune analyses	Analyses may be done instead of will be done.	Clarification

Clarifications, Additions, Corrections		
Section Number and Name	**Description of Change**	**Rationale**
Attachment 1: Selected major protocol deviations for analyses purposes	Remove the inclusion/exclusion criteria with no impact in the efficacy and safety analyses from the list of major protocol deviations	Select the necessary conditions for a participant to be part of the per protocol population.
Attachment 2: Adverse events of Special Interest	Update the PT	Meddra version has changed: from version 23.1 to version 25.1

Amendment 1

Overall rationale for the SAP Amendment: This amendment aims to align the Statistical Analysis Plan (SAP) to the ISA Protocol Amendment #5 issued on July 30, 2021 and the ISA Protocol Amendment #6 issued on September 30, 2021 and the ISA Protocol Amendment #7 issued on November 26, 2021where the main changes in the study design include to remove JNJ-6379 as study intervention, to add a new nucleos(t)ide analog (NA) re-treatment criterion for participants who discontinued NA treatment during follow-up, and to include more frequent monitoring for participants who discontinued NA treatment during follow-up, to update the criteria for post-treatment monitoring and for NA re-treatment for participants who discontinued NA treatment during follow-up and to a fixed 36-week duration of the induction phase.

The primary reason for removing JNJ-6379 was based on new data from recent interim analyses of the REEF-1 (73763989HPB2001) and REEF-2 (73763989PAHPB2002) studies, have shown an unfavorable benefit-risk profile of JNJ-6379 in combination with JNJ-3989+NA compared to JNJ-3989+NA alone (Negative impact of JNJ-6379, when combined with JNJ-3989+NA, on HBsAg reduction and adverse renal profile). Therefore, the Sponsor has decided to discontinue treatment with JNJ-6379 in all ongoing clinical studies effective immediately. Participants currently on treatment with JNJ-6379 will be contacted and requested to stop taking JNJ-6379, while continuing treatment with NA and JNJ-3989. For newly enrolled participants after urgent safety measurement (USM), JNJ-6379 will no longer be included in the treatment regimen.

The main reason for additional NA re-treatment criterion is a severe clinical alanine aminotransferase (ALT) flare that was reported following discontinuation of NA treatment in a virologically suppressed HBeAg negative participant on long-term TDF treatment who was randomized to the control arm (placebo + placebo + NA) in the REEF-2 study. The participant presented with hepatitis B virus (HBV) DNA levels that increased rapidly, before any relevant changes in liver markers were noted. Discontinuation of NA treatment followed the protocol-defined criteria and was in line with recent European Association for the Study of the Liver (EASL) treatment guidelines.[1] Flares following NA discontinuation are not unexpected, but the rapid

evolution and clinical deterioration seen in this participant who was anti-HBe antibody positive at screening and had no history or evidence of liver cirrhosis was unforeseeable.

The main reason for updating the criteria for post-treatment monitoring and NA re-treatment for patients who discontinued NA treatment is triggered by a case of hepatitis B reactivation with subacute hepatic failure (initially reported as severe clinical ALT flare) following NA treatment cessation as per protocol in the REEF-2 (73763989PAHPB2002) study which led to listing of the patient for high urgency liver transplantation. The patient received a donor liver at Week 14 post-stopping NA and has since then showed an uneventful post-operative recovery.

Two cohorts have been introduced to distinguish between participants enrolled prior to or after ISA Protocol Amendment #5. All participants enrolled prior to ISA Protocol Amendment #5 will comprise Cohort 1, of which some may be randomized to either study intervention Arm 1 or Arm 2. Protocol Amendment #5 was not implemented due to the USM and no participants will be receiving Protocol Amendment #5 treatment, the participants enrolled after approval of ISA Protocol Amendment #6 will comprise Cohort 2.

Main changes and their rationale are clarified in the table below.

Section Number and Name	Description of Change	Rationale
Section 1.2 Trial Design	The study design was updated such that participants (Cohort 2) will receive JNJ-3989+NA for a fixed duration of 36 weeks (induction phase) instead of a response-guided treatment duration. The induction phase will be followed by a 12-week consolidation phase during which PegIFN-α2a will be added to the treatment regimen for all participants. JNJ-6379 was discontinued in all ongoing clinical studies effective immediately.	Based on preliminary 48-week treatment data from the REEF-1 study and insights from EASL 2021, PegIFN-α2a will be added to the treatment regimen for all participants, to increase the potential of achieving functional cure. New data from recent interim analyses of the REEF-1 (73763989HPB2001) and REEF-2 (73763989PAHPB2002) studies, have shown an unfavorable benefit-risk profile of JNJ-6379 in combination with JNJ-3989+NA compared to JNJ-3989+NA alone.
Section 1.4 Sample Size Determination	With the introduction of the new study design in Protocol Amendment 6 (single-arm), no formal sample size re-calculation was performed.	Alignment of the sample size justification for Cohort 2 to the new design elements.
Section 2.1.1 Analysis Phase	Analysis Phase start date and end date have been updated.	Alignment to the new fixed-duration induction phase; separation of definition of start/stop dates for participants in Cohort 1 (pre- or post-amendment) and in Cohort 2.

Section Number and Name	Description of Change	Rationale
Section 3.3.2 Interim Analyses	The second IA is planned when all participants have completed Week 48 or discontinued earlier.	To align IA to the new design Week 48 (End of Treatment) in the ISA Protocol Amendment #6.
Section 5 Efficacy	The efficacy for Cohort 1 will be evaluated on the treated population set. A secondary analysis of efficacy will be performed combining the data from participants who received PegIFN-α2a but not JNJ-6379 in Cohort 1 with data of Cohort 2.	To align with trial design changes in the ISA Protocol Amendment #6.
Section 5.3.1.1.2 NA Re-Treatment Criteria and Monitoring After Stopping of NA	Update of follow-up procedures and criteria for re-initiation of NA treatment and criteria for post-treatment monitoring and NA re-treatment for patients who discontinued NA treatment	For clarification as per ISA Protocol Amendment #6 and #7.
Section 6.2.4 Physical Examination	Head, neck, and thyroid were added to complete physical examination	For completeness
Attachment 1: Selected Major protocol Deviations for Analysis Purposes	List was updated to incorporate the updated inclusion/exclusion criteria as per ISA protocol amendment #6.	For completeness

ABBREVIATIONS

ADY	analysis relative day
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomic and therapeutic class
ATEOC	analysis time point (Week) for EOC
ATEOI	analysis time point (Week) for EOI
AUC_{24h}	area under the concentration-time curve at 24 hours
BMI	body mass index
CHB	chronic hepatitis B
C_{24h}	concentration 24 hours after administration
CI	confidence interval
Cmax	maximum concentration
CRF	case report form
CV	coefficient of variation
DAIDS	division of acquired immunodeficiency syndrome
DNA	deoxyribonucleic acid
DR	data review
DRC	data review committee
EASL	european association for the study of the liver
ECG	electrocardiogram
EOC	end of consolidation phase
EOI	end of induction phase
EOS	end of study
EOT	end of treatment
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EQ-5D-5L	5-Level EuroQol 5-Dimension
FEPO4	urine fractional excretion of phosphate
FU	follow-up
GGT	Gamma-glutamyltransferase
HBQOL	hepatitis B Quality of Life
HBcrAg	hepatitis B core-related antigen
HBs	hepatitis B surface
HBeAg	hepatitis B envelope antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HBV DNA	hepatitis B virus deoxyribonucleic acid
HBV RNA	hepatitis B virus ribonucleic acid
ICS	intracellular cytokine staining
iFLEP	independent flares expert panel
IA	interim analysis
IFN	interferon
IQR	interquartile range
IRT	item response theory
ISR	injection site reaction
ITT	intent-to-treat
IU/mL	international units per milliliter
IWRS	interactive website response system
LiPA	line probe assay
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MAR	missing at random
MAV	minimum acceptable value
MCS	mental component summary

MedDRA	medical dictionary for regulatory activities
MH	Mantel-Haenszel
MI	multiple imputation
mITT	modified intent-to-treat
mTreated	modified treated
MSE	missing score estimation
NA	nucleos(t)ide analog
NGS	next generation sequencing
PBMC	peripheral blood mononuclear cell
PCS	physical component summary
PD	pharmacodynamic(s)
PegIFN-α2a	pegylated interferon alpha-2a
PGIC	Patient Global Impression of Change
PK	pharmacokinetic(s)
PoC	proof of concept
PP	per protocol
PRO	patient-reported outcomes
Q4W	every 4 weeks
qd	once daily
QTc	corrected QC interval
QTcF	QT interval corrected for heart rate according to Fridericia
QW	once weekly
RBP	rentinol binding protein
RGT	response-guided treatment
RR	Interval between R wave of one heartbeat and R wave of preceding heartbeat
RT	reference timepoint
SAE	serious adverse event
SAP	statistical analysis plan
SCr	serum creatinine
SD	standard deviation
SF-36v2	Short Form 36 version 2
SPO4	serum phosphate
T4	thyroxine
TAF	tenofovir alafenamide
TD	target detected
TEAE	treatment-emergent adverse event
TeD	tenofovir disoproxil
TND	target not detected
TNF	tumor necrosis factor
TSH	thyroid stimulating hormone
TV	target value
ULN	upper limit of normal
UACR	urine albumin to creatinine ratio
UPCR	urine protein to creatinine ratio
USM	urgent safety measurement
VAS	Visual Analog Scale
WBC	white blood cell

1. INTRODUCTION

This statistical analysis plan (SAP) for the 73763989PAHPB2005 phase 2 trial describes the statistical analyses and definitions to assess the efficacy and safety of study interventions including JNJ-73763989, pegylated interferon alpha-2a (PegIFN-α2a), Nucleos(t)ide analogs (NA) regimen with or without JNJ-56136379 in patients with HBeAg positive chronic hepatitis B (CHB) virus infection and ALT ≤2x ULN who are not currently being treated for their HBV infection (i.e., who had <9 months of prior treatment which ended at least 12 months before screening, including treatment-naïve patients). In the rest of the document the abbreviations JNJ-3989 and JNJ-6379 are used to refer to the treatments JNJ-73763989 and JNJ-56136379, respectively. JNJ-6379 was initially part of the study intervention but has been removed as study intervention with the implementation of an urgent safety measure, as described in Protocol Amendment 6.

This study is part of the platform trial PLATFORMPAHPB2001 in participants with CHB. The protocol amendment for 73763989PAHPB2005 constitutes the Intervention Specific Appendix that describes all the specific and/or additional features of this study complementing the common design elements of the platform trial described in the Master Protocol.

This SAP is to be interpreted in conjunction with the clinical protocol Amendment-6 finalized on 30 September 2021, and with the Master Protocol Amendment-3 for PLATFORMPAHPB2001 finalized on 21 January 2021.

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

1.1. Trial Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of a treatment regimen of JNJ-3989 + PegIFN-α2a + NA.	• Proportion of participants with HBsAg seroclearance 24 weeks after stopping all study interventions of the consolidation phase and without restarting NA treatment.
Secondary	
• To evaluate the safety and tolerability of the study intervention.	• Safety and tolerability including but not limited to the proportion of participants with (serious) adverse events (S)AEs and abnormalities in clinical laboratory tests (including hematology, blood biochemistry, blood coagulation, urinalysis, urine chemistry, and renal biomarkers), 12-lead electrocardiograms (ECGs), vital signs, and physical examinations throughout the study.
• To evaluate the efficacy of the study intervention during the treatment period.	• Proportion of participants reaching HBsAg <10 IU/mL at the end induction phase (Week 36).

Objectives	Endpoints
	• Proportion of participants meeting the NA treatment completion criteria at the end of the consolidation phase.
• To evaluate the efficacy of the study intervention during the follow-up (FU) phase.	• Proportion of participants with HBsAg seroclearance 48 weeks after stopping all study interventions of the consolidation phase and without restarting NA treatment. • Proportion of participants with HBV DNA <LLOQ 48 weeks after stopping all study interventions of the consolidation phase and without restarting NA treatment. • Frequency of viral and/or biochemical flares and/or clinical flares. • Proportion of participants requiring NA re-treatment.
• To evaluate efficacy of the study intervention as measured by blood markers (such as HBsAg, HBeAg, HBV DNA, and alanine aminotransferase [ALT]) during study intervention and follow-up.	• Proportion of participants with (sustained) reduction, suppression, and/or seroclearance considering single and multiple markers (such as HBsAg, HBeAg, HBV DNA, and ALT). • Proportion of participants with HBsAg and HBeAg seroconversion. • Change from baseline over time in HBsAg, HBeAg, and HBV DNA. • Time to achieve HBsAg seroclearance, and/or HBV DNA <LLOQ. • Proportion of participants with HBeAg, HBsAg, and HBV DNA levels and/or changes from baseline below/above different cut-offs.
• To evaluate the frequency of virologic breakthrough.	• Proportion of participants with virologic breakthrough.
• To evaluate the efficacy of NA re-treatment in participants who meet the criteria for NA re-treatment.	• Proportion of participants who reach HBV DNA undetectability after re-start of NA treatment during follow-up.
• To evaluate the pharmacokinetics (PK) of JNJ-3989 (ie, JNJ-3976 and JNJ-3924) and optionally of JNJ 6379, NA and/or PegIFN-α2a.	• PK parameters of JNJ-3976 and JNJ-3924. • Optionally, PK parameters of JNJ 6379, NA and/or PegIFN-α2a compared to historical data.
Exploratory	
• To identify baseline and on-treatment markers associated with efficacy.	• Association of baseline characteristics and baseline/on-treatment viral blood markers (such as age, and baseline/on-treatment

Objectives	Endpoints
	HBsAg levels) with selected efficacy variables.
• To explore changes in the severity of liver disease.	• Changes in fibrosis (according to Fibroscan liver stiffness measurements) at end-of-study intervention (EOSI) and end of follow-up versus baseline.
• To explore efficacy of the study intervention in terms of changes in HBV RNA and HBcrAg levels.	• Changes from baseline in HBV RNA and HBcrAg levels during the study intervention and follow-up.
• To explore the impact of study intervention on participants' physical and emotional functioning, and health-related quality of life using patient-reported outcomes (PROs) during study intervention and follow-up.	• Changes over time in score on the Short Form 36 version 2 (SF-36v2). • Changes over time in score on the Hepatitis B Quality of Life (HBQOL) Instrument. • Changes over time in the 5-Level EuroQol 5-Dimension (EQ-5D-5L) Visual Analog Scale (VAS) score and Index score. • Changes over time on the Patient Global Impression of Change (PGIC).
• To explore the relationship between plasma PK parameters (JNJ-3976, JNJ-3924, optionally JNJ 6379, 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, JNJ-3924, and optionally JNJ 6379, NA, and/or PegIFN-α2a) and selected efficacy and/or safety endpoints, as applicable.
• To explore the effect of PegIFN-α2a coadministration on the PK of JNJ-3989 (optional PK substudy).	• Effect of PegIFN-α2a coadministration on the PK of JNJ-3976 and JNJ-3924.
• To explore the HBV genome sequence during study intervention and follow-up.	• Assessment of intervention-associated mutations.
• To explore HBV-specific T-cell responses during study intervention and follow-up.*	• Changes from baseline in HBV-specific peripheral blood T-cell responses.

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

1.2. Trial Design

This is a Phase 2a, randomized, open-label, multicenter, parallel-group, interventional study to evaluate the efficacy, pharmacokinetics, safety, and tolerability of treatment with JNJ-3989+ PegIFN-α2a +NA regimen with or without JNJ-6379 in patients with HBeAg positive chronic HBV infection and ALT ≤2x ULN who are not currently being treated for their HBV infection (i.e., who had <9 months of prior treatment which ended at least 12 months before screening,

including treatment-naïve patients). After completing this study, participants may have the option to enroll into a long-term follow-up study.

A target of approximately 60 adult participants (including approximately 33 after implementation of Protocol Amendment #6), 18-55 years (inclusive) of age (with a maximum of approximately 10 participants >45 to ≤55 years of age), with CHB who are HBeAg positive, who are not currently treated for their HBV infection (including treatment-naïve patients), have HBV DNA ≥20,000 IU/mL and have ALT ≤2x ULN at screening will be enrolled in this study. It is targeted to enroll at least 30% participants with HBV DNA ≥10^7 IU/mL and normal ALT at screening in the study.

The study will be conducted in 4 phases:

- A screening phase (4 weeks [if necessary, can be extended to a maximum of 6 weeks decided on a case-by-case basis and in agreement with the sponsor]).
- An induction phase:
    - Prior to Protocol Amendment #5: response-guided treatment (RGT) of 36-60 weeks (inclusive).

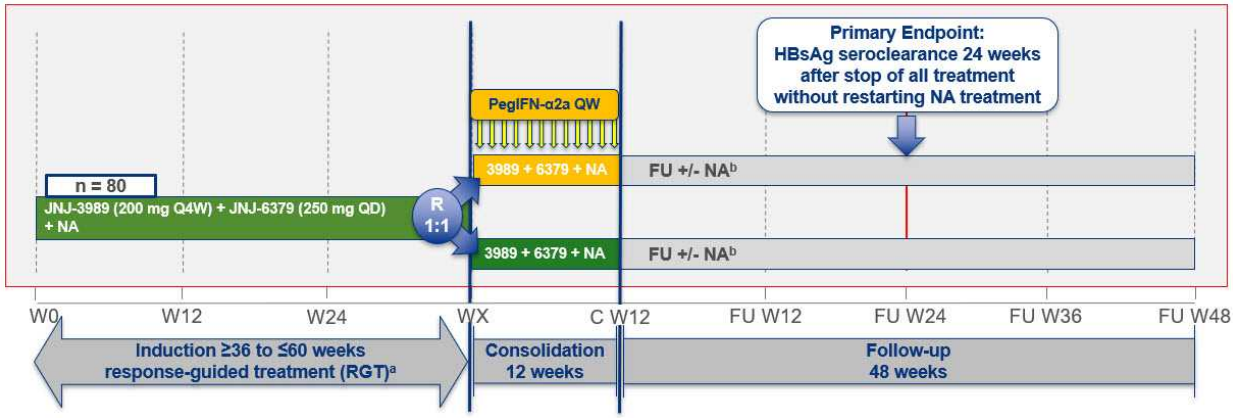
      Note: Participants who already passed the Week 36 visit before Protocol Amendment #5 is in effect, will enter the consolidation phase at the next scheduled visit.
    - As of Protocol Amendment #5: fixed duration of 36 weeks for all participants.
- A consolidation phase (12 weeks).
- A follow-up (FU) phase (48 weeks).

The total duration of individual participation will be between 100 and 126 weeks. Of note, participants enrolled after Protocol Amendment #5 will be between 100 and 102 weeks; and the participants enrolled before Protocol Amendment #5 may have a longer induction phase and a total study duration up to 126 weeks.

To distinguish between participants enrolled prior to or after Protocol Amendment #5 is in effect, the terms Cohort 1 and Cohort 2 will be used. All participants enrolled prior to the Protocol Amendment #5 will comprise Cohort 1. RGT criterion is defined as having HBsAg <10 IU/mL. Protocol Amendment #5 was not implemented due to the USM and no participants will be receiving Protocol Amendment #5 treatment, the participants enrolled after approval of Amendment #6 will comprise Cohort 2.

The schematics of the trial changes per Protocol Amendment #5 are presented in Figure 1 and Figure 2 to show the history of protocol amendment.

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



a End of the induction phase is defined by either meeting the study defined RGT criterion (HBsAg <10 IU/mL) or reaching study Week 60, whichever comes first. The RGT criterion will be assessed from Week 36 onwards, and the assessment will always be based on lab results from the previous study visit (4 weeks earlier).

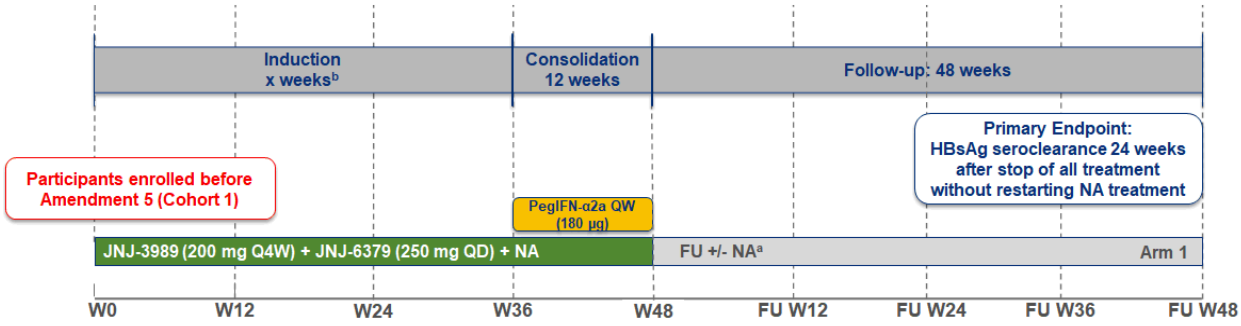
b If NA treatment completion criteria (HBsAg <10 IU/mL, and HBeAg-negative, and HBV DNA <LLOQ, and ALT <3x ULN) have been met at consolidation Week 12, NA will be stopped at the next scheduled visit (ie, FU Week 2), otherwise NA treatment will continue during the complete follow-up phase.

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

Cohort 1: Participants enrolled before Protocol Amendment #5 is in effect

Per Amendment #5, participants who did not yet reach the Week 36 visit will have PegIFN-α2a added to their treatment regimen at Week 36 for 12 weeks.

Participants who already passed the Week 36 visit and/or were randomized to the group without PegIFN-α2a, will have PegIFN-α2a added to their treatment regimen at the next scheduled visit. After 12 weeks, treatment with NA, PegIFN-α2a, JNJ-3989 and JNJ-6379 (if applicable) will be stopped.

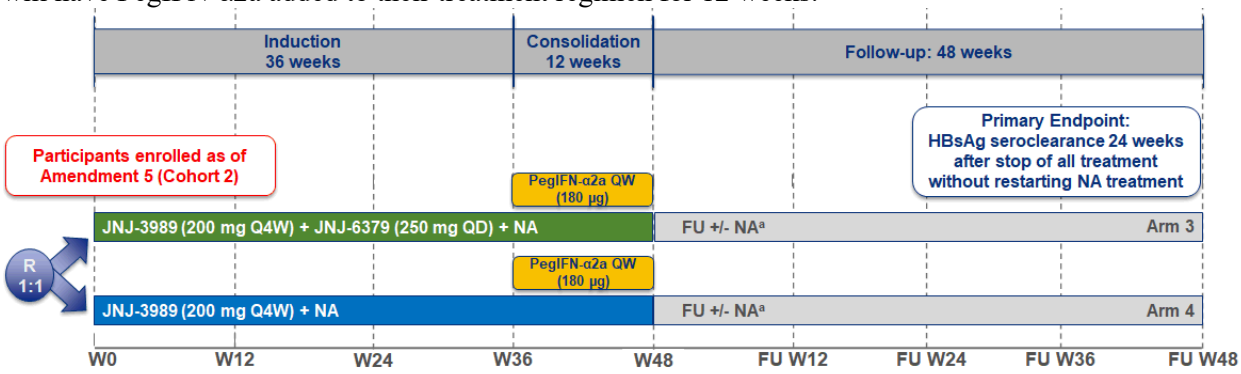


a If NA treatment completion criteria (HBsAg <10 IU/mL, and HBeAg-negative, and HBV DNA <LLOQ, and ALT <3x ULN) have been met at consolidation Week 12, NA will be stopped at the next scheduled visit (ie, FU Week 2), otherwise NA treatment will continue during the complete follow-up phase.

b Depending on the approval date of Amendment #5, the induction phase can be longer than 36 weeks for some of these participants.

Cohort 2: Participants enrolled under Protocol Amendment #5 is in effect

Per Amendment #5, participants will be randomized in a 1:1 ratio at the start of the induction phase to either receive JNJ-3989 + JNJ-6379 + NA or JNJ-3989 + NA for 36 weeks. At Week 36 all participants will have PegIFN-α2a added to their treatment regimen for 12 weeks.

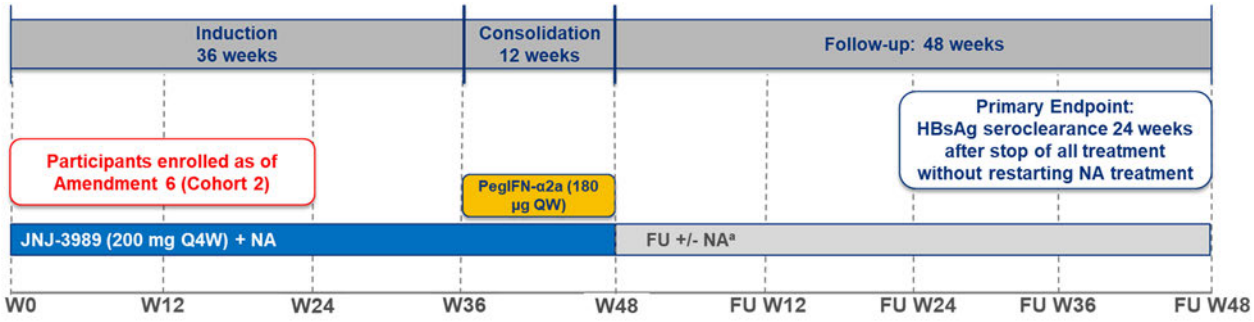


[a] If NA treatment completion criteria (HBsAg <10 IU/mL, and HBeAg-negative, and HBV DNA <LLOQ, and ALT <3x ULN) have been met at consolidation Week 12, NA will be stopped at the next scheduled visit (ie, FU Week 2), otherwise NA treatment will continue during the complete follow-up phase.

With the implementation of an urgent safety measure, as described in Protocol Amendment 6, participants previously enrolled had to immediately stop JNJ-6379 treatment, because of the removal of JNJ-6379 as study intervention. They were to continue with JNJ-3989+NA treatment up to the end of the induction phase and then enter the 12-week consolidation phase during which PegIFN-α2a was added to their treatment regimen.

Because of the urgent removal of JNJ-6379 as study intervention, none of the participants enrolled under Protocol Amendment #5 did receive JNJ-6379.

Figure 3: Schematic Overview of Cohort 2 of the Study – As of Protocol Amendment 6



[a] If NA treatment completion criteria (HBsAg <10 IU/mL, and HBeAg-negative, and HBV DNA <LLOQ, and ALT <3x ULN) have been met at consolidation Week 12, NA will be stopped at the next scheduled visit (ie, FU Week 2), otherwise NA treatment will continue during the complete follow-up phase.

As of Protocol Amendment 6, the study will continue as a single-arm study (JNJ-3989+NA+PegIFN-α2a), as schematized in Figure 3. All newly enrolled participants will receive JNJ-3989+NA for 36 weeks (induction phase) and will then enter the 12-week consolidation phase during which they will have PegIFN-α2a added to their treatment regimen.

Key: ALT: alanine aminotransferase; C: consolidation; DNA: deoxyribonucleic acid; FU: follow-up; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; JNJ-3989: JNJ-73763989; JNJ-6379: JNJ-56136379; n: number of participants; LLOQ: lower limit of quantification; NA: nucleos(t)ide analog; PegIFN-α2a: pegylated interferon alpha-2a; R: randomization; RGT: response-guided treatment; ULN: upper limit of normal; Q4W: once every 4 weeks; qd: once daily; QW: once weekly; W: week; WX: last visit of the induction phase (≥W36 and ≤W60) equivalent to Day 1 of the consolidation phase.

The induction and consolidation phase have been updated as below:

- Before Protocol Amendment #5, enrolled participants will enter an induction phase with triple combination treatment (JNJ-3989 + JNJ-6379 + NA) for a response-guided treatment duration of ≥36 weeks to ≤60 weeks. End of the induction phase is defined by either meeting the study defined RGT criterion (HBsAg <10 IU/mL) or reaching study Week 60, whichever comes first. The RGT criterion will be assessed from Week 36 onwards at each study visit, and the assessment will always be based on lab results from the previous study visit. Participants will be randomized in a 1:1 ratio to one of the following intervention arms in the 12-week consolidation phase: JNJ-3989+JNJ-6379+NA+PegIFN-α2a (Cohort 1, Arm 1) or JNJ-3989+JNJ-6379+NA (Cohort 1, Arm 2).

  Note: Participants enrolled before Protocol Amendment #5 is in effect will switch to the new study design as soon as Protocol Amendment #5 is in effect. The details are in the Figure 2 Cohort 1.

- Per Protocol Amendment #5, participants will be randomized at baseline in a 1:1 ratio to one of the following intervention arms: JNJ-3989+JNJ-6379+NA (Cohort 2, Arm 3) or JNJ-3989+NA (Cohort 2, Arm 4). Upon completion of the 36-week induction phase, all participants will enter the 12-week consolidation phase during which they will have PegIFN-α2a added to their treatment regimen.

  Note: With the implementation of an urgent safety measure, as described in Protocol Amendment 6, participants previously enrolled had to immediately switch to the new study design. Participants had to stop JNJ-6379 treatment immediately and continue with JNJ-3989+NA treatment up to the end of the induction phase and will then enter the 12-week consolidation phase during which they will have PegIFN-α2a added to their treatment regimen.

- As of Protocol Amendment 6, the study will continue as a single-arm study (JNJ-3989+NA+PegIFN-α2a). All newly enrolled participants will receive JNJ-3989+NA for 36 weeks (induction phase) and will then enter the 12-week consolidation phase during which they will have PegIFN-α2a added to their treatment regimen.

At the end of the consolidation phase, all participants will enter the FU phase and stop treatment with JNJ-3989+PegIFN-α2a. If NA treatment completion criteria (HBsAg <10 IU/mL, and HBeAg-negative, and HBV DNA <LLOQ, and ALT <3x upper limit of normal [ULN]) have been met at consolidation Week 12, NA will also be stopped at the next scheduled visit (ie, FU Week 2), otherwise NA treatment will continue during the complete FU phase. Participants will be monitored closely during the 48-week FU phase and should restart NA treatment in accordance with the NA re-treatment criteria.

As of protocol Amendment #6, study intervention consists of:

- 200 mg JNJ-3989 (SC injection Q4W)
- 245 mg tenofovir disoproxil (tablets qd) – ***Note:*** tenofovir disoproxil may be supplied as fumarate or maleate
- 180 µg PegIFN-α2a (SC injection, QW)

Note: Most participants enrolled before Protocol Amendment #6 was in effect, also received 250 mg JNJ-6379 (tablets qd) as part of their study intervention.

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

A data review committee (DRC) will be commissioned for this study. In addition, an Independent Flare Expert Panel (IFLEP) will be appointed.

1.3. Statistical Hypotheses for Trial Objectives

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

1.4. Sample Size Determination

According to the initial study design, the plan was to enroll 80 participants in the study to achieve at least 70 participants to be randomized in a 1:1 ratio to one of the 2 intervention arms after completion of the induction phase. Based on the number of participants currently enrolled, participants who already passed the Week 36 visit and/or were randomized to the group without PegIFN-α2a by the time Protocol Amendment 6 is in effect, will have PegIFN-α2a added to their treatment regimen at the next scheduled visit and will enter the 12-week consolidation phase. For the purpose of the statistical analyses, all participants enrolled prior to Protocol Amendment #5 will comprise “Cohort 1”. Protocol Amendment #5 was not implemented due to the USM and no participants will be receiving Protocol Amendment #5 treatment. All participants enrolled after approval of Protocol Amendment 6 will comprise “Cohort 2”.

With the introduction of the new study design in Protocol Amendment 6 (single-arm), no formal sample size re-calculation was performed. The targeted total sample size (Cohort 1 and Cohort 2 combined) was set to approximately 60 participants. With a sample size of 33 participants in Cohort 2 and assuming a 10% dropout rate, 30 participants in Cohort 2 would be expected to have data for the primary efficacy endpoint at 24 weeks after stopping all study interventions of the consolidation phase and without restarting NA treatment.

If at least 15 (50%) participants are responders, this sample size will allow to conclude with 90% confidence that the true response rate is at least 0.34, with a confidence interval (CI) width of 0.322 (90% CI: 0.339 - 0.661).

1.5. Randomization and Blinding

Randomization

For participants in Cohort 1, a distinction will be made depending on the timing when the ISA protocol Amendment #6 will be in effect. Protocol Amendment #5 was not implemented due to the USM and no participants will be receiving Protocol Amendment #5 treatment.

- If a participant of Cohort 1 is in between Week 36 and 60 and met the RGT criteria prior to Amendment #5 approval, then he/she will be randomly assigned in a 1:1 ratio to 1 of 2 intervention arms (Arm 1 = JNJ-3989+JNJ-6379+NA+PegIFN-α2a; or Arm 2 = JNJ-3989+JNJ-6379+NA). The randomization is stratified by screening HBV DNA level ($\geqslant 10^7$ IU/mL OR $<10^7$ IU/mL) and timing of meeting the study defined RGT criterion (at Week 36 OR after Week 36 up to Week 48 OR after Week 48 up to Week 60 OR not met before or at Week 60) for participants in Cohort 1.

- If a participant of Cohort 1 has not yet reached Week 36, or did not meet RGT criteria up to Week 60 prior to Amendment #5 approval, then he/she will not be randomized, but will have PegIFN-α2a added to his/her treatment regimen at the next scheduled visit. After 12 weeks, treatment with NA, PegIFN-α2a, JNJ-3989 and JNJ-6379 will be stopped, regardless of the actual duration of induction (which may exceed 36 weeks).

For participants in Cohort 2 as of Protocol Amendment #6, the study will continue as a single-arm study (JNJ-3989+NA+PegIFN-α2a). All newly enrolled participants will receive JNJ-3989+NA for 36 weeks (induction phase) and will then enter the 12-week consolidation phase during which they will have PegIFN-α2a added to their treatment regimen.

Blinding

As this is an open-label study, blinding procedures are not applicable.

2. GENERAL ANALYSIS DEFINITIONS

The SAP will use throughout the document the following definitions:

The term "**induction phase**" corresponds to the first treatment phase of the study starting with enrollment into induction phase of flexible duration of 36-60 weeks (inclusive) for Cohort 1 and starting with randomization or enrollment into the induction phase of a fixed duration of 36 weeks for Cohort 2.

The term "**consolidation phase**" corresponds to the second treatment phase of the study starting with the first PegIFN-α2a intake with a fixed duration of 12 weeks for both cohorts.

- *Study treatment/intervention* refers to: JNJ-3989, JNJ-6379, NA (TeD, or TAF) and PegIFN-α2a prior to Protocol Amendment #6; JNJ-3989, NA (TeD, or TAF) and PegIFN-α2a as of Protocol Amendment #6.
- *Study agent* refers to: JNJ-3989, JNJ-6379, and PegIFN-α2a prior to Protocol Amendment #6; JNJ-3989 and PegIFN-α2a as of Protocol Amendment #6.

- *Study intervention arm* will be specified with Cohort 1 and Cohort 2 which are distinguished between participants enrolled prior to or after Protocol Amendment #6 as the Protocol Amendment #5 was not implemented due to the USM and no participants will be receiving Protocol Amendment #5 treatment. All participants enrolled prior to the Protocol Amendment #5 will comprise Cohort 1. The participants enrolled after approval of Amendment #6 who will comprise Cohort 2. The Study intervention arm in the SAP will be
  - Cohort 1:
    - JNJ-3989 + JNJ-6379 + NA + PegIFN-α2a
    - JNJ-3989 + NA + PegIFN-α2a
  - Cohort 2:
    - JNJ-3989 + NA + PegIFN-α2a

2.1. Analysis Phases and Visit Windows

2.1.1. Analysis Phase

The analysis phases are defined in Table 1 below.

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 (excluding PegIFN-α2a)
Induction phase	**Cohort1:** Date of first study agent intake (excluding PegIFN-α2a)	**Cohort1:** **Participants who are randomized:** Min{Max[Date of first PegIFN-α2a intake, Date of randomization] -1 day, cut-off date[b]} **Participants who are not randomized but receive PegIFN-α2a:** Min[Date of first PegIFN-α2a intake-1 day, cut-off date[b]] **Participants who are not randomized and did not receive PegIFN-α2a:** Min{Min[JNJ-3989 discontinuation date[a], early study withdrawal visit date, max(Week 36 to 60 visit date from induction phase)] + 5 days[a], cut-off date[b]}
	Cohort 2: Date of first study agent intake (excluding PegIFN-α2a)	**Cohort 2:** **Participants who receive PegIFN-α2a:** Min[Date of first PegIFN-α2a intake – 1 day, cut-off date[b]] **Participants who did not receive PegIFN-α2a:** Min{Min[JNJ-3989 discontinuation date[a], early study withdrawal visit date, Week 36 visit date from induction phase] + 5 days[a], cut-off date[b]}

Analysis phase	*Start date*	*End date*
Consolidation phase	**Cohort 1:** **Participants who receive PegIFN- α2a:** Date of first PegIFN-α2a intake **Participants who did not receive PegIFN- α2a:** date of any study agent intake after Max[Week 36 to 60 visit date] Otherwise: Missing	**Cohort1:** **Participants who did not withdraw from the study prior to the Consolidation Week (CW) 12 visit date:** Min{Max[last intake date of any study agent (excluding NA), CW[c]12], JNJ-3989 discontinuation date[a]} + 5 days[a] or cut-off date[b], whichever occurs first **Participants who withdrew from the study prior to the Consolidation Week 12 visit date:** Min[JNJ-3989 discontinuation date[a], early study withdrawal visit date] + 5 days[a] or cut-off date[b], whichever occurs first Otherwise: Missing
	Cohort 2: **Participants receive PegIFN- α2a:** Date of first PegIFN-α2a intake **Participants who did not receive PegIFN- α2a:** Date of any study agent intake after Week 36 visit date Otherwise: Missing	**Cohort 2;** **Participants who did not withdraw from the study prior to the Consolidation Week 12 visit date:** Min{Max[last intake date of any study agent (excluding NA), CW12], JNJ-3989 discontinuation date[a]} + 5 days[a] or cut-off date[b], whichever occurs first **Participants who withdrew from the study prior to the Consolidation Week 12 visit date:** Min[JNJ-3989 discontinuation date[a], early study withdrawal visit date] + 5 days[a] or cut-off date[b], whichever occurs first Otherwise: Missing
Follow-up	**Participants who did not withdraw informed consent during induction or consolidation phase:** Max[End date of induction phase, End date of consolidation phase] +1 Otherwise: Missing	Max[study discontinuation date, study completion date] or cut-off date[b], whichever occurs first Otherwise: Missing

[a] Addition of 5 days is only applicable for JNJ-3989 discontinuation due to Adverse Events and Concomitant Medications.
[b] Cut-off dates will be defined to match the prespecified timepoints for DRC safety monitoring, interim analyses and the primary and final analyses, respectively.
[c] CW = Consolidation Week

2.1.2. Relative Day by Study Phase

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

2.1.2.1. Induction Phase Relative Day

Induction start date (Induction Day 1) is defined in the Table 1 Induction phase. All efficacy and safety assessments during the induction phase will be assigned an analysis study day relative to this date.

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

Induction ADY=visit date – Induction start date+1

for visits on or after induction Day 1, and

Induction ADY=visit date – Induction start date

for visits before induction Day 1 (Screening phase).

There is no 'induction Day 0'.

2.1.2.2. Consolidation Relative Day

Consolidation start date (Consolidation Day 1) is defined in the Table 1 Consolidation phase.

All efficacy and safety assessments during the consolidation phase will be assigned an analysis study day relative to this date.

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

Consolidation ADY=visit date – Consolidation start date+1

for visits on or after consolidation Day 1. There is no 'consolidation Day 0'.

2.1.2.3. Follow Up Relative Day

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

FU ADY=visit date – FU start date+1

for visits on or after FU Day 1.

2.1.3. Analysis Visits and Time Points

All visits for all assessments (safety, efficacy or PK) will be uniquely allocated within each phase to an analysis time point based on the target day according to Table 2. All assignments will be made in chronological order. Once a visit is assigned to a visit window (Time interval in Table 2) it will no longer be used for a later time point except for the end of induction (EOI), which is the same visit as the consolidation baseline, the end of consolidation (EOC) and the end of study (EOS) visits, if applicable. If two or more visits fall within the same interval in the same phase, only one measurement will be selected for the analysis time point per phase in order to have only one evaluation per participant, except for the production of the spaghetti plots for which all measures will be displayed. The following rules will be applied:

1. The measurement closest to the target day in that phase will be used.

2. If the measurements fall equidistant from the target day, the last measurement in chronological order within the interval will be used per phase.

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.

The listings will include all measurements, also those multiple assessments within the same visit window/phase.

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

Because of the different scenarios for Cohort 1 vs Cohort 2 participants, a flag called Analysis Timepoint EOI (ATEOI) is created for each participant to identify the potentially different time point of end of induction phase. Similarly, an additional variable will be generated to identify the analysis timepoint for End of Consolidation (ATEOC).

Note: For the selection of the patient-reported outcome (PRO) measurements the above algorithm needs to be performed on the entire questionnaire (filled in at a specific date and time) and not on the individual questions /items (i.e., not mixing answers from different questionnaires).

Table 2 provides the analysis time points, time intervals for each visit per analysis phase.

Table 2: Analysis Time Points and Time Intervals by Analysis Phase

a) Screening and Induction Phases (Cohort 1 and 2)

Analysis phase	Target day	Analysis time point (Week)			Analysis time point (label)	Time interval (Induction days)
		Cohort 1a[a]	Cohort 1b[b]	Cohort 2[c]		
Screening	-∞	-1	-1	-1	Screening	<0
Induction	1	0	0	0	Baseline	Pre-dose: 1
	15	2	2	2	Week 2	[2,22]
	29	4	4	4	Week 4	[23,36]
	43	6	6	6	Week 6	[37,50]
	57	8	8	8	Week 8	[51, 71]
	85	12	12	12	Week 12	[72, 99]
	113	16	16	16	Week 16	[100, 127]
	141	20	20	20	Week 20	[128, 155]
	169	24	24	24	Week 24	[156, 183]
	197	28	28	28	Week 28	[184, 211]
	225	32	32	32	Week 32	[212, 239]
	253	36[a]	36[b]	36[c]	Week 36	[240, 267]
	281	40[a]	N/A	N/A	Week 40	[268, 295]
	309	44[a]	N/A	N/A	Week 44	[296, 323]
	337	48[a]	N/A	N/A	Week 48	[324,351]
	365	52[a]	N/A	N/A	Week 52	[352, 379]
	393	56[a]	N/A	N/A	Week 56	[380, 407]
	421	60[a]	N/A	N/A	Week 60	[408, 435]
	last visit in induction phase	61[a, d]	37[b, d]	37[c, d]	EOI[d]	

[a] If the participant was enrolled prior to the Protocol Amendment #5 was in effect (Cohort 1) and has already passed the Week 36 visit and/or has been randomized to the group without PegIFN-α2a, then he/she will have PegIFN-α2a added to their treatment regimen at the next scheduled visit. The EOI visit could occur between Week 36 and Week 60 (inclusive).
[b] If the participant was enrolled prior to the Protocol Amendment #5 was in effect (Cohort 1) and did not pass the Week 36 visit, he/she will have PegIFN-α2a added to their treatment regimen at Week 36.
[c] If the participants was enrolled after the Protocol Amendment #6 (Cohort 2), he/she will have PegIFN-α2a added to their treatment regimen at Week 36.
[d] End of induction phase (EOI) visit will be the last visit in Induction phase.
N/A=not applicable

b) Consolidation Phases (Cohort 1 & 2)

Analysis phase	Target day	Analysis time point (Week)			Consolidation Analysis time points (label)	Time interval (Consolidation days) [h]
		Cohort 1a[e]	Cohort 1b[f]	Cohort 2[g]		
Consolidation	1	ATEOI[i]+1	36	36	C Baseline	1
	15	ATEOI[i]+1	38	38	C Week 2	[1,22]
	29	ATEOI[i]+3	40	40	C Week 4	[23,36]
	43	ATEOI[i]+5	42	42	C Week 6	[37,50]
	57	ATEOI[i]+7	44	44	C Week 8	[51, 71]
	85	ATEOI[i]+11	48	48	C Week 12	[72, 99]
	last visit in consolidation phase	ATEOI[i]+12[e, j]	49[f, j]	49[g, j]	EOC[j]	

[e] Analysis time point for Cohort 1 will be based on end date of the induction phase in the Table 2 a) above.
[f] Analysis time point for Cohort 1 will be based on end date of the induction phase in the Table 2 a) above.
[g] Analysis time point for Cohort 2 will be based on end date of the induction phase in the Table 2 a) above.
[h] Relative to Consolidation start date (see the Table 1).
[i] ATEOI = Analysis time point (Week) for EOI.
[j] End of consolidation (EOC) visit will be the last post baseline visit in the Consolidation phase.

c) Follow-Up Phase (Cohort 1 & 2)

Analysis phase (FU)	Target day	Analysis time point (Week)			Analysis time point (label)	Time interval (FU days) [n]
		Cohort 1a[k]	Cohort 1b[l]	Cohort 2[m]		
Follow-up	15	ATEOC[o]+1	50	50	FU Week 2	[1, 22]
	29	ATEOC[o]+3	52	52	FU Week 4	[23, 43]
	57	ATEOC[o]+7	56	56	FU Week 8	[44, 71]
	85	ATEOC[o]+11	60	60	FU Week 12	[72, 99]
	113	ATEOC[o]+15	64	64	FU Week 16	[100, 127]
	141	ATEOC[o]+19	68	68	FU Week 20	[128, 155]
	169	ATEOC[o]+23	72	72	FU Week 24	[156, 183]
	197	ATEOC[o]+27	76	76	FU Week 28	[184, 211]
	225	ATEOC[o]+31	80	80	FU Week 32	[212, 239]
	253	ATEOC[o]+35	84	84	FU Week 36	[240, 267]
	281	ATEOC[o]+39	88	88	FU Week 40	[268, 295]
	309	ATEOC[o]+43	92	92	FU Week 44	[296, 323]
	337	ATEOC[o]+47	96	96	FU Week 48	[324, +∞]
	last visit in the study	999[k, p]	999[l, p]	999[m, p]	EOS[p]	

[k,] Analysis time point for Cohort 1 will be based on end date of the induction and consolidation phase.
[l] Analysis time point for Cohort 1 will be based on end date of the induction and consolidation phase.
[m] Analysis time point for Cohort 2 will be based on end date of the induction and consolidation phase.
[n] Relative to follow-up start date.

[o] ATEOC = Analysis time point (Week) for EOC.
[p] End of study (EOS) visit (last available data during the follow-up) will be the last visit in the study.

2.2. Baseline

2.2.1. Study Baseline

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

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

The baseline defined above is the study baseline and will be used for all analysis throughout the induction, consolidation and follow up phases.

2.2.2. Consolidation Baseline Timepoint

For the participants who receive PegIFN- α2a, the consolidation baseline assessment is defined as the date of first PegIFN- α2a intake. For the participants who did not receive PegIFN- α2a, the consolidation baseline will be defined as the date of any study agent intake after Max[Week 36 to 60 visit date] for Cohort 1 and the date of any study agent intake after Week 36 visit date for Cohort 2.

2.3. Analysis Sets

Due to a potential impact of future Coronavirus Disease 2019 (COVID-19) pandemics on the study data collection, study treatment adherence and study conduct, the modified treated (mTreated) analysis set and the modified intent-to-treat analysis (mITT) set are defined to target the estimation of the treatment effect without the pandemic-related influences.

If there is a relevant difference (5% of total population or more participants in total) from the ITT analysis vs the mITT analysis set, then, the mTreated, and mITT will be used. However, if there is less than 5% difference, then the Treated and ITT, will be used.

Treated analysis set: All participants who received at least 1 dose of study treatment within this ISA.

Modified Treated analysis set (mTreated): All participants who received at least one dose of study treatment, excluding participants who have no efficacy assessment for the primary endpoint (24 weeks after stopping all study treatment of the consolidation phase) because of COVID-19 or similar pandemics related reasons (e.g., missed visits due to travel restriction, shortage of lab kits at the planned visit, missed collection of blood sample at key time points for the primary analysis endpoint, etc.).

Intent-to-Treat analysis set (ITT): All participants who were randomized or enrolled and who received at least 1 dose of consolidation phase study intervention within this ISA.

Modified Intent-to-Treat analysis set (mITT): All participants who were randomized or enrolled and received at least one dose of the consolidation phase study intervention excluding those participants impacted by the pandemic defined as those participants who, because of COVID-19 or similar pandemics related reasons, withdrew prematurely from the study prior to FU Week 24 or had no efficacy assessment for the primary endpoint (24 weeks after stopping all study interventions of the consolidation phase). COVID-19 or similar pandemics related reasons may include for example missed visits due to travel restriction, shortage of lab kits at the planned visit, missed collection of blood sample at key time points for the primary analysis endpoint, etc.

Safety analysis set: All participants who received at least one dose of study intervention. Participants will be analyzed according to the study intervention they actually received.

***Per protocol analysis set (PP)*:** All participants in the ITT analysis set who do not have any of the selected major protocol deviations that may affect the assessment of efficacy in terms of the primary endpoint at 24 weeks after stopping all study interventions of the consolidation phase. The selected major protocol deviations for efficacy analysis purposes that will be used to identify the participants included in the PP set are described in Section 4.5 and Attachment 1: Selected Major Protocol Deviations for Analysis Purposes. Participants will be analyzed according to the study intervention they were randomly assigned to.

***Pharmacokinetics analysis set (PK)*:** The PK analysis set is defined as subjects who have received at least 1 dose of any of the study interventions and have at least 1 valid blood sample drawn for PK analysis.

2.4. On-treatment and off-treatment periods

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

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

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

2.5. Definition of Subgroups

The following demographic and screening/baseline characteristics will be used to define subgroups of interest for efficacy analyses (primary endpoint and key secondary endpoint) and selected safety analyses (see Section 6).

2.5.1. Subgroups for Efficacy Analyses

- Age categories: 18 years -≤30 years, >30 years
- Race: Asian, non-Asian
- ALT level at baseline: normal, >ULN
- HBsAg level at baseline:
  - <10,000 IU/mL
  - ≥10,000 IU/mL-<100,000 IU/mL
  - ≥100,000 IU/mL
- HBV DNA level at screening:
  - $<10^7$ IU/mL
  - $\geq 10^7$ IU/mL
- Immune tolerant at baseline
  - Yes: HBV DNA level > 7 log10 IU/mL and ALT ≤ULN
  - No: HBV DNA level ≤ 7 log10 IU/mL or ALT >ULN
- Pegylated Interferon responder definition #1
  - First, compare the ALT maximum value between Consolidation Baseline and FU Week 4 with the last value of ALT before or at the first Pegylated Interferon intake date. If the increase in ALT is >=100%, then the patient is considered as a "responder" to Pegylated Interferon. If the increase in ALT is <100%, then the patient is considered as a "non-responder" to Pegylated Interferon. Only patients who have received at least one dose of Pegylated interferon are considered.
- Pegylated Interferon responder definition #2

A linear regression model using the four last HBsAg measures before Consolidation Baseline is performed to estimate predicted value of HBsAg at CW12. If a decline higher that 0.5 log10 HBsAg is observed compared to the predicted value, then the patient is considered as a "responder" to Pegylated Interferon. Only patients who have received at least one dose of Pegylated interferon are considered.

2.5.2. Subgroups for Safety Analyses

- Sex: Male, Female
- Race: Asian, non-Asian

- Body mass index (BMI) group: Underweight <18.5, Normal ≥18.5 - <25, Overweight ≥25 - <30, and Obese ≥30
- Age categories: 18 years - ≤30 years, >30 years

2.6. 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.

2.6.1. 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 in induction phase.
  - The day of the first study treatment administration in induction phase, if the month/year of the AE onset date is the same as the month/year of the first study treatment administration in induction phase but the month/year of the AE resolution date is different.
  - The earliest between the day of the first study treatment administration date in induction phase 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 in induction phase 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 treatment administration in induction phase.
  - Month and day of the first study treatment administration in induction phase, 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 treatment administration in induction phase.
  - 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.

2.6.2. 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.

2.6.3. Concomitant Medication Dates

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

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

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

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

In case of a completely missing start date, the concomitant therapy will be considered as having started before the trial, unless the eCRF indicates 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 indicates as not ongoing.

2.6.4. Dates of Alcohol Consumptions

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

- the 15th of the month, if only the day is missing.
- the 30th of June, if only the year is available.
- if the imputed start date is after the end date, further adjustment of the imputed start date is required. It will be imputed as the end date

- if end date is completely missing and marked as Ongoing then impute with Date of first study agent intake (excluding PegIFN-α2a) for Cohort 1 and randomization date or date of first study agent intake (excluding PegIFN-α2a) for Cohort 2. Otherwise, no imputation if completely missing

3. DATA REVIEW COMMITTEE AND INTERIM ANALYSES

3.1. Data Review Committee

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

3.2. Independent Flares Monitoring

Flares in this study will be adjudicated by the independent Flares Expert Panel (iFLEP). The iFLEP flare adjudication results are sent to the DRC Chairperson, and the information will include conclusions and review history for each flare. Additional details are provided in the iFLEP Charter document. Flares are defined in Section 5.3.1.1.9.

3.3. Data Reviews and Interim Analyses

3.3.1. Data Reviews

Data review meetings will take place as follows:

- The first data review will be performed after approximately 20 participants completed 4 weeks of treatment.
- The second data review will be performed after approximately 40 participants completed 12 weeks of treatment.
- Thereafter, data reviews will occur quarterly.
- An additional data review will occur once 10 participants have completed 4 weeks of consolidation phase treatment with PegIFN-α2a. This data review may be part of a quarterly data review/the second data review if the timing of the 10 participants target coincides with a scheduled quarterly review/the second data review, otherwise, this data review will occur as a separate review.

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

Besides the safety variables listed above, selected efficacy parameters for review may include values and changes from baseline over time in HBV disease blood markers (e.g., HBV DNA,

HBeAg, and HBsAg), proportion of participants with virologic breakthrough, flares, and proportion of participants with HBsAg seroclearance.

3.3.2. Interim Analyses

Two interim analyses (IAs) are planned to assess safety and evaluate the time course of different safety and efficacy markers to support the sponsor's interactions with health authorities, as well as to inform internal decisions about additional studies and/or investigation of other treatment combination regimens.

The first IA is planned when 50% of the participants have completed Week 24 of the induction phase or discontinued earlier. The second IA is planned when all participants have completed Week 48, which corresponds to Consolidation Week 12, or discontinued earlier.

The primary analysis will be conducted at the time when all participants have completed FU Week 24 or discontinued earlier.

Both primary and interim analyses will be based on all data available at the 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 (FU Week 48) or discontinued earlier.

3.3.3. Analysis Overview of Data Reviews, Interim Analysis, Primary and Final Analyses

The overview of data domains and specific endpoints that will be provided to the DRC for review is provided in Table 3. Details on the type of summaries and analyses of both efficacy and safety variables are described in the following sections.

Table 3: Overview of Data Summaries and Different Analyses: Data Reviews, Planned Interims, Primary and Final Analyses

	DR1 (N=20 w/ Induction Week 4 data)	DR2 (N=40 w/ Induction Week 12 data)	DR quarterly[a]	IA1 Week 24 data (50% of the total participants)	IA2[b] Week 48 data (100% of the total participants)	Primary analysis/ FU Week 24 (100% of the total participants)	Final analysis/ FU Week 48 (100% of the total participants)
Subject Information							
Baseline & Demographic characteristics	X	X	X	X	X	X	X
Disposition and Study Populations	X	X	X	X	X	X	X
Extent of Exposure	X	X	X	X	X	X	X
Safety							
TEAEs, SAEs, AE of interest, fatal AEs, AEs causing treatment discontinuation	X	X	X	X	X	X	X
Laboratory Tests	X	X	X	X	X	X	X
ECG		X	X	X	X	X	X
Vital signs		X	X	X	X	X	X

	DR1 (N=20 w/ Induction Week 4 data)	DR2 (N=40 w/ Induction Week 12 data)	DR quarterly[a]	IA1 Week 24 data (50% of the total participants)	IA2[b] Week 48 data (100% of the total participants)	Primary analysis/ FU Week 24 (100% of the total participants)	Final analysis/ FU Week 48 (100% of the total participants)
Efficacy							
Proportion of participant with HBsAg seroclearance over time during FU phase			X		X	X	X
Proportion of participants with HBsAg seroclearance over time during induction phase		X	X	X	X	X	X
Proportion of participants with HBsAg seroclearance over time during consolidation phase			X	X	X	X	X
Proportion of participants with HBV DNA <LLOQ		X	X	X	X	X	X
Proportion of participants with HBsAg seroconversion			X	X	X	X	X
Proportion of participants with HBeAg seroconversion			X	X	X	X	X
HBsAg, HBeAg, HBV DNA: Values and changes over time Proportions of participants reaching given cut-offs		X	X	X	X	X	X
Virologic breakthrough	X	X	X	X	X	X	X
Flares[c]: Viral, Biochemical, Clinical	X	X	X	X	X	X	X
Correlation baseline characteristics with baseline/on-treatment viral blood markers				X	X	X	X
HBV RNA and HBcrAg Values and changes over time Proportions of participants reaching given cut-offs			X	X	X	X	X
Change in T-cell response[d]			X			X	X
Time to event analyses							X
Viral Genome Sequence Analysis [e]							
Viral genome sequence						X	X
HBV genotype						X	X
Hepatitis B Quality of Life							
HRQoL: Values and change over time Proportion of participants experiencing a clinically important improvement or worsening from baseline							X

[a] Applies to the additional DR of 10 participants having completed 4 WKs of consolidation phase treatment
[b] Applicable to potential additional IAs before the final analysis
[c] Viral and Clinical flares will be summarized for the DR quarterly and IAs
[d] If there are available data, it will be analyzed
[e] A separate virology report may be prepared

4. SUBJECT INFORMATION

All the summaries will be done by cohort on the Treated, ITT, and safety analysis set unless specified otherwise for a specific display. The PegIFN-α2a ITT, mTreated, mITT and mPegIFN-α2a ITT analysis sets may be used as indicated in Section 2.3.

4.1. Disposition Information

The number and percentage of participants who are screened, screened failure and reason for that screening failure will be tabulated by cohort and combined cohort (JNJ-3989+NA+PegIFN-α2a). Only an all participants group (total N) will be provided.

For Cohort 1, a summary of the number of participants enrolled in the induction phase, enrolled and not treated in the induction phase, randomized/enrolled and treated in the consolidation phase, randomized/enrolled but not treated in the consolidation phase, entered in the FU phase, entered and not met the NA treatment completion criteria, entered and not retreated with NA in the FU phase, will be summarized.

For Cohort 2, a summary of the number of participants, randomized/enrolled in the induction phase, randomized/enrolled and not treated in the induction and/or consolidation phase, entered in the FU phase, entered and not met the NA treatment completion criteria, entered and not retreated with NA in the FU phase, will be summarized.

Completion/withdrawal information, study disposition and treatment disposition will be summarized by cohort.

An overview of the study disposition will be provided by analysis phase, cohort 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. The number and percentage of participants under each analysis phase (i.e., induction phase, consolidation phase and follow-up phase) by cohort will also be tabulated.

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, cohort and overall. The incidences of treatment discontinuation reasons will also be summarized by analysis phase, cohort and overall.

A listing including information (i.e., cohort, 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 which prematurely discontinue from the study and/or study treatment will be included. Information on NA discontinuation and/or re-treatment will also be included.

4.2. Demographic and Baseline Characteristics

Tabulations of demographic and baseline characteristics will be presented by cohort, combined cohort and overall. Continuous variables will be summarized by descriptive statistics including the

number of participants, mean, standard deviation, standard error, median, range and interquartile range. Categorical/binary variables will be summarized by counts and percentages.

4.2.1. Demographic Characteristics

The following demographic characteristics will be summarized by cohort, combined cohort and overall.

- Sex: Male, Female, Undifferentiated, Unknown
- Age (years)
- Age categories: 18 years - ≤30 years, >30 - ≤45years, >45 years - ≤55 years
- Race: American Indian or Alaska Native, Asian (Japanese, Other Asian), Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple, Not reported
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not Reported
- Region: Asia (Japan and Taiwan), Europe (France, Germany, Russia, Spain, Turkey and UK), North America (Canada and US)
- Height at baseline (cm)
- Weight at baseline (kg)
- Body mass index (BMI) at baseline (kg/m^2) = weight at baseline (kg) / (height at baseline $(m))^2$ (rounded to 1 decimal)
- BMI group: Underweight <18.5, Normal ≥18.5-<25, Overweight ≥25-<30 and Obese ≥30
- History of Tobacco use: Yes/No
- Alcohol consumption:
  - Type of Substance (Beer, Wine, Distilled Spirits): Current/Former/Never
  - Type of Substance (Beer, Wine, Distilled Spirits) Duration (Months) = (stop date – start date +1)/30.4375; rounded to 1 decimal
  - Standard drinks containing alcohol (weekly period)

4.2.2. Baseline Characteristics

For the viral activity parameters (e.g., HBeAg, HBsAg, HBV DNA, HBV RNA, HBcrAg, anti-HBs antibody, anti-HBe antibody), baseline values are used unless specified differently.

- Prior exposure to NA versus treatment
- Duration of HBV infection (Years) = (date of first study agent administration – date of HBV infection +1)/365.25; rounded to 1 decimal
- Time since HBV diagnosis (Years) = (date of first study agent administration – date of HBV diagnosis+1)/365.25; rounded to 1 decimal
- Mode of HBV infection: Sexual transmission, intravenously injectable drug use, blood transfusion, Hemophilia-associated injection, occupational exposure, mother to child transmission, unknown and other

- HBeAg at baseline (qualitative): positive, negative, borderline
- HBeAg at baseline (quantitative): values in IU/mL and log_{10} IU/mL
- HBeAg category at baseline (quantitative: IU/mL):
  - Participants with HBeAg > ULOQ
  - Participants with HBeAg ≤ ULOQ
  - Participants with HBeAg <3 log_{10} IU/mL
  - Participants with HBeAg ≥3 log_{10} IU/mL
  - Participants with HBeAg <4 log_{10} IU/mL
  - Participants with HBeAg ≥4 log_{10} IU/mL
- HBsAg at baseline (qualitative): positive, negative
- HBsAg at baseline (quantitative): values in IU/mL and log_{10} IU/ml
- HBsAg category at baseline (quantitative: IU/mL):
  - Participants with HBsAg > ULOQ
  - Participants with HBsAg ≤ ULOQ
  - Participants with HBsAg <1,000 IU/mL
  - Participants with HBsAg ≥1,000 IU/mL-<10,000 IU/mL
  - Participants with HBsAg ≥10,000 IU/mL-<100,000 IU/mL
  - Participants with HBsAg ≥100,000 IU/mL
- HBV DNA at baseline (quantitative): values in IU/mL and log_{10} IU/mL
- HBV DNA category at baseline (quantitative: IU/mL):
  - Participants with HBV DNA < 10^7 IU/mL
  - Participants with HBV DNA ≥ 10^7IU/mL
- HBV RNA at baseline (quantitative): values in copies/mL and log_{10} copies/mL
- HBV RNA category at baseline (quantitative: copies/mL):
  - Participants with HBV RNA target not detected (TND)
  - Participants with HBV RNA < limit of detection (LOD)
  - Participants with HBV RNA < 1,000 copies /mL
  - Participants with HBV RNA ≥1,000-< 10,000 copies /mL
  - Participants with HBV RNA ≥ 10,000-<1,000,000 copies /mL
  - Participants with HBV RNA ⩾1,000,000-<10,000,000 copies /mL
  - Participants with HBV RNA ⩾10,000,000 copies /mL
  - Participants with HBV RNA < LLOQ

  - Participants with HBV RNA ≥ LLOQ
- Hepatitis B core related antigen (HBcrAg) at baseline (quantitative): values in log U/mL
- HBcrAg category at baseline (quantitative: log U/mL):
  - Participants with HBcrAg <3 log U/mL
  - Participants with HBcrAg≥3 log U/mL-<4 log U/mL
  - Participants with HBcrAg≥4 log U/mL-<9 log U/mL
  - Participants with HBcrAg≥9 log U/mL
- Alanine Transferase (ALT) at baseline:
  - Baseline ALT values (U/L)
  - Participants with normal ALT
- Fibroscan score at baseline (quantitative: kPa)
- Fibrosis Stage: F0, F1, or F2
- HBV genotype: Genotype A, B, C, D, E, F, G, H, I, J and Unknown
- Anti-HBs antibody (quantitative) at baseline: values in mIU/mL and $\log_{10}$ mIU/mL
- Anti-HBs antibody category at baseline (quantitative: mIU/mL):
  - Participants with Anti-HBs antibody level > LLOQ
  - Participants with Anti-HBs antibody level ≤ LLOQ
  - Participants with Anti-HBs antibody level >10 mIU/mL
  - Participants with Anti-HBs antibody level >100 mIU/mL
- Anti-HBs antibody (qualitative) at baseline: positive, negative
- Anti-HBe antibody (qualitative) at baseline: positive, negative

4.3. Medical History

A tabulation of the general medical history coded terms will be provided by body system class and by cohort.

4.4. Prior and Concomitant Medications

All medications will be coded using the World Health Organization-Drug Dictionary. Tabulations will include prior and concomitant medications which are defined as follows:

(i) Prior medications are defined as medications with a start date occurring before the date of Induction Day 1 regardless of when dosing of the medication ended.

(ii) Concomitant medications are defined as medications received on or after Induction Day 1, medication that was received before initial dosing and continued after initial dosing of the study interventions, or medication with missing stop date.

Medication that started before the Induction Day 1 and continued afterwards will be summarized both as prior and, separately, as concomitant medication. All concomitant medications will be displayed by cohort and allocated to one or multiple analysis phases depending on their start date and end date and also taking into account the eCRF flag to indicate if it is taken before/after study start or still ongoing.

(iii) Concomitant medications of interest include the following categories:

- Oral contraceptives (hormonal contraceptive of systemic use)
- Medications that impact immune system (e.g., corticosteroids, cyclosporin, interferon)
- Medications that can be subject to CYP3A4 induction or CYP3A4 inhibition

A frequency tabulation of prior medications, and concomitant medications will be shown by Anatomical Therapeutic Chemical (ATC) class level 2, level 4 and preferred terms by cohort. The proportion of participants who received at least one concomitant medication will also be summarized. A listing of prior medications, concomitant medications, and concomitant medications of interest, respectively, will be also provided.

4.5. Protocol Deviations

Only major protocol deviations will be summarized by cohort, combined cohort and overall.

Major protocol deviations will be based on clinical review, but not limited to, the following criteria: (1) entered but did not satisfy inclusion/exclusion criteria, (2) received wrong treatment or incorrect dose, (3) received a disallowed concomitant treatment, (4) efficacy not done at schedule visit, (5) developed withdrawal criteria but not withdrawn, (6) other. Protocol deviations will be closely monitored during the execution of the study and the final set of protocol deviation criteria will be finalized before the primary analysis database lock.

All major protocol deviations will be tabulated by coded term by cohort for the Treated, and ITT analysis set. 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 1: Selected Major Protocol Deviations for Analysis Purposes) will be identified and finalized prior to the primary database lock to define the Per-Protocol analysis set (Section 2.3). The number and percentage of ITT participants who are included in the PP analysis set will be summarized, accompanied by number and percentage of ITT participants who are excluded from the PP analysis set with the incidence of the major protocol deviations.

4.6. Extent of Exposure

Extent of exposure to study treatments will be summarized and presented based on the safety analysis set. The total duration of exposure during the induction and consolidation phase will be calculated by each study treatment separately and summarized descriptively. Exposure of each

study treatment will also be summarized across induction and consolidation phase. The duration of treatment with NA will be summarized also for the follow up phase by cohort.

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

Induction and consolidation phase separately:

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

Consolidation phase only:

- PegIFN-α2a: [Min (Date of the last PegIFN-α2a administration in the given phase +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 in the given phase + 1] /7

Total exposure to JNJ-3989, JNJ-6379, and NA for the overall treatment period (induction and consolidation phase) will be calculated as the sum of total exposure in induction, and consolidation phase.

Cut-off dates will be defined to match the prespecified timepoints for DRC periodical data reviews, interim analyses and the primary analysis, respectively (see Section 3).

The number and percentage of participants who skipped any dose of JNJ-3989 or JNJ-6379 or NA or PegIFN-α2a will be summarized separately for each study treatment during the induction and consolidation phase. 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 presented.

For FU, the total duration will add up the weeks of NA treatment. Those participants who stopped NA treatment at or before consolidation Week 12 (end of consolidation phase) and never restarted NA treatment thereafter will be counted as having zero weeks of NA exposure during the FU phase.

4.7. Treatment Compliance

Treatment compliance will be summarized for the safety analysis set for each study treatment except NA.

Treatment compliance for induction and consolidation phase (%) is defined as follows.

Induction Phase (Cohort 1)

- For JNJ-3989: (Total number of injections received/Total number of injections supposed to be received [a]) * 100%
- For JNJ-6379: (Total medication intake / 4 *7 *X) * 100%
  - As the 250 mg daily dose of JNJ-6379 consists of 4 tablets (2 tablets of 100 mg strength and 2 tablets of 25 mg strength). The numerator representing the total medication intake for JNJ-6379 is calculated as:
  - Total medication intake = (Total number of tablets dispensed–Total number of tablets returned).

[a] for each participant, the individual RGT length (weeks) determines the number of injections supposed to be received.

X: is the number of weeks on 6379 (end date of JNJ-6379 – start date of JNJ-6379) for each participant

Treatment compliance during induction phase will also be summarized descriptively by the timing of meeting the RGT criterion (categories are defined in Section 5.3.1.1.1).

Induction Phase (Cohort 2)

- For JNJ-3989: (Total number of injections received/ 9) * 100%

Consolidation Phase

- For JNJ-3989: (Total number of injections received/ 3) * 100%
- For PegIFN-α2a: (Total number of injections received/ 12) * 100%

5. EFFICACY

All efficacy data will be analyzed by cohort, combined cohort and overall, analysis phase and over time (when applicable). The primary analysis set will be the ITT analysis set for the primary efficacy endpoint, and the Treated analysis set for the rest efficacy endpoints. A secondary analysis set (combined cohort) will be performed combining the data from participants who received PegIFN-α2a but not JNJ-6379 in Cohort 1 with data of Cohort 2 by analysis phase, the PegIFN-α2a ITT analysis set will be used. This combined cohort is for the selected efficacy endpoints. The mTreated, mITT, and mPegIFN-α2a ITT will be used if relevant difference between the sets exist (see Section 2.3). Selected efficacy endpoints will be also analyzed using the PP analysis set (see definition in Section 2.3). Efficacy assessments over time will be performed at the analysis time points defined in Section 2.1.

5.1. Analysis Specifications

All efficacy endpoints will be summarized descriptively by analysis phase, cohort, combined cohort and overall. In general, continuous variables will be summarized using descriptive statistics

including the number of participants, mean, standard deviation (SD), standard error (SE), confidence interval (CI), median, and range. The confidence level is detailed in Section 5.1.1. 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.

Participants who have taken at least one dose of JNJ-6379 during induction phase could be referred as being part of Trt-1 group and the other participants who have never taken JNJ-6379 as being part of Trt-2 group.

5.1.1. Level of Significance

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

5.1.2. Data Handling Rules

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

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

HBV parameter	LLOQ	ULOQ	Imputed Values	
			If value< LLOQ	If value> ULOQ
HBsAg	0.05 IU/mL	249,750.00 IU/mL with dilution	0.025 IU/mL [a]	274,725.00 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	7.0 $\log_{10}$ U/mL w/o dilution 9.0 $\log_{10}$ U/mL with dilution	2.7 $\log_{10}$ U/mL	7.7 $\log_{10}$ U/mL[b][c] w/o dilution 9.9 $\log_{10}$ U/mL [b] with dilution
HBV DNA	20 IU/mL	170,000,000 IU/mL w/o dilution	If target detected: 15 IU/mL If target not detected: 5 IU/mL**	187,000,000[b][c] IU/mL w/o dilution
HBV RNA*	LLOQ = 2.939 $\log_{10}$ cp/mL (i.e., 869 cp/mL) LOD = 1.398 $\log_{10}$ cp/mL	NAP	If <LOD or target not detected then 1.114 $\log_{10}$ cp/mL (i.e., 13 cp/mL)	NAP

HBV parameter	LLOQ	ULOQ	Imputed Values	
			If value< LLOQ	If value> ULOQ
	(i.e., 25 cp/mL)			
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 indicated in this table

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

5.2. Primary Efficacy Endpoint

5.2.1. Definition

The primary efficacy endpoint, also known as “functional cure”, is the proportion of participants with HBsAg seroclearance 24 weeks after stopping all study interventions at the end of the consolidation phase and without restarting NA treatment.

5.2.2. Analysis Methods

All participants who do not achieve HBsAg seroclearance 24 weeks off-treatment during FU and/or require NA re-treatment within any time prior to FU Week 24 are considered treatment non-responders for the purpose of the primary endpoint analysis. The primary endpoint will be summarized with the point estimate and its 90% CI by using the Clopper-Pearson exact method by cohort.

5.2.2.1. Missing Data Handling

Missing data will be handled with three approaches: observed data analysis, missing as non-responder, and LOCF.

5.2.2.1.1. Observed Case Data

Participants who have missing HBsAg values at FU Week 24 will not be used for the analysis.

5.2.2.1.2. Missing as Non-Responder

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

5.2.2.1.3. Last Observation Carried Forward (LOCF)

The third approach to handle missing data is based on the LOCF principle (single imputation). If the HBsAg value at FU Week 24 is missing and NA treatment has not been restarted, then LOCF in conjunction with the next available observation imputation will be applied. The available non-missing HBsAg value closest to the time point which is no earlier/later than 12 weeks prior/after to the FU Week 24 time point will be used. Participants who do not have data within the analysis window of ±12 weeks around the FU Week 24 assessment will be defined as non-responders.

5.2.3. Subgroup Analyses of Primary Efficacy Endpoint

The primary efficacy endpoint will be summarized descriptively using the number and percentage of participants by cohort by each subgroup of interest (Section 2.5.1).

5.2.4. Per-Protocol Analysis

The analysis of the primary efficacy endpoint will be performed on the PP set, as defined in Section 2.3, using observed case data.

The proportion of responders will be summarized descriptively using the number and percentage of participants by cohort.

5.3. Secondary Endpoints

See Section 1.1 for a list of the secondary endpoints.

5.3.1. Definitions

5.3.1.1. Binary Endpoints

5.3.1.1.1. Reaching HBsAg <10 IU/mL During the Induction Phase

The participant has reached HBsAg <10 IU/mL at the end the induction phase, and the assessment will always be based on lab results.

5.3.1.1.2. NA Treatment Completion Criteria

5.3.1.1.2.1. NA Treatment Completion Criteria During the Study

NA treatment completion criteria are defined as follows:

- HBsAg <10 IU/mL, and
- HBeAg-negative (<LLOQ), and
- HBV DNA <LLOQ, and
- ALT <3x upper limit of normal [ULN]

The NA completion criteria will be assessed based on clinical laboratory tests and summarized at consolidation Week 12 and during FU phase.

5.3.1.1.2.2. NA Re-Treatment Criteria and Monitoring After Stopping of NA

Participants who meet the NA treatment completion criteria will be monitored closely during the follow-up phase.

After stopping NA treatment, participants should be monitored as follows:

- Regular monitoring visits will be every 4 weeks during the follow-up phase in accordance with the schedule of activities.
- A post-treatment HBV DNA value of >20,000 IU/mL should trigger re-testing of ALT/aspartate aminotransferase (AST), HBV DNA, and total and direct bilirubin within a maximum of 7 days from receipt of the data and further repeats as necessary (i.e., weekly until HBV DNA returns to <20,000 IU/mL).
- A post-treatment HBV DNA value of >2,000 IU/mL (but <20,000 IU/mL) should trigger a re-test within 14 days from receipt of the data and further repeats as necessary (i.e., every other week until HBV DNA returns to <2,000 IU/mL).
- A post-treatment ALT value of >5x ULN should trigger re-testing of ALT, AST, alkaline phosphatase (ALP), total and direct bilirubin, International Normalized Ratio (INR), albumin, and HBV DNA on a weekly basis until ALT and AST levels have returned to <5x ULN.

After stopping NA treatment, participants should re-start NA treatment:

- Immediately with signs of decreasing liver function based on laboratory findings (eg, INR, direct bilirubin) or clinical assessment (e.g., ascites, hepatic encephalopathy).
- Immediately with an HBV DNA value of >100,000 IU/mL (irrespective of confirmation and/or ALT increase).
- With confirmed post-treatment HBeAg seroreversion (HBeAg positive after it was negative at NA completion).
- With confirmed* post-treatment increases in HBV DNA >2,000 IU/mL and ALT >5x ULN.
- With confirmed* post-treatment increases in HBV DNA >20,000 IU/mL.

** At least 4 weeks apart – frequency of visits as described above.*

Note: Additional re-testing and/or earlier restarting of NA treatment is at the investigator's discretion, even if the above cut-offs are not yet met.

In case NA treatment is re-started, participants will be followed until the end of the study or until clinical stabilization, whichever comes later.

Participants who actually re-started NA treatment and monitoring after stopping of NA will be identified based on the 'Study Drug Administration for NA' CRF page.

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

5.3.1.1.3. HBsAg Seroclearance

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

HBsAg seroclearance will be evaluated over all time points when assessed.

HBsAg seroclearance will be also evaluated when assessed at all time points after stopping all study interventions (regardless when intervention was stopped) and without restarting NA treatment.

If the HBsAg value at FU Week 12 is missing, the next available observation will be used. The next non-missing lab test no later than FU Week 24 will be imputed.

If the HBsAg value at FU Week 24 is missing, the LOCF in conjunction with the next available observation imputation approach will be used. The available non-missing lab test closest to FU Week 24 which is no earlier/later than 12 weeks from the actual time point of interest (FU Week 12 and FU Week 36, respectively) will be imputed.

If the HBsAg value at FU Week 36 is missing, the LOCF in conjunction with the next available observation imputation approach will be used. The available non-missing lab test closest to FU Week 36 which is no earlier/later than 12 weeks from the actual time point of interest (FU Week 24 and FU Week 48, respectively) will be imputed.

If the HBsAg value at FU Week 48 is missing, the LOCF will be used with the condition that no value earlier than FU Week 36 may be carried forward.

For all other time points, seroclearance will be analyzed as observed case without imputation.

5.3.1.1.4. HBeAg Seroclearance

Seroclearance of HBeAg is defined as a (quantitative) HBeAg level <LLOQ and is assessed for participants HBeAg positive at baseline only.

5.3.1.1.5. HBsAg and HBeAg Seroconversion

Seroconversion of HBsAg is defined as having achieved HBsAg seroclearance (as quantitative HBsAg level <LLOQ) and appearance of anti-HBs antibodies, defined as a baseline anti-HBs (quantitative) <LLOQ and a post-baseline assessment ≥LLOQ.

Seroconversion of HBeAg is defined as having achieved HBeAg seroclearance (as quantitative HBeAg level < LLOQ) and appearance of anti-HBe antibodies, defined as a baseline anti-Hbe antibodies (qualitative) with a "NEGATIVE" result and a post-baseline assessment with “POSITIVE” result.

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

5.3.1.1.6. Suppressed HBV DNA

HBV DNA < LLOQ (HBV DNA detectable or HBV DNA TND) will be evaluated all time points when assessed after stopping all study interventions at the end of the consolidation phase and without restarting NA treatment.

HBV DNA < LLOQ (HBV DNA detectable or HBV DNA TND) will be also evaluated when assessed at all time points after stopping all study interventions (regardless when intervention was stopped) and without restarting NA treatment.

If the HBV DNA value at FU Week 12 is missing, the next available observation will be used. The next non-missing lab test no later than FU Week 24 will be imputed.

If the HBV DNA value at FU Week 24 is missing, the LOCF in conjunction with the next available observation imputation approach will be used. The available non-missing lab test closest to FU Week 24 which is no earlier/later than 12 weeks from the actual time point of interest (FU Week 12 and FU Week 36, respectively) will be imputed.

If the HBV DNA value at FU Week 36 is missing, the LOCF in conjunction with the next available observation imputation approach will be used. The available non-missing lab test closest to FU Week 36 which is no earlier/later than 12 weeks from the actual time point of interest (FU Week 24 and FU Week 48, respectively) will be imputed.

If the HBV DNA value at FU Week 48 is missing, the LOCF approach will be used with the condition that no value earlier than FU Week 36 may be carried forward.

For all other time points, HBV DNA will be analyzed as observed case without imputation.

5.3.1.1.7. Thresholds Based on HBsAg, HBeAg, HBV DNA and Multiple Markers

Thresholds for **HBsAg** values:

- <1000 IU/mL
- <100 IU/mL
- <10 IU/mL
- <1 IU/mL
- <0.05 IU/mL

Thresholds for **HBsAg** decreases 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

Thresholds for **HBeAg** values (assessed for participants HBeAg Positive at baseline only):

- < 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** decreases from baseline (assessed for participants HBeAg Positive at baseline only):

- ≥ 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

Thresholds for **HBV DNA** values:

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

Thresholds for **HBV DNA** decreases 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

5.3.1.1.8. Virologic Breakthrough

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

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

5.3.1.1.9. Flares

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

a) **Virologic flare** is defined as follows:

Virologic flare will be assessed only for those participants who are off-treatment and had HBV DNA < LLOQ at the last observed time point on all study treatments.

The start of a confirmed virologic flare is defined as the first date of two consecutive visits with HBV DNA > 200 IU/mL. The end date of the same confirmed virologic flare is defined as the first date when HBV DNA value returns to ≤ 200 IU/mL or the date of NA treatment restart, whichever comes first. Each virologic flare will be categorized based on the confirmed (i.e., two consecutive values) peak HBV DNA above any of the three thresholds within the start and end date of that flare as follows: 20,000 IU/mL 2,000 IU/mL and 200 IU/mL

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

b) **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 time point of meeting the biochemical flare criteria) while the participant does not receive any of the study interventions. The end date of the same off-treatment biochemical flare is defined as the first date when there is a 50% reduction from the peak ALT and/or AST level & < 3x ULN.

- 1 (Yes) = confirmed** ALT and/or AST ≥ 3x ULN and ≥ 3x nadir (i.e., lowest value observed during off-treatment period up to the time point of meeting the biochemical flare criteria)

- 0 (No) = otherwise

c) **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 time point of meeting the biochemical flare criteria) while the participant receives any of the study interventions. The end date of the same on-treatment biochemical flare is defined as the first date when there is a 50% reduction from the peak ALT and/or AST level & < 3x ULN, regardless of stopping the study interventions.

- 1 (Yes) = confirmed** ALT and/or AST ≥ 3x ULN and ≥ 3x nadir (i.e., lowest value observed on-treatment period up to the time point of meeting the biochemical flare criteria)

- 0 (No) = otherwise

d) **Clinical flare** is defined as follows:

A clinical flare occurs either when a virologic flare and biochemical flare overlap in time or when a biochemical flare starts within 4 weeks following the end of a virologic flare. The start date of a clinical flare is defined as the minimum start date of the virologic flare and the biochemical flare. The end date of a clinical flare is defined as the maximum end date of the virologic flare and biochemical flare, i.e., the later date between HBV DNA returns to ≤200 IU/mL and 50% reduction from the peak ALT and/or AST level & < 3x ULN .

- 1 (Yes)= confirmed** HBV DNA > peak threshold and confirmed** ALT and/or AST ≥ 3x ULN and confirmed** ≥ 3x nadir (i.e., lowest value observed during off-treatment period up to the time point of meeting the flare criteria).

- 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 breakthrough in Section 5.3.1.1.8. On-treatment will be defined as the time period in which the participant receives any of the study interventions. Off-treatment will be defined as the period after stopping all study interventions (including NA). In addition, the proportion of subjects with off-treatment virologic flares, ALT and clinical flare for subjects who met NA treatment completion criteria and stopped NA will be shown.

5.3.1.2. Values and Changes Over Time Endpoints

5.3.1.2.1. HBsAg, HBeAg, HBV DNA and ALT

Actual values (original unit and log_{10} transformed values) and changes from baseline (log_{10} transformed values) over time in HBsAg, HBeAg (for participants HBeAg positive at baseline only), HBV DNA and ALT (actual values only) will be evaluated.

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

The change from baseline value to nadir (i.e., maximum decrease for each participant) in HBsAg, HBeAg and HBV DNA will be evaluated at three intervals: on-treatment nadir, during follow-up nadir, and entire study duration nadir.

5.3.1.3. Time to Event Endpoints

5.3.1.3.1. Time to First HBsAg Seroclearance

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

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

5.3.1.3.2. Time to First HBV DNA < LLOQ

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

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

5.3.2. Analysis Methods

Statistical analyses of all secondary endpoints will be performed by cohort using Treated analysis set. The selected secondary endpoints efficacy analyses will use combining the data from participants who received PegIFN-α2a but not JNJ-6379 in Cohort 1 with data of Cohort 2, the PegIFN-α2a ITT analysis set will be used. If applicable, additional statistical analyses (descriptive statistics and spaghetti plots) may be added for each of the following subgroups: participants who

received at least one dose of JNJ-6379 and an induction phase duration of ≤36 weeks, participants who received at least one dose of JNJ-6379 and an induction phase duration >36 weeks, participants who never received JNJ-6379. The mTreated and mPegIFN-α2a ITT will be used if relevant difference between the sets exists (see Section 2.3).

5.3.2.1. Binary Outcomes

The number and proportion (%) of participants achieving the endpoints will be summarized. The associated 90% CI may also be included.

5.3.2.1.1. NA Treatment Completion Criteria

5.3.2.1.1.1. NA Treatment Completion Criteria During the Study

The count and proportion of participants who met the NA treatment completion criteria (as defined Section 5.3.1.1.2.1) and at any time during the study, regardless of the treatment duration, will be summarized by cohort.

Starting at consolidation Week 12, the incidence of participants who did not meet the NA treatment completion criteria will be summarized by cohort and at each timepoint during the study, accompanied by the distribution of each of the 4 criteria that is not met. The NA treatment completion criteria are based on a threshold for the laboratory tests of ALT, HBV DNA, HBeAg and HBsAg as defined in Section 5.3.1.1.2.1.

The count and proportion of participants who met the NA treatment completion criteria (as defined in Section 5.3.1.1.2.1) at any time during the FU phase, regardless of the treatment duration, will be summarized by cohort. All of NA treatment completion criteria will be checked based on clinical laboratory tests in FU phase.

A listing including the participants who do not meet the NA completion criteria at consolidation Week 12, and the NA completion criteria will be generated. A bar chart for including the participants who do not meet the NA completion criteria at consolidation Week 12 will be generated.

5.3.2.1.1.2. NA Re-Treatment Criteria and Monitoring After Stopping of NA

The number and proportion of participants who meet the criteria for NA re-treatment at any time during FU will be summarized descriptively by cohort. Only the subset of ITT participants who meet the NA treatment completion criteria at any time during the study and actually stop NA treatment will be included in the analysis (as defined in Section 5.3.1.1.2.2).

The proportion of participants who actually re-started NA treatment and monitoring after stopping of NA on the basis of the ‘Study Drug Administration for NA’ CRF page will be summarized separately over time by cohort.

In addition, the proportion of participants who met the above criteria according to the flag on the CRF page of 'NA Re-treatment Criteria Assessment' during the follow-up phase will be summarized over time by cohort.

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

A listing including all participants who meet the NA re-treatment criteria and monitoring after stopping of NA will be generate. This listing will also include information whether they actually re-started NA treatment (re-started/not restarted).

5.3.2.1.2. HBsAg Seroclearance

The proportion of participants achieving HBsAg seroclearance over time will be summarized by cohort and analysis phase. Separate analyses will be performed for participants who completed treatment as planned (at the end of consolidation phase), and regardless when treatment was stopped.

The proportion of participants with HBsAg seroclearance at the end of consolidation treatment will be tabulated by cohort.

The proportion of participants with HBsAg seroclearance will be evaluated at all off-treatment time points, respectively, after stopping all study interventions and without restarting NA treatment. In an additional summary, these proportions will be calculated with the denominator including only on those participants who have reached the off-treatment timepoint, and have stopped all interventions including NA and have not restarted NA prior to the timepoint of interest.

5.3.2.1.3. HBsAg and HBeAg Seroconversion

The number and proportion of participants who achieve HBsAg and HBeAg seroconversion will be summarized descriptively by cohort and analysis phase over time.

For participants achieving HBsAg seroconversion, descriptive statistics will be calculated for the level of anti-HBs antibodies at the timepoint when achieving the HBsAg seroconversion by cohort. In an additional summary, the level of anti-HBs antibodies at the specific timepoint (i.e., end of consolidation, FU Week 24, FU Week 36 and FU Week 48) will be summarized for the subset of the participants achieving HBsAg seroconversion at any time before or at that given timepoint by cohort.

5.3.2.1.4. Suppressed HBV DNA

The proportion of participants achieving HBV DNA <LLOQ (overall and separately for HBV DNA detectable and HBV DNA TND) will be summarized by cohort and analysis phase over time.

The proportion of participants with HBV DNA<LLOQ (overall and separately for HBV DNA detectable and HBV DNA TND) will be evaluated at each of the off-treatment time points,

respectively, after stopping all study interventions and without restarting NA treatment. In an additional summary, these proportions will be calculated with the denominator including only on those participants who have reached the off-treatment timepoint, and have stopped all interventions including NA and have not restarted NA prior to the timepoint of interest.

The proportion of participants who reach HBV DNA <LLOQ (overall and separately for HBV DNA detectable and HBV DNA TND) after restart of NA treatment during follow-up will also be tabulated by cohort.

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

5.3.2.1.5. Thresholds based on HBsAg, HBeAg, HBV DNA and Multiple Markers

The proportion of participants achieving the cut-offs as defined in Section 5.3.1.1.7 will be summarized by cohort and analysis phase over time.

Cumulative percentage of participants achieving any given decrease from baseline in HBsAg, HBeAg and HBV DNA respectively at the end of induction, end of consolidation, and all FU time points, separately, will be presented graphically.

For the thresholds based on multiple markers, the number and proportion of participants who meet the blood marker reduction/seroclearance thresholds at all FU time points, respectively, after stopping all study interventions (including NA) and not having NA re-treated will be summarized descriptively by cohort for each marker and each threshold listed in Section 5.3.1.1.7.

5.3.2.1.6. Virologic Breakthrough

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

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

5.3.2.1.7. Flares

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

For on-treatment biochemical flares, the incidence of flares causing treatment discontinuation will be summarized by cohort. Further, for off-treatment flares, the count and percentage of participants

who experienced a flare followed by NA re-treatment will be summarized by flare type and cohort. Similarly, the incidence of flares followed by the achievement of HBsAg seroclearance (at any time) will be summarized by flare type and cohort.

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

5.3.2.2. Values and Change Over Time Endpoints

5.3.2.2.1. HBsAg, HBeAg, HBV DNA and ALT

Descriptive statistics on actual values (original unit and log_{10} transformed values), changes from baseline (log_{10} transformed values), changes from consolidation reference time point (log_{10} transformed values) over time in HBsAg, HBeAg, HBV DNA and ALT will be summarized by cohort and analysis phase. Mean (+/- SE) plots of the actual values, change from baseline (log_{10} transformed) and change from consolidation reference time point (log_{10} transformed) will be presented over time per blood marker by cohort and analysis phase.

In addition, the change from baseline value to the nadirs (i.e., maximum decrease for each participant) will be summarized descriptively by cohort. Box plots of the changes to nadir in HBsAg, HBeAg and HBV DNA will display the distribution by cohort.

Descriptive statistics on actual values (original unit and log_{10} transformed values) and changes from baseline (log_{10} transformed values) at end of consolidation in HBsAg, HBeAg, HBV DNA and ALT (original unit), respectively, will be summarized by cohort, by NA treatment completion criteria status at the end of consolidation phase, by functional cure status at FU Week 24 and 48, and for participants who achieved functional cure 24 weeks after stopping all study interventions regardless of meeting the NA completion criteria) and at the end of FU phase.

Cross-tabulations overtime and overall of quantitative versus qualitative HBsAg and HBeAg values, respectively, will also be presented.

Spaghetti plots for both absolute values and changes from baseline of HBsAg, HBeAg, HBV DNA and ALT will be presented over time (all data collected including unscheduled visit, all data within the same time interval, see Section 2.1.3) per blood marker by cohort and by selected subgroups (e.g. HBV Genotype), by NA treatment completion criteria status at the end of consolidation phase, by functional cure status at FU Week 24 and 48, and for participants who achieved functional cure 24 weeks after stopping all study interventions regardless of meeting the NA completion criteria) and at the end of FU, separately, will be presented graphically.

Shift tables in HBV DNA categories from baseline will also be summarized by cohort and analysis phase.

5.3.2.3. Time to Event Endpoints

All time to event variables will be analyzed for all treated participants.

5.3.2.3.1. Time to First HBsAg Seroclearance

Time to first HBsAg seroclearance will be summarized. The Kaplan-Meier method will be used to estimate and plot the cumulative incidence. The median time with 90% CI will be estimated using Kaplan-Meier method.

In addition, the number and percentage of participants who had an event or were censored will be reported.

5.3.2.3.2. Time to First HBV DNA < LLOQ

Time to HBV DNA < LLOQ will be analyzed following the methodology in Section 5.3.2.3.1.

5.4. Exploratory Endpoints

5.4.1. Definitions

5.4.1.1. Binary and Categorical Endpoints

5.4.1.1.1. End of Follow-up Phase HBsAg response

The number and proportion of participants with sustained response according to the below different definitions will be summarized descriptively by cohort, combined cohort, overall and by analysis phase.

End of follow-up phase HBsAg Response definition #1:

- For participants with Follow-up Week 48 data: participants who had a >1 $\log_{10}$ decline from baseline in HBsAg at Follow-up Week 48 and HBsAg < 1000 IU/mL at Follow-up Week 48

- For participants without Follow-up Week 48 data: participants who had a >2 $\log_{10}$ decline from baseline in HBsAg at Follow-up Week 24 or a >1.5 $\log_{10}$ decline from baseline in HBsAg at Follow-up Week 36 (most recent value used) and HBsAg < 1000 IU/mL at the last available timepoint.

End of follow-up phase HBsAg Response definition #2:

- For participants who had a >1 $\log_{10}$ decline from baseline in HBsAg at the last Follow-up visit: among the 3 most recent visits, the difference between $\log_{10}$ HBsAg at 2 of the 3 last visits and 1 of the 3 last visits is < 0.2, and the difference between log10 HBsAg at 3 of the 3 last visits and 1 of the 3 last visits is < 0.2.

End of follow-up phase HBsAg Response definition #3:

- For participants with a >1 $\log_{10}$ decline from baseline in HBsAg at the last Follow-up visit: among the 3 most recent visits, the difference between $\log_{10}$ HBsAg at 2 of the 3

last visits and 1 of the 3 last visits is <0.2, and the difference between log_{10} HBsAg at 3 of the 3 last visits and 1 of the 3 last visits is <0.2 and had HBsAg <1,000 IU/mL at the last available timepoint.

End of follow-up phase HBsAg Response definition #4:

- Three categories regarding the difference between HBsAg level at the last Follow-up timepoint from CW12:
    - >0.2 log_{10} decrease: Decreasing level
    - ≤0.2 log_{10} increase or ≤0.2 log_{10} decrease: Stable level
    - >0.2 log_{10} increase: Increasing level

5.4.1.1.2. Treatment Failure

A participant will be defined as off-treatment failure if he/she never had HBsAg seroclearance 24 weeks after stopping all study interventions at the end of the consolidation phase and without restarting NA treatment.

5.4.1.1.3. Thresholds of HBV RNA and HBcrAg Levels

Thresholds for **HBV RNA** values:

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

Thresholds for **HBV RNA** decreases from baseline:

- ≥ 1 log IU/mL
- ≥ 2 log IU/mL
- ≥ 3 log IU/mL
- ≥ 4 log IU/mL
- ≥5 log IU/mL

Thresholds for **HBcrAg** values:

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

Thresholds for **HBcrAg** decreases from baseline:

- ≥ 1 log IU/mL
- ≥ 2 log IU/mL

- ≥ 3 log IU/mL
- ≥ 4 log IU/mL
- ≥ 5 log IU/mL
- ≥ 6 log IU/mL

5.4.1.1.4. Thresholds Based Multiple Markers for participants who completed NA Treatment

Thresholds based on multiple markers:

- **HBsAg<LLOQ and HBV DNA**
  - HBsAg<LLOQ and HBV DNA<LLOQ**
  - HBsAg < LLOQ and HBV DNA < LLOQ for target detected
  - HBsAg < LLOQ and HBV DNA < LLOQ for target not detected
  - HBsAg<LLOQ and HBV DNA≥LLOQ
- **HBsAg≥LLOQ and HBV DNA<2,000 IU/ml**
  - HBsAg≥LLOQ and HBV DNA<LLOQ**
  - HBsAg ≥ LLOQ and HBV DNA < LLOQ for target detected
  - HBsAg ≥ LLOQ and HBV DNA < LLOQ for target not detected
  - HBsAg ≥ LLOQ and HBV DNA < LLOQ for target detected and not detected
  - HBsAg ≥ LLOQ and LLOQ ≤ HBV DNA < 2,000 IU/mL
  - HBsAg ≥LLOQ and HBV DNA <2,000 IU/mL
  - 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 ≥LLOQ and HBV DNA ≥2,000 IU/mL
  - HBsAg <100 IU/mL and HBV DNA < LLOQ
  - 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

** HBV DNA<LLOQ will be summarized by DNA target detected, TND and overall.

Due to the exploratory objectives of this Phase 2 study, additional blood marker reduction/seroclearance thresholds may be added at a later point in time according to the clinical interest.

5.4.1.1.5. Anti-HBe Antibodies

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

5.4.1.2. Values and Change Over Time Endpoints

5.4.1.2.1. HBV RNA and HBcrAg

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

Change will be defined as: value at a given time point minus baseline value.

The change from baseline value to nadir (i.e., maximum decrease for each participant) in HBV RNA and HBcrAg will be evaluated at three intervals: on-treatment nadir, during follow-up nadir, and entire study duration nadir by met the NA treatment completion criteria and stopped NA or did not meet and did not stop NA.

5.4.1.2.2. Anti-HBs Antibodies

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

Change from baseline is defined as: value at a given time point minus baseline value. Participants who have positive and negative Anti-HBs values will be evaluated over time.

5.4.1.2.3. Liver Stiffness Measurements

Severity of liver disease at the end of study intervention and follow-up versus baseline will be evaluated by the actual values and changes in fibrosis according to Fibroscan liver stiffness measurements. Change will be defined as: value at a given time point minus baseline value.

5.4.1.3. Endpoints for Correlation

5.4.1.3.1. Association between several endpoints after the beginning of the consolidation phase

Correlations between the following endpoints will be evaluated for participants who received at least one dose of Pegylated Interferon:

- Maximum ALT increase (U/L) vs Maximum HBV DNA increase (log10 IU/mL) between Consolidation Baseline and FU Week 4

- Maximum ALT increase (U/L) vs Maximum Neutrophils (10^9/L) decrease between Consolidation Baseline and FU Week 4

- Maximum ALT increase (U/L) vs Maximum HBsAg decrease (log10 IU/mL) between Consolidation Baseline and FU Week 4

- Additional HBsAg decline (log10 IU/mL) at CW12 vs Maximum Neutrophils decrease between Consolidation Baseline and FU Week 4

- Additional HBsAg decline (log10 IU/mL) at CW12 vs Maximum ALT increase (U/L) between Consolidation Baseline and FU Week 4

To evaluate the additional HBsAg decline (log10 IU/mL) at CW12, a linear regression model using the four last HBsAg measures before Consolidation Baseline is performed to estimate Predicted value of HBsAg at CW12.

5.4.2. Analysis Methods

Statistical analyses of all exploratory endpoints will use descriptive statistics. Treated analysis set will be used. The selected exploratory endpoints efficacy analyses will use combining the data from participants who received PegIFN-α2a but not JNJ-6379 in Cohort 1 with data of Cohort 2, the PegIFN-α2a ITT analysis set will be used. If applicable, additional statistical analyses (descriptive statistics and spaghetti plots) may be added for each of the following subgroups: participants who received at least one dose of JNJ-6379 and an induction phase duration ≤36 weeks, participants who received at least one dose of JNJ-6379 and an induction phase duration > 36 weeks, participants who never received JNJ-6379. The mTreated and mPegIFN-α2a ITT will be used if relevant difference between the sets exists (see Section 2.3).

5.4.2.1. Binary Endpoints

Please see the section 5.3.2.1.

5.4.2.1.1. Treatment Failure

The number and proportion of off-treatment failure participants, as defined in Section 5.4.1.1.2, will be summarized descriptively by cohort.

5.4.2.1.2. Thresholds based on HBV RNA and HBcrAg Levels

The number and proportion of participants achieving the cut-offs as defined 5.4.1.1.3 will be summarized by cohort and analysis phase over time.

Cumulative percentage of participants achieving any given decrease from baseline in HBV RNA and HBcrAg respectively at the end of induction, end of consolidation, and all FU time points, separately, will be presented graphically.

5.4.2.1.3. Anti-HBe Antibodies

The number and proportion of participants having anti-HBe positive/negative values will be summarized by cohort and analysis phase over time.

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

5.4.2.1.4. Thresholds Based Multiple Markers for participants who completed NA Treatment

The number and proportion of participants who meet the blood marker reduction/seroclearance thresholds at all FU time points, respectively, after stopping all study interventions (including NA) and not having NA re-treated will be summarized descriptively by cohort for each marker and each threshold listed in Section 5.4.1.1.4.

5.4.2.2. Values and Change Over Time Endpoints

5.4.2.2.1. HBV RNA and HBcrAg

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, and HBV DNA as described in Section 5.3.2.2.1, including the change from baseline value to nadir (i.e., maximum decrease for each participant) and the various graphical displays.

Only the participants with HBV RNA values ≥LOD+ 0.5 $\log_{10}$ cp/mL (i.e., ≥2.99 $\log_{10}$ cp/mL) at baseline will be included in this analysis. Similarly, additional analyses only for participants with HBV RNA values ≥LOD+ 1.0 $\log_{10}$ cp/mL and ≥LOD+ 2.0 $\log_{10}$ cp/mL, respectively, will be summarized.

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

5.4.2.2.2. Anti-HBs Antibodies

The values of and changes from baseline in anti-HBs antibodies will be summarized only descriptively in a similar manner as described for values and changes from baseline over time in other blood disease markers in Section 5.3.2.2.1.

Additionally, for all ITT participants with positive anti-HBs antibodies at baseline who will reach HbsAg seroclearance (as defined in Section 5.3.1.1.3), descriptive statistics will be calculated for the change of anti-HBs antibodies level from baseline at the timepoint when achieving the HbsAg seroclearance by cohort. In an additional summary, the change of anti-HBs antibodies level from baseline at the specific timepoint (i.e., Week 12 of the consolidation phase, FU Week 4, Week 12, Week 24, Week 36 and Week 48) will be summarized descriptively for the subset of the participants achieving HbsAg seroclearance at any time before or at that given timepoint by cohort.

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

5.4.2.2.3. Liver Stiffness Measurements

Severity of liver disease at the end of consolidation phase and follow-up versus baseline will be evaluated by the changes in fibrosis according to Fibroscan liver stiffness measurements.

The changes from baseline at end of consolidation phase and end of follow-up will be summarized using descriptive statistics (n, mean, SE, 90% CI, median, minimum, maximum) by cohort

At each assessment time point, a frequency distribution of severity scores will be produced by cohort. A graphical display will also illustrate the findings.

5.4.2.3. Endpoints for Correlation

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

Correlations will be evaluated graphically using scatter plots, and heat maps displaying such potential associations by cohort and/or selected subgroups.

The following correlation coefficients will be calculated 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.

6. SAFETY

All safety analyses will be performed using the safety analysis set. All assessments will be presented by analysis phase and cohort for safety analysis set. All summaries will be only descriptive, and no inferential methods will be used for safety.

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

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

6.1. Adverse Events

6.1.1. Definitions

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 21.1 or higher). Treatment-emergent Aes (TEAE) are all Aes with a start date on or after the first administration of study

treatment or any ongoing event that worsens in severity, intensity or frequency after the first administration of study treatment. If the event date and/or resolution date is recorded as partial or completely missing, then the imputation rules described in Section 2.6.1 will apply.

6.1.2. Analysis Methods

The adverse events will be summarized by cohort and by analysis phase. Adverse events will be allocated to phases based on their start date. If the start date of an event falls between (or on) the start and stop date of an analysis phase, the AE will be attributed to that phase (treatment-emergent principle). For imputation of partially/fully missing dates please see Section 2.6.1. In case of a completely missing start date, the event is allocated to the induction study intervention phase, except if the end date of the AE falls before the first administration of study treatment in induction phase (Induction Day 1).

An overview table will summarize the incidence of TEAEs classified in the following categories: Aes, serious Aes, related Aes, Aes leading to treatment discontinuation, and fatal Aes by presenting by the number and percentage of participants who experienced at least one of such AE. The overview Aes table will be also presented stratified by the subgroup of interests identified in Section 2.5.2.

AE relationship to study treatment is grouped into either related or not related category. A related AE is defined as with possible, probable, or very likely relationship with study treatment; not related, otherwise.

All adverse events will be presented in a descending order by incidence based on all participants (Total column). The following TEAEs tables will be included in the analysis:

- All TEAEs
- Serious TEAEs
- At least grade 3 TEAEs
- At least grade 2 TEAEs and related
- TEAEs leading to treatment discontinuation
- Related TEAEs

All serious TEAE, related TEAE, TEAE leading to death, TEAE leading to treatment or study discontinuation, TEAE of at least grade 3, or adverse events of special interest (AESIs) will be listed separately. Listings will include all information collected on the Adverse Event CRF pages (e.g. information on time of onset, duration of events, time of resolution, concomitant therapies and relationship to study treatment).

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

6.1.3. Adverse Events of Special Interest (AESI)

Incidence of treatment-emergent AESI will be summarized by cohort and analysis phase. The AESI include:

- ALT/AST elevations
- JNJ-3989 related Injection Site Reactions
- Renal complications
- Hematologic abnormalities (platelet count, hemoglobin, reticulocytes, neutrophil count)
- Cholesterol increase

The list of all preferred terms belonging to ALT/AST elevations, renal complications, cholesterol increase, and hematologic abnormalities is provided in Attachment 2: Adverse events of special interest list of preferred terms. Injection site reactions will be identified using the eCRF Injection Site Reaction form.

6.2. Clinical Laboratory Tests

6.2.1. Definitions

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	RBC Indices: Mean corpuscular volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Hematology Coagulation	Activated Partial Thromboplastin Time (APTT) Fibrinogen (FIBRINO) Prothrombin Intl. Normalized Ratio (INR) Prothrombin Time (PT)		
Clinical Chemistry	Sodium Potassium Chloride Bicarbonate Blood urea nitrogen Creatinine 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 Cystatin C	

Table 5: Laboratory Parameters

Laboratory Category	Parameters	
	Note: Creatinine clearance (eGFR calculated by the CKD-EPI formula) will be assessed. eGFR will also be assessed with the CKD-EPI-Cystatin C equation (Inker LA et al., 2012).	
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	
Thyroid function tests	TSH T4	
Other optional tests in response to ALT flare	Testing for HIV-1 and -2, and hepatitis A, C, and E Testing for CMV, HSV, EBV infection Ig-Electrophoresis	

The laboratory abnormalities will be determined according to the criteria specified in the DAIDS Toxicity Grading Scale (see Clinical Protocol Appendix 9, DAIDS Table) or in accordance with the normal ranges of the clinical laboratory if no gradings are available.

An assessment is treatment-emergent if the toxicity grade/abnormality worsened as compared to the grade/abnormality at baseline; this also includes the shift from abnormally high to abnormally low and vice-versa. Post-reference toxicities/abnormalities are always treatment-emergent with regard to missing toxicities/abnormalities at baseline. The abnormalities 'Abnormally high' and 'Abnormally low' are considered equally important.

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.

6.2.2. Analysis Methods

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

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

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 2.5.2.

Plots of mean (+/- SE) values and changes from baseline over time for selected laboratory parameters will be presented. Spaghetti-plots for selected laboratory parameters may be presented over time.

Additional spaghetti plots may be added for each of the following subgroups: participants who received at least one dose of JNJ-6379 and an induction phase duration ≤36 weeks, participants who received at least one dose of JNJ-6379 and an induction phase duration > 36 weeks, participants who never received JNJ-6379.

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

6.2.3. Renal Safety

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

6.2.3.1. eGFR

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

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

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

Differences between the two types of eGFR calculations will be assessed. Cross-tabulation of eGFR creatinine (<10%, 10-<30%, 30-<50% and ≥50% decrease from baseline) versus eGFR cystatin C (<10%, 10-<30%, 30-<50% and ≥50% decrease from baseline) will be presented over time.

6.2.3.1.1. Proximal Renal Tubular Function Proteinuria by Quantitative Assessment

Total urine protein, total urine albumin, UPCR and UACR will be summarized by cohort 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 cohort. The evolution over time of total urine protein and total urine albumin will also be presented.

6.2.3.1.2. Proteinuria by Urinalysis (Dipstick)

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

6.2.3.1.3. 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 cohort 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 retinal binding protein to creatinine ratio results in the following categories overtime will be tabulated:

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

6.2.3.1.4. Phosphate Excretion

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

FEPO4 will be calculated as follows:

- Based on unadjusted serum creatinine:

  FEPO4 (%) = (SCr × UPO4) / (SPO4 × Ucr) × 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 cohort and visit using descriptive statistics. Median (Q1, Q3) change from baseline in FEPO4 over time will be plotted by cohort.

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

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

Baseline Subclinical renal proximal tubulopathy

Potential Markers of Renal Proximal Tubulopathy at Baseline are:

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).

6.2.4. Electrocardiogram

6.2.4.1. Definitions

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

The abnormalities in ECG parameters will be determined according to the criteria specified in the Cardiovascular Safety – Abnormalities Table (see Clinical Protocol Appendix 7, Cardiovascular

Safety- Abnormalities Table). Abnormalities on actual values are provided for HR, PR, QRS and QTcF. Additional abnormalities on change from baseline will be provided for QTcF. No abnormalities will be defined for actual uncorrected QT values. Uncorrected QT ≥ 500 ms will be flagged and only shown in listings.

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

For each parameter, a "worst-case" analysis will be performed by using the worst abnormality and time point per participant. Worst-case will be derived within each 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).

6.2.4.2. Analysis Methods

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

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

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

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

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

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

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

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 cohort and analysis phase on safety analysis set.

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

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

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

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.

6.2.5. Vital Signs and Body Temperature

6.2.5.1. Definitions

The following parameters measurements will be analyzed:

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

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

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

For each parameter, a “worst-case” analysis will be performed by using the worst abnormality and time point per participant. Worst-case will be derived within each 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).

6.2.5.2. Analysis Methods

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 by cohort and analysis phase on safety analysis set.

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 cohort and analysis phase on safety analysis set.

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

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

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

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

6.2.6. Physical Examination

The complete physical examination including the head, neck, and thyroid findings and abnormalities will be listed.

7. VIRAL GENOME SEQUENCE ANALYSIS

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

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

Sequencing of the HBV genome will be performed to monitor HBV variants present at the time points indicated in Section 7.1.

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

7.1. Time Points and Samples

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

- Time Point of Sequence at Baseline (BLSEQ): Last available pre-first dose time point in the study with sequence data available
- Time Point of Sequence at End of Study Agent (last available on-treatment time point, with a specific focus on subjects not meeting the NA treatment completion criteria)
- Time Point of Sequence at Virologic Breakthrough: time point with sequence data available closest to the time point of virologic breakthrough (FTPT) (See Section 5.3.1.1.8 for virologic breakthrough definition)
- Time Point of Sequence at Virologic Flare: time point with sequence data available closest to the time point of Virologic flare (See Section 5.3.1.1.9 for virologic flare definition)
- Time Point of Sequence at End of Study (ESSEQ): last available off-treatment post-baseline time point in the study with sequence data available
- Time Point of Sequence at Re-treatment during Post-treatment Follow-up: time point with sequence data available closest to time point where re-treatment criteria is met (See Section 5.3.1.1.2.2)
- Aggregated Post-Baseline Study Period (ASSEQ): entire post-baseline study period, aggregate of all available time points in the study with sequence data available
- Aggregated Post-Baseline Treatment Period (ATSEQ): entire post-baseline treatment period, aggregate of all available post-baseline time points during the treatment phase with sequence data available
- Aggregated Off-treatment follow-up period: entire period with no drug taken, aggregate of all available time points during the off-treatment period with sequence data available

7.2. Definitions

(Baseline) Genetic variations (i.e., aka baseline polymorphisms) are defined as changes (on the amino acid or nucleotide level) in the subject viral sequence compared to a HBV genotype specific reference viral sequence and/or the universal HBV reference sequence (NCBI ID X02763). The reference sequence to be used is provided in the database. The reference viral sequences to be used are:

Virus	Genotype	NCBI genbank accession	NGS isolate name	Sanger genbank accession	Sanger isolate name
HBV	A	X02763	adw2	X02763	adw2
HBV	B	AB219428	PNN3	D00329	pJDW233
HBV	C	GQ924620	M38	AB014362	03D03HCC
HBV	D	AF121240	11066	V01460	ayw
HBV	E	AB106564	GA325	X75657	ayw4
HBV	F	AY090458	70H	X75658	adw4q

Virus	Genotype	NCBI genbank accession	NGS isolate name	Sanger genbank accession	Sanger isolate name
HBV	G	AF160501	IG29227	AB064311	USG825
HBV	H	FJ356716	CL150171	AY090460	LAS2523
HBV	I	EU833891	H4536-07		

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

Emerging viral variation: If at certain position a genetic variation is absent at baseline but present at later time point, the genetic variation is considered to be emerging at that time point. For NGS, emerging will be defined based on the frequency of variant at baseline and at the later time point. "Absent at baseline" is defined as a frequency of variant below 1% (<1%). "Present at later point" is defined as a frequency of variant equal or greater that 15% (≥15%) at the later time point.

Enriched genetic variations: are exclusively defined for NGS analysis. If at a certain position a genetic variation has a frequency of variant of ≥1% but <15% at baseline and a frequency of variant of ≥15% at a later time point and an increase in read frequency of ≥15%.

7.3. Parameters to Analyze

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

- Number (%) of subjects with a substitution at a specific position.
- Number (%) of subjects with a specific substitution.
- Number (%) of subjects with a specific substitution profile
- Number (%) of subjects with substitutions on amino acid level (overall and by HBV genotype (A, B, C, D, E, F, G, H, I, J and Unknown))
  - at positions of interest in the major hydrophilic loop of HBsAg.
- Number (%) of subjects with substitutions on nucleotide level
  - at the binding site positions of JNJ-3989 (i.e., JNJ-3976 and JNJ-3924) (overall and by HBV genotype (A, B, C, D, E, F, G, H, I, J and Unknown)).
  - in the precore (genome position 1896) and basal core promotor (genome positions 1762/1764) region (overall, by HBV genotype (A, B, C, D, E, F, G, H, I, J and Unknown) and by baseline HBeAg status)
- Number (%) of subjects with treatment-emergent and enriched substitutions on amino acid level at post-baseline time points (as defined in Section 7.1) by substitution profile
  - at HBV core protein position of interest (list of 15 POI),
  - at positions of interest in the polymerase region,

- Number (%) of subjects with treatment-emergent and treatment-enriched substitutions on nucleotide level at post-baseline time points (as defined in Section 7.1) by substitution profile
  - at the binding site positions of JNJ-3989 (overall and by HBV genotype (A, B, C, D, E, F, G, H, I and J)).

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

In the sequence analysis, sequences will be mapped to the respective genotype specific reference sequences after which nt changes and aa substitutions will be annotated compared to the respective genotype specific reference (see Table in Section 7.2). In addition, the X02763 (HBV genotype A), which is the master reference sequence of the HBV db, will be used as universal reference sequence. Focus of analysis and reporting of results will be on comparison versus Universal reference sequence

All NGS data will be collected using a nt and aa read frequency cut-off of ≥0.01. For the analysis of baseline nt changes and/or aa substitutions in terms of frequency of variant and impact on treatment outcome, a read frequency cut-off of ≥0.15 will be used. The analysis of treatment-emergent nt changes or aa substitutions will consider nt changes or aa substitutions absent at baseline (<0.01 read frequency) but present at a read frequency of ≥0.15 at later time points. Virology analyses based on NGS data will also evaluate treatment-enriched nt changes and aa substitutions, defined as present at baseline with a read frequency ≥0.01 but <0.15 and with an increase in read frequency of at least 0.15 post-baseline. A minimum increase in read frequency of 0.15 compared to baseline excludes small, potentially technical variations in the read frequency of minority nt changes and aa substitutions which are not expected to have clinical relevance. In addition, for subjects with treatment failure nt changes and aa substitutions detected with a read frequency ≥0.01 at baseline, at time of failure and at end of study will be described in a listing. The persistence of treatment-emergent nt changes and aa substitutions will be evaluated using a cut-off of ≥0.15 and ≥0.01.

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

7.4. Positions & Genetic Variations of Interest

On the nucleotide level:

In the basal core promotor region:

- 1762 and 1764 (Eco numbering will be used)

In the precore region:

- 1896 (Eco numbering will be used)

In the JNJ-3989 binding pocket positions:

- JNJ-3976 (S Trigger)
    - Long list (N=21): 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, and 279
- JNJ-3924 (X Trigger)
    - Long list (N=21): 1779, 1780, 1781, 1782, 1783, 1784, 1785, 1786, 1787, 1788, 1789, 1790, 1791, 1792, 1793, 1794, 1795, 1796, 1797, 1798, and 1799
- In the JNJ-3976/JNJ-3924
- Combination of JNJ-3989 binding site positions JNJ-3976 and/or JNJ-3924

Amino acid level:

In the HBV core protein (based on putative binding pocket [Bourne C. et al., 2006 & Katen S.P. et al., 2013])

- Short list (n=15): 23, 24, 25, 29, 30, 33, 37, 105, 106, 109, 110, 118, 124, 127, 128.
    - Due to an insertion of 12 amino acids in the N-terminal part of core, the 15 HBV Core Protein positions of interest for HBV genotype G are 35, 36, 37, 41, 42, 45, 49, 117, 118, 121, 122, 130, 136, 139, 140

In the pol/RT protein:

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

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

HBV GT-A		HBV-GT-B/C/F/H/I		HBV GT-D		HBV-GT-E/G	
POL number	RT number	POL number	RT number	POL number	RT number	POL number	RT number
517	169	515	169	504	169	514	169
521	173	519	173	508	173	518	173
528	180	526	180	515	180	525	180
529	181	527	181	516	181	526	181
532	184	530	184	519	184	529	184
542	194	540	194	529	194	539	194
550	202	548	202	537	202	547	202
552	204	550	204	539	204	549	204
584	236	582	236	571	236	581	236
598	250	596	250	585	250	595	250

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

- Amino acids 99 to 169

7.5. Analysis Methods

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

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

For comparison of amino acid or nucleotide levels to universal HBV reference sequences descriptive summaries will be performed by subgroups (HBeAg status at screening and HBV genotypes) by cohort. For comparison of amino acid or nucleotide levels to HBV genotype-specific reference sequences, descriptive summaries will only be performed by HBV genotypes and by cohort.

7.5.1. Baseline

The frequency of variant of baseline genetic variations, i.e., the number of subjects with baseline genetic variations, will be tabulated in frequency outputs (n, %), based on NGS data (1% and 15% cut-off), and the genetic variations will be listed for all subjects.

Subgroup analysis by the presence of baseline genetic variations will be tabulated to evaluate the impact on treatment efficacy (efficacy categories including but not limited to functional cure, treatment failure).

7.5.2. Post-Baseline

- Time of Virologic Breakthrough (if applicable)

For subjects with virologic breakthrough, the incidence of treatment emergent (NGS) and treatment enriched genetic variations (with primary focus on substitutions) will be tabulated in frequency outputs (n, %) and the genetic variations will be listed for all subjects with paired baseline and post-baseline sequencing data.

The return to baseline for subjects with virologic breakthrough and treatment-emergent genetic variations at time of virologic breakthrough may be tabulated in frequency outputs based on NGS data, as well as the treatment-emergent genetic variations in subjects who did not return to baseline.

- Time of End of Treatment

For subjects who don't meet the NA treatment completion criteria, the incidence of treatment emergent and treatment enriched variants (with primary focus on substitutions) will be tabulated

in frequency outputs (n, %) and the genetic variations will be listed for all subjects with paired baseline and post-baseline sequencing data.

The return to baseline for subjects who don't meet the NA treatment completion criteria and treatment-emergent genetic variations end of treatment may be tabulated in frequency outputs based on NGS data, as well as the treatment-emergent genetic variations in subjects who did not return to baseline.

- Time of Virologic /Clinical Flare (if applicable)

For subjects with virologic/clinical flare, the incidence of treatment emergent (NGS) and treatment enriched genetic variations (with primary focus on substitutions) will be tabulated in frequency outputs (n, %) and the genetic variations will be listed for all subjects with paired baseline and post-baseline sequencing data.

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

- Time of Re-treatment during Post-treatment Follow-up (if applicable)

For subjects who meet re-treatment criteria during follow-up, the incidence of treatment emergent and treatment enriched variants (with primary focus on substitutions) will be tabulated in frequency outputs (n, %) and the genetic variations will be listed for all subjects with paired baseline and post-baseline sequencing data.

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

- Other Post-Baseline

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

7.5.3. Over the Study Period

For all subjects, listings with relevant baseline disease and demographic characteristics, session info, all genetic variations at baseline, at time of virologic breakthrough (if applicable), at end of induction phase, at the end of consolidation phase and at end of FU will be presented.

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

7.6. HBV genotype

Plasma samples for HBV genotyping were taken at screening and tested using the INNO-LiPA HBV genotyping assay. In addition, plasma samples were taken at baseline to determine the HBV genotype using the HBV full genome sequence and phylogenetic analysis.

The number and percentage of subjects by HBV genotype for study analysis will be tabulated. In addition, cross-tabulations per HBV genotype will compare the HBV genotypes determined by the INNO-LiPA HBV genotyping assay and by using the HBV full genome sequence.

8. OTHER ANALYSIS

8.1. Pharmacokinetics

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

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

To assess the effect of PegIFN-α2a on JNJ-3989, the PK parameters of JNJ-3976, and JNJ-3924 coadministered with PegIFN-α2a at Week 8 (or 4) of the consolidation phase will be compared to those of JNJ-3976, and JNJ-3924 at Week 24 (or 28 or 32) of the induction phase as reference. The primary PK parameters are C_{max} and AUC_{24h} on the logarithmic scale. A mixed effects model will be fitted to log-transformed PK parameters with phase (induction or consolidation) as a fixed effect and subject as a random effect.

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

Population PK analysis of concentration-time data of JNJ-3976, and JNJ-3924, and, optionally, of JNJ-6379, NA and/or PegIFN-α2a may be performed using non-linear mixed effects modeling. Data may be combined with selected Phase 1 and/or 2 studies to support a relevant structural model. Available participant characteristics (e.g., demographics, laboratory variables, genotypes) will be included in the model as necessary. Details will be given in a population PK analysis plan and results of the population PK analysis, if applied, will be presented in a separate report.

8.2. Pharmacokinetic/Pharmacodynamic Relationships

Relationships of PK parameters for JNJ-3989, JNJ-3924, and, optionally, of JNJ-6379, Nas and/or PegIFN-α2a, as applicable, with selected efficacy and with selected safety endpoints will be evaluated, applying graphical tools and, if feasible, statistical models.

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

Effect of PegIFN-α2a coadministration on the PK of JNJ-3976, JNJ-3924, and JNJ-6379 if applicable, will be presented in a separate report.

8.3. Immune Analyses

Descriptive statistics (n, mean, SD, SE, CV, geometric mean, median, minimum, and maximum) may be used to describe the magnitude of the gamma interferon (IFN-γ) T-cell response or the CD4+ and CD8+ T-cell responses (expressing at least 1 cytokine such as interleukin [IL]-2, tumor necrosis factor [TNF]-α or IFN-γ specific to any HBV antigen) as defined by ELISpot and/or ICS, respectively. Changes from baseline (if present) may also be tabulated for PBMCs during study intervention and follow-up. The proportion (%) of CHB patients 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, may be determined. Changes from baseline in HBV-specific peripheral blood T-cell responses may be summarized and tabulated.

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

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

9. PATIENT-REPORTED OUTCOMES

The impact of HBV/HDV treatment on participants will be assessed using PROs at predefined time points. The following PRO instruments will be used: Hepatitis B Quality of Life (HBQOL), Short Form 36 version 2 (SF-36), and EQ-5D-5L. All PRO analyses will be performed using the ITT analysis set.

9.1. Hepatitis B Quality of Life Instrument (HBQOL)

9.1.1. Definition

The HBQOL version 1 is a 31-item disease-specific instrument designed to measure HRQoL for participants with CHB.

Each item is scored on a 5-level response scale ranging from 1 through 5. Each response is transformed along a 0 to 100-point scale, where lower scores denote less HRQOL impact, and higher scores denote more HRQOL impact (i.e., 0=best score; 100=worst score), as follows:

Level 1 – 0 points

Level 2 – 25 points

Level 3 – 50 points

Level 4 – 75 points

Level 5 – 100 points

The items are combined to form 7 subscales, as follows:

Psychological Well-Being (8 Items): Anxious (F6), Frustrated (F4), Sad (F3), Angry (F7), Less Enjoyable (F10), Scared (F13), Bad (F9), Isolated (F8)

Anticipation Anxiety (6 Items): Concern Failure (C1), Concern Cancer (C2), Concern Worsen (C15), Concern Serious (C12), Concern Survival (C9), Concern Flare (C5)

Vitality (5 Items): Tiredness (P1), Worn Out (F5), Muscle Aches (P3), Memory Problems (P2), Unproductive (F12)

Stigma (6 Items): Concern Embarrassed (C14), Ashamed (F1), Concern Self-Conscious (C10), Concern Socially Isolated (C11), Concern Boss (C3), Stigmatized (F2)

Vulnerability (3 Items): Concern Eat (C13), Concern Sick Easily (C6), Concern Medicines (C8)

Transmission (3 Items): Concern Transmit Sex (C7), Concern Transmit Child (C4), Sex Difficult (F11)

Viral Response (4 Items): Concern Transmit Sex (C7), Concern Transmit Child (C4), Concern Eat (C13), Concern Medicines (C8)

Each subscale score is simply calculated as the average score among the items included in that subscale. In addition to the 7 subscales, there is a single global score that reflects the results on all 31 items. The global score is the average score among all the items in the HBQOL. Responses are transformed along a 0 to 100-point scale, where lower scores denote less HRQOL impact, and higher scores denote more HRQOL impact (i.e., 0=best score; 100=worst score).

For example, consider these sample scores for items in the vulnerability scale:

Item Number	Item Name	Raw Score	Scaled Score
C13	Concern eat	2	25
C6	Concern sick easily	4	75
C8	Concern medicines	3	50
		Average	**50**

The score on this subscale is 50 out of a possible score of 100, where higher scores denote more severe negative impact of HBV on HRQOL.

9.1.2. Analysis Methods

Descriptive statistics of the actual values and change from baseline values at each timepoint (including baseline, Week 24, end of induction, end of consolidation phase, FU Week 24 and FU Week48) for the derived scores will be displayed for subscales/domains and global score by analysis phase and by cohort. The proportion of participants experiencing a clinically important improvement or worsening from baseline (if applicable) at each timepoint will be calculated by analysis phase and by cohort. Clinically important improvement = change from baseline >= 10, Clinically important worsening = change from baseline <= -10. Other change from baseline values will be categorized as 'No clinically important change'. Analyses will also be performed on the changes from baseline at specific time points (end of consolidation phase, FU Week 24 and FU Week 48) as appropriate for different subgroups: participants with HBsAg seroclearance 24 weeks and 48 weeks after completion of consolidation phase treatment, in patients stopping NA (at FU Week 2) without restarting NA treatment, versus those without HBsAg seroclearance at those time points.

9.2. Short Form 36 version 2

9.2.1. Definition

The SF-36 is a 36-item generic PRO instrument designed to measure physical and mental health status. Participants self-report on items that have between 2-6 response options per item using Likert-type responses (e.g., none of the time, some of the time). The SF-36 is scored and interpreted using two summary scores – Physical Component Summary (PCS) and Mental Component Summary (MCS) – and eight domain subscales:

- PF: Physical functioning
- RP: Role limitations due to physical health problems
- BP: Bodily pain
- SF: Social functioning
- MH: General mental health, covering psychological distress & well-being
- RE: Role limitations due to emotional problems
- VT: Vitality, energy and fatigue
- GH: General health perceptions

Although SF-36v2 PCS and MCS scores include information from all 8 SF-36 domain subscales, the PCS score gives more weight to physical aspects of health status as represented in the Physical functioning, Physical role limitations, Pain, and General health perception domain scores. The MCS score gives more weight to the emotional and mental and social aspects of health status as assessed by the Vitality, Social function, Social role limitations, and Mental health domain scores.

A scoring algorithm will be used to convert the raw scores into the eight dimensions listed above. The total domain scores of domain scales will be transformed into a range from zero where the respondent has the worst possible health to 100 where the respondent is in the best possible health. The scores (0-100) will then be standardized using means and standard deviation from 2009 U.S. general population and converted to norm-based scores using a T-score transformation (mean = 50, SD = 10). The two component scores will be derived as linear combination of the standardized (2009 U.S. norm) scores using weights from principal component analysis. Each component score will be transformed to the corresponding PCS T-score and MCS T-score (mean = 50 and SD = 10)

The domain scale scores, and component summary scores will be calculated using the Quality Metric Health Outcomes™ Scoring Software, version 4.5.1 or a later version and the OPTUM scoring software (Third Party vendor). In case of missingness the Full Missing Score Estimation (MSE) method or Item Response Theory (IRT) will be used, if applicable, for imputation of missing values (Maruish, 2011).

9.2.2. Analysis Methods

Descriptive statistics of the actual values and change from baseline values at each timepoint (including baseline and available analysis time point) for the derived PCS, MCS and 8 domain scores will be displayed by analysis phase and by cohort.

The number (and percentage) of participants with clinically important improvement/ worsening will be presented for SF-36 v2 components (PCS score, MCS score and 8 domain scores (T-scores):

- Clinical Important Improvement = change from baseline ≥ 5
- Clinical Important Worsening = change from baseline ≤ -5.
- Other changes from baseline values are categorized as ‘No Clinically Important Change’.

9.3. 5-Level EuroQol 5-Dimension Questionnaire

9.3.1. Definition

The EQ-5D-5L questionnaire is a generic health-related quality-of-life assessment that evaluates a participant’s self-rated health state on 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Additionally, a VAS records the participant’s self-rated health on a vertical VAS where the endpoints are labelled ‘best imaginable health state’ (100) and ‘worst imaginable health state’ (0).

The EQ-5D-5L questionnaire will be analyzed in 3 ways:

- EQ-5D descriptive system scores (5 scores reflecting each of the 5 dimensions).

  An assessment that evaluates a subject's self-rated health state on 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) with 5 possible levels (no problems (level code = 1), slight problems (level code = 2), moderate problems (level code = 3), severe problems (level code = 4), extreme problems (level code = 5)).

  EQ-5D VAS a continuous score ranging from 0 to 100 (with a possible range from 0 [worst imaginable health] to 100 [best imaginable health]);

  This information can be used as a quantitative measure of health outcome as judged by the subject.

- EQ-5D Valuation index summarizes the information of the 5 dimensions of the descriptive system as below.

  a. Assign the level code 1, 2, 3, 4 and 5 to each level of the 5 dimensions (see above)

  b. Create a health state for each patient-time point combination. A health state is a combination of 5 level codes; one level code for each dimension.

  E.g., health state 12543 indicates 'no problems in walking about, slight problems washing or dressing myself, unable to do my usual activities, severe pain or discomfort, moderately anxious or depressed'.

  c. Assign an index value (valuation index) to each observed health state. Based on the origin of the subjects, another method can be used.

Missing Data:

If – for a questionnaire – one (or more) dimensions of the descriptive system are missing, then

- The EQ-5D VAS will be tabulated if not missing
- The valuation index will not be tabulated
- The non-missing dimensions of EQ-5D descriptive system will be summarized

If – for a questionnaire – the EQ-5D VAS is missing then the EQ-5D descriptive system and validation index will be tabulated if complete.

9.3.2. Analysis Methods

For the EQ-5D descriptive system, descriptive statistics on the actual value and change from baseline will be presented by analysis phase and by cohort.

For the EQ-5D VAS and for the Valuation index, descriptive statistics for the actual and change from baseline values at each time point will be displayed. In addition, mean changes from baseline will be explored as appropriate for different subgroups: participants with HBsAg seroclearance 24 weeks and 48 weeks after completion of consolidation phase treatment, in patients stopping NA

(at FU Week 2) without restarting NA treatment, versus those without HBsAg seroclearance at those time points.

The clinically important thresholds of 7 and 10 will be used to interpret the mean change from baseline in the VAS.

The number (and percentage) of participants with clinically important improvement/ worsening will be presented for EQ-5D VAS:

- Clinical Important Improvement = change from baseline ≥ 7, and also for ≥ 10
- Clinical Important Worsening = change from baseline ≤ -7, and also for ≤ -10.
- Other changes from baseline values are categorized as 'No Clinically Important Change'.

A cumulative distribution function of the EQ-5D VAS will be drawn at different time points (baseline and changes from baseline).

9.4. Patient Global Impression of Change Scale (PGIC)

9.4.1. Definition

The PGIC scale is a single-item PRO scale aimed at assessing the participant's perceptions of change (improvement or worsening) in how they feel overall compared to the beginning of the study. Response options include: "Much better", "Better", "A little better", "No change", "A little worse", "Worse", "Much worse".

9.4.2. Analysis Methods

The tabulation of the number and percentage of participants at each response level will be displayed per time point by analysis phase and by cohort.

10. REFERENCES

1. European Association for the Study of the Liver. EASL clinical practice guidelines on the Management of chronic hepatitis B virus infection. J Hepatol. 2017;67(2):370-398.
2. Bourne, C. R., Finn, M. G., & Zlotnick, A. (2006). Global structural changes in hepatitis B virus capsids induced by the assembly effector HAP1. Journal of virology, 80(22), 11055-11061.
3. Brooks ST, Whitely E, Egger M, Smith GD, Mulheran PA, Peters TJ. Subgroup analyses in randomized trials: risks of subgroup-specific analyses; power and sample size for the interaction test. J Clin Epidemiol. 2004;229-236.
4. Graham JW, Olchowski A E, Gilreath T D, How Many Imputations are Really Needed? Some Practical Clarifications of Multiple Imputation Theory, Prev Sci . 2007 Sep;8(3):206-13
5. Honaker J, King G et al.. Amelia II: A Program for Missing Data. Journal of Statistical Software, 45, 7, Pp. 1-47.
6. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, Coresh J, Levey AS; CKD-EPI Investigators. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012 Jul 5;367(1):20-9.
7. Katen, S. P., Tan, Z., Chirapu, S. R., Finn, M. G., & Zlotnick, A. (2013). Assembly-directed antivirals differentially bind quasiequivalent pockets to modify hepatitis B virus capsid tertiary and quaternary structure. Structure, 21(8), 1406-1416.
8. King G., Honaker J., Joseph A., et al. Analyzing Incomplete Political Science Data: An Alternative Algorithm for Multiple Imputation. American Political Science Review, Vol. 95:49-69.
9. Klumpp, K., Lam, A. M., Lukacs, C., Vogel, R., Ren, S., Espiritu, C., … & Efimov, A. (2015). High-resolution crystal structure of a hepatitis B virus replication inhibitor bound to the viral core protein. Proceedings of the National Academy of Sciences, 112(49), 15196-15201.
10. Lui K.J., Kelly C. A Revisit on Tests for Homogeneity of the Risk Difference, Biometrics, 2000; 56:309-315.
11. Mantel N and Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959;22:719-748.
12. Maruish M. E. (Ed.). User's manual for the SF-36v2 Health Survey (3rd ed.). Lincoln, RI:QualityMetric Incorporated.
13. Qiu, Z., Lin, X., Zhou, M., Liu, Y., Zhu, W., Chen, W., ... & Huang, M. (2016). Design and synthesis of orally bioavailable 4-methyl heteroaryldihydropyrimidine based hepatitis B virus (HBV) capsid inhibitors. Journal of medicinal chemistry, 59(16), 7651-7666.
14. Ratitch B., Lipkovitch I., O'Kelly M. (2013), Combining Analysis Results from Multiply Imputed Categorical Data, PhasrmaSUG, Paper SP03.
15. Tu, J., Li, J. J., Shan, Z. J., & Zhai, H. L. (2017). Exploring the binding mechanism of Heteroaryldihydropyrimidines and Hepatitis B Virus capsid combined 3D-QSAR and molecular dynamics. Antiviral research, 137, 151-164.
16. Zhou, Z., Hu, T., Zhou, X., Wildum, S., Garcia-Alcalde, F., Xu, Z., ... & Shen, F. (2017). Heteroaryldihydropyrimidine (HAP) and sulfamoylbenzamide (SBA) inhibit hepatitis B virus replication by different molecular mechanisms. Scientific reports, 7, 42374.

ATTACHMENT 1: SELECTED MAJOR PROTOCOL DEVIATIONS FOR ANALYSIS PURPOSES

The major protocol deviations that may affect the assessment of efficacy will be updated to reflect protocol amendment and 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 A01(M01) not met: Participant was <specify> years old.	Entered but did not satisfy criteria	Yes
1.1	Inclusion criterion A01.1(M01) not met: Participant was <specify participant's age> years old.	Entered but did not satisfy criteria	Yes
2	Inclusion criterion M02 not met: a) Participant didn't have PE, medical review, vital signs and 12-lead ECG performed at screening; b) The abnormalities found on the basis of PE, medical review, vital signs and 12-lead ECG performed at screening, are not consistent with the underlying illness in the study population.	Entered but did not satisfy criteria	No
3	Inclusion criterion A03 (M03d) not met: Chronic HBeAg positive HBV infection was not documented by HBsAg positivity at screening and/or chronicity was not documented by serum HBsAg positivity, HBeAg positivity or HBV DNA positivity documented transition event., or by alternative markers of chronicity. Inclusion criterion 3 not met: participant a) was not treatment naïve b) was not HBeAg positive c) did not have serum HBV DNA at screening ⩾20,000 IU/mL or d) did not have ALT ≤2x ULN at screening and at least once >6 months prior to screening.	Entered but did not satisfy criteria	Yes
3.1	Inclusion criterion A03 1 (M03d) not met: Chronic HBeAg positive HBV infection was not documented by HBsAg positivity at screening and/or chronicity was not documented by serum HBsAg positivity, HBeAg positivity or HBV DNA positivity documented transition event., or by alternative markers of chronicity. Inclusion criterion 3 not met. a) Participant is currently treated (defined as having received <9 months of NA treatment≥12 months prior to screening) including treatment-naïve participants b) was not HBeAg positive c) did not have serum HBV DNA at screening ≥20,000 IU/mL or d) did not have normal ALT at screening and at least once >6 months prior to screening.	Entered but did not satisfy criteria	Yes
3.2	Inclusion criterion A03 2 (M03d) not met: Chronic HBeAg positive HBV infection was not documented by HBsAg positivity at screening and/or chronicity was not documented by serum HBsAg positivity, HBeAg positivity or HBV DNA positivity documented transition event., or by alternative markers of chronicity. Inclusion criterion 3 not met. a) Participant is currently treated (defined as having received <9 months of NA treatment≥12 months prior to screening) including treatment-naïve participants b) was not HBeAg positive c) did not have serum HBV DNA at screening ≥20,000 IU/mL or d) did not have ALT<2x ULN at screening and at least once >6 months prior to screening.	Entered but did not satisfy criteria	Yes
4	Inclusion criterion M04 not met:	Entered but did not satisfy criteria	No

Sequence No.	Protocol Deviation Description (DVTERM)	Protocol Deviation Coded Term (DVDECOD)	Exclude from PP
	Participant has a BMI >35.0 kg/ m² or <18.0 kg/ m²..		
5	Inclusion A05 (M05) not met: Participant (or legally acceptable representative) did not provide consent to participate in the study.	Entered but did not satisfy criteria	Yes
6	Inclusion criterion M06 not met: Participant provided an optional DNA sample which was analyzed; however, she/he did not sign a separate ICF.	Entered but did not satisfy criteria	No in general, but Yes for the Optional DNA (Pharmacogenomics DNA) sample data
7	Inclusion criterion A07 (M07) not met: Participant does not agree to remain on a highly effective method while receiving study intervention and until 90 days after last dose.	Entered but did not satisfy criteria	No
13	Inclusion criterion A13 not met: Participant does not have < specify the missing data> a. Fibroscan liver stiffness measurement =<9.0 kPa within 6 months prior to screening or at the time of screening b. and a liver biopsy result classified as Metavir F0-F2 within 1 year prior to screening or at the time of screening.	Entered but did not satisfy criteria	Yes
14	Inclusion criterion A14 not met: Participant participated in the PK sub study, but she/he did not sign a separate ICF.	Entered but did not satisfy criteria	No I
15	Exclusion criterion A01 (M01) met: Participant has evidence of <specify the infection: hepatitis A virus infection (hepatitis A antibody IgM), HCV infection (HCV antibody), hepatitis D virus (HDV) infection (HDV antibody), hepatitis E virus (HEV) infection (hepatitis E antibody IgM), or HIV-1 or HIV-2 infection (confirmed by antibodies)> at screening.	Entered but did not satisfy criteria	Yes
15.1	Exclusion criterion A01.1 (M01) met: Participant has evidence of *<specify the infection hepatitis A virus infection (hepatitis A antibody IgM), HCV infection (HCV antibody), hepatitis D virus (HDV) infection (HDV antibody), hepatitis E virus (HEV) infection (hepatitis E antibody IgM), or HIV-1 or HIV-2 infection (confirmed by antibodies)>* at screening (and no negative HIV RNA test).	Entered but did not satisfy criteria	Yes
15.2	Exclusion criterion A01.2 (M01) met: Participant has evidence of *<specify the infection hepatitis A virus infection (hepatitis A antibody IgM), HCV infection (HCV antibody), hepatitis D virus (HDV) infection (HDV antibody), hepatitis E virus (HEV) infection (hepatitis E antibody IgM), or HIV-1 or HIV-2 infection (confirmed by antibodies)>* at screening (and no negative HIV RNA test). Patients confirmed with HIV-1 or HIV-2 infection on antiretroviral treatment.	Entered but did not satisfy criteria	Yes
16	Exclusion criterion M02.1 met: Participant has evidence of hepatic decompensation at any time point prior to or at the time of screening: a. Total bilirubin >1.5xULN[a], OR b. Direct bilirubin >1.2xULN[a], OR c. Prothrombin time >1.3xULN[a] (unless caused by anticoagulation therapy or vitamin K deficiency), OR d. Serum albumin <3.2 g/dL[a], OR e. History of clinical symptoms of hepatic decompensation (e.g., ascites, jaundice, hepatic encephalopathy or coagulopathy, especially if resulting in a Child-Pugh classification B or C at the time clinical symptoms present or at screening). [a] Not explained by anything other than hepatic decompensation.	Entered but did not satisfy criteria	Yes
17	Exclusion Criterion M03 met: Participant has a history or evidence of hepatic decompensation, including but not limited to: portal hypertension, ascites, hepatic encephalopathy, esophageal varices. <Specify>.	Entered but did not satisfy criteria	Yes
18	Exclusions Criterion M04 met:	Entered but did not satisfy criteria	Yes

Sequence No.	Protocol Deviation Description (DVTERM)	Protocol Deviation Coded Term (DVDECOD)	Exclude from PP
	Participants with evidence of liver disease of non-HBV etiology. This includes but is not limited to hepatitis infections mentioned in exclusion criterion A01, drug- or alcohol-related liver disease, autoimmune hepatitis, hemochromatosis, Wilson's disease, α-1 antitrypsin deficiency, primary biliary cholangitis, primary sclerosing cholangitis, Gilbert's syndrome (mild cases are allowed, see exclusion criterion A02a) or any other non-HBV liver disease considered clinically significant by the investigator. <specify>.		
19	Exclusion Criterion M05 met: Participant with signs of HCC or clinically relevant renal abnormalities on an abdominal ultrasound performed within 6 months prior to screening or at the time of screening. The Participant is included if HCC / abnormal ultrasound results have been ruled out.	Entered but did not satisfy criteria	Yes
20	Exclusion Criterion A06 (M06) met: Participant has one or more of the following laboratory abnormalities at screening as defined by the Division of Acquired Immunodeficiency Syndrome (DAIDS) Toxicity Grading Scale a. Estimated glomerular filtration rate (e.g.FR) <80 mL/min/1.73 m^2 at screening, calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; b. Pancreatic lipase elevation ≥grade 3; c. Pancreatic amylase elevation ≥grade 3; d. Hemoglobin ≤10.9 g/dL (males), ≤10.4 g/dL (females); e. Platelet count ≤lower limit of normal (LLN); f. Alpha-fetoprotein >100 ng/mL; g. Any other laboratory abnormality considered to be clinically significant by the investigator (also see inclusion criterion A03).	Entered but did not satisfy criteria	No
21	Exclusion Criterion M07 met: Participant has hemoglobin A1c value >8% <specify value> at screening.	Entered but did not satisfy criteria	No
22	Exclusion criterion M08 met: Participant has a history of malignancy within <specify number of years>years before screening.	Entered but did not satisfy criteria	No
23	Exclusion criterion M09.1 met: Participant has an abnormal sinus rhythm (heart rate <45 or >100 beats per minute [bpm]); QT interval corrected for heart rate according to Fridericia's formula (QTcF) >450 ms for males and >470 ms for females; QRS interval ≥120 ms; PR interval >220 ms; abnormal conduction; or any other clinically significant abnormalities on a 12-lead ECG at screening. <Specify details>.	Entered but did not satisfy criteria	No
24	Exclusion Criterion M10 met: Participant has a history of or current cardiac arrhythmias (e.g., extrasystole, tachycardia at rest), history of risk factors for Torsade de Pointes syndrome (e.g , hypokalemia, family history of long QT Syndrome) or history or other clinical evidence of significant or unstable cardiac disease (e.g., angina, congestive heart failure, myocardial infarction, diastolic dysfunction, significant arrhythmia and/or coronary heart disease), moderate to severe valvular disease, or uncontrolled hypertension at screening.<specify significant, unstable cardiac disease, moderate to severe valvular disease or uncontrolled hypertension> at screening.	Entered but did not satisfy criteria	No
25	Exclusion Criterion M11 met: Participant has a current or previous illness for which, in the opinion of the investigator and/or sponsor, participation would not be in the best interest of the particip'nt'<current or previous> illness that might interfere with the study: <specify illness>.	Entered but did not satisfy criteria	No
26	Exclusion Criterion M12 met: Participant received an organ transplant (except for skin, hair, or cornea transplants) <specify details>.	Entered but did not satisfy criteria	No
27	Exclusion Criterion M13 met: Participant has a history of clinically significant skin disease requiring regular or periodic treatment. <specify skin disease>.	Entered but did not satisfy criteria	No

Sequence No.	Protocol Deviation Description (DVTERM)	Protocol Deviation Coded Term (DVDECOD)	Exclude from PP
28	Exclusion Criterion M14 met Participant has a history of clinically relevant alcohol or drug abuse within 12 months of screening.	Entered but did not satisfy criteria	No
29	Exclusion Criterion M15 met: Participant has a history of clinically relevant drug rash: <specify drug rash>.	Entered but did not satisfy criteria	No
30	Exclusion Criterion A16 (M16) met: Participant has taken a disallowed therapy before the planned first dose of study intervention as noted in Section 6.5 of the Protocol, Concomitant Therapy before the planned first dose of study intervention.: <specify disallowed therapy>.	Entered but did not satisfy criteria	If classified as major protocol deviation, excluded from PP set.
31	Exclusion Criterion M17 met: Participant received <invasive investigational medical device within 3 months> Or received an investigational intervention or a biological product, immunoglobulin or other blood product not intended for the treatment of HBV within 6 months or 5 half-lives (whichever is longer), before the planned first dose of study intervention, Or is currently enrolled in an interventional clinical study with an investigational product.	Entered but did not satisfy criteria	If classified as major protocol deviation, excluded from PP set.
32	Exclusion Criterion A18 (M18) met: Participant is *<pregnant, breast-feeding or planning to become pregnant>* while on study treatment or within 90 days after the last dose.	Entered but did not satisfy criteria	No
33	Exclusion Criterion A19 (M19) met: Male Participant is planning to father a child while enrolled in this study or within 90 days after the last dose of JNJ-3989 and JNJ-6379.	Entered but did not satisfy criteria	No
34	Exclusion Criterion M20 met: Participant had major surgery within 12 weeks before screening, has not fully recovered of surgery or planned surgery: <specify surgery and date >.	Entered but did not satisfy criteria	No
35	Exclusion Criterion M21 met: Participant is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator <specify the investigator or study site>.	Entered but did not satisfy criteria	No
36	Exclusion Criterion M22.1 met: Participant is vulnerable.	Entered but did not satisfy criteria	Yes
37	Exclusion Criterion A23 met: Participant has a known <specify allergy, hypersensitivity or intolerance to JnJ-3989 or JnJ-6379 or their excipients >.	Entered but did not satisfy criteria	No
37.1	Exclusion Criterion A23.1 met: Participant has a known *<specify allergy, hypersensitivity or intolerance to JnJ-3989 or its excipients>*.	Entered but did not satisfy criteria	No
38	Exclusion Criterion A24 met: Participant has a known contraindication to the use of tenofovir disoproxil <provide details>.	Entered but did not satisfy criteria	No
39	Exclusion Criterion A25 met: Participants has a contraindication to the use of PegIFN-α2a as per prescribing information <provide details>	Entered but did not satisfy criteria	No
39.1	Exclusion Criterion A25.1 met: Participant has a contraindication to the use of PegIFN-α2a as per prescribing information *<provide details>*.	Entered but did not satisfy criteria	No
39.2	Exclusion Criterion A25.2 met: Participants has a contraindication to the use of PegIFN-α2a as per prescribing information *<provide details>*.	Entered but did not satisfy criteria	No
39.3	Exclusion Criterion A25.4 met:	Entered but did not satisfy criteria	No

Sequence No.	Protocol Deviation Description (DVTERM)	Protocol Deviation Coded Term (DVDECOD)	Exclude from PP
	Participants has a contraindication to the use of PegIFN-α2a as per prescribing information <*provide details*>.		
40	Participant used disallowed medication (i.e., HBV antiviral medicines as defined in description of this criterion) from 12 months prior to screening until end of follow-up: <*specify treatment, dose, unit, frequency, reason administered*>.	Received a disallowed concomitant treatment	If classified as major protocol deviation, excluded from PP set.
41	Participant used disallowed medication (as defined in description of this criterion) from 6 months prior to baseline until end of follow-up: <*specify treatment, dose, unit, frequency, reason administered*>.	Received a disallowed concomitant treatment	If classified as major protocol deviation, excluded from PP set.
42	Participant used disallowed medication (i e., any investigational agent other than the study intervention taken in the context of this study) from 6 months prior to screening until end of follow-up: <*specify treatment, dose, unit, frequency, reason administered*>.	Received a disallowed concomitant treatment	If classified as major protocol deviation, excluded from PP set.
42.1	Participant used disallowed medication (i e., any investigational agent other than the study intervention taken in the context of this study) from 6 months prior to screening until end of follow-up: <*specify treatment, dose, unit, frequency, reason administered*>.	Received a disallowed concomitant treatment	If classified as major protocol deviation, excluded from PP set.
43	Participant used disallowed medication (as defined in description of this criterion) from screening until end of follow-up: <*specify treatment, dose, unit, frequency, reason administered*>.	Received a disallowed concomitant treatment	If classified as major protocol deviation, excluded from PP set.
43.1	Participant used disallowed inhibitor/medication (as defined in description of this criterion) from screening until end of follow-up: <*specify treatment, dose, unit, frequency, reason administered*>.	Received a disallowed concomitant treatment	If classified as major protocol deviation, excluded from PP set.
44	Participant used disallowed inhibitor/medication (as defined in description of this criterion) from 1 month prior to screening until end of follow-up: <*specify treatment, dose, unit, frequency, reason administered*>.	Received a disallowed concomitant treatment	If classified as major protocol deviation, excluded from PP set.
44.1	Participant used disallowed inhibitor/medication (as defined in description of this criterion) from 1 month prior to screening until end of follow-up: <*specify treatment, dose, unit, frequency, reason administered*>.	Received a disallowed concomitant treatment	If classified as major protocol deviation, excluded from PP set.
45	Participant used disallowed Ethinylestradiol-containing contraceptives from 1 week prior to baseline until 12 weeks after EOSI: <*specify treatment, dose, unit, frequency, reason administered*>.	Received a disallowed concomitant treatment	If classified as major protocol deviation, excluded from PP set.
46	Participant did not receive dose of study drug <*specify the study medication JNJ-3989/JNJ-6379/ NA/ PegIFN-α2a*> within window <*specify out of window duration*>.	Received a disallowed concomitant treatment	If classified as major protocol deviation, excluded from PP set.
46.1	Participant did not receive dose of study drug <*specify the study medication JNJ-3989/ NA/ PegIFN-α2a*> within window <*specify out of window duration*>.	Received a disallowed concomitant treatment	If classified as major protocol deviation, excluded from PP set.
47	Participant missed <*specify number of doses*> dose of study drug JNJ-3989 at <*specify visit*>.	Received wrong treatment or incorrect dose	If classified as major protocol deviation, excluded from PP set.
48	Participant missed JNJ-6379: more than 5 doses or 3 consecutive doses within a four week period <*specify number of missed dose/consecutive dose*> within <*specify duration of missed dose*>	Received wrong treatment or incorrect dose	If classified as major protocol deviation, excluded from PP set.
48.1	Participant was administered (a) dose(s) of JNJ-6379 after approval of CTPA6.	Received wrong treatment or incorrect dose	If classified as major protocol deviation, excluded from PP set.
49	Participant missed NA treatment for more than 5 doses within a four week period. <*specify number of missed dose*> within <*specify duration of missed dose*>	Received wrong treatment or incorrect dose	If classified as major protocol deviation, excluded from PP set.
50	Participant missed 2 or more PegIFN-α2a doses <*specify number of missed dose*>.	Received wrong treatment or incorrect dose	If classified as major protocol deviation, excluded from PP set.
51	Participant received expired study medication <JNJ-3989/ JNJ-6379/ NA/ PegIFN-α2a>.	Other	If classified as major protocol deviation, excluded from PP set.
52	Study treatment <JNJ-3989, JNJ-6379/ NA/ PegIFN-α2a> was not <prepared/ handled/ stored> in line with intervention-specific pharmacy manual/ study site investigational product and procedures manual <specify the incorrect preparation/handling/storage conditions>.	Other	If classified as major protocol deviation, excluded from PP set.
52.1	Study treatment <*JNJ-3989, NA/ PegIFN-α2a*> was not <*prepared/ handled/ stored*> in line with intervention-specific pharmacy manual/ study site investigational product and procedures manual <*specify the incorrect preparation/handling/storage conditions*>.	Other	If classified as major protocol deviation, excluded from PP set.
53	Participant has event of "signs of decreasing liver function" based on laboratory or clinical findings but did not start NA treatment.	Received wrong treatment or incorrect dose	If classified as major protocol deviation, excluded from PP set.

Sequence No.	Protocol Deviation Description (DVTERM)	Protocol Deviation Coded Term (DVDECOD)	Exclude from PP
53.1	Participant has event of "signs of decreasing liver function" based on laboratory or clinical findings or HBV DNA value of >1,000,000 IU/mL (irrespective of confirmation and/or ALT increase) but did not start NA treatment.	Received wrong treatment or incorrect dose	If classified as major protocol deviation, excluded from PP set.
54	Participant has confirmed HBeAg seroreversion but did not start NA treatment.	Received wrong treatment or incorrect dose	If classified as major protocol deviation, excluded from PP set.
55	Participant has a confirmed post-treatment increase in HBV DNA >2,000 IU/mL and ALT >5 x ULN over a period of at least 4 weeks, but did not start NA treatment.	Received wrong treatment or incorrect dose	If classified as major protocol deviation, excluded from PP set.
55.1	Participant has a confirmed post-treatment increase in HBV DNA >2,000 IU/mL and ALT >5 x ULN over a period of at least 4 weeks, but did not start NA treatment.	Received wrong treatment or incorrect dose	If classified as major protocol deviation, excluded from PP set.
56	Participant has a confirmed post-treatment increase in HBV DNA >20,000 IU/mL over a period of at least 4 weeks, but did not start NA treatment.	Received wrong treatment or incorrect dose	If classified as major protocol deviation, excluded from PP set.
57	Participant has received a Covid-19 vaccine on the same day as PegIFN-α2a administration.	Other	If classified as major protocol deviation, excluded from PP set.
58	Patients met at least one criteria of discontinuation of study intervention but did not stop	Developed withdrawal criteria but not withdrawn	Yes
71	<*Specify study specific procedure(s)*> <*was/were*> conducted prior to signing an informed consent form.	Other	If classified as major protocol deviation, excluded from PP set.
72	<*Specify screening procedure(s)*> <*was/were*> not performed within <*28 days or 42 days*> before first study drug administration.	Other	If classified as major protocol deviation, excluded from PP set.
73	Screen failed Participant was rescreened without agreement with the sponsor.	Other	If classified as major protocol deviation, excluded from PP set.
74	Study <specify the visit which> procedure not done at scheduled Visits.	Other	If classified as major protocol deviation, excluded from PP set.
75	Efficacy evaluation <*specify assessment*> not done at scheduled Visits.	Other	If classified as major protocol deviation, excluded from PP set.
76	Study Visits <*specify visit*> not performed per protocol.	Other	If classified as major protocol deviation, excluded from PP set.
77	Potential confusion between cross-over sites participating in REEF-studies.	Other	If classified as major protocol deviation, excluded from PP set.
78	Site reported protocol deviation not specified elsewhere.	Other	If classified as major protocol deviation, excluded from PP set.
79	<*Specify visit(s)*>: <*specify blood, serum or urine, e.g., PK Samples, PMBC Sample*> sample were collected in error however not destroyed.	Other	If classified as major protocol deviation, excluded from PP set.
80	Study Visits <*specify visit*> not performed per protocol.	Other	If classified as major protocol deviation, excluded from PP set.

ATTACHMENT 2: ADVERSE EVENTS OF SPECIAL INTEREST LIST OF PREFERRED TERMS

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

Adverse Event of Special Interest	Source	Preferred Term
		Glomerulonephropathy
		Nephrolithiasis
Cholesterol increase	Dyslipidaemia (SMQ), (MedDRA v25.1)	Blood cholesterol abnormal
		Blood cholesterol esterase increased
		Blood cholesterol increased
		Dyslipidaemia
		High density lipoprotein abnormal
		High density lipoprotein decreased
		High density lipoprotein increased
		Hypercholesterolaemia
		Hyperlipidaemia
		Hypo HDL cholesterolaemia
		Intermediate density lipoprotein decreased
		Intermediate density lipoprotein increased
		LDL/HDL ratio decreased
		LDL/HDL ratio increased
		Lipid metabolism disorder
		Lipids abnormal
		Lipids increased
		Lipoprotein abnormal
		Lipoprotein increased
		Low density lipoprotein abnormal
		Low density lipoprotein decreased
		Low density lipoprotein increased
		Non-high-density lipoprotein cholesterol decreased
		Non-high-density lipoprotein cholesterol increased
		Primary hypercholesterolaemia
		Remnant hyperlipidaemia
		Remnant-like lipoprotein particles increased
		Total cholesterol/HDL ratio abnormal
		Total cholesterol/HDL ratio decreased
		Total cholesterol/HDL ratio increased
		Very low density lipoprotein abnormal
		Very low density lipoprotein decreased
		Very low density lipoprotein increased
Hematologic abnormalities	(Modified) Haematopoietic cytopenias affecting more than one type of blood cell (SMQ), (MedDRA v25.1)	Aplastic anaemia
		Autoimmune aplastic anaemia
		Bicytopenia

Adverse Event of Special Interest	Source	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
		Full Blood count abnormal
		Blood disorder
		Bone marrow disorder
		Bone marrow infiltration
		Bone marrow myelogram abnormal
		Bone marrow necrosis
		Haematotoxicity
		Myelodysplastic syndrome
		Myelodysplastic syndrome transformation
		Myelofibrosis
		Myeloid metaplasia
		Plasmablast count decreased
		Scan bone marrow abnormal
	(Modified) Haematopoietic erythropenia (SMQ), (MedDRA v25.1)	Aplasia pure red cell
		Aplastic anaemia
		Erythroblast count decreased
		Erythroid maturation arrest
		Erythropenia
		Hypoplastic anaemia
		Microcytic anaemia
		Proerythroblast count decreased
		Red blood cell count decreased
		Reticulocyte count decreased
		Reticulocytopenia
		Anaemia
		Erythroblast count abnormal
		Erythropoiesis abnormal
		Haematocrit abnormal
		Haematocrit decreased

Adverse Event of Special Interest	Source	Preferred Term
		Haemoglobin abnormal
		Haemoglobin decreased
		Leukoerythroblastic anaemia
		Normochromic anaemia
		Normochromic normocytic anaemia
		Normocytic anaemia
		Proerythroblast count abnormal
		Red blood cell count abnormal
		Reticulocyte count abnormal
		Reticulocyte percentage decreased
	(Modified) Haematopoietic leukopenia (SMQ), (MedDRA v25.1)	Agranulocytosis
		Band neutrophil count decreased
		Band neutrophil percentage decreased
		Basophil count decreased
		Basophilopenia
		B-lymphocyte count decreased
		Cyclic neutropenia
		Eosinopenia
		Eosinophil count decreased
		Febrile neutropenia
		Granulocyte count decreased
		Granulocytes maturation arrest
		Granulocytopenia
		Idiopathic neutropenia
		Leukopenia
		Lymphocyte count decreased
		Lymphopenia
		Metamyelocyte count decreased
		Monoblast count decreased
		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

Adverse Event of Special Interest	Source	Preferred Term
		White blood cell count decreased
		Basophil count abnormal
		Basophil percentage decreased
		B-lymphocyte abnormalities
		B-lymphocyte count abnormal Differential white blood cell count abnormal
		Eosinophil count abnormal
		Eosinophil percentage decreased
		Full blood count abnormal
		Granulocytes abnormal
		Leukopenia neonatal
		Lymphocyte count abnormal
		Lymphocyte percentage abnormal
		Lymphocyte percentage decreased
		Monocyte count abnormal
		Monocyte percentage decreased
		Mononuclear cell count decreased
		Myeloblast percentage decreased
		Myelocyte percentage decreased
		Myeloid maturation arrest
		Neutrophil count abnormal
		Neutrophil percentage decreased
		Plasma cell disorder
		Plasma cells absent
		White blood cell analysis abnormal
		White blood cell count abnormal
		White blood cell disorder
	(Modified) Haematopoietic thrombocytopenia (SMQ), (MedDRA v25.1)	Acquired amegakaryocytic thrombocytopenia
		Megakaryocytes decreased
		Platelet count decreased
		Platelet maturation arrest
		Platelet production decreased
		Platelet toxicity
		Thrombocytopenia
		Megakaryocytes abnormal
		Platelet count abnormal
		Platelet disorder
		Plateletcrit abnormal
		Plateletcrit decreased