Janssen Research & Development

Statistical Analysis Plan

A Phase 2b, Multicenter, Double-blind, Active-controlled, Randomized Study to Investigate the Efficacy and Safety of Different Combination Regimens Including JNJ-73763989 and/or JNJ-56136379 for the Treatment of Chronic Hepatitis B Virus Infection

The REEF-1 Study

Protocol 73763989HPB2001; Phase 2b

JNJ-73763989 and JNJ-56136379

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

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AMENDMENT HISTORY

Document History	
Document	**Date**
Amendment 2	19 May 2022
Amendment 1	02 December 2020
Original SAP	27 November 2019

Amendment 2 (this document)

Overall rationale for the Amendment:

This administrative amendment incorporates additional clarifications on endpoints, data handling rules, and analysis timepoints and intervals that have previously been documented in the Data Presentation Specification for past interim analyses.

Clarifications, Additions, Corrections		
Section Number and Name	**Description of Change**	**Rationale**
Section 2.1 Analysis Phases and Visit Windows	Revised footnote describing cut-off dates and added table for follow-up and extended follow-up periods.	To provide clarification for cut-off date definition, and to include description for follow-up and extended follow-up visit windows.
Section 5.1.2 Data Handling Rules	Revised ULOQ and Imputed Values data cutpoints for HBsAg and HBeAg.	Update from Central Laboratory.
Section 5.2.5 Subgroup Analyses of Primary Efficacy Endpoint	Added sentence describing how to address the scenario of the model not converging.	Initial analysis of the data found that in some subgroup analyses there was an issue with model convergence. This was alleviated when the interaction term was removed from the model.
Section 5.3.5 Other Analyses of The Key Secondary Endpoint	Description added for how to handle missing data at week 72 for HBsAg for analysis #3.	To be aligned with other analyses defined in Section 5.3.5.
Section 5.4.1.1 At Week 48 and At Week 96	Added methodology for how missing data is handled for HBsAg at Week 48.	To provide description for analysis methodology for the handling of missing data.
Section 5.4.4 NA Re-Treatment During Follow-Up	Modified criteria for NA re-treatment during follow-up.	Updated due to Protocol Amendment #4 which modified the criteria for post-treatment monitoring and for nucleos(t)ide analog (NA) re-treatment for participants who discontinued NA treatment at Week 48 due to an urgent safety measure.

Clarifications, Additions, Corrections		
Section Number and Name	**Description of Change**	**Rationale**
Section 5.4.12 ALT Decrease and Normalization Section 5.4.13 ALT Normalization After NA Re-Treatment	Updated definition for ALT elevation.	Definition updated to account for subjects who may have ALT= ULN
Section 5.4.14.1 Flares Definition	Added new definitions for virologic, biochemical, and clinical flares.	The definition of Flares was updated after the approval of the SAP (REEF-1 SAP Amendment 1 dated 09 December 2020). Updates included to clearly define the start and stop time points of the flare, as well as an update to the nadir for biochemical and clinical flares
Section 5.4.15.1Virologic Breakthrough Definition	Updated definition for virologic breakthrough.	Additional clarification needed in definition.
Section 7.4 Positions & Genetic Variations of Interest	Added lists of genetic variations for JNJ-3976 and JNJ-3924	Updated list requested by Virology.

Amendment 1

Overall rationale for the Amendment: Due to the global impact of the pandemic Coronavirus Disease 2019 (COVID-19), the study team has decided to define the primary analysis set for efficacy as the **modified** Intent-to-Treat (mITT) population, which excludes from the ITT set all 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 Week 44, or had no efficacy assessment for the primary endpoint. Based on the current estimates, the study has also slightly over enrolled approximately 5% of the planned total sample size to protect the study power. Furthermore, clarifications, additions and corrections were made throughout the SAP.

Main Changes		
Section Number and Name	**Description of Change**	**Rationale**
Section 1.4 Sample Size Justification	Approximately 5% over enrollment was added	In response to COVID-19, to help mitigate the attrition rate and early treatment discontinuations.

Section 2.3 Analysis Sets	Added definition of mITT analysis set. mITT applied to different summaries and analyses throughout the SAP accordingly. Added definition of PP1 and PP2 analysis sets. PP1 and PP2 applied to different summaries and analyses of primary and key secondary endpoints.	To obtain a more accurate treatment effect estimate removing the impact COVID-19 To align intercurrent events with corresponding estimand.

Clarifications, Additions, Corrections		
Section Number and Name	**Description of Change**	**Rationale**
Section 2.5.3 Concomitant Medication Dates	Added additional rule on imputation of partial dates.	Clarification
Section 5.1.2 Data Handling Rules	ULOQ updated for HBsAg and HBeAg	Update from Central Laboratory
Section 5.2 Primary Efficacy Endpoint	Clarified the endpoint definition	Align the definition to the protocol wording of NA stopping criteria
Section 5.2 Primary Efficacy Endpoint and 5.3 Key Secondary Endpoint	Expanded text in the estimand section. Updated intercurrent events and added multiple missing data handling rules. Added Supplementary estimands and estimators.	To structure the efficacy analyses of the primary endpoint and key secondary endpoint in alignment with the estimand framework following the ICH E9-R1 guidance and to align the estimands with other clinical trial SAPs within hepatitis disease area.
Section 5.2 Primary Efficacy Endpoint	Removed reference to statistical software	Different statistical pieces of software for different steps of the primary efficacy endpoint analysis will facilitate the implementation of the predefined unchanged methods
Section 5.2 Primary Efficacy Endpoint and 5.3 Key Secondary Endpoint	Removed Wilson score CI	Wilson score approach does not account for stratification factors. Hence a method for verification of homogeneous treatment effect across randomization stratification factors was added as an additional sensitivity estimator for the primary endpoint.

Clarifications, Additions, Corrections		
Section Number and Name	**Description of Change**	**Rationale**
Section 5.4.3.3 Time to NA Treatment Completion Section 5.4.11 Time to Seroclearance Section 5.4.14.2 Time to Flare	Change 95% CI of the hazard ratio to 90% CI of the hazard ratio	Correction of typo of the confidence level
Section 5.4.14.1 Definition	Clinical flare definition changed from "1 (Yes)= confirmed** HBV DNA ≥ threshold" to "1 (Yes)= confirmed** HBV DNA > threshold"	Correction of typo in the mathematical symbol
Section 6.2 Clinical Laboratory Tests	Added imputation rules for laboratory data in the event of "<", ">", "≥" and "≤" being contained in the character result value.	Clarification
Section 6.2.3 Creatinine and Glomerular Filtration	Added new section on Creatinine and Glomerular Filtration	Added new safety analyses on renal function following IDMC recommendation
Section 7.3 Parameters to Analyze	Added J and Other genotypes to be analyzed	Added for completeness
ATTACHMENT 2	Added attachment 2 to identify the preferred terms for adverse events of special interest.	Added for completeness
Throughout the document	Clarification of text	Typographical corrections or improved language for clarity and precision
Throughout the document	Added/removed analyses	Updated analyses for completeness and internal consistency.

ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomic and therapeutic class
BMI	body mass index
CHB	chronic hepatitis B
CI	confidence interval
CRF	case report form
CV	coefficient of variation
DAIDS	division of acquired immunodeficiency syndrome
ECG	electrocardiogram
EOS	end of study
EOT	end of treatment
eCRF	electronic case report form
ETV	entecavir
HBQOL	hepatitis B Quality of Life
HBcrAg	hepatitis B core-related antigen
HBe	hepatitis B envelope
HBs	hepatitis B surface
HBeAg	hepatitis B envelope antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HBV DNA	hepatitis B virus deoxyribonucleic acid
HBV RNA	hepatitis B virus ribonucleic acid
HIV-1(-2)	human immunodeficiency virus type 1 (type 2)
ICE	intercurrent event
ICS	intracellular cytokine staining
IDMC	independent data monitoring committee
iFLEP	independent flares expert panel
IQR	interquartile range
ISR	injection site reaction
ITT	Intent-to-treat
IU/mL	international units per milliliter
IWRS	interactive website response system
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MCP-Mod	multiple comparisons procedure-modeling
MCT	multiple contrast test
MedDRA	medical dictionary for regulatory activities
MH	Mantel-Haenszel
mITT	modified intent-to-treat
MSR	Modeling and Simulation Report
NA	nucleos(t)ide analog
NGS	next generation sequencing
PBMC	peripheral blood mononuclear cell
PC	precore
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	per protocol
PRO	patient-reported outcomes
QTcF	QT interval corrected for heart rate according to Fridericia
RR	Interval between R wave of one heartbeat and R wave of preceding heartbeat
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
$SigE_{max}$	sigmoid E_{max}

TEAE	treatment-emergent adverse event
TAF	tenofovir alafenamide
TD	target detected
TDF	tenofovir disoproxil fumarate
TND	target not detected
TNF	tumor necrosis factor
ULN	upper limit of normal
WBC	white blood cell

1. INTRODUCTION

This statistical analysis plan (SAP) for study 73763989HPB2001 (REEF-1) describes the definitions of analysis sets, derived variables and statistical methods to assess the efficacy and safety of study interventions including the combinations of JNJ-73763989 (doses of 40 mg, 100 mg, or 200 mg) or placebo, and/or JNJ-56136379 (250 mg) or placebo, and Nucleos(t)ide analogs (NA) to treat HBeAg-positive and HBeAg-negative chronic HBV-infected participants who (1) are currently not being treated for their HBV infection (including treatment-naïve participants) or (2) who are virologically suppressed by current NA treatment. 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.

This SAP is to be interpreted in conjunction with the clinical protocol Amendment-2 finalized on 27 January 2020.

This is a Phase 2b, randomized, double-blind, double-dummy, active-controlled, dose-finding, parallel, multicenter, interventional study in HBeAg-positive and -negative chronic HBV-infected participants to evaluate the efficacy, safety, and pharmacokinetic (PK) of the study interventions.

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 establish the dose-response relationship for antiviral activity of 3 doses of JNJ-3989+NA and to evaluate the efficacy of combination regimens of JNJ-3989+NA (with and without JNJ-6379) and of JNJ-6379+NA.	• Proportion of participants meeting the NA treatment completion criteria at Week 48.
Secondary	
• To evaluate the safety and tolerability of the study intervention throughout the study.	• Proportion of participants with (S)AEs and abnormalities in clinical laboratory tests (including hematology, blood biochemistry, blood coagulation, urinalysis, urine chemistry, and renal biomarkers), 12-lead ECGs, and vital signs.
• To evaluate the efficacy of the study intervention during the follow-up phase.*	• Proportion of participants with HBsAg seroclearance 24 weeks after completion of all study intervention at Week 48. • Proportion of participants with HBsAg seroclearance 48 weeks after completion of all study intervention at Week 48. • Proportion of participants with HBV DNA <LLOQ 24 and 48 weeks, respectively, after

Objectives	Endpoints
	completion of all study intervention at Week 48. • Proportion of participants meeting the NA treatment completion criteria during follow-up. • Proportion of participants with HBsAg seroclearance 24 and 48 weeks, respectively, after completion of NA treatment at any time during follow-up. • Frequency of flares. • Proportion of participants requiring NA re-treatment during follow-up.
• To evaluate efficacy as measured by blood markers (such as HBsAg, HBeAg,** HBV DNA, and 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 and HBeAg** seroclearance. • Proportion of participants with HBsAg levels and/or changes from baseline below/above different cut-offs (eg, HBsAg <100 IU/mL or >1 $\log_{10}$ IU/mL reduction in HBsAg from baseline). • Proportion of HBeAg-positive participants with HBeAg** levels and/or changes from baseline below/above different cut-offs. • Proportion of participants with HBV DNA levels and/or changes from baseline below/above different cut-offs (eg, <LLOQ of the assay). • Proportion of participants with ALT decrease and normalization.
• 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 PK of JNJ-3989, JNJ-6379, and NA, as applicable.	• PK parameters of JNJ-3989, JNJ-6379, and NA, as applicable.

Objectives	Endpoints
Exploratory	
• To explore changes in the severity of liver disease at the end of follow-up versus screening/baseline.	• Changes in fibrosis (according to Fibroscan liver stiffness measurements).
• To explore the relationship between PK parameters (JNJ-3989 and/or JNJ-6379 and/or NA) and selected pharmacodynamic (PD) parameters of efficacy and/or safety, as applicable.	• Relationship between various PK parameters (JNJ-3989 and/or JNJ-6379 and/or NA) and selected efficacy and/or safety endpoints, as applicable.
• To explore efficacy as measured by HBV RNA and HBcrAg during study intervention and follow-up.	• Changes from baseline in HBV RNA and HBcrAg levels. • Time to reach undetectability of HBV RNA and HBcrAg.
• To explore the impact of the baseline HBeAg and treatment status factors on efficacy as measured by primary and secondary endpoints.	• Proportion of participants meeting the NA treatment completion criteria at Week 48. • Proportion of participants with HBsAg seroclearance 24 weeks after completion of all study intervention at Week 48. • Proportion of participants with HBsAg seroclearance 48 weeks after completion of all study intervention at Week 48. • Proportion of participants with HBV DNA <LLOQ 24 and 48 weeks after completion of all study intervention at Week 48. • Proportion of participants meeting the NA treatment completion criteria during follow-up. • Proportion of participants with HBsAg seroclearance 24 and 48 weeks after completion of NA treatment at any time during follow-up. • Frequency of flares. • Proportion of participants requiring NA re-treatment during follow-up.
• To explore the association between viral and host baseline factors with efficacy and safety.	• Correlation of viral and host baseline characteristics (such as HBV genotype, baseline HBV DNA levels, age, gender, body mass index [BMI]) with selected efficacy and safety variables.
• To explore changes in the HBV genome sequence during study intervention and follow-up.	• Emergence of intervention-associated mutations.

Objectives	Endpoints
• To explore the effect of any baseline variation in the HBV genome on efficacy.	• Correlation of HBV genome sequence with selected efficacy parameters.
• To explore HBV-specific T-cell responses during study intervention and follow-up.	• Changes from baseline in HBV-specific peripheral blood T-cell responses.
• To explore the impact of study intervention on participants' health-related quality of life (HRQoL), self-stigma, and impression of change using patient-reported outcomes (PROs) during study intervention and follow-up.	• Changes over time in score on the Hepatitis B Quality of Life (HBQOL) scale and subscales. • Changes over time in score on the HBV-specific self-stigma PRO scale. • Participants' impression of change on the Patient Global Impression of Change (PGIC) scale.

[*] The follow-up phase has a maximum duration of 96 weeks.
[**] in HBeAg-positive participants only

1.2. Trial Design

A target of 450 adult male and female participants, 18 to 65 years of age (inclusive), will be randomized in a 2:2:2:2:1:1 ratio to one of the following intervention arms:

- Arm 1: JNJ-3989 (100 mg) + JNJ-6379 (250 mg qd) + NA (N=90)
- Arm 2: JNJ-3989 (200 mg) + Placebo + NA (N=90)
- Arm 3: JNJ-3989 (100 mg) + Placebo + NA (N=90)
- Arm 4: JNJ-3989 (40 mg) + Placebo + NA (N=90)
- Arm 5: Placebo + JNJ-6379 (250 mg qd) + NA (N=45)
- Arm 6 (control): Placebo + Placebo + NA (N=45)

NA treatment refers to entecavir (ETV), or tenofovir disoproxil fumarate (TDF), or tenofovir alafenamide (TAF). Treatment duration with JNJ-3989/placebo and/or JNJ-6379/placebo is of 48 weeks. Participants who meet the NA treatment completion criteria at Week 48 will also stop NA treatment and be monitored closely during the follow-up phase. NA treatment may be re-started at any time if protocol-defined NA re-treatment criteria will be met.

The study will be conducted in the following phases:

- **Screening phase**: 4 weeks. If necessary, eg, for operational reasons, the screening phase may be extended up to a maximum of 6 weeks on a case-by-case basis and in agreement with the sponsor.
- **Double-blind study intervention phase**: from Day 1 (ie, baseline) up to Week 48.
- **Follow-up phase**: for 48 weeks after the end of investigational intervention. For participants who complete NA treatment during follow-up, the follow-up phase will be extended to 48 weeks after the end of NA treatment. The follow-up phase has a maximum duration of 96 weeks.

Participants will be considered to have completed the study if they have completed the assessments of the end of study visit ([Extended] Follow-up Week 48).

An Independent Data Monitoring Committee (IDMC) was commissioned for this study to monitor and review data in an unblinded manner on a regular basis to ensure the continuing safety of the study participants. The committee will meet periodically to review unblinded data, as well as the results from the interim analyses (IAs) at prespecified time points (see Section 3). A separate IDMC SAP describes details of the safety and efficacy analyses included in the IDMC periodical data reviews.

In addition, an independent Flare Expert Panel (iFLEP) was appointed for flares monitoring and adjudication. Details on the IDMC and iFLEP activities are described in their respective charter.

1.3. Statistical Hypotheses for Trial Objectives

Based on the primary efficacy endpoint, the proportion of participants meeting the NA treatment completion criteria at Week 48, the primary hypotheses are as follows:

- Any of the combination regimens is more efficacious than NA treatment alone.
  - There is a positive dose-response signal across the 3 doses of JNJ-3989 (40, 100, and 200 mg) on the background of NA compared with NA treatment alone.
  - One or both combination regimens JNJ-3989+JNJ-6379+NA and JNJ-6379+NA are more efficacious than NA treatment alone.
- The combination regimen of JNJ-3989 (100 mg)+JNJ-6379+NA is more efficacious than JNJ-3989 (100 mg)+NA and/or JNJ-6379+NA regimens.

1.4. Sample Size Justification

The total study sample size is 450 participants with a 2:2:2:2:1:1 randomization ratio, where 90 participants will be randomly allocated to each of the arms including a JNJ-3989 dose (Arms 1 to 4) and 45 participants will be randomly assigned to each of the arms with no JNJ-3989 component (Arms 5 and 6). Due to the global impact of the pandemic Coronavirus Disease 2019 (COVID-19) and the use of the modified ITT analysis set as primary set for the efficacy analyses, study enrollment was extended by approximately 5% of participants.

Statistical power to test a dose-response signal (max trend test) was assessed using the generalized version of the MCP-Mod (Pinheiro J. et al., 2014) applied to the binary primary efficacy endpoint on the logit scale using data from Arms 2, 3, and 4 (JNJ-3989 at 200, 100, and 40 mg dose, respectively +NA), and Arm 6 (placebo+placebo+NA) as control. The “max trend test” is to test the null hypothesis that none of the doses is better than control (i.e. the flat dose response curve).The power to reject the null hypothesis is ≥85% under all 5 candidate dose-response models for an absolute response rate of the highest dose of JNJ-3989 of at least 25% (one-sided alpha level of 5%). In addition, assuming a response rate of 5% in control Arm 6, the study sample size provides a statistical power ≥84% to detect a difference of ≥20% in the primary endpoint between Arm 1 and Arm 6, and power ≥76% for at least a 20% delta between Arm 5 and Arm 6, using a fixed sequence approach for controlling for multiplicity.

The testing among the regimens (Arm 1, 3, and 5) will be performed using the min test approach control for the one-sided Type 1 error of 0.05. The chosen study sample size and randomization allocation provides acceptable power levels also for the comparison of different combination regimens, ie, JNJ-3989+JNJ-6379+NA (Arm 1, 100-mg dose of JNJ-3989) versus JNJ-3989+NA (Arm 3, 100-mg dose of JNJ-3989), and versus JNJ-6379+NA (Arm 5), respectively. For example, for the same delta of 25% between Arm 1 and Arm 3 and between Arm 1 and Arm 5, the power to conclude that Arm 1 is statistically superior to Arm 3 and Arm 5 is 87%, assuming a response rate of 25% in both Arm 3 and 5. Details are provided in Section 9 of the protocol Amendment 1.

1.5. Randomization and Blinding

Randomization

Central randomization is implemented in this study. Participants are randomly assigned to 1 of 6 intervention arms with a ratio of 2:2:2:2:1:1 (Arms 1:2:3:4:5:6). The randomization is stratified by HBeAg status at screening (positive versus negative) and by treatment history (not currently treated versus virologically suppressed).

Blinding

At Week 48 or earlier at the time of treatment discontinuation, it will be communicated to the investigators whether the participants were allocated to either an intervention arm (Arms 1 to 5) or the control arm (Arm 6) to determine which follow-up visit schedule will be followed. Only at Week 72, randomization codes (for Arms 1 to 5) will be fully disclosed to the investigators. The sponsor will be fully unblinded at the time of the primary analysis (all participants have completed Week 48 or discontinued early).

Sponsor personnel involved in the pharmacokinetic and pharmacodynamic modelling will have access to the pharmacokinetic and pharmacodynamic data before formal unblinding for the primary analysis. Sponsor personnel involved in trial conduct, data management, and statistics will not have access to these data prior to the primary analysis. The sponsor will be fully unblinded at the time of the primary analysis which will be conducted at the time when all participants have completed Week 48 or discontinued earlier.

2. GENERAL ANALYSIS DEFINITIONS

The SAP will use throughout the document the following definitions:

- *Study treatment* refers to: JNJ-3989, JNJ-6379, placebo and NA (ETV, TDF, or TAF)
- *Study agent* refers to: JNJ-3989, JNJ-6379, or placebo
- *Study intervention arm* refers to*:*

  Arm 1: JNJ-3989 (100 mg) + JNJ-6379 (250mg qd) + NA

  Arm 2: JNJ-3989 (200 mg) + placebo + NA

  Arm 3: JNJ-3989 (100 mg) + placebo + NA

  Arm 4: JNJ-3989 (40 mg) + placebo + NA

Arm 5: placebo + JNJ-6379 (250mg qd) + NA

Arm 6: placebo + placebo + NA

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
Double-blind Study intervention	Date of first study agent intake	The maximum of last intake of JNJ-3989/placebo, last intake of JNJ-6379/placebo and Week 48 date + 5 days or cut-off date*, whichever comes first
Follow-up	End of the double-blind study intervention phase + 1 day	If the participant stops NA treatment at/up to Week 48, study termination date (date of last contact) or cut-off date*, whichever comes first
		If the participant completes NA treatment post Week 48 during the follow-up phase, (date of the last NA intake + 5 days) or cut-off date*, whichever comes first
		If the participant never completes NA treatment during follow-up phase, trial termination date (date of last contact) or cut-off date*, whichever comes first
Extended Follow-up #	End of the follow-up phase + 1 day	Trial termination date (date of last contact) or cut-off date*, whichever comes first

Note: +5 days is only attributed to adverse events and concomitant medications.
*Cutoff dates will be defined to match the prespecified timepoints for IDMC safety monitoring, interim analysis and the primary analysis, respectively.
The extended follow-up phase is only for the participants who completed the NA treatment during the follow-up phase

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. Double Blind Relative Day

Double Blind (DB) start date (DB Day 1) is defined as the date of first study intervention intake. If the date of the first study treatment administration differs among the treatments (e.g. JNJ-3989, JNJ-6379, or NA), the earliest administration date/time is used. All efficacy and safety assessments during the double-blind phase will be assigned an analysis study day relative to this date.

The DB study day in the double-blind treatment phase (ADY) is defined as:

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

for visits on or after DB Day 1, and

DB ADY=visit date – DB start date

for visits before DB Day 1 (Screening phase).

There is no 'DB Day 0'.

2.1.2.2. 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

2.1.2.3. Extended Follow Up Relative Day

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

EFU ADY=visit date – EFU start date+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 analysis relative day (ADY) compared with the target day based on 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 treatment (EOT) and the end of study (EOS) visits. 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. 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 treatment (i.e. EOT) and end of study (i.e. EOS) time points will be included in all analysis over time unless stated otherwise.

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 Double-Blind Phases**

Analysis phase	Target day	Analysis time point (Week)	Analysis time point (label)	Time interval (days)
Screening	-∞	-1	Screening	<0
Double-Blind	1	0	Baseline	Pre-dose
	8	1	Week 1	[2,11]
	15	2	Week 2	[12,22]
	29	4	Week 4	[23,36]
	43	6	Week 6	[37,50]
	57	8	Week 8	[51, 71]
	85	12	Week 12	[72, 99]
	113	16	Week 16	[100, 127]
	141	20	Week 20	[128, 155]
	169	24	Week 24	[156, 183]
	197	28	Week 28	[184, 211]
	225	32	Week 32	[212, 239]
	253	36	Week 36	[240, 267]
	281	40	Week 40	[268, 295]
	309	44	Week 44	[296, 323]
	337	48	Week 48	[324,350]
	last visit in double-blind phase	49 [a]	EOT [a]	

[a] End of treatment (EOT) visit will be the last post-baseline visit in double-blind phase.

b) **Follow-Up Phase**

Analysis phase (FU)	Target day	Analysis time point (Week)	Analysis time point (label)	Time interval (days)[a] (Arm 1-5 and Arm 6 [NA stopped])	Time interval (days)[a] (Arm 6 [NA continued])
Follow-up [a]	15	50	Follow-up Week 2	[1, 22]	
	29	52	Follow-up Week 4	[23,36]	
	43	54	Follow-up Week 6	[37,50]	
	57	56	Follow-up Week 8	[51, 71]	
	85	60	Follow-up Week 12	[72, 99]	[1, 99]
	113	64	Follow-up Week 16	[100, 127]	
	141	68	Follow-up Week 20	[128, 155]	
	169	72	Follow-up Week 24	[156, 190]	[100, 190]
	197	76	Follow-up Week 28	[191, 204]	
	211	78	Follow-up Week 30	[205, 218]	
	225	80	Follow-up Week 32	[219, 232]	
	253	84	Follow-up Week 36	[233, 274]	[191, 274]
	281	88	Follow-up Week 40	[275, 288]	
	295	90	Follow-up Week 42	[289, 302]	
	309	92	Follow-up Week 44	[303, 316]	
	337	96	Follow-up Week 48	[317, +∞]	[275, +∞]

c) Extended Follow-Up Phase

Analysis phase (EFU)	Target day	Analysis time point (Week)	Analysis time point (label)	Time interval (days) [a]
Extended Follow-up	15	102	Ext Follow-up Week 2	[1, 22]
	29	104	Ext Follow-up Week 4	[23,36]
	43	106	Ext Follow-up Week 6	[37,50]
	57	108	Ext Follow-up Week 8	[51, 71]
	85	112	Ext Follow-up Week 12	[72, 99]
	113	116	Ext Follow-up Week 16	[100, 127]
	141	120	Ext Follow-up Week 20	[128, 155]
	169	124	Ext Follow-up Week 24	[156, 190]
	197	128	Ext Follow-up Week 28	[191, 204]
	211	130	Ext Follow-up Week 30	[205, 218]
	225	132	Ext Follow-up Week 32	[219, 232]
	253	136	Ext Follow-up Week 36	[233, 274]
	281	140	Ext Follow-up Week 40	[275, 288]
	295	142	Ext Follow-up Week 42	[289, 302]
	309	144	Ext Follow-up Week 44	[303, 316]
	337	148	Ext Follow-up Week 48	[317, +∞]
	last visit in the study	999 [a]	EOS [a]	

[a] End of study (EOS) visit (last available data during the extended follow-up) will be the last visit in the study.

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

2.3. Analysis Sets

All randomized analysis set: All participants who were randomized in the study. Participants will be analyzed according to the study intervention they were randomly assigned to.

Intent-to-Treat analysis set (ITT): All participants who are randomized and received at least one dose of any of the study treatments. Participants will be analyzed according to the study intervention they were randomly assigned to.

Modified Intent-to-Treat analysis set (mITT): All participants who were randomized in the study and received at least one dose of study treatment 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 Week 44, or had no efficacy assessment for the primary endpoint. COVID-19 or similar pandemics related reasons may include for example missed visits due to travel restriction, shortage of lab kits at the planned visit, missed collection of blood sample at key time points for the primary efficacy endpoint, etc. Participants will be analyzed according to the study intervention they were randomly assigned to.

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

***Per protocol analysis set 1 (PP1)*:** 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 Week 48. 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 (column **PP1**). Participants will be analyzed according to the study intervention they were randomly assigned to.

***Per protocol analysis set 2 (PP2)*:** 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 key secondary endpoint at Week 72. 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 (column **PP2**). 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 treatments and have at least 1 valid blood sample drawn for PK analysis.

2.4. 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 Sections 6.1.2 and 6.2.2).

2.4.1. Subgroups for Efficacy Analyses

- Sex: Male, Female
- Age categories: ≤ 45 years, > 45 years
- Race: Asian, non-Asian
- Geographical region: Asia, Europe, North America, South America
- Has never received HBV treatment (only currently not treated):
  - Yes
  - No
- Type of NA at study entry (only for virologically suppressed participants):
  - Tenofovir Disoproxil Fumarate (TDF)
  - Tenofovir Alafenamide Fumarate (TAF)
  - Entecavir (ETV)
- Hepatitis B e Antigen (HBeAg) status at screening (qualitative):
  - Positive

  - Negative
- Treatment history:
  - Currently not being treated
  - Virologically suppressed
- HBsAg level at baseline:
  - <1,000 IU/mL
  - ≥1,000 IU/mL-<10,000 IU/mL
  - ≥10,000 IU/mL
- HBV DNA level at baseline (only for currently not treated):
  - <100,000 IU/mL
  - ≥100,000 IU/mL
- HBV RNA level at baseline:
  - < 1,000 copies /mL
  - ≥1,000-<10,000 copies /mL
  - ≥10,000 copies /mL
- HBcrAg level at baseline:
  - <3 log U/mL
  - ≥3 log U/mL-<4 log U/mL
  - ≥4 log U/mL
- HBsAg Antibody (Anti-HBs) level at baseline:
  - <10 mIU/mL
  - ≥10 mIU/mL
- Alanine Transferase (ALT) at baseline: ≤ 1.0 ULN, > 1.0 ULN - <2.5 ULN, ≥ 2.5 ULN
- HBV genotype assessed at screening and tested using the INNO-LiPA or sequence based HBV genotyping data: Genotype A, B, C, D, E, F, G, H, I, J and Unknown
- Combination of HBeAg status at screening and treatment history:
  - Positive/Currently not being treated
  - Positive/Virologically suppressed
  - Negative/Currently not being treated
  - Negative/Virologically suppressed
- Combination of HBeAg status at screening and age categories:
  - Positive/≤ 45 years
  - Positive/> 45 years
  - Negative/≤ 45 years

  - Negative/> 45 years
- Combination of HBeAg status at screening and HBsAg level at baseline:
  - Positive/<1,000 IU/mL
  - Positive/≥1,000 IU/mL-<10,000 IU/mL
  - Positive/≥10,000 IU/mL
  - Negative/<1,000 IU/mL
  - Negative /≥1,000 IU/mL-<10,000 IU/mL
  - Negative /≥10,000 IU/mL
- Combination of treatment history and age categories:
  - Currently not being treated /≤ 45 years
  - Currently not being treated /> 45 years
  - Virologically suppressed /≤ 45 years
  - Virologically suppressed /> 45 years
- Combination of treatment history and HBsAg level at baseline:
  - Currently not being treated /<1,000 IU/mL
  - Currently not being treated /≥1,000 IU/mL-<10,000 IU/mL
  - Currently not being treated /≥10,000 IU/mL
  - Virologically suppressed /<1,000 IU/mL
  - Virologically suppressed /≥1,000 IU/mL-<10,000 IU/mL
  - Virologically suppressed /≥10,000 IU/mL

2.4.2. Subgroups for Safety Analyses

- Age categories: ≤ 45 years, > 45 years
- Type of NA at study entry (only for virologically suppressed participants):
  - Tenofovir Disoproxil Fumarate (TDF)
  - Tenofovir Alafenamide Fumarate (TAF)
  - Entecavir (ETV)
- Treatment history:
  - Currently not being treated
  - Virologically suppressed

2.5. 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.

2.5.1. Adverse Event Onset Date and Resolution Date

Partial AE onset dates will be imputed as follows:

- If the AE onset date is missing the day only, it will be set to:
  - The first day of the month when the AE occurred, if month/year of the AE onset date is different than the month/year of the first administration of study treatment date.
  - The day of the first study treatment administration, if the month/year of the AE onset date is the same as the month/year of the first study treatment administration but the month/year of the AE resolution date is different.
  - The earliest between the day of the first study treatment administration date and day of AE resolution date, if month/year of the AE onset are the same as both the month/year of the first study drug administration and the AE resolution date.
- If the AE onset date is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, as long as this date is on or after the first study drug administration.
  - Month and day of the first study treatment administration, if this date is in the same year of AE onset date.
  - December 31 if the AE onset date year is prior to the year of the first study drug administration.
  - The AE resolution date.
- Completely missing onset dates will not be imputed.

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

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

2.5.2. 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.

2.5.3. Concomitant Medication Dates

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

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

If the medication was taken prior to study start (DB 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 (DB 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.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

The IDMC will conduct unblinded periodic data reviews to ensure the continuing safety of the study participants during the entire course of the study. The IDMC 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. The timepoints of the safety reviews, and further details on the safety data and selected efficacy (HBV disease blood markers) are specified in a separate document, the IDMC SAP. Details on the roles and responsibilities of the IDMC, as well as data reviews and the flows of communication, are documented in the IDMC charter.

The IA timepoints are described in the following section.

3.1. Interim Analyses

The primary analysis will be conducted at the time when all participants have completed Week 48 or discontinued earlier.

Interim analyses will be conducted to monitor safety and evaluate the time course of different disease markers to support the sponsor's internal decision-making, interactions with health

authorities, as well as inform decisions about additional studies and/or investigation of other treatment combinations. Three IAs are planned when:

- All participants have completed Week 60 visit or discontinued earlier.
- All participants have completed Week 72 visit or discontinued earlier.
- All participants have completed Week 96 visit or discontinued earlier.

One additional IA may be performed at the sponsor's discretion when all participants, who completed NA treatment at Week 48 of follow-up, have completed Week 120, i.e. Week 24 of the extended follow-up, or discontinued earlier. As all IAs follow the primary analysis, they will be conducted by the sponsor. Both primary and interim analyses will be based on all data available at the predefined cut-off time, including 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 or discontinued earlier.

This SAP covers the definitions of analysis sets, derived variables and statistical methods for the primary, interim and final analyses of this study.

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 IDMC 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 5.4.14.

4. SUBJECT INFORMATION

All the summaries will be done on the ITT analysis set unless specified otherwise for a specific display.

4.1. Disposition Information

The number and percentage of participants who are screened, screened failure and reason for that screening failure will be tabulated. Only an all participants group (total N) will be provided.

A summary of the number of participants randomized, randomized and not treated, in the safety, ITT, mITT, and PP sets, respectively, will be summarized by intervention arm.

Completion/withdrawal information, study disposition and treatment disposition will be summarized for the ITT, mITT, and safety sets (only for mITT and ITT set if the safety set is identical to ITT).

An overview of the study disposition will be provided by intervention arm 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 phase (i.e. double-blind study intervention phase, follow-up phase and Extended follow-up phase) 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 cutoff (except the final analysis) will be presented by treatment and intervention arm. The incidences of treatment discontinuation reasons will also be summarized by study intervention arm for each treatment and overall.

A listing including information (i.e. the date of last study visit, the last study 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 the NA treatment completion, 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 intervention arm and overall for the mITT, ITT and PP analysis sets. Continuous variables will be summarized by descriptive statistics (for example may include the number of participants, mean, standard deviation, standard error, median, range and interquartile range). Categorical/binary variables will be summarized by counts and percentages.

Additional summaries will be presented by the 2 randomization stratification factors (HBeAg status at screening and treatment history). The randomization stratification factors are reported by IWRS and also entered in the Electronic Case Report Form (eCRF). A cross–tabulation of the stratification factors collected by the IWRS vs. eCRF will also be provided by intervention arm to identify any mismatch. In case of discrepancies between the 2 sources, the randomization factors as entered in the eCRF will be used in the analyses/summaries.

4.2.1. Demographic Characteristics

The following demographic characteristics will be summarized by study intervention arm and overall.

- Sex: Male, Female
- Age (years)
- Age categories: ≤30 years, >30-≤ 45years, > 45 years-≤60 years, >60 years
- Race: American Indian or Alaska Native, Asian (Japanese, Other Asian), Black or African American, Native Hawaiian or Other Pacific Islander, White, Not reported
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not Reported
- Region: Asia (China, Japan, and Other Asian Country), Europe, North America, South America
- 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)
- Body mass index group: Underweight <18.5, Normal ≥18.5-<25, Overweight ≥25-<30 and Obese ≥30
- History of Tobacco use: Yes/No

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.

- Duration of HBV infection (Years) = (date of randomization – date of HBV infection +1)/365.25; rounded to 1 decimal
- Time since HBV diagnosis (Years) = (date of randomization – 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
- Treatment history: not currently treated, virologically suppressed
- History of IFN-alpha (All participants): Yes, No
- History of Lamivudine, Telbivudine, Adefovir (All participants): Yes, No
- Has never received HBV treatment (only for currently not treated participants): Yes, No
- Type of NA at study entry (only for virologically suppressed participants): TDF, TAF, ETV
- HBeAg status at screening: positive, negative
- HBeAg at baseline (quantitative): values in IU/mL and log10 IU/mL (for HBeAg positive participants only)
- HBsAg at baseline (quantitative): values in IU/mL and log10 IU/mL
- HBsAg category at baseline (quantitative: IU/mL):
  - Participants with HBsAg <500 IU/mL
  - Participants with HBsAg <1,000 IU/mL
  - Participants with HBsAg <10,000 IU/mL
  - Participants with HBsAg ≥10,000 IU/mL
- HBV DNA at baseline (quantitative): values in IU/mL and log10 IU/mL
- HBV DNA category at baseline (quantitative: IU/mL):
  - Participants with HBV DNA < LLOQ (20 IU/mL) target detected (TD) or target not detected (TND)
  - Participants with HBV DNA < LLOQ (20 IU/mL) target detected
  - Participants with HBV DNA < LLOQ (20 IU/mL) target not detected

  - Participants with HBV DNA < 60 IU/mL
  - Participants with HBV DNA < 2,000 IU/mL
  - Participants with HBV DNA < 20,000 IU/mL
  - Participants with HBV DNA < 100,000 IU/mL
  - Participants with HBV DNA ≥ 100,000 IU/mL
- HBV RNA (quantitative): values in copies/mL and log10 copies/mL
- HBV RNA category at baseline (quantitative: copies/mL):
  - Participants with HBV RNA TND
  - Participants with HBV RNA < limit of detection (LOD)
  - Participants with HBV RNA < 1000 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
- HBsAg Antibody (Anti-HBs) status at baseline (qualitative): Positive, Negative
- HBsAg Antibody (Anti-HBs) at baseline (quantitative): values in mIU/mL and log10 mIU/mL
- HBsAg Antibody (Anti-HBs) category at baseline (quantitative: mIU/mL):
  - Participants with Anti-HBs<10 mIU/mL
  - Participants with Anti-HBs≥10 mIU/mL
- HBeAg Antibody (Anti-HBe) status at baseline (qualitative): Positive, Negative
- Alanine Transferase (ALT) at baseline:
  - Baseline ALT values (U/L)
  - Baseline ALT toxicity grade according to DAIDS
  - Baseline ALT categorization (≤ 1.0 ULN, > 1.0 ULN to <2.5 ULN, ≥ 2.5 ULN)
- Fibroscan score at baseline (quantitative: kPa)
- Fibrosis Stage: F0, F1, or F2
- HBV genotype (using the INNO-LiPA or sequence based HBV genotyping data): Genotype A, B, C, D, E, F, G, H, I, J, and Unknown

4.3. Medical History

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

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 DB Day 1 regardless of when dosing of the medication ended.

(ii) Concomitant medications are defined as medications received on or after DB 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 DB Day 1 and continued afterwards will be summarized both as prior and, separately, as concomitant medication. All concomitant medications will be 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 intervention arm. In addition, the concomitant medications and cconcomitant medications of interest will be summarized by analysis phase. 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.

Protocol deviations and violations will be based on clinical review, but not limited to, the following criteria: (1) entered but did not satisfy criteria, (2) received wrong treatment or incorrect dose, (3) received a disallowed concomitant treatment, (4) developed withdrawal criteria but not withdrawn, (5) 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 intervention arm for the 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) will be identified and finalized prior to database lock to define the Per-Protocol analysis sets 1 and 2 (Section 2.3). The number and percentage of ITT participants who are included in the PP1 and PP2 analysis sets will be summarized by intervention arm, accompanied by number and percentage of ITT participants who are excluded from the PP1 and PP2 analysis sets 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 DB phase will be calculated by each study treatment (JNJ-3989/corresponding placebo, JNJ-6379/corresponding placebo, and NA) separately and summarized descriptively by intervention arm. The duration of treatment with NA will be summarized also for the follow up phase by intervention arm.

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

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

Cutoff dates will be defined to match the prespecified timepoints for IDMC 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/placebo or JNJ-6379/placebo or NA will be summarized separately for each study treatment by intervention arm during the DB phase. Additionally, the number and percentage of participants who missed 2 or more JNJ-3989/placebo injections, or who missed more than 5 JNJ-6379/placebo doses within a four week period, or who missed more than 5 doses of NA within a four week period.

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

4.7. Treatment Compliance

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

Treatment compliance (%) is defined as follows.

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

For JNJ-6379/placebo: (Total medication intake / 4 *7 *48) * 100%

As the 250 mg daily dose of JNJ-6379/placebo consists of 4 tablets (2 tablets of 50 mg strength and 2 tablets of 25 mg strength), the denominator is 1,344 tablets= 4*7*48. The numerator representing the total medication intake for JNJ-6379/placebo is calculated as:

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

5. EFFICACY

All efficacy data will be analyzed by intervention arm, analysis phase and over time (when applicable). The primary analysis set will be the mITT analysis set (see definition in Section 2.3). Selected efficacy endpoints will be also analyzed using the ITT, and PP analysis sets, respectively (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 study intervention arm. In general, continuous variables will be summarized using descriptive statistics (for example, may include the number of participants, mean, standard deviation (SD), 90% confidence interval (CI), median, and range). Binary or categorical variables will be summarized using the number and percentage of participants in each category. For time-to-event variables, a summary table including number of participants included in the analysis, number of participants censored, 25th and 75th percentiles and median time-to event will be shown. Descriptive summaries may be presented by the 2 randomization stratification factors, HBeAg status at screening and treatment history for the primary and key secondary endpoints and selected other secondary endpoints. Graphic displays will also be used to summarize the data.

5.1.1. Level of Significance

The study addresses two separate research questions:

1) Dose finding: the comparisons of 3 doses of JNJ-3989+NA (Arms 2, 3, and 4) against NA treatment alone (Arm 6) and other comparisons of active regimens (Arm 1 and Arm 5) vs Arm 6,

2) Regimen finding: the comparisons of the combination regimen of JNJ-3989 (100 mg) +JNJ-6379 +NA (Arm 1) vs each of the mono components JNJ-3989 (100 mg) and JNJ-6379, respectively, on the background of NA (Arm 3 and Arm 5).

For the primary efficacy endpoint analysis, the Type 1 error rate is controlled at 0.05 one-sided level for multiple comparisons within each separate research question differently and independently.

For the comparisons against the control, a fixed sequence approach is used where the first step implements the multiple contrast test of the MCP-Mod methodology (applied to Arms 2, 3, 4, and 6) to detect a trend test among the JNJ-3989 doses (40 mg, 100 mg and 200 mg), under the null hypothesis of no differences across the four arms, which is followed by the pairwise comparison of Arm 1 vs Arm 6, followed by the pairwise comparison of Arm 5 vs Arm 6. Based on the fixed sequence principle, each step must be found statistically significant at a one-sided 0.05 level in order to proceed to the next step.

For the comparisons among the regimens (Arms 1, 3, and 5), the min test principle is used. The JNJ-3989+JNJ-6379+NA combination regimen Arm 1 will be declared statistically superior to the dual regimens (Arm 3 and Arm 5) if both tests of Arm 1 vs Arm 3 and Arm 1 vs Arm 5 demonstrate statistical significance at the one-sided 0.05 level.

For the key secondary endpoint, the same multi-step testing strategy as the one implemented for the primary efficacy endpoint described above, using MCP-Mod and additional treatment arms pairwise comparisons against control in a fixed sequence, as well as the min test approach separately for between-regimen comparisons, will be used for this key secondary endpoint. However, the comparisons with NA control in the testing strategy applied to this efficacy endpoint will be made against the NA historical control benchmark of 5%, instead of the study NA control arm (Arm 6).

For the key secondary efficacy endpoint (functional cure at week 72), the tests to compare the JNJ-3989+JNJ-6379+NA regimen against theJNJ-3989+NA and JNJ-6379+NA combination regimens, respectively, will be performed at a one-sided 0.025 alpha level. This more stringent significance level aims to support for regulatory consideration the selection of the combination regimen to be studied in confirmatory studies.

All other efficacy analyses will be based on one-sided alpha level of 0.05, and/or 90% confidence interval (CI) will be presented, with no multiplicity adjustment, unless otherwise specified.

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 3.

Table 3: Data Handling Rules for HBV Virology and Serology Assessments

HBV parameter	LLOQ	ULOQ	Imputed Values	
			If value< LLOQ ULOQ	If value>
HBsAg	0.05 IU/mL	124,925.00 IU/mL w/o dilution 249,750.00 IU/mL with dilution	0.025 IU/mL [(a)]	137,417.50 IU/mL w/o dilution [(b)] 274,725.00 IU/mL [(b)] with dilution
HBeAg	0.11 IU/mL	1,400.00 IU/mL w/o dilution 7,000.00 IU/mL with dilution	0.055 IU/mL [(a)]	1,540.00IU/mL[(b)] w/o dilution 7,700.00 IU/mL[(b)] with dilution
HBcrAg	3.0 Log10 U/mL	7.0 Log10 U/mLw/o dilution 9.0 Log10 U/mL with dilution	2.7 Log10 U/mL	7.7 Log10 U/mL[(b)(c)] w/o dilution 9.9 Log10 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)] w/o dilution
HBV RNA*	LLOQ = 4.04 log10 cp/mL LOD = 2.49 log10 cp/mL	NAP	If < LOD or target not detected then 2.19 log10 cp/mL	NAP
Anti-HBs	5mIU/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

Key: NAP=Not applicable

(a) LLOQ/2

(b) ULOQ+(ULOQ/10)

(c) If the original result >UL0Q 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 is defined as the proportion of participants meeting the NA treatment completion criteria **at Week 48**.

A participant will be defined as responder in meeting the NA treatment completion criteria at Week 48, if the following criteria are met based on the clinical laboratory tests performed **at Week 44**:

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

Note: In case of ALT elevation ≥3x ULN at Week 44, the ALT re-test before Week 48 may be performed. If the ALT re-test meets the criteria above, the participant will be considered as responder as satisfying the NA treatment completion criteria.

Note: Quantitative HBeAg assessment is only performed at Week 44 for participants who are HBeAg positive at screening. Therefore, if a participant is HBeAg negative at screening, they are assumed to be negative at Week 44 for the purpose of the primary endpoint.

5.2.2. Main Estimand for The Primary Endpoint

Primary Study Objective: To establish the dose-response relationship for antiviral activity of 3 doses of JNJ-3989+NA and to evaluate the efficacy of combination regimens of JNJ 3989+NA (with and without JNJ-6379) and of JNJ-6379+NA.

Scientific question: in the adult population with chronic HBV infection

a) what is the benefit of any of the JNJ-3989 doses (40mg, 100mg or 200 mg) (Arms 2-4) administered in combination with NA for 48 weeks in terms of antiviral HBV replication and liver inflammation compared with Placebo+NA?

b) what is the benefit of JNJ-3989 100 mg+JNJ-6379+NA (Arm 1) and JNJ-6379+NA (Arm 5) for 48 weeks in terms of antiviral HBV replication and liver inflammation compared with Placebo+NA?

c) what is the benefit of JNJ-3989 100mg+NA with or without JNJ-6379 (Arm 1, 3) or JNJ-6379+NA (Arm 5) administered for 48 weeks in terms of antiviral HBV replication and liver inflammation?

A) The primary estimand for the primary endpoint is characterized by the following attributes:
Study Intervention:

- Arm 1: JNJ-3989 (100 mg) + JNJ-6379 (250 mg qd) + NA
- Arm 2: JNJ-3989 (200 mg) + Placebo + NA
- Arm 3: JNJ-3989 (100 mg) + Placebo + NA
- Arm 4: JNJ-3989 (40 mg) + Placebo + NA
- Arm 5: Placebo + JNJ-6379 (250 mg qd) + NA

- Arm 6: Placebo + Placebo + NA

B) Study Population: HBeAg-positive and -negative chronic HBV-infected patients who are not being treated for their HBV infection (including treatment-naïve participants) or are virologically suppressed by being treated with NA.

C) Variable: Response status defined as meeting the NA treatment completion criteria (responders) at Week 48 as defined in Section 5.2.1.

D) Intercurrent events:

- Treatment discontinuation prior to Week 48:
  - if the participant discontinued treatment prior to Week 44, then s/he will be considered non-responder (composite strategy).
  - if the participant discontinued treatment between Week 44 and Week 48 but ALT, HBV DNA, HBeAg (only for the participants with HBeAg positive status at baseline), and HBsAg assessments for primary endpoint are available, all data will be used regardless of occurrence of the intercurrent event (treatment policy strategy).
- Major protocol deviations affecting efficacy: ATTACHMENT 1 identifies the deviations considered intercurrent event (in the Per Protocol set 1 column [PP1] for the primary efficacy endpoint). Participants with such deviations and who have missing data for the primary endpoint at Week 48 will be considered as non-responders (composite strategy). For all other deviations not considered intercurrent events, the data are used regardless of the occurrence of major protocol deviations (treatment policy strategy).
- Deaths prior to Week 48 are handled in a composite strategy as participants who die prior to Week 48 will be considered as non-responders.

E) Population-level summary: Difference in proportion of responders at Week 48 between study intervention arms.

5.2.2.1. Main Estimator

5.2.2.1.1. Analysis Methods

5.2.2.1.1.1. Scientific Question Part a: JNJ-3989 Dose Response Trend Test and Dose Response Model Estimation

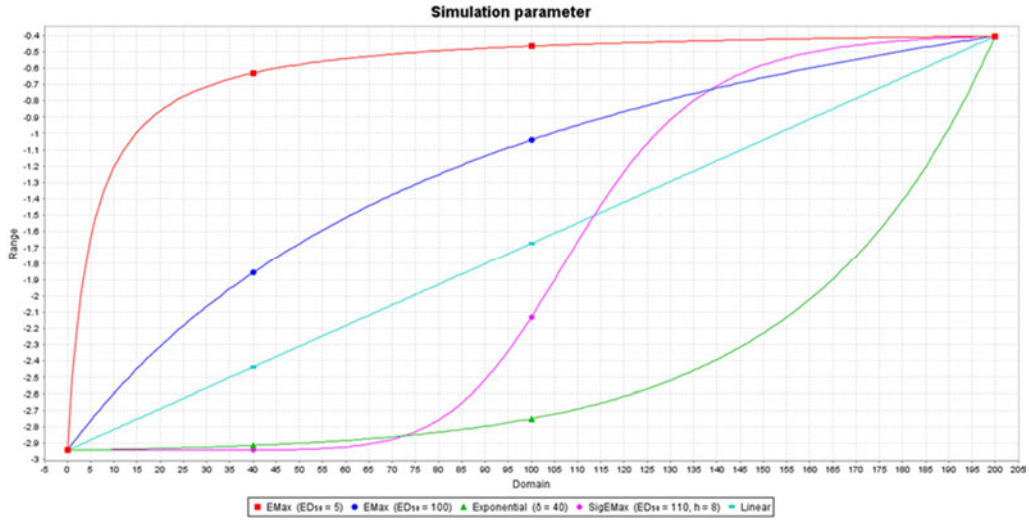
Statistical Model: For the JNJ-3989 dose-finding objective, a hybrid methodology that combines aspects of multiple testing with modeling techniques (MCP-Mod) will be used for evaluating a dose-response trend and estimating the dose-response relationship of 3 JNJ-3989 doses in combination with NA (Arm 2, 3 and 4) versus NA treatment alone (control Arm 6). Because the primary efficacy endpoint is binary, the generalized MCP-Mod approach (Pinheiro J. et al, 2014) will be used on the logit scale. Following the notation in Pinheiro et al (2014), the "dose-response parameter" estimates and their variance-covariance matrix will be obtained from a logistic regression with JNJ-3989 dose treated as a factor, where Arm 6 corresponds to "JNJ-3989 dose=0

mg". The Firth's penalized likelihood method (Firth D., 1993 & Heinze G. et al., 2002) will be used in the logistic regression to reduce possible bias which could arise in the presence of a zero response rate at one or more dose levels

If one or more prespecified models are found to be significant (multiple contrast test approach), a significant trend test among Arms 2, 3, 4, and 6 (JNJ-3989 40 mg, 100 mg and 200 mg and NA control), under the null hypothesis of no differences across the 4 arms will be declared.

A set of 5 candidate models (see Figure 1) was prespecified as possible dose-response shapes in terms of the logit of the primary efficacy endpoint. The 5 candidate models are the EMax1 (ED50=5 mg), EMax2 (ED50=100 mg), Linear, Exponential (d=40) and Sigmoid Emax model (ED50=110 mg, h=8). A dose-response trend is established when the maximum of the t-test statistics exceeds the critical value at the one-sided 0.05 alpha.

Figure 1: Candidate Dose-response Models on the Logit Scale



Characterization of the dose-response model: The model averaging techniques (Bornkamp B. et al., 2009) across the candidate models will be utilized to derive the dose-response shape and to evaluate the desired dose(s) of JNJ-3989 (modeling step). The estimated dose response curve and the corresponding 90% confidence band will be plotted against the JNJ-3989 dose range of 0 mg to 200 mg.

5.2.2.1.1.2. Scientific Question Part b: Pairwise Comparisons vs Control Arm

After a positive significant dose-response signal is established for the combination regimen JNJ-3989+NA, the testing procedure continues in a fixed sequence to control the type 1 error in presence of multiple testing, with the comparison of Arm 1 (JNJ-3989+JNJ-6379+NA) with control Arm 6 at a one-sided alpha of 0.05. If Arm 1 is found statistically superior to control Arm 6, then the combination regimen JNJ-6379+NA (Arm 5) is compared to control Arm 6 at 0.05 one-sided alpha level. The Mantel-Haenszel (MH) test (Mantel N. et al., 1959) for the difference of 2 proportions adjusted for the 2 randomization stratification factors (treatment history

status and screening HBeAg status) will be used at one-sided 0.05 alpha level in each of the above mentioned pairwise comparisons.

5.2.2.1.1.3. Scientific Question Part c: Comparisons Among Combination Regimens

For the regimen-finding objective, the statistical comparisons among the regimens (Arm 1, 3, and 5) will be performed using the min test approach to control for the Type I error rate at the one-sided 0.05 alpha level. The JNJ-3989+JNJ-6379+NA combination regimen will be declared statistically superior to the dual regimens if both tests of Arm 1 vs Arm 3 and Arm 1 vs Arm 5 demonstrate statistical significance at the one-sided 0.05 level. The Mantel-Haenszel test for the difference of 2 proportions adjusted for the 2 randomization stratification factors will be applied.

5.2.2.1.2. Data Included

All available data from mITT analysis set, after taking into account all the intercurrent events and applying the intercurrent event strategies specified in Section 5.2.2, will be included.

5.2.2.1.3. Assumptions

- Missing Data for ALT, HBV DNA, and HBsAg are Missing at Random (MAR)
- The treatment effect is homogeneous across strata

5.2.2.1.4. Missing Data Handling Rule

Participants who withdraw from the study prior to Week 48 will be considered as non-responders.

If a participant remains in the study after experiencing a major protocol deviation (defined for the purpose of efficacy analyses and is an intercurrent event [ICE]) and has missing Week 44 lab value(s) (ALT, HBV DNA, HBeAg [screening positive participants] and HBsAg), then the imputation to non-response will be applied. If the value for the primary endpoint at Week 44 is available, then such data will be used to determine their response status.

For the participants still in the study at Week 48 or for participants that have neither discontinued treatment early nor experienced any major protocol violations (defined for the purpose of efficacy analyses and is an intercurrent event), and ALT, HBV DNA, HBeAg (screening positive participants) and/or HBsAg values missing at Week 44, then the primary method to handle missing data will be the Multiple Imputation (MI) approach (Ratitch B. et al., 2013) under the assumption of MAR will be applied in a joint multivariate fashion to leverage the correlation between ALT, HBV DNA, and HBsAg values over time.

The multiple imputation (MI) multivariate model will use all available data and be applied to the continuous ALT, HBV DNA, HBeAg (screening positive participants) and HBsAg values (not the binary endpoint). Of note, also the pre-ICE data for those subjects who experienced an ICE will be included in the MI model; but for these subjects the response status will be applied according to the ICE strategies before running the MI model.

If a subject is HBeAg negative at screening, s/he is considered HBeAg negative also at Week 48 for the purpose of determining the status of the primary efficacy endpoint. Because the quantitative HBeAg assessments are collected only for participants who are HBeAg positive at screening, two separate MI models are defined as follows:

For subjects HBeAg positive at screening: The model will include treatment, the 2 randomization factors and the available non-missing log-transformed HBV DNA, log-transformed HBeAg values, log-transformed ALT values and HBsAg (values < LLOQ, TND or TD will be first substituted following rules described in Table 3) for each scheduled time point (Week) and the following demographic and baseline characteristics (King G. et al., & Honaker J. et al.): age, gender, and baseline log value for HBV DNA level, baseline log HBsAg level, baseline HBeAg level, and baseline log ALT level.

For subjects HBeAg negative at screening: The model will include treatment, the 2 randomization factors and the available non-missing log-transformed HBV DNA, log-transformed ALT, and log-transformed HBsAg (values < LLOQ, TND or TD will be first substituted following rules described in Table 3) for each scheduled time point (Week) and the following demographic and baseline characteristics (King G. et al., & Honaker J. et al.): age, gender, and baseline log transformed value for HBV DNA level, baseline log HBsAg level and baseline log ALT level.

A total of 200 datasets (comprising both HBeAg positive and negative subjects at screening) will be generated where both intermittent and monotone missing ALT, HBV DNA, and/or HBsAg values will be imputed for each subject relying on non-missing data from all other subjects within the same treatment group. Once the 200 completed datasets are generated by filling in the missing data with samples from the imputation model, the primary endpoint response status (binary variable) will be derived using both imputed and observed ALT, HBV DNA, HBeAg, and HBsAg values at Week 44.

For the MCP-step, the max trend test will be obtained for each of the imputed datasets and the multiplicity adjusted p-value associated with the largest T-test statistic will be saved. All p-values will be transformed to a Z-test statistic using the inverse cumulative distribution function of the standard normal distribution. The resulting 200 Z-test statistics and their standard error of 1 will be combined into an overall Z test result, using SAS PROC MIANALYZE.

For Mod-step, model averaging techniques across all 5 candidate models will apply to each imputed dataset and produce the weighted estimates of the treatment effect across the JNJ-3989 dose range (0 mg to 200 mg). The standard errors will be obtained using bootstrapping techniques and then combined into one result using PROC MIANALYZE. The final response estimates on the logit scale for each dose level in the range 0 mg to 200 mg and their 90% CI will be back transformed to the original scale of proportion of responders and plotted with the corresponding 90% confidence band.

For pairwise comparisons of Arms 1 vs 6 and Arm 5 vs 6, as well as the comparisons amongst combination regimens (Arms1, 3, and 5), the MH test will be performed for each dataset to generate individual estimates of the difference in proportions and the standard error adjusted on

stratification factors. Then the results from these multiple imputed datasets are combined (pooled) for obtaining the overall inference and p-value in a way that accounts for the variability between imputations (Ratitch B. et al., 2013)

Depending on the amount of missing data, the number of imputed datasets to be generated will be increased appropriately from the planned 200 to ensure robustness in the MI results and relative efficiency (Graham JW. et al., 2007).

5.2.2.2. Sensitivity Estimators of the Main Estimand

Sensitivity analyses will be conducted by constructing three sensitivity estimators for the primary estimand as defined in Section 5.2.2. One estimator will test the assumption of homogeneous treatment effect across the 2 randomization stratification factors, and the 2 other ones will use different missing data imputation rules.

5.2.2.2.1. Sensitivity Estimator 1 For the Main Estimand (Homogeneity Assumption)

Homogeneity will be assessed for scientific question part b, comparison vs control arm. For this sensitivity estimator 1, the same included data, missing data assumption (MAR), and missing data handling rule (multiple imputation) as well as the same approach to control the Type I error rate (Section 5.1.1) will be applied. The assumption for homogeneity of treatment effect across the stratification factors will be tested and, if heterogeneity is found statistically significant, a different statistical model is used to define the sensitivity estimator.

5.2.2.2.1.1. Assumptions

- Missing Data for HBV RNA, ALT, and HBsAg are Missing at Random
- The treatment effect is non-homogeneous across strata

5.2.2.2.1.2. Analysis Methods

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

Any heterogeneity found to be statistically significant will be explored using the following statistical model for the sensitivity estimator 1.

Statistical model: A logistic regression model on the primary efficacy endpoint using the 2 randomization stratification factors and interaction terms. The model will include intervention arm, treatment history status and HBeAg status at screening as factors, and the intervention arm-by-factor interaction terms.

5.2.2.2.2. Sensitivity Estimator 2 For the Main Estimand (LOCF)

For this sensitivity estimator 2, the same statistical model (MCP-Mod and stratum-adjusted MH test), data included and approach to control the Type I error rate will be used as for the main

estimator (Section 5.2.2.1). The assumption for missing data and the rule to handle missing data have changed.

5.2.2.2.2.1. Assumptions

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

5.2.2.2.2.2. Missing Data Handling Rule

For sensitivity estimator 2, participants who withdraw from the study prior to Week 48 will be considered as non-responders. After taking into account all the intercurrent events and applying the intercurrent event strategies specified in Section 5.2.2, if a subject who did not experience any ICEs has missing response status for the primary efficacy endpoint then the LOCF approach will be used as follows.

If any of the lab parameters values (used to define response status per primary efficacy endpoint) are missing at Week 44, the Last Observation Carried Forward (LOCF). The non-missing value closest to Week 44 will be selected among the non-missing values which are no earlier than 4 weeks prior. The imputed values will be chosen to be all at the same timepoint. If 2 non-missing laboratory values are equidistant, the later observation will be preferred.

For Mod-step, model averaging techniques across the statistically significant candidate models obtained from the MCP step will be used to derive the dose-response shape (Mod step).

5.2.2.2.3. Sensitivity Estimator 3 For the Main Estimand (Tipping Point)

For this sensitivity estimator 3, the same statistical model (MCP-Mod, stratum-adjusted MH test), data included and approach to control the Type I error rate will be used as for the main estimator (Section 5.2.2.1). The assumption for missing data and the rule to handle missing data have changed.

5.2.2.2.3.1. Assumptions

- Missing Data for HBV RNA, ALT, and HBsAg are Missing Not at Random (MNAR)
- The treatment effect is homogeneous across strata

5.2.2.2.3.2. Missing Data Handling Rule

For sensitivity estimator 3, the tipping point approach with the exhaustive scenario's analysis will be applied.

Instead of imputing non-response for missing data, the following method will be utilized to vary the imputation of response for missing data. For participants with missing response data at Week 48, responder status will be imputed in an increasing manner by participant count for each treatment group. Specifically, for each participant with missing primary endpoint at Week 48, a responder/non-responder status will be imputed starting with the scenario where all participants

are non-responders up to the scenario where all participants are responders. This would include all possible scenario combinations of responder/non-responder status for all missing data, including scenarios where participants on any active Arm have worse outcomes than participants on placebo+placebo+NA. Within the exhaustive scenarios list, the 'worst case scenario' will be one of the cases where all participants with missing Week 48 data in the active regimen arms will be imputed to 'non-responders' and all participants with missing data at Week 48 in the placebo+placebo+NA arm will be imputed to "responders". For each scenario, the same statistical model (MCP-Mod, stratum-adjusted MH test), will be used as for the main estimator of pairwise comparisons (Section 5.2.2.1.1.2). will be performed. A graphical display of the p-values for the different hypotheses testing will summarize the results across all scenarios for this sensitivity estimator 3.

5.2.2.3. Supplementary Estimators of the Main Estimand

Supplementary analyses to better interpret the primary analysis results will be conducted by constructing additional estimators for the main estimand of the primary endpoint as defined in Section 5.2.2. This estimator will be based on the ITT set (instead of mITT).

To provide a comprehensive interpretation of the study results and the impact of COVID-19 pandemic, the following supplementary estimator will utilize the ITT analysis set.

5.2.2.3.1. Supplementary Estimator 1 (ITT Analysis Set + MI)

For this supplementary estimator, the same estimand defined in Section 5.2.2, statistical model (MCP-Mod, and stratum-adjusted MH test), assumptions and approach to control the Type I error rate, and the same MI rule to handle missing data will be used as for the main estimator (Section 5.2.2.1).

5.2.2.3.1.1. Data Included

All available data from ITT analysis set, after taking into account all the intercurrent events and applying the intercurrent event strategies specified in Section 5.2.2, will be included.

5.2.2.3.1.2. Supplementary Estimator 2 (ITT Analysis Set + LOCF)

For this supplementary estimator, the same estimand defined in Section 5.2.2, statistical model (MCP-Mod, and stratum-adjusted MH test), assumptions and approach to control the Type I error rate will be used as for the main estimator (Section 5.2.2.1). For Mod-step, model averaging techniques across the statistically significant candidate models obtained from the MCP step will be used to derive the dose-response shape (Mod step).

The missing data approach will follow the LOCF approach as described in Section 5.2.2.2.2.

5.2.2.3.1.3. Supplementary Estimator 3 (ITT Analysis Set + Tipping Point)

For this supplementary estimator, the same estimand defined in Section 5.2.2, statistical model (MCP-Mod, and stratum-adjusted MH test), assumptions and approach to control the Type I error rate will be used as for the main estimator (Section 5.2.2.1).

This supplementary estimator will use the tipping point approach as described in Section 5.2.2.2.3.

5.2.3. Supplementary Estimand 1 (Missing as Non-Response)

A) Study Intervention:

- Arm 1: JNJ-3989 (100 mg) + JNJ-6379 (250 mg qd) + NA
- Arm 2: JNJ-3989 (200 mg) + Placebo + NA
- Arm 3: JNJ-3989 (100 mg) + Placebo + NA
- Arm 4: JNJ-3989 (40 mg) + Placebo + NA
- Arm 5: Placebo + JNJ-6379 (250 mg qd) + NA
- Arm 6: Placebo + Placebo + NA

B) Study Population: HBeAg-positive and -negative chronic HBV-infected patients who are not being treated for their HBV infection (including treatment-naïve participants) or are virologically suppressed by NA treatment.

C) Variable: Response status defined as meeting the NA treatment completion criteria (responders) at Week 48 as defined in Section 5.2.1.

D) Intercurrent events:

- Treatment discontinuation prior to Week 48: if the participant discontinued treatment prior to Week 48 s/he will be considered as non-responder (composite strategy).
- Major protocol deviations affecting efficacy: ATTACHMENT 1 identifies the deviations considered intercurrent event (Per Protocol set 1 [PP1] for the primary efficacy endpoint). Participants with such deviations and who have missing data for the primary endpoint at Week 48 will be considered as non-responders (composite strategy).
- Deaths prior to Week 48 are handled in a composite strategy as participants who die prior to Week 48 will be considered as non-responders.

E) Population-level summary: Difference in proportion of responders at Week 48 between study intervention arms.

5.2.3.1. Main Estimator

5.2.3.1.1. Analysis Methods

Statistical Model

The same MCP-Mod approach and stratum-adjusted MH test on the difference of proportions as described for the main estimator of the primary estimand will be used (see Section 5.2.2.1).

For Mod-step, model averaging techniques across the statistically significant candidate models obtained from the MCP step will be used to derive the dose-response shape (Mod step).

5.2.3.1.2. Data Included

All available data from mITT analysis set, after taking into account all the intercurrent events and applying the intercurrent event strategies specified in the previous Section 5.2.3, will be included.

An additional analysis of this estimand will be performed using the ITT analysis set, after taking into account all the intercurrent events and applying the intercurrent event strategies specified in the previous Section 5.2.3, will be included.

5.2.3.1.3. Assumptions

- Missing Data for ALT, HBV DNA, and HBsAg are missing not at random
- The treatment effect is homogeneous across strata

5.2.3.1.4. Missing Data Handling Rule

Participants who withdraw from the study prior to Week 48 will be considered as non-responders. All participants with missing data for the determination of the primary endpoint status will be imputed as non-responders.

5.2.4. Supplementary Estimand 2 (Per-Protocol Analysis Set)

A) Study Intervention:

- Arm 1: JNJ-3989 (100 mg) + JNJ-6379 (250 mg qd) + NA
- Arm 2: JNJ-3989 (200 mg) + Placebo + NA
- Arm 3: JNJ-3989 (100 mg) + Placebo + NA
- Arm 4: JNJ-3989 (40 mg) + Placebo + NA
- Arm 5: Placebo + JNJ-6379 (250 mg qd) + NA
- Arm 6: Placebo + Placebo + NA

B) Study Population: HBeAg-positive and -negative chronic HBV-infected patients who are not being treated for their HBV infection (including treatment-naïve participants) or are virologically suppressed by NA treatment and who are able to tolerate the treatment regimen and will comply with the treatment schedule as prescribed.

C) Variable: Response status defined as meeting the NA treatment completion criteria (responders) at Week 48 as defined in Section 5.2.1.

D) Intercurrent events:

- Treatment discontinuation prior to Week 48: if the participant discontinued treatment prior to Week 48 s/he will be considered as non-responder (composite strategy).
- Deaths prior to Week 48 are handled in a composite strategy as participants who die prior to Week 48 will be considered as non-responders.

E) Population-level summary: Difference in proportion of responders at Week 48 between study intervention arms.

5.2.4.1. Main Estimator

5.2.4.1.1. Analysis Methods

Statistical Model
Similar MCP-Mod and stratum-adjusted MH test on the difference of proportions as described for the main estimator of the primary estimand will be used (see Section 5.2.2.1).

5.2.4.1.2. Data Included

All available data from randomized participants that are included in the PP1 analysis set will be used, after taking into account the intercurrent events and applying the intercurrent event strategies specified in Section 5.2.4.

To complement this analysis because of its inherent bias and allow a better interpretation of the results, the proportions of participants excluded from the PP1 analysis set will be summarized by intervention arm and by type of major protocol deviation.

5.2.4.1.3. Assumptions

- The treatment effect is homogeneous across strata

5.2.4.1.4. Missing Data Handling Rule

Participants who withdraw from the study prior to Week 48 will be considered non-responders. For the participants still in the study at Week 48 or for participants that have neither discontinued treatment early nor experienced any major protocol violations as listed in ATTACHMENT 1 (PP1 column), but ALT, HBV DNA, and/or HBsAg values missing at Week 44, then the primary method to handle missing data will be the imputation to non-responder.

5.2.5. Subgroup Analyses of Primary Efficacy Endpoint

The potential association between the primary endpoint and the randomization stratification factors will be explored by a multivariate logistic regression model and exploration of the interaction terms using observed case data. The model will include intervention arm, treatment history and HBeAg status at screening, as factors, and the intervention arm-by-treatment history and intervention arm-by-HBeAg status interaction terms. If the model does not converge, then the interaction term may be removed from the model as a means to facilitate model convergence. The primary endpoint estimates for each intervention arm will be derived from this model and presented graphically with their 90% CI in a forest plot.

In addition, for assessment of internal consistency and investigation of homogeneity of the treatment effect in the primary efficacy endpoint across other subgroups (as defined in Section 2.4.1), similarly to what is described above, a multivariate logistic regression model (Brooks ST. et al., 2004) will be estimated for each subgroup variable at a time. The factors in the model will be intervention arm, treatment history, HBeAg status at screening and the subgroup

variable as factors, and the intervention arm-by-subgroup variable as the interaction-term (Brooks ST. et al., 2004). Corresponding 90% CIs will be also calculated without multiplicity adjustment for each intervention arm. Statistical analysis of treatment heterogeneity between subgroups will be conducted by assessing the significance of the interaction term. The forest plot will present graphically the primary endpoint estimate, its 90% CI resulting from the model across intervention arms by the prespecified subgroups.

5.3. Key Secondary Endpoint

5.3.1. Definition

The key secondary endpoint is the proportion of participants having HBsAg seroclearance 24 weeks after stopping all study interventions at Week 48. This endpoint will be called as "functional cure" at week 72 interchangeably in the rest of this document.

A participant will be defined as having achieved functional cure (FC) at Week 72 if he/she has:

- met the criteria for stopping NA treatment at Week 48, and
- had HBsAg seroclearance at Week 72 (i.e. 24 weeks after stopping all study interventions), and
- not required NA re-treatment between Weeks 48 and 72.

Seroclearance of HBsAg is defined as HBsAg level<LLOQ. It can be noted that a participant may achieve HBsAg seroclearance prior to Week 72, but the HBsAg level<LLOQ has to be shown at Week 72 to be counted as responder.

5.3.2. Main Estimand of The Key Secondary Endpoint

Study Objective: To evaluate the efficacy of the study intervention 24 weeks off-treatment.

Scientific Question: in the adult population with chronic HBV infection

a) what is the benefit of any of the JNJ-3989 doses (40mg, 100mg or 200 mg) (Arms 2-4) administered in combination with NA for 48 weeks in terms of functional cure 24 weeks after stopping all study interventions compared with historical control (5%)?

b) what is the benefit of JNJ-3989 100 mg+JNJ-6379+NA (Arm 1) and JNJ-379+NA (Arm 5) for 48 weeks in terms of functional cure 24 weeks after stopping all study interventions compared with Historical Control (5%)?

c) what is the benefit of JNJ-3989 100mg+NA with or without JNJ-6379 (Arm 1, 3) or JNJ-6379+NA (Arm 5) administered for 48 weeks in terms of functional cure 24 weeks after stopping all study interventions?

A) Study Intervention:

- Arm 1: JNJ-3989 (100 mg) + JNJ-6379 (250 mg qd) + NA

- Arm 2: JNJ-3989 (200 mg) + Placebo + NA
- Arm 3: JNJ-3989 (100 mg) + Placebo + NA
- Arm 4: JNJ-3989 (40 mg) + Placebo + NA
- Arm 5: Placebo + JNJ-6379 (250 mg qd) + NA
- Historical Control value of 5%

B) Study Population: HBeAg-positive and -negative chronic HBV-infected patients who are not being treated for their HBV infection (including treatment-naïve patients) or are virologically suppressed by being treated with NA.

C) Variable: Response status defined as participants who meet the criteria defining functional cure at Week 72 (responders) as in Section 5.3.1

D) Intercurrent events:

- Treatment discontinuation prior to Week 48: if the participant discontinued treatment prior to Week 48 then s/he will be considered non-responder (composite strategy).
- Major protocol deviations affecting efficacy: ATTACHMENT 1 identifies the deviations considered intercurrent event (in per protocol set 2 column [PP2]). Participants with such deviations and who have missing data for the endpoint will be considered as non-responders (composite strategy). For all other deviations not considered intercurrent events, the data are used regardless of the occurrence of major protocol deviations (treatment policy strategy).
- Deaths prior to Week 72 are handled in a composite strategy as participants who die prior to Week 72 will be considered as non-responders.
- NA re-treatment between Week 48 and 72: the participant will be counted as non-responder (composite strategy).

E) Population-level summary: Difference in proportion of participants with functional cure status at Week 72 between study intervention arms**.**

5.3.2.1. Main Estimator

5.3.2.1.1. Analysis Methods

5.3.2.1.1.1. Scientific Question Part a: JNJ-3989 Dose Response Trend Test and Dose Response Model Estimation

For the comparisons against NA control, the same multi-step testing strategy as the one implemented for the primary efficacy endpoint (see Sections 5.1.1 and 5.2.2.1.1), using MCP-Mod and additional intervention arms pairwise comparisons against NA control in a fixed sequence, will be used to control the type 1 error for multiple testing. However, the comparisons with NA control in the testing strategy applied to this efficacy endpoint will be made against the NA historical control benchmark of 5%, instead of the study NA control arm (Arm 6).

The choice of 5% as the historical NA control percentage for the HBsAg seroclearance 24 weeks after 48-week NA treatment was based on the results of a meta-analysis (Slaets L. et al., 2020) of historical data available for more than 15 years of NA treatment in 3 different subgroups based on treatment history and HBeAg status. The upper limit of the 95% prediction interval of the percentage of seroclearance at the end of 48-week NA treatment, based on the meta-analytical predictive probability distribution, was the largest (4.17%) in the subgroup of treatment-naïve HBeAg-positive patients (see Table 8 in the Protocol Amendment 1). As the current study enrolls participants in all subgroups of treatment history and HBeAg status, the value of 5% is considered a conservative estimate. Given that the percentage of HBsAg seroclearance at the end of 48 weeks of NA treatment is not expected to differ substantially from that percentage 24 weeks later, the 5% value derived from this meta-analysis provides an adequate historical control point estimate of the functional cure endpoint.

The MCP-Mod analysis will use 5% as the point estimate for the functional cure rate of the historical control group. In simulations on the logit scale under the assumption that the null hypothesis is globally true, a variance of 0.0275 (on the logit scale) afforded a match between the observed and nominal Type-I error rate. For this value the simulated Type 1 error rate was 0.043 (upper 99% CI: 0.044). Further details are described in a separate document, the Modeling and Simulation Report (MSR) for this study.

Therefore, within the MCP-Mod framework, the MCP analysis to test the null hypothesis that none of the 3 JNJ-3989 doses (40 mg, 100 mg, and 200 mg)+NA is better than historical control NA (i.e. the flat dose response curve) will assume:

- the point estimate for the response rate of the “JNJ-3989 dose=0 mg historical NA” is 0.05,
- the estimated variance, on the logit scale, of the point estimate for the response rate of the “JNJ-3989 dose=0 mg historical NA” historical group is 0.0275.

Characterization of the dose-response model: The model averaging techniques (Bornkamp B. et al., 2009) across the candidate models will be utilized to derive the dose-response shape and to evaluate the desired dose(s) of JNJ-3989 (modeling step). The estimated dose response curve and the corresponding confidence band will be plotted against the JNJ-3989 dose range of 0 mg to 200 mg.

5.3.2.1.1.2. Scientific Question Part b: Pairwise Comparisons vs Historical Control

For the pairwise comparison against the fixed historical control value of 5% for Arms 1 and Arm 5, respectively, the Clopper-Pearson test will be used at one-sided 0.05 alpha level, based on a fixed sequence testing approach as described in Section 5.1.1.

5.3.2.1.1.3. Scientific Question Part c: Comparisons Among Combination Regimens

For the regimen-finding objective, the testing among the regimens (Arm 1, 3, and 5) will be performed at a one-sided 0.025 alpha level using the min test approach to provide evidence of superior efficacy of the triple regimen Arm 1 over the dual regimens Arm 3 and Arm 5, for

regulatory consideration. This analysis is performed at a more stringent α-level because it aims to support the selection of the combination drug therapy to be studied in confirmatory studies. The JNJ-3989+JNJ-6379+NA combination regimen Arm 1 will be declared statistically superior to the dual regimens Arm 3 and Arm 5, if both tests of Arm 1 vs Arm 3 and Arm 1 vs Arm 5 demonstrate statistical significance at the one-sided 0.025 level. The Mantel-Haenszel test for the difference of 2 proportions adjusted for the 2 randomization stratification factors will be applied.

Further, the functional cure efficacy endpoint will be summarized for the control Arm 6 with the point estimate paired with its 90% CI using the Clopper-Pearson exact method to assess the consistency with the assumed historical control value of 5%.

5.3.2.1.2. Data Included

All available data from mITT analysis set, is included after taking into account all the intercurrent events and applying the intercurrent event strategies specified in Section 5.3.2.

5.3.2.1.3. Assumptions

- Missing Data for HBsAg are Missing at Random (MAR)
- The treatment effect is homogeneous across randomization stratification strata

5.3.2.1.4. Missing Data Handling Rule

Participants who withdraw from the study prior to Week 72 will be considered as non-responders.

If a participant remains in the study after experiencing a major protocol deviation (defined for the purpose of efficacy analyses and is an intercurrent event) and has missing Week 72 value, then the imputation to non-response will be applied. If the value for the endpoint at Week 72 is available, then such data will be used to determine their response status.

For the participants still in the study at Week 72 or for participants that have neither discontinued treatment early nor experienced any major protocol violations (defined for the purpose of efficacy analyses and is an intercurrent event), and HBsAg values missing at Week 72, then the primary method to handle missing data will be the Multiple Imputation (MI) approach (Ratitch B. et al., 2013) under the assumption of MAR will be applied to a model for continuous HBsAg log values over time.

The MI model will use all available data and be applied to the continuous log-transformed HBsAg values (not the binary endpoint). Of note, also the pre-ICE data for those subjects who experienced an ICE will be included in the MI model; but for these subjects the response status will be applied according to the ICE strategies before running the MI model.

The model will include treatment, the 2 randomization factors and the available non-missing log-transformed HBsAg (values < LLOQ, TND or TD will be first substituted following rules described in Table 3) for each scheduled time point (Week) and the following demographic and baseline characteristics (King G. et al., & Honaker J. et al.): age, gender, and baseline log-transformed value for HBsAg level.

A total of 200 datasets will be generated where both intermittent and monotone missing HBsAg values will be imputed for each subject relying on non-missing data from all other subjects within the same treatment group. Once the 200 completed datasets are generated by filling in the missing data with samples from the imputation model, the key secondary endpoint response status (binary variable) will be derived using both imputed and observed HBsAg values at Week 72.

For the MCP-step, the max trend test will be obtained for each of the imputed datasets and the multiplicity adjusted p-value associated with the largest T-test statistic will be saved. All p-values will be transformed to a Z-test statistic using the inverse cumulative distribution function of the standard normal distribution. The resulting 200 Z-test statistics and their standard error of 1 will be combined into an overall Z test result, using SAS PROC MIANALYZE.

For Mod-step, model averaging techniques across all 5 candidate models will apply to each imputed dataset and produce the weighted estimates across all models of the treatment effect across the JNJ-3989 dose range (0 mg and 200 mg). The standard errors will be obtained using bootstrapping techniques and then combined into one result using PROC MIANALYZE. The final response estimates on the logit scale for each dose level in the range 0 mg to 200 mg and their 90% CI will be back transformed to the original scale of proportion of responders and plotted with the corresponding 90% confidence band.

For pairwise comparisons against the fixed historical control value of 5% for Arm 1 and Arm 5, the estimated proportion with the asymptotic standard error will be obtained for each dataset. Then the results from these multiple imputed datasets are combined (pooled) for obtaining the overall inference and p-value in a way that accounts for the variability between imputations (Ratitch B. et al., 2013). Depending on the amount of missing data, the number of imputed datasets to be generated will be increased appropriately to ensure robustness in the results (Graham JW. et al., 2007).

For comparisons amongst combination regimens (Arms 1, 3, and 5), the MH test will be performed for each dataset to generate individual estimates of the difference in proportions and the standard error adjusted on stratification factors. Then the results from these multiple imputed datasets are combined (pooled) for obtaining the overall inference and p-value in a way that accounts for the variability between imputations (Ratitch B. et al., 2013). Depending on the amount of missing data, the number of imputed datasets to be generated will be increased appropriately from the planned 200 to ensure robustness in the MI results.

5.3.2.2. Sensitivity Estimators of the Main Estimand of the Key Secondary Endpoint

Sensitivity analyses will be conducted by constructing three sensitivity estimators for the key secondary primary estimand as defined in Section 5.3.2. One estimator will test the assumption of homogeneous treatment effect across the 2 randomization stratification factors, and the 2 other ones will use different missing data imputation rules.

5.3.2.2.1. Sensitivity Estimator 1 For the Main Estimand (LOCF) of the Key Secondary Endpoint

For this sensitivity estimator 2, the same statistical model (Clopper-Pearson and stratum-adjusted MH test), data included and approach to control the Type I error rate will be used as for the main estimator (Section 5.3.2.1). The assumption for missing data and the rule to handle missing data have changed.

5.3.2.2.1.1. Assumptions

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

5.3.2.2.1.2. Missing Data Handling Rule

For sensitivity estimator 2, participants who withdraw from the study prior to Week 72 will be considered as non-responders. After taking into account all the intercurrent events and applying the intercurrent event strategies specified in Section 5.3.2, if a subject who did not experience any ICEs has missing response status for the key secondary efficacy endpoint then the LOCF approach will be used as follows.

If the HBsAg value is missing at Week 72, the Last Observation Carried Forward (LOCF) in conjunction with the next available observation imputation approach will be used. The non-missing value closest to Week 72 will be selected among the non-missing values which are no earlier than 12 weeks prior or no later than 12 weeks after Week 72. If 2 non-missing laboratory values are equidistant, the later observation will be preferred.

For Mod-step, model averaging techniques across the statistically significant candidate models obtained from the MCP step will be used to derive the dose-response shape (Mod step).

5.3.2.2.2. Sensitivity Estimator 2 For the Main Estimand (Tipping Point) of the Key Secondary Endpoint

For this sensitivity estimator 3, the same statistical model (MCP-Mod, Clopper-Pearson and stratum-adjusted MH test), data included and approach to control the Type I error rate will be used as for the main estimator (Section 5.3.2.1). The assumption for missing data and the rule to handle missing data have changed.

5.3.2.2.2.1. Assumptions

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

5.3.2.2.2.2. Missing Data Handling Rule

For sensitivity estimator 3, the tipping point approach with the exhaustive scenario's analysis will be applied.

Instead of imputing non-response for missing data, the following method will be utilized to vary the imputation of response for missing data. For participants with missing response data at Week

72, responder status will be imputed in an increasing manner by participant count for each treatment group. Specifically, for each participant with missing data at Week 72, a responder/non-responder status will be imputed starting with the scenario where all participants are non-responders up to the scenario where all participants are responders. This would include all possible scenario combinations of responder/non-responder status for all missing data, including scenarios where participants on any active Arm have worse outcomes than participants on placebo+placebo+NA. Within the exhaustive scenarios list, the 'worst case scenario' will be one of the cases where all participants with missing Week 72 data in the active regimen arms will be imputed to 'non-responders' and all participants with missing data at Week 72 in the placebo+placebo+NA arm will be imputed to "responders". For each scenario, the same statistical model (MCP-Mod, Clopper-Pearson, and stratum-adjusted MH test), will be used as for the main estimator of comparisons vs historical control and comparisons amongst the combination regimens (Section 5.3.2.1.1) will be performed. A graphical display of the pvalue significance will summarize the results across all scenarios for this sensitivity estimator 3.

5.3.2.3. Supplementary Estimators of the Main Estimand of the Key Secondary Endpoint

Supplementary analyses to better interpret the results will be conducted by constructing additional estimators for the main estimand of the key secondary endpoint as defined in Section 5.3.2. This estimator will be based on the ITT set (instead of mITT).

To provide a comprehensive interpretation of the study results and the impact of COVID-19 pandemic on the functional cure at Week 72, the following supplementary estimator will utilize the ITT analysis set.

5.3.2.3.1. Supplementary Estimator 1 (ITT Analysis Set + MI)

For this supplementary estimator, the same estimand defined in Section 5.3.2, statistical model (MCP-Mod, and stratum-adjusted MH test), assumptions and approach to control the Type I error rate, and the same MI rule to handle missing data will be used as for the main estimator (Section 5.3.2.1).

5.3.2.3.1.1. Data Included

All available data from ITT analysis set, after taking into account all the intercurrent events and applying the intercurrent event strategies specified in Section 5.3.2, will be included.

5.3.2.3.2. Supplementary Estimator 2 (ITT Analysis Set + LOCF)

For this supplementary estimator, the same estimand defined in Section 5.3.2, statistical model (MCP-Mod, and stratum-adjusted MH test), assumptions and approach to control the Type I error rate will be used as for the main estimator (Section 5.3.2.1). For Mod-step, model averaging techniques across the statistically significant candidate models obtained from the MCP step will be used to derive the dose-response shape (Mod step).

The missing data approach will follow the LOCF approach as described in Section 5.3.2.2.1.

5.3.2.3.3. Supplementary Estimator 3 (ITT Analysis Set + Tipping Point)

For this supplementary estimator, the same estimand defined in Section 5.3.2, statistical model (MCP-Mod, and stratum-adjusted MH test), assumptions and approach to control the Type I error rate will be used as for the main estimator (Section 5.3.2.1).

This supplementary estimator will use the tipping point approach as described in Section 5.3.2.2.2.

5.3.2.3.4. Supplementary Estimator 4 of the Key Secondary Endpoint (Missing as Non-Response)

For this supplementary estimator, the same estimand defined in Section 5.3.2, statistical model (MCP-Mod, and stratum-adjusted MH test), assumptions and approach to control the Type I error rate will be used as for the main estimator (Section 5.3.2.1).

For Mod-step, model averaging techniques across the statistically significant candidate models obtained from the MCP step will be used to derive the dose-response shape (Mod step).

5.3.2.3.4.1. Assumptions

- Missing Data for ALT, HBV DNA, and HBsAg are missing not at random
- The treatment effect is homogeneous across strata

5.3.2.3.4.2. Missing Data Handling Rule

Participants who withdraw from the study prior to Week 72 will be considered as non-responders. All participants with missing data for the determination of the key secondary endpoint status will be imputed as non-responders.

5.3.3. Supplementary Estimand 1 of the Key Secondary Endpoint (Per-Protocol Analysis Set)

A) Study Intervention:

- Arm 1: JNJ-3989 (100 mg) + JNJ-6379 (250 mg qd) + NA
- Arm 2: JNJ-3989 (200 mg) + Placebo + NA
- Arm 3: JNJ-3989 (100 mg) + Placebo + NA
- Arm 4: JNJ-3989 (40 mg) + Placebo + NA
- Arm 5: Placebo + JNJ-6379 (250 mg qd) + NA
- Historical Control 5%

B) Study Population: HBeAg-positive and -negative chronic HBV-infected patients who are not being treated for their HBV infection (including treatment-naïve participants) or are virologically suppressed by NA treatment and who are able to tolerate the treatment regimen and will comply with the treatment schedule as prescribed.

C) Variable: Response status defined as participants who meet the criteria defining functional cure at Week 72 (responders) as defined in Section 5.3.1.

D) Intercurrent events:

- Treatment discontinuation prior to Week 48: if the participant discontinued treatment prior to Week 48 then s/he will be considered non-responder (composite strategy).
- Deaths prior to Week 72 are handled in a composite strategy as participants who die prior to Week 72 will be considered as non-responders.
- NA re-treatment between Week 48 and 72: the participant will be counted as non-responder (composite strategy).

E) Population-level summary: Difference in proportion of participants with functional cure status at Week 72 between study intervention arms.

5.3.3.1. Main Estimator

5.3.3.1.1. Analysis Methods

Statistical Model
Similar MCP-Mod and stratum-adjusted MH test on the difference of proportions as described for the main estimator of the main estimand will be used (see Section 5.3.2.1).

5.3.3.1.2. Data Included

All available data from randomized participants that are included in the PP2 analysis set will be used, after taking into account the intercurrent events and applying the intercurrent event strategies specified in Section 5.3.3.

To complement this analysis because of its inherent bias and allow a better interpretation of the results, the proportions of participants excluded from the PP2 analysis set will be summarized by intervention arm and by type of major protocol deviation.

5.3.3.1.3. Assumptions

- The treatment effect is homogeneous across strata

5.3.3.1.4. Missing Data Handling Rule

Participants who withdraw from the study prior to Week 72 will be considered non-responders. For the participants still in the study at Week 72 or for participants that have neither discontinued treatment early nor experienced any major protocol violations as listed in ATTACHMENT 1 (PP1 column), but HBsAg values missing at Week 72, then the primary method to handle missing data will be the imputation to non-responder.

5.3.4. Supplementary Estimand 2 of Key Secondary Efficacy Endpoint (vs NA Control Arm)

A) Study Intervention:

- Arm 1: JNJ-3989 (100 mg) + JNJ-6379 (250 mg qd) + NA
- Arm 2: JNJ-3989 (200 mg) + Placebo + NA
- Arm 3: JNJ-3989 (100 mg) + Placebo + NA
- Arm 4: JNJ-3989 (40 mg) + Placebo + NA
- Arm 5: Placebo + JNJ-6379 (250 mg qd) + NA
- Arm 6: Placebo + Placebo + NA

B) Study Population: HBeAg-positive and -negative chronic HBV-infected patients who are not being treated for their HBV infection (including treatment-naïve patients) or are virologically suppressed by being treated with NA.

C) Variable: Response status defined as participants who meet the criteria defining functional cure at Week 72 (responders) as in Section 5.3.1.

D) Intercurrent events:

- Treatment discontinuation prior to Week 48: if the participant discontinued treatment prior to Week 48 then s/he will be considered non-responder (composite strategy).
- Major protocol deviations affecting efficacy: ATTACHMENT 1 identifies the deviations considered intercurrent event (in per protocol set 2 column [PP2]). Participants with such deviations and who have missing data for the endpoint will be considered as non-responders (composite strategy). For all other deviations not considered intercurrent events, the data are used regardless of the occurrence of major protocol deviations (treatment policy strategy).
- Deaths prior to Week 72 are handled in a composite strategy as participants who die prior to Week 72 will be considered as non-responders.
- NA re-treatment between Week 48 and 72: the participant will be counted as non-responder (composite strategy).

E) Population-level summary: Difference in proportion of subjects with functional cure status at Week 72 between study intervention arms**.**

5.3.4.1. Main Estimator

To assess the functional cure rate against the observed proportion in the control Arm 6, for this estimator, the same statistical model (MCP-Mod, and stratum-adjusted MH test), data included, assumptions, and MI approach for handling missing data and approach to control the Type I error rate will be used as for the main estimator of the main estimand for the primary endpoint (Section 5.2.2.1). The MCP-Mod approach and pairwise statistical tests to compare with control will be based on the data from Arm 6 instead of historical control fixed value of 5%. The MCP-step will use the actual data from Arm 6, and statistical test to compare Arm 1 and Arm 5 to control will be the MH test as it compares 2-sample proportions.

5.3.4.1.1. Data Included

All available data from mITT analysis set, is included after taking into account all the intercurrent events and applying the intercurrent event strategies specified in Section 5.3.4.

An additional analysis of this estimand will be performed using the ITT analysis set, after taking into account all the intercurrent events and applying the intercurrent event strategies specified in the previous Section 5.3.4, will be included.

5.3.4.1.2. Assumptions

- Missing Data for HBsAg are Missing At Random (MAR)
- The treatment effect is homogeneous across randomization stratification strata

5.3.4.1.3. Missing Data Handling Rule

Participants who withdraw from the study prior to Week 72 will be considered as non-responders. For other missing data, the same datasets resulting from the MI approach as described in Section 5.3.2.1.4 will be used.

5.3.5. Other Analyses of The Key Secondary Endpoint

The following secondary analyses will be performed for the functional cure rate 24 weeks off treatment.

1. A participant will be defined as having achieved functional cure if he/she has:

   - completed 48 weeks of treatment, and
   - met the criteria for stopping NA treatment at Week 48, and
   - had HBsAg seroclearance between Week 60-72, inclusive, in case of early withdrawal, and
   - not required NA re-treatment in the 12-24 weeks after stopping all study intervention.

   If the HBsAg value at Week 72 is missing (including the case of early withdraw from the study prior to Week 72), the last/earliest available lab test no earlier/later than 12 weeks prior/after Week 72 will be used in the imputation (Week 60 and 84, respectively).

2. Participants with HBsAg seroclearance 24 weeks after stopping all study interventions (regardless of the actual duration of treatment and regardless of meeting the criteria for stopping NA treatment) without restarting NA treatment will be considered as having achieved FC. A participant will be defined as having achieved functional cure if he/she has:

   - stopped all study treatment at some point in time, and
   - had HBsAg seroclearance 24 weeks after stopping all study interventions, and
   - not required NA re-treatment in the 24 weeks after stopping all study intervention.

   If the HBsAg value 24 weeks after treatment completion is missing, the LOCF in conjunction with the next available observation imputation approach will be used with a 12-week window prior/after the timepoint of 24 weeks post stopping all treatments.

The following analyses of functional cure rate will be based on different analysis sets, i.e., a subset of mITT, ITT and PP2 analysis set.

3. Functional cure rate at Week 72 will be calculated for the subset of those participants in the selected analysis set who are responders for the primary efficacy endpoint (i.e. the denominator is the count of participants meeting the NA treatment completion criteria at Week 48, Section 5.2.1).

   If the HBsAg value at Week 72 is missing (including the case of early withdraw from the study prior to Week 72), the last/earliest available lab test no earlier/later than 12 weeks prior/after Week 72 will be used in the imputation (Week 60 and 84, respectively).

Descriptive summary and 90% CIs will be performed for the secondary analyses. The differences in functional cure rate between intervention arms will be summarized using Mantel-Haenszel method adjusted for the 2 randomization stratification factors. No adjustment for multiplicity will be made in these secondary analyses.

5.3.6. Subgroup Analyses of The Key Secondary Endpoint

The potential association between the functional cure rate and the randomization stratification factors will be explored by a multivariate logistic regression model and exploration of the interaction terms using observed case data. The model will include intervention arm, treatment history and HBeAg status at screening, as factors, and the intervention arm-by-treatment history and intervention arm-by-HBeAg status interaction terms. The functional cure estimates for each intervention arm will be derived from this model and presented graphically with their 90% CI in a forest plot. In addition, for assessment of internal consistency and investigation of homogeneity of the treatment effect in functional cure across other subgroups (as defined in Section 2.4.1), the same logistic regression approach as defined in Section 5.2.5 will be used.

5.4. Other Secondary Endpoints

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

In addition, the potential association between treatment outcome and baseline factors will be explored by multivariate logistic regression model in a similar fashion as described in Section 5.2.5.

5.4.1. HBsAg Seroclearance

HBsAg seroclearance will be evaluated over all time points when assessed, with emphasis at the following time points:

- at Week 48
- at Week 96 (ie, 48 weeks after completion of all study interventions at Week 48) without restarting NA treatment,

- 12 weeks after stopping all study interventions (regardless when intervention was stopped) without restarting NA treatment, and
- 24 weeks after stopping all study interventions (regardless when intervention was stopped) without restarting NA treatment, and
- 36 weeks after stopping all study interventions (regardless when intervention was stopped) without restarting NA treatment, and
- 48 weeks after stopping all study interventions (regardless when intervention was stopped) without restarting NA treatment

Proportions at the time points listed in the above bullets will be analyzed using the Mantel-Haenszel test and 90% CIs stratified for treatment history status and screening HBeAg status.

5.4.1.1. At Week 48 and At Week 96

The proportion of participants achieving HBsAg seroclearance at EOT (Week 48), and at Week 96 (48 weeks after completion of all study interventions at Week 48) will be summarized by intervention arm. A participant will be defined as responder at Week 96 (with HBsAg seroclearance 48 weeks after completion of all study intervention at Week 48) if he/she has completed 48 weeks of treatment AND met the criteria for stopping NA treatment at Week 48 AND not required NA re-treatment between Week 48 and Week 96 AND had HBsAg seroclearance at Week 96. If the HBsAg value at Week 96 is missing, the LOCF approach will be used with the condition that no value earlier than Week 84 may be carried forward.

Those participants who did not meet the NA stopping criteria at Week 48 OR did not complete 48 weeks of treatment OR did not reach seroclearance at Week 96 will be defined as non-responders for Week 96. The participants who has no HBsAg value between Week 84 and 96 or required NA re-treatment prior to Week 96 will be considered as non-responder as well.

If the HBsAg value at Week 48 is missing, the LOCF approach will be used with the condition that no value earlier than Week 40 may be carried forward. Those participants who did not meet the NA stopping criteria at Week 48 OR did not complete 48 weeks of treatment OR did not reach seroclearance at Week 48 will be defined as non-responders for Week 48. The participants who has no HBsAg value between Week 40 and 48 or will be considered as non-responder as well.

5.4.1.2. After 12, 24, 36, and 48 Weeks Off Treatment

The HBsAg seroclearance will be evaluated at each of the following timepoints separately: 12, 24, 36 and 48 Weeks after stopping all study interventions at any time. Participants with HBsAg seroclearance 12, 24, 36 and 48 Weeks, respectively, after stopping all study interventions and without restarting NA treatment thereafter, will be considered as having achieved this endpoint regardless of meeting the NA stopping criteria and of treatment duration. Of note, HBsAg seroclearance may be achieved prior to the Week 12, 24, 36, or 48, respectively, but must be observed at the given week of interest.

The CRF pages of ‘Treatment Disposition of JNJ-3989’, ‘Treatment Disposition of JNJ-6379’ and ‘Treatment Disposition of ETV, TDF or TAF’ will be checked to ensure all treatment actually

stopped. In addition, the CRF page of 'NA Re-treatment Criteria Assessment' will be checked to ensure no NA re-treatment required within 12, 24, 36 and 48 Weeks, respectively, after stopping all study interventions.

If the HBsAg value at 12 weeks after stopping all study interventions is missing, the next available observation will be used. The next non-missing lab test no later than 24 weeks after stopping all study interventions will be imputed.

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

If the HBsAg value at 48 weeks after stopping all study interventions is missing, the LOCF imputation approach will be used. The last available lab test no earlier than 36 weeks after stopping all study interventions will be carried forward.

The following analysis will be repeated for 4 different timepoints: 12, 24, 36, and 48 weeks after stopping all study interventions. The proportion of participants who achieve HBsAg seroclearance at a given point (e.g. 12 weeks after stopping all study interventions) will be summarized stratified by meeting the NA completion criteria (yes, or no) at the time when they stopped all study interventions.

5.4.2. Suppressed HBV DNA

HBV DNA <LLOQ will be evaluated over all time points when assessed, with emphasis at the following time points:

- 12 weeks after stopping all study interventions (regardless when intervention was stopped) without restarting NA treatment, and
- 24 weeks after stopping all study interventions (regardless when intervention was stopped) without restarting NA treatment, and
- 36 weeks after stopping all study interventions (regardless when intervention was stopped) without restarting NA treatment, and
- 48 weeks after stopping all study interventions (regardless when intervention was stopped) without restarting NA treatment

Proportions will be analyzed using the Mantel-Haenszel test and 90% CIs stratified for treatment history status and screening HBeAg status.

HBV DNA TND will be evaluated at the same time points with the same methodology described above.

5.4.2.1. Suppressed HBV DNA After Stopping Study Interventions

The proportion of participants with HBV DNA <LLOQ will be evaluated at each of the following time points separately: 12, 24, 36 and 48 weeks, respectively, after stopping all study interventions at any time during the study and without restarting NA treatment thereafter.

In addition, the proportion of participants with HBV DNA TND will be evaluated at each of the following time points separately: 12, 24, 36 and 48 weeks, respectively, after stopping all study interventions at any time during the study and without restarting NA treatment thereafter will be calculated and summarized separately.

If the HBV DNA value at 12 weeks after stopping all study interventions is missing, the next available observation will be used. The next non-missing lab test no later than 24 weeks after stopping all study interventions will be imputed.

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

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

If the HBV DNA value at 48 weeks after stopping all study interventions is missing, the LOCF imputation approach will be used. The last available lab test no earlier than 36 weeks after stopping all study interventions will be carried forward.

5.4.2.2. Suppressed HBV DNA After NA Re-Treatment

Proportion of participants who reach HBV DNA<LLOQ after NA re-treatment during follow-up will be summarized by intervention arm. In addition, proportion of participants who reach HBV DNA TND after NA re-treatment during follow-up will be summarized by intervention arm.

Re-start of NA treatment during follow-up will be checked according to the CRF page of 'NA Re-treatment Criteria Assessment' in follow-up phase. In addition, the CRF page of 'Study Drug Administration for ETV, TDF or TAF' will be checked to ensure the actual re-start of NA treatment during follow-up.

5.4.3. NA Treatment Completion Criteria

5.4.3.1. NA Treatment Completion Criteria During The Study

The count and proportion of participants who met the NA treatment completion criteria (as defined in Section 5.2.1) at any time during the study, regardless of the treatment duration, will be summarized by intervention arm.

Starting at Week 44, the incidence of participants who did not meet the NA treatment completion criteria will be summarized by intervention arm 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 5.2.1.

5.4.3.2. NA Treatment Completion Criteria During FU

The count and proportion of participants who met the NA treatment completion criteria (as defined in Section 5.2.1) at any time during the FU phase, regardless of the treatment duration, will be summarized by intervention arm. All of NA treatment completion criteria will be checked based on clinical laboratory tests in FU phase.

5.4.3.3. Time to NA Treatment Completion

Time to meet NA completion criteria is defined as the number of days between the date of first study intervention intake and the date of meeting NA completion criteria regardless of whether the participant actually discontinued treatment (i.e. the date of meeting NA completion criteria – the date of first study intervention intake + 1). The participants who withdrew early from the study before meeting NA completion criteria or who did not meet NA completion criteria will be censored at the last available lab assessment with non-missing ALT, HBV DNA, HBeAg and HBsAg results.

Time to meet NA completion criteria will be summarized by intervention arm. The Kaplan-Meier method will be used to estimate and plot the cumulative incidence by each intervention arm. The log-rank test will be performed to compare among the intervention arms. The median time with 90% CI will be estimated using Kaplan-Meier method. In addition, the hazard ratio and the corresponding 90% confidence interval will be estimated based on a stratified Cox's regression model by the 2 randomization stratification factors

5.4.4. NA Re-Treatment During Follow-Up

The number and proportion of participants who meet the criteria for NA re-treatment at any time during FU will be summarized descriptively by intervention arm. Only the subset of 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.

The proportion of participants who actually re-started NA treatment during the follow-up phase on the basis of the 'Study Drug Administration for ETV, TDF or TAF' CRF page will be summarized separately over time (e.g. FU Week12, 24, 48, etc.) by intervention arm.

Due to the Protocol Amendment #4 to update the criteria for NA re-treatment for participants who discontinued NA treatment at Week 48, the participants who met NA re-treatment criteria in follow-up will also be listed along with their respective criterion. The proportion of participants who met the criteria according to the flag on the CRF page of 'NA Re-treatment Criteria Assessment' during the follow-up phase was summarized over time by intervention arm prior to Protocol Amendment 4 approval.

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

5.4.5. HBsAg, HBeAg, and HBV DNA

5.4.5.1. Values and Changes Over Time

HBsAg and HBeAg will be summarized by treatment history (not currently treated and virologically suppressed) and overall, and HBV DNA will only be summarized by treatment history.

Descriptive statistics on actual values (original unit and log10 transformed values) and changes from baseline (log10 transformed values) over time in HBsAg, HBeAg and HBV DNA will be summarized by intervention arm. Mean (+/- SE) plots of the actual values and the change from baseline (log10 transformed) will be presented over time per blood marker by intervention arm.

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

Change from baseline based on log10 transform for quantitative HBsAg, HBeAg and HBV DNA will be analyzed using mixed effects model for repeated measures [MMRM]) including intervention arm, analysis time point (week), and 2 randomization stratification factors (HBeAg status at screening [positive versus negative] and treatment history [not currently treated versus virologically suppressed]) and baseline blood marker categorical variable as fixed effects. In addition, the above model will be augmented with an intervention arm-by-analysis week interaction term (i.e. treatment-by-time interaction term) to evaluate the change of treatment effect over time and the intervention arm-by-baseline interaction term. The covariance structure will include a random intercept at the level of the participant to capture between-participant variability, while within-participant variability will be captured with an unstructured (type=UN) covariance matrix. In case of convergence problems, simpler variance-covariance structures such as Toeplitz or AR (1) will be considered. The selection of any of these structures will be determined after exploration of the observed correlation structure. The LS mean of change from baseline, standard error (SE), 90% confidence interval (CI) and p-values will be provided.

Descriptive statistics on actual values (original unit and log10 transformed values) and changes from baseline (log10 transformed values) at end of treatment in HBsAg, HBeAg and HBV DNA, respectively, will be summarized by study intervention arm by outcome response (i.e. by NA

treatment completion criteria status at Week 48, by functional cure status at Week 72, and by partial cure status at Week 72, and for participants who achieved functional cure 24 weeks after stopping all study interventions regardless of meeting the NA completion criteria).

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, and HBV DNA will be presented over time per blood marker by intervention arm and by selected subgroups (e.g. HBeAg status at baseline, HBV Genotype) and by outcome response (i.e. by NA treatment completion criteria status at Week 48, by functional cure status at Week 72, and by partial cure status at Week 72).

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

5.4.5.2. HBsAg Thresholds

The following cut-offs for HBsAg values and decreases from baseline will be used in separate summaries over time by intervention arm. The number and proportion of participants who meet those HBsAg thresholds during the study will be summarized descriptively by intervention arm and analysis phase over time.

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 log10 IU/mL
- ≥ 0.5 log10 IU/mL
- ≥ 1 log10 IU/mL
- ≥ 2 log10 IU/mL
- ≥ 3 log10 IU/mL
- ≥ 4 log10 IU/mL

Cumulative percentage of participants achieving any given decrease from baseline in HBsAg at Week 72 and at Week 96, separately, will be presented graphically.

5.4.5.3. HBeAg Thresholds

The following cut-offs for HBeAg values and decreases from baseline will be used in separate summaries over time by intervention arm for the subset of participants with HBeAg positive at baseline. The number and proportion of participants who meet those HBeAg thresholds during the study will be summarized descriptively by intervention arm and analysis phase over time.

Thresholds for **HBeAg** values:

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

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

Thresholds for **HBeAg** decreases from baseline:

- ≥ 0.3 log10 IU/mL
- ≥ 0.5 log10 IU/mL
- ≥ 1 log10 IU/mL
- ≥ 2 log10 IU/mL
- ≥ 3 log10 IU/mL

Cumulative percentage of participants achieving any given decrease from baseline in HBeAg at Week 72 and at Week 96, separately, will be presented graphically.

5.4.5.4. HBV DNA Thresholds

The values and decreases from baseline of HBV DNA will be summarized by treatment history (not currently treated and virologically suppressed).

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

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 log10 IU/mL
- ≥ 2 log10 IU/mL
- ≥ 3 log10 IU/mL
- ≥ 4 log10 IU/mL
- ≥ 5 log10 IU/mL

Cumulative percentage of participants achieving any given decrease from baseline in HBV DNA at Week 72 and at Week 96, separately, will be presented graphically.

5.4.6. Thresholds Based on Multiple Markers

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

- **HBsAg<LLOQ and HBV DNA**
  - HBsAg<LLOQ and HBV DNA<LLOQ**
  - HBsAg<LLOQ and HBV DNA≥LLOQ
- **HBsAg≥LLOQ and HBV DNA<2,000 IU/ml**
  - HBsAg≥LLOQ and HBV DNA<LLOQ**
  - HBsAg≥LLOQ and LLOQ ≤HBV DNA<2,000 IU/ml (See partial cure in Section 5.4.7)
- **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

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

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

5.4.7. Partial Cure

Partial cure will be evaluated at each of the following time points separately: 24 weeks and 48 weeks after stopping all study interventions. A participant will be defined as having achieved partial cure if he/she has:

- Stopped all study interventions at any time, and
- had HBV DNA level < 2,000 IU/ml quantifiable at the given week of interest, and
- had HBsAg ≥LLOQ at the given week of interest, and
- not required NA re-treatment after stopping all study interventions.

The number and proportion of participants who achieve partial cure during the study will be summarized descriptively by intervention arm at 24 weeks and 48 weeks after stopping all study interventions, respectively. Of note, HBV DNA level < 2,000 IU/ml may be achieved prior to the Week 24 (or 48) but must be observed at the given week of interest. Proportions will be analyzed using the Mantel-Haenszel test and 90% CIs stratified for treatment history status and screening HBeAg status.

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

If the HBV DNA value at 48 weeks after stopping all study interventions is missing, the LOCF imputation approach will be used. The last available lab test no earlier than 36 weeks after stopping all study interventions will be carried forward.

5.4.8. Treatment Failure

Treatment failures will be summarized separately on-treatment, off-treatment, and overall.

A participant will be defined as on-treatment failure if he/she never met the criteria for stopping NA treatment during the study. The number and proportion of on-treatment failure participants will be summarized descriptively by intervention arm over time (i.e. at Week 48, Week 60, Week 72 and Week 96, respectively) and at the time of EOT.

A participant will be defined as off-treatment failure if he/she required NA re-treatment after stopping all study interventions. The number and proportion of off-treatment failure participants will be summarized descriptively by intervention arm over time (i.e. at 12, 24 and 48 weeks after stopping all study interventions, respectively).

5.4.9. HBsAg Seroconversion

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

Seroclearance of HBsAg is defined as (quantitative) HBsAg<LLOQ. Appearance of anti-HBs antibodies is defined as a baseline anti-HBs antibodies (quantitative) <LLOQ and a post-baseline assessment ≥LLOQ. A sensitivity analysis will be conducted using the threshold of 10mIU/mL, i.e. appearance of anti-HBs antibodies is defined as a baseline anti-HBs antibodies (quantitative) <10 mIU/mL and a post-baseline assessment ≥10 mIU/mL.

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

The number and proportion of participants who achieve HBsAg seroconversion will be summarized descriptively by intervention arm and analysis phase.

For participants achieving HBsAg seroconversion, descriptive statistics will be calculated for the level of anti-HBs antibodies at the timepoint when achieving the HBsAg seroconversion by intervention arm. In an additional summary, the level of anti-HBs antibodies at the specific timepoint (i.e. Week 48, Week 72, Week 96) will be summarized for the subset of the participants achieving HBsAg seroconversion at any time before or at that given timepoint by intervention arm.

In addition, the number and proportion of participants with appearance of anti-HBs antibodies but without seroclearance of HBsAg will also be summarized by intervention arm and analysis phase.

5.4.10. HBeAg Seroconversion

Seroconversion of HBeAg is defined as having achieved HBeAg seroclearance together with appearance of anti-HBe antibodies. The seroconversion of HBeAg will be summarized for the subset of participants with HBeAg positive at baseline.

Seroclearance of HBeAg is defined as (quantitative) HBeAg <LLOQ. Appearance of anti-HBe antibodies is defined as a baseline anti-HBe antibodies (qualitative) with a "NEGATIVE" result and a post-baseline assessment with “POSITIVE” result.

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

The number and proportion of participants who achieve HBeAg seroconversion will be summarized by intervention arm and analysis phase.

In addition, the number and proportion of participants with appearance of anti-HBe antibodies but without seroclearance of HBeAg will also be summarized by intervention arm and analysis phase.

5.4.11. Time to Seroclearance

For the time-to-event endpoints described in the subsections of the following efficacy-related Sections 5.4 and 5.5, the Kaplan-Meier method will be used to estimate and plot the cumulative incidence by each intervention arm. The log-rank test will be performed to compare among the intervention arms. The median time with 90% CI will be estimated using Kaplan-Meier method. In addition, the hazard ratio and the corresponding 90% confidence interval will be estimated based on a stratified Cox's regression model by the 2 randomization stratification factors. In addition, the number and percentage of participants who had an event or were censored will be reported by intervention arm. The estimated survival curves from the stratified Cox model will be plotted for intervention arms by strata. The interaction between intervention arm and stratification factors will be explored graphically. To explore the impact of selected baseline factors in addition of study intervention, multivariate (including all baseline factors together) and univariate (each baseline factor at a time) stratified Cox models will be performed.

5.4.11.1. Time to HBsAg Seroclearance

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

In addition, time to the first occurrence of HBsAg <10 IU/mL (i.e. the date of the first occurrence of HBsAg <10 IU/mL – the date of first study intervention intake + 1), HBsAg <100 IU/mL (i.e. the date of the first occurrence of HBsAg <100 IU/mL – the date of first study intervention intake + 1), time to the first occurrence of HBsAg decline ≥ 2.0 log10 IU/mL (i.e. the date of the first occurrence of HBsAg < HBsAg decline ≥ 2.0 log10 IU/mL – the date of first study intervention intake + 1) and time to the first occurrence of HBsAg decline ≥ 3.0 log10 IU/mL (i.e. the date of the first occurrence of HBsAg < HBsAg decline ≥ 3.0 log10 IU/mL – the date of first study intervention intake + 1) will also be evaluated.

5.4.11.2. Time to HBeAg Seroclearance

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

5.4.12. ALT Decrease and Normalization

The number and proportion of participants who achieve ALT normalization on treatment and off treatment but without restarting NA treatment will be summarized descriptively by intervention

arm and analysis phase, over time, only for the subjects who had ALT elevation (ALT ≥ULN) at baseline. A participant with ALT elevation at baseline achieves ALT normalization if his/her ALT value post-baseline is <ULN at any given time point.

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

5.4.13. ALT Normalization After NA Re-Treatment

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

5.4.14. Flares

5.4.14.1. Definition

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 date of a confirmed virologic flare is defined as the first date of two consecutive visits with HBV DNA > 200 IU/mL. The end date of the same confirmed virologic flare is defined as the first date when HBV DNA value returns to ≤200 IU/mL or the date of 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) Biochemical flare is defined as follows:

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

The start date of a confirmed biochemical flare is defined as the first date of two consecutive visits with ALT and/or AST ≥3x ULN and ≥3x nadir. The end date of the same confirmed biochemical flare is defined as the first date when there is a 50% reduction from the peak ALT and/or AST level & <3x ULN.

c) Clinical flare is defined as follows:

Clinical flare will be assessed with both derivations specified above for virologic flare.

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

A clinical flare occurs when a virologic flare and biochemical flare overlap in time. However, if there is no overlap in time, a clinical flare occurs when a virologic flare ends prior to a biochemical flare starting, and the end date of the virologic flare is within 4 weeks of the biochemical flare start date. 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, e.g., the later date of HBV DNA ≤200 IU/mL and 50% reduction from the peak ALT and/or AST level & <3x ULN.

** 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 5.4.15.1. 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 time period after stopping all study interventions (including NA).

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 study intervention arm. Additionally, for each participant the total number of flares the participant experienced will be counted by type and overall, respectively. Such counts will be used to summarize the distribution of the total number of flares both by type and across types by intervention arm.

For on-treatment biochemical flares, the incidence of flares causing treatment discontinuation will be summarized by intervention arm. Further, for off-treatment flares, the count and percentage of participants who experienced a flare followed by NA re-treatment will be summarized by flare type and intervention arm. Similarly, the incidence of flares followed by the achievement of HBsAg seroclearance (at any time) will be summarized by flare type and intervention arm.

5.4.14.2. Time to Flare

Time to on-treatment flare and time to off-treatment flare will be summarized for each type of flare by intervention arm separately.

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

Time to off-treatment flare will be defined as the number of days between the date of last study intervention intake and the date of the first occurrence of off-treatment flare (i.e. the date of experiencing the first off-treatment flare of each type- the date of last study intervention intake). The participants who withdrew early from the study before experiencing off-treatment flare or who

did not experience off-treatment flare will be censored at the last available blood markers or liver enzymes assessment.

The Kaplan-Meier method will be used to estimate and plot the cumulative incidence by each intervention arm. The log-rank test will be performed to compare among the intervention arms. The median time with 90% CI will be estimated using Kaplan-Meier method. In addition, the hazard ratio and the corresponding 90% confidence interval will be estimated based on a stratified Cox's regression model by the 2 randomization stratification factors. In addition, the number and percentage of participants who had an event or were censored will be reported by intervention arm.

5.4.15. Virologic Breakthrough

5.4.15.1. Definition

HBV virological breakthrough is defined as having a confirmed on-treatment HBV DNA increase by >1 log10 from nadir level (lowest level reached during treatment) in participants who did not have on-treatment HBV DNA level below the lower limit of quantification (LLOQ) or a confirmed on-treatment HBV DNA level >200 IU/mL in participants who had on-treatment HBV DNA level below the lower limit of quantification (LLOQ). Confirmed HBV DNA increase/level means that the criterion should be fulfilled at 2 or more consecutive time points or at the last observed time point.

On-treatment will be defined as the time period in which the participant receives any of the study interventions (including NA).

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

5.4.15.2. Time to Virologic Breakthrough

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

5.5. Exploratory Endpoints

5.5.1. Changes in Fibrosis

To explore the changes in the severity of liver disease at the end of follow-up versus screening/baseline, the changes in fibrosis (according to Fibroscan liver stiffness measurements) will be summarized using descriptive statistics (for example, may include n, mean, SD, 90% CI, median, minimum, maximum) by intervention arm. The comparison among intervention arms will

be done using ANCOVA with intervention arm, randomization stratification factors as main effects in the model and baseline score as covariate.

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

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

5.5.2. HBV RNA and HBcrAg

5.5.2.1. Values and Changes Over Time

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

The values of and changes from baseline in HBV RNA and HBcrAg, respectively, will be summarized only descriptively over time in a similar manner as for values and changes from baseline over time in HBsAg, HBeAg, and HBV DNA as described in Sections 5.4.5.1, including the change from baseline value to nadir (i.e. maximum decrease for each participant) and the various graphical displays.

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

5.5.2.2. HBV RNA Thresholds

The number and proportion of participants who meet the HBV RNA thresholds below during the study will be summarized descriptively by intervention arm and analysis phase over time.

Thresholds for **HBV RNA** values:

- < TND (target not detected)
- < LOD
- < LLOQ
- <1000 IU/mL

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

- ≥ 1.0 Log IU/mL
- ≥ 2.0 Log IU/mL
- ≥ 3.0 Log IU/mL

5.5.2.3. HBcrAg Thresholds

The number and proportion of participants who meet the **HBcrAg** thresholds below during the study will be summarized descriptively by intervention arm and analysis phase over time.

Thresholds for **HBcrAg** values:

- < 3.0 LogU/mL

- < 4.0 LogU/mL

Thresholds for **HBcrAg** decreases from baseline:

- ≥ 1.0 Log U/mL
- ≥ 2.0 Log U/mL
- ≥ 3.0 Log U/mL

5.5.3. Time to Undetectability

The following time-to-event variables will be analyzed in a similar manner as for the time to event endpoints described in the Section 5.4.11.

5.5.3.1. Time to Undetectability of HBV DNA

Time to undetectability of HBV DNA is defined as the duration from the date of first study intervention intake to the date of the first occurrence of undetectability of HBV DNA (i.e. the date of the first occurrence of HBV DNA<LLOQ – the date of first study intervention intake + 1). The participant who did not achieve undetectability or who early withdrew from the study before achieving undetectability of HBV DNA will be censored at the last HBV DNA assessment before the date of withdrawal. Only the participants with HBV DNA≥ LLOQ at baseline will be included in this analysis.

5.5.3.2. Time to Undetectability of HBV RNA

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

5.5.3.3. Time to Undetectability of HBcrAg

Time to undetectability of HBcrAg is defined as the duration from the date of first study intervention intake to the date of the first occurrence of undetectability of HBcrAg (i.e. the date of the first occurrence of HBcrAg<LLOQ – the date of first study intervention intake + 1). The participant who did not achieve undetectability or who early withdrew from the study before achieving undetectability of HBcrAg will be censored at the last HBcrAg assessment before the date of withdrawal. Only the participants with HBcrAg values ≥ LLOQ+ 0.5 Log10 U/mL (i.e. ≥3.5 Log10 U/mL) at baseline will be included in this analysis.

5.5.4. Anti-HBs Antibodies

5.5.4.1. Changes from Baseline

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 5.4.5.1.

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

5.5.4.2. Time to Appearance of Anti-HBs Antibodies

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

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

Time to appearance of anti-HBs antibodies will be analyzed in a similar manner as for the time to event endpoints described in Section 5.4.11.

5.5.4.3. Assessment of Positive Anti-HBs Antibodies at Baseline

For all participants with positive anti-HBs antibodies at baseline who will reach HBsAg seroclearance (as defined in Section 5.3.1), descriptive statistics will be calculated for the change of anti-HBs antibodies level from baseline at the timepoint when achieving the HBsAg seroclearance by intervention arm. In an additional summary, the change of anti-HBs antibodies level from baseline at the specific timepoint (i.e. Week 48, Week 72, Week 96) will be summarized descriptively for the subset of the participants achieving HBsAg seroclearance at any time before or at that given timepoint by intervention arm.

5.5.5. Anti-HBe Antibodies

The number and proportion of positive and negative values in anti-HBe antibodies will be summarized over time.

Shift tables from baseline will also be provided at each time point.

5.5.5.1. Time to Appearance of Anti-HBe Antibodies

Appearance of anti-HBe antibodies is defined as a baseline anti-HBe antibodies (qualitative) with a "NEGATIVE" result and a post-baseline assessment with “POSITIVE” result. Only participants who are negative for the anti-HBe antibodies at baseline will be included in the analysis.

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

Time to appearance of anti-HBe antibodies will be analyzed in a similar manner as for the time to event endpoints described in the Section 5.4.11.

6. SAFETY

All safety analyses will be performed using the safety analysis set. All assessments will be presented by analysis phase, unless other specified. All summaries will be descriptive, and no inferential methods will be used to compare intervention arms 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.

As a result of the IDMC ongoing reviews to ensure the continuing safety of study participants, additional safety analyses may be generated at the discretion of the Sponsor.

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 2.5.1 will apply.

6.1.2. Analysis Methods

The adverse events will be summarized by intervention arm 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 a study phase, the AE will be attributed to that phase (treatment-emergent principle). For imputation of partially/fully missing dates please see Section 2.5.1. In case of a completely missing start date, the event is allocated to the double-blind study intervention phase, except if the end date of the AE falls before the first administration of study treatment (DB 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 intervention arm 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 2.4.2.

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 discontinuation, TEAE of at least grade 3, or 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 and Rash questionnaire will be tabulated by study intervention arm and overall.

6.1.3. Adverse Events of Special Interest

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

The adverse events of special interest include:

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

The list of all preferred terms belonging to ALT/AST elevations, renal complications, cholesterol increase, and hematologic abnormalities is provided in ATTACHMENT 2. 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 4.

Table 4: Laboratory Parameters

Laboratory Category	Parameters		
Hematology	Platelet count RBC count Hemoglobin Hematocrit Reticulocyte count Reticulocyte index	RBC Indices: Mean corpuscular volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Hematology Coagulation	Activated partial thromboplastin time Prothrombin Intl. normalized ratio Prothrombin time		
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	
	Note: Creatinine clearance (eGFR calculated by the CKD-EPI formula) will be assessed.		
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		

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

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 (for example, may include n, mean, SD, minimum, median, and maximum) will be calculated for each laboratory analyte for observed values and changes from baseline at each scheduled time point by intervention arm and study phase.

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

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

A tabulation of percentage and number of the participants who have treatment-emergent worst toxicity grades and treatment-emergent worst abnormalities per parameter and analysis phase will be included. The incidence table of worst toxicity grade abnormality in laboratory parameters will be also presented stratified by the subgroup of interests identified in Section 2.4.2.

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

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

6.2.3. Creatinine and Glomerular Filtration

Unless otherwise specified, time points to be evaluated for these creatinine and glomerular filtration analyses will be Baseline, Week 12, Week 24, Week 36 and Week 48.

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-<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]) will also be presented.

6.2.3.2. Proximal Renal Tubular Function

Proteinuria by Quantitative Assessment

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

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

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

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

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

Proteinuria by Urinalysis (Dipstick)

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

Other Renal Biomarkers

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

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

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

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

Phosphate excretion

Other renal biomarkers include FEPO4 that will be summarized by intervention arm 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 intervention arm and visit using descriptive statistics. Median (Q1, Q3) change from baseline in FEPO4 over time will be plotted by intervention arm.

Subclinical renal proximal tubulopathy

Potential Markers of Renal Proximal Tubulopathy are:

1. Confirmed increase in serum creatinine ≥ 0.40 mg/dL from baseline.

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

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

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

Baseline Subclinical renal proximal tubulopathy

Potential Markers of Renal Proximal Tubulopathy at Baseline:

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

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

6.3. Electrocardiogram

6.3.1. 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)

The abnormalities in ECG parameters will be determined according to the criteria specified in the Cardiovascular Safety – Abnormalities Table (see Clinical Protocol Appendix 6, 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).

6.3.2. 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 intervention arm.

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

A cross-tabulation of the worst abnormalities (on actual values) versus baseline per parameter by study phase will be presented including also the number of participants per abnormality. A tabulation of number and percentage of the participants who have treatment-emergent worst

abnormalities per parameter (i.e. for HR, PR, QRS and QTcF) and analysis phase will also be presented.

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

- Frequency tabulations of categorized corrected QT/QTc change from baseline (<=30 msec, >30- <=60 msec, >60 msec) and categorized corrected QT/QTc interval values (<=450 msec, >450- <=480 msec, >480-<= 500 msec, >500 msec) per timepoint will be presented by intervention arm.
- Listings including all parameters for participants with at least one treatment-emergent abnormality (on actual values or change from baseline), including all findings (e.g. interpretation, rhythm, or technical findings) for participants with uncorrected QT values ≥ 500 ms will be provided separately.

6.4. Vital Signs and Body Temperature

6.4.1. Definitions

The following parameters measurements will be analyzed:

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

The abnormalities in vital signs will be determined according to the criteria specified in the Cardiovascular Safety – Abnormalities Table (see Clinical Protocol Appendix 6).

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).

6.4.2. Analysis Methods

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

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

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

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

- A tabulation of percentage and number of the participants who have treatment-emergent worst abnormalities per parameter and study phase will be included.
- A listing including all parameters for participants with at least one treatment-emergent abnormality (on actual values or change from baseline) is provided. Additional vital signs assessments corresponding to the rash eCRF pages will be only listed as applicable.

6.5. Physical Examination

The physical examination findings and abnormalities will be listed.

7. VIRAL GENOME SEQUENCE ANALYSIS

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 ETV or TDF 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 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 5.4.15.1 for virologic breakthrough definition)
- Time Point of Sequence at Virologic Flare: time point with sequence data available closest to the time point of Virologic flare (see Section 5.4.14.1 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 5.4.4)
- 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

The sequencing of samples after baseline 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.

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
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 Other))
  - in the HBV core protein,
  - at HBV core protein positions of interest,
  - at positions of interest in the RT-domain of the polymerase,
  - at positions of interest in the major hydrophilic loop of HBsAg.
- Number (%) of subjects with substitutions on nucleotide level
  - at the binding site positions of JNJ-3989 (i.e. JNJ-3976 and JNJ-3924) (overall and by HBV genotype (A, B, C, D, E, F, G, H, I, J and Other)).
  - 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 Other) 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 28 and 15 POI),
  - at positions of interest in the polymerase region,
  - at positions of interest in the major hydrophilic loop of HBsAg.
- 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.

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 (eg, 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 (ECoRI numbering will be used)

In the precore region:

- 1896 (ECoRI numbering will be used)

In the basal core/precure region

- Combination of basal core promotor and/or precore region

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
  - Short list (N=17): 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, and 278
- 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
  - Short list (N=17): 1782, 1783, 1784, 1785, 1786, 1787, 1788, 1789, 1790, 1791, 1792, 1793, 1794, 1795, 1796, 1797, and 1798
- 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])

- Long list (n=47): 18, 19, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 37, 38, 102, 103, 105, 106, 107, 109, 110, 111, 114, 115, 116, 117, 118, 119, 122, 123, 124, 125, 126, 127, 128, 129, 131, 132, 133, 134, 136, 137, 138, 139, 140, 141
- Due to an insertion of 12 amino acids in the N-terminal part of core, the 47 HBV Core Protein positions of interest for HBV genotype G are 30, 31, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 49, 50, 114, 115, 117, 118, 119, 121, 122, 123, 126, 127, 128, 129, 130, 131, 134, 135, 136, 137, 138, 139, 140, 141, 143, 144, 145, 146, 148, 149, 150, 151, 152, 153.

Based on some recent more detailed published structural data (Klumpp K. et al., 2015, Qiu Z. et al., 2016, Zhou Z. et al., 2017, & Tu J. et al., 2017) , and some in house structural analysis, a more shortened list of core positions of interest can be defined:

- Short list (n=28): 23, 24, 25, 29, 30, 33, 37, 38, 102, 105, 106, 109, 110, 118, 122, 124, 125, 127, 128, 129, 132, 133, 134, 137, 138, 139, 140, 141
  - Due to an insertion of 12 amino acids in the N-terminal part of core, the 28 HBV Core Protein positions of interest for HBV genotype G are 35, 36, 37, 41, 42, 45, 49, 50, 114, 117, 118, 121, 122, 130, 134, 136, 137, 139, 140, 141, 144, 145, 146, 149, 150, 151, 152, 153
- 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

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

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. 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) intervention arm. For comparison of amino acid or nucleotide levels to HBV genotype-specific reference sequences, descriptive summaries will only be performed by subgroup HBV genotypes and intervention arm.

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, partial 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 will 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 will 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 will 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

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 will 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 study treatment, and at end of study will be generated.

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

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. PHARMACOKINETICS/PHARMACODYNAMICS

8.1. Pharmacokinetics

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

8.2. Pharmacokinetic/Pharmacodynamic Relationships

Relationships of PK parameters for JNJ-3989, JNJ-6379, and/or NAs (ETV, TAF and/or TDF), 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.

8.3. Immune Response

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

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

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

9. PATIENT-REPORTED OUTCOMES

The impact of study intervention on participants' HRQoL, self-stigma level, and impression of change will be assessed using PROs at predefined time points. The following PRO instruments will be used: the HBQOL scale, an HBV-specific self-stigma PRO scale, and the PGIC scale. All PRO analyses will be performed using the ITT analysis set.

9.1. Hepatitis B Quality of Life Instrument (HBQOL)

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 (ie, 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.

Descriptive statistics of the actual values and change from baseline values at each timepoint (including baseline and available analysis time point) for the derived scores will be displayed for subscales/domains and global score by intervention arm. The proportion of participants experiencing a clinically important improvement or worsening from baseline (if applicable) at each timepoint will be calculated by intervention arm. Analyses will also be performed on the changes from baseline at specific time points (Week 48, 72, 96, etc.) as appropriate for different subgroups: participants who meet the NA treatment completion criteria at Week 48 versus those who do not, and participants with versus participants without HBsAg seroclearance 24 weeks and 48 weeks after completion of all study intervention at Week 48.

In addition, effect sizes will be calculated to measure the magnitude of difference between means in all different intervention arms using an ANCOVA, with intervention arm, and 2 randomization stratification factors, as main effect in the model, and the two 2-way intervention arm-stratification factor interaction terms, and baseline as covariate. The LS means of the change from baseline on the analysis time points with estimates, SE, 90% CI, p-values will be presented. A graphical representation may be used to display the adjusted mean change from baseline.

9.2. HBV-specific Self-stigma PRO Scale

The HBV-specific self-stigma scale is an hepatitis B-specific PRO instrument designed to assess the experience and impact of self-stigma. The current version consists of 37 items. The items cover aspects of self-stigma such as a) devaluation, inferiority, and worthlessness, b) marginalization and alienation, c) secrecy and concealment, d) shame and guilt, and e) withdrawal and social

isolation. Each of the 37 items is graded on a 5-point Likert scale (1="Never", 2="Rarely", 3="Sometimes", 4="Often", and 5="Always").

The analyses will be performed in a similar manner as described in Section 9.1.

9.3. Patient Global Impression of Change Scale (PGIC)

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".

The tabulation of the number and percentage of participants at each response level will be displayed per time point for each intervention arm. The comparison among the intervention arms will be done using Mann–Whitney U test.

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ATTACHMENT 1

Selected Major Protocol Deviations for analysis Purposes: The major protocol deviations that may affect the assessment of efficacy will be finalized prior to the primary analysis database lock. Two Per Protocol sets are identified: PP1 to be used for the primary efficacy endpoint (at Week 48) analysis and PP2 for the key secondary efficacy endpoint (at Week 72) analysis. The major deviations that are selected to exclude participants from the PP sets are listed below. The flag of Intercurrent Event is added to each deviation for facilitating the implementation of the estimands for the primary and key secondary efficacy endpoints.

Sequence No.	Protocol Deviation Description (DVTERM)	Protocol Deviation Coded Term (DVDECOD)	Exclude from PP1	Intercurrent Event PP1	Exclude from PP2	Intercurrent Event PP2
1	Inclusion criterion 3 not met: Chronic HBV infection was not documented by serum HBsAg positivity at screening and/or chronicity was not documented by serum HBsAg positivity at least 6 months prior to screening, or by alternative markers of chronicity.	Entered but did not satisfy criteria	Yes	No	Yes	No
2	Inclusion criterion 4 not met: Participant who is currently not treated does not have a. Serum HBV DNA at screening more than or equal to 2,000 IU/mL for HBeAg-negative participants and greater than or equal to 20,000 IU/mL for HBeAg-positive participants and/or b. ALT levels at screening less than 10x ULN AND greater than ULN on 2 sequential measurements at least 3 months apart.	Entered but did not satisfy criteria	Yes	No	Yes	No
3	Inclusion Criterion 5 not met: Participant is not suppressed and/or a. Participant is not on stable NA treatment (ETV, TDF, or TAF) for greater than or equal to 6 months prior to screening and/or not having the same dose for ≥3 months prior to screening b. Participant is not having serum HBV DNA <60 IU/mL on two sequential measurements at least 6 months apart (one of which is at screening) c. Participant is not having ALT values ≤2x ULN on two sequential.	Entered but did not satisfy criteria	Yes	No	Yes	No
4	Inclusion Criterion 6 not met: Participant has HBsAg ≤100 IU/mL at screening.	Entered but did not satisfy criteria	Yes	No	Yes	No
5	Exclusion Criterion 1 met: Participant has evidence of hepatitis A virus infection (hepatitis A antibody IgM), HCV infection (HCV antibody), HDV infection (HDV antibody), or hepatitis E virus infection (hepatitis E antibody IgM), or HIV-1 or HIV 2 infection (confirmed by antibodies) at screening.	Entered but did not satisfy criteria	Yes	No	Yes	No
6	Exclusion Criterion 2 met: Participant has Total bilirubin >1.5x ULN or Direct bilirubin >1.2x ULN or Prothrombin time >1.3x ULN or Serum albumin <3.2 g/dL within 12 months prior to screening.	Entered but did not satisfy criteria	Yes	No	Yes	No
7	Exclusion Criterion 3 met:	Entered but did not satisfy criteria	Yes	No	Yes	No

Sequence No.	Protocol Deviation Description (DVTERM)	Protocol Deviation Coded Term (DVDECOD)	Exclude from PP1	Intercurrent Event PP1	Exclude from PP2	Intercurrent Event PP2
	Participant has a history or evidence of hepatic decompensation <*Specify*>.					
8	Exclusion Criterion 4 met: Participant has evidence of <*specify liver disease of non-HBV etiology*>.	Entered but did not satisfy criteria	Yes	No	Yes	No
9	Subject used disallowed medication at any time 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 PP1 set.	Yes	If classified as major protocol deviation, excluded from PP2 set.	Yes
10	Subject used disallowed medication from 6 months prior to screening until end of follow-up: <*specify treatment, dose, unit, frequency, reason administered*>.	Received a disallowed concomitant treatment	If classified as major protocol deviation, excluded from PP1 set.	Yes	If classified as major protocol deviation, excluded from PP2 set.	Yes
11	Subject used disallowed medication from 6 months prior to screening until end of follow-up: <*specify treatment, dose, unit, frequency, reason administered*>.	Received a disallowed concomitant treatment	If classified as major protocol deviation, excluded from PP1 set.	Yes	If classified as major protocol deviation, excluded from PP2 set.	Yes
12	Subject used disallowed medication 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 PP1 set.	Yes	If classified as major protocol deviation, excluded from PP2 set.	Yes
13	Subject used disallowed medication 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 PP1 set.	Yes	If classified as major protocol deviation, excluded from PP2 set.	Yes
14	Subject used disallowed medication from 1 week prior to baseline until 12 weeks after EOS intervention: <specify *treatment, dose, unit, frequency, reason administered*>.	Received a disallowed concomitant treatment	If classified as major protocol deviation, excluded from PP1 set.	Yes	If classified as major protocol deviation, excluded from PP2 set.	Yes
15	Received wrong treatment of study drug JNJ-6379: *was randomized to receive JNJ-6379 but received placebo or vice versa*	Received wrong treatment or incorrect dose	If classified as major protocol deviation, excluded from PP1 set.	Yes	If classified as major protocol deviation, excluded from PP2 set.	Yes
16	Received wrong treatment of study drug JNJ-3989: *incorrect dose or placebo when randomized to active (and vice versa)*	Received wrong treatment or incorrect dose	If classified as major protocol deviation, excluded from PP1 set.	Yes	If classified as major protocol deviation, excluded from PP2 set.	Yes
17	Subject did not receive dose of study drug JNJ-3989 within window: Subject missed two consecutive injections or missed more than 2 injections.	Received wrong treatment or incorrect dose	If classified as major protocol deviation, excluded from PP1 set.	Yes	If classified as major protocol deviation, excluded from PP2 set.	Yes
18	Subject missed more than 5 JNJ-6379/ Placebo doses within a four week period	Received wrong treatment or incorrect dose	If classified as major protocol deviation, excluded from PP1 set.	Yes	If classified as major protocol deviation, excluded from PP2 set.	Yes
19	Subject missed NA treatment for more than 5 doses within a four week period.	Received wrong treatment or incorrect dose	If classified as major protocol deviation, excluded from PP1 set.	Yes	If classified as major protocol deviation, excluded from PP2 set.	Yes
20	Subject received expired study medication <*JNJ-3989, JNJ--6379, NA or placebo*>.	Received wrong treatment or incorrect dose	If classified as major protocol deviation, excluded from PP1 set.	Yes	If classified as major protocol deviation, excluded from PP2 set.	Yes

Sequence No.	Protocol Deviation Description (DVTERM)	Protocol Deviation Coded Term (DVDECOD)	Exclude from PP1	Intercurrent Event PP1	Exclude from PP2	Intercurrent Event PP2
21	Subject has event of signs of decreasing liver function based on laboratory or clinical findings, but did not start NA treatment.	Received wrong treatment or incorrect dose	If classified as major protocol deviation, excluded from PP1 set.	Yes	If classified as major protocol deviation, excluded from PP2 set.	Yes
22	Subject has confirmed HBeAg seroreversion, but did not start NA treatment.	Received wrong treatment or incorrect dose	If classified as major protocol deviation, excluded from PP1 set.	Yes	If classified as major protocol deviation, excluded from PP2 set.	Yes
23	Subject has a confirmed post-treatment increase in HBV DNA >2,000 IU/mL and ALT >5 x ULN over a period of at least 4 weeks, but did not start NA treatment	Received wrong treatment or incorrect dose	If classified as major protocol deviation, excluded from PP1 set.	Yes	If classified as major protocol deviation, excluded from PP2 set.	Yes
24	Subject has a confirmed post-treatment increase in HBV DNA >20,000 IU/mL over a period of at least 4 weeks, but did not start NA treatment	Received wrong treatment or incorrect dose	If classified as major protocol deviation, excluded from PP1 set.	Yes	If classified as major protocol deviation, excluded from PP2 set.	Yes
25	Subject has confirmed signs of hepatic decompensation <*specify*> but subject continued study treatment.	Developed withdrawal criteria but not withdrawn	Yes	Yes	Yes	Yes
26	The subject has confirmed HBV virological breakthrough but continued study treatment.	Developed withdrawal criteria but not withdrawn	Yes	Yes	Yes	Yes
27	Accidental unblinding of treatment group of a subject or a blinded staff member prior to planned unblinding at <*specify visit*>.	Other	If classified as major protocol deviation, excluded from PP1 set.	No	If classified as major protocol deviation, excluded from PP2 set.	No
28	Study < specify the visit which >procedure not done at scheduled Visits.	Other	If classified as major protocol deviation, excluded from PP1 set.	No	If classified as major protocol deviation, excluded from PP2 set.	No
29	Efficacy evaluation not done at Week 44 visit	Other	Yes	No	No	No
30	Efficacy evaluation not done at Week 72 visit	Other	No	No	Yes	No
31	Study Visits not performed per protocol.	Other	If classified as major protocol deviation, excluded from PP1 set.	No	If classified as major protocol deviation, excluded from PP2 set.	No

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 v23.1)	Alanine aminotransferase abnormal
		Alanine aminotransferase increased
		Aspartate aminotransferase abnormal
		Aspartate aminotransferase increased
		Hepatic enzyme abnormal
		Hepatic enzyme increased
		Hepatic function abnormal
		Hypertransaminasaemia
		Liver function test abnormal
		Liver function test increased
		Transaminases abnormal
		Transaminases increased
Renal Complications	(Modified) Acute renal failure (SMQ) broad (MedDRA v23.1)	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

Adverse Event of Special Interest	Source	Preferred Term
		Renal tubular necrosis
		Urine output decreased
		Nephropathy
		Nephropathy toxic
		Glomerulonephropathy
		Nephrolithiasis
Cholesterol increase	Dyslipidaemia (SMQ), (MedDRA v23.1)	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

Adverse Event of Special Interest	Source	Preferred Term
		Very low density lipoprotein increased
Hematologic abnormalities	(Modified) Haematopoietic cytopenias affecting more than one type of blood cell (SMQ), (MedDRA v23.1)	Aplastic anaemia Autoimmune aplastic anaemia Bicytopenia Bone marrow failure Cytopenia Febrile bone marrow aplasia Full blood count decreased Gelatinous transformation of the bone marrow Immune-mediated pancytopenia Pancytopenia Panmyelopathy Aspiration bone marrow abnormal Biopsy bone marrow abnormal Blood count abnormal Blood disorder Bone marrow disorder Bone marrow infiltration Bone marrow myelogram abnormal Bone marrow necrosis Bone marrow toxicity Haematotoxicity Myelodysplastic syndrome Myelodysplastic syndrome transformation Myelofibrosis Myeloid metaplasia Plasmablast count decreased Scan bone marrow abnormal
Hematologic abnormalities	(Modified) Haematopoietic erythropenia (SMQ), (MedDRA v23.1)	Aplasia pure red cell Aplastic anaemia Erythroblast count decreased Erythroid maturation arrest Erythropenia Hypoplastic anaemia Microcytic anaemia Proerythroblast count decreased

Adverse Event of Special Interest	Source	Preferred Term
		Red blood cell count decreased
		Reticulocyte count decreased
		Reticulocytopenia
		Anaemia
		Erythroblast count abnormal
		Erythropoiesis abnormal
		Haematocrit abnormal
		Haematocrit decreased
		Haemoglobin abnormal
		Haemoglobin decreased
		Leukoerythroblastic anaemia
		Normochromic anaemia
		Normochromic normocytic anaemia
		Normocytic anaemia
		Proerythroblast count abnormal
		Red blood cell count abnormal
		Reticulocyte count abnormal
		Reticulocyte percentage decreased
Hematologic abnormalities	(Modified) Haematopoietic leukopenia (SMQ), (MedDRA v23.1)	Agranulocytosis
		Band neutrophil count decreased
		Band neutrophil percentage decreased
		Basophil count decreased
		Basophilopenia
		B-lymphocyte count decreased
		Cyclic neutropenia
		Eosinopenia
		Eosinophil count decreased
		Febrile neutropenia
		Granulocyte count decreased
		Granulocytes maturation arrest
		Granulocytopenia
		Idiopathic neutropenia
		Leukopenia
		Lymphocyte count decreased
		Lymphopenia
		Metamyelocyte count decreased
		Monoblast count decreased
		Monocyte count decreased
		Monocytopenia

Adverse Event of Special Interest	Source	Preferred Term
		Myeloblast count decreased
		Myelocyte count decreased
		Neutropenia
		Neutropenic infection
		Neutropenic sepsis
		Neutrophil count decreased
		Promyelocyte count decreased
		Pure white cell aplasia
		T-lymphocyte count decreased
		White blood cell count decreased
		Basophil count abnormal
		Basophil percentage decreased
		B-lymphocyte abnormalities
		B-lymphocyte count abnormal
		Differential white blood cell count abnormal
		Eosinophil count abnormal
		Eosinophil percentage decreased
		Full blood count abnormal
		Granulocytes abnormal
		Leukopenia neonatal
		Lymphocyte count abnormal
		Lymphocyte percentage abnormal
		Lymphocyte percentage decreased
		Monocyte count abnormal
		Monocyte percentage decreased
		Mononuclear cell count decreased
		Myeloblast percentage decreased
		Myelocyte percentage decreased
		Myeloid maturation arrest
		Neutrophil count abnormal
		Neutrophil percentage decreased
		Plasma cell disorder
		Plasma cells absent
		White blood cell analysis abnormal
		White blood cell count abnormal
		White blood cell disorder
Hematologic abnormalities	(Modified) Haematopoietic thrombocytopenia (SMQ), (MedDRA v23.1)	Acquired amegakaryocytic thrombocytopenia
		Megakaryocytes decreased

Adverse Event of Special Interest	Source	Preferred Term
		Platelet count decreased
		Platelet maturation arrest
		Platelet production decreased
		Platelet toxicity
		Thrombocytopenia
		Megakaryocytes abnormal
		Platelet count abnormal
		Platelet disorder
		Plateletcrit abnormal
		Plateletcrit decreased