Janssen Research & Development

Statistical Analysis Plan

Intervention-specific Appendix 2 to Master Protocol PLATFORMPAHPB2001

A Randomized, Double blind, Placebo-controlled Phase 2b Study to Evaluate Efficacy, Pharmacokinetics, and Safety of 48-week Study Intervention With JNJ 73763989+JNJ 56136379+Nucleos(t)ide Analog (NA) Regimen Compared to NA Alone in HBe Antigen negative Virologically Suppressed Participants With Chronic Hepatitis B Virus Infection

The REEF-2 Study

Protocol 73763989PAHPB2002; Phase 2b

JNJ-73763989 and JNJ-56136379

Status: Approved
Date: 08 July 2022
Prepared by: Janssen Research & Development, a division of Janssen Pharmaceutica NV
Document No.: EDMS-ERI-200976680, 2.0

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

TABLE OF CONTENTS

AMENDMENT HISTORY

Document History	
Document	**Date**
Amendment 1	This document
Original SAP	05 February 2021

Overall rationale for Amendment 1: 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**
2.1.1 Analysis Phase	Revised logic for deriving the end date of the Double-blind phase.	Previous logic did not account for subjects potentially continuing NA treatment after end of Double-blind phase.
2.1.3 Analysis Visits and Time Points	Revised Table 2 to incorporate new visits at Follow-up Weeks 28, 32, 40, and 44.	Protocol Amendment 3 (finalized 30 September 2021) added new visits to allow more frequent monitoring of NA re-treatment criteria.
5.1.2 Data Handling Rules	Revised ULOQ and Imputed Values data cutpoints for HBsAg and HBeAg.	Update from Central Laboratory.
5.3.1.1.5 HBsAg and HBV DNA cut-offs	Added new HBV DNA cut-off: 100,000 IU/mL.	Cut-off added to align with revised NA re-treatment criteria in Protocol Amendment 4 (finalized 26 November 2021).
5.3.1.1.6 Flares 5.3.2.1.3 Flares	Revised definitions for virologic, biochemical, and clinical flares.	The definition of flares was updated after approval of the original SAP (dated 05 February 2021). Updates included to clearly define the stop time of the flare. Biochemical flares was also updated to account for summarizing flares after NA re-treatment. A new HBV DNA threshold was added for virologic and clinical flares (Derivation 1): 100,000 IU/mL.
5.3.1.1.7 Virologic Breakthrough	Updated definition for virologic breakthrough.	Additional clarification needed in definition.
5.3.1.1.9 ALT Normalization	Updated definition for ALT elevation.	Definition updated to account for subjects who may have ALT=ULN.

Clarifications, Additions, Corrections		
Section Number and Name	**Description of Change**	**Rationale**
5.3.1.2 Continuous Endpoints	Specified analysis of changes in HBsAg from both EOT and Week 48 in follow-up.	Additional analysis for HBsAg was decided to be performed after approval of the original SAP (dated 05 February 2021)
5.3.1.3.1 First HBsAg Seroclearance 5.4.1.3 Time to Event Endpoints	Some time-to-event endpoints will also be analyzed by censoring at NA re-treatment.	Sensitivity analysis.
5.4.1.1.5 Treatment Failure	Defined treatment failure at Week 96.	The original SAP defined treatment failure only at Week 72, yet described analyses of treatment failure at Weeks 72 and 96.
7.4 Positions & Genetic Variations of Interest	Added lists of genetic variations for JNJ-3976 and JNJ-3924.	Updated list requested by Virology.
Attachment 1. Selected Major Protocol Deviations For Analysis Purposes	Specified how to determine if a subject has the major protocol deviation “Efficacy evaluation not done at Week 72” as listed in Attachment 1 Sequence No. 25.	Algorithm updated to not only check DV.DVCRIT records, but also the central lab data.

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
DB	double blind
ECG	electrocardiogram
EOS	end of study
EOT	end of treatment
eCRF	electronic case report form
ETV	entecavir
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
ISA	intervention-specific appendix
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
MedDRA	medical dictionary for regulatory activities
MH	Mantel-Haenszel
mITT	modified intent-to-treat
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
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 the 73763989PAHPB2002 phase 2b trial describes the statistical analyses and definitions to assess the efficacy and safety of study interventions including JNJ-73763989 (200 mg), JNJ-56136379 (250 mg), and Nucleos(t)ide analogs (NA) in hepatitis B e antigen (HBeAg) negative virologically suppressed participants with chronic hepatitis B (CHB). 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 study is part of the platform trial PLATFORMPAHPB2001in participants with CHB. The protocol amendment for 73763989PAHPB2002 constitutes the Intervention-specific Appendix (ISA) that describes all the specific and/or additional features of this study complementing the common design elements of the platform trial described in the Master Protocol.

This SAP is to be interpreted in conjunction with the ISA Amendment-2 finalized on 27 January 2020, and with the Master Protocol Amendment-2 for PLATFORMPAHPB2001 finalized on 27 January 2020.

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 Intention-to-Treat (mITT) analysis set, 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 72, or had no efficacy assessment for the primary endpoint.

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

1.1. Trial Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of 48-week study intervention with JNJ-3989+JNJ-6379+NA regimen compared to NA alone.	• Proportion of participants with HBsAg seroclearance at Week 72 (ie, 24 weeks after completion of all study interventions at Week 48) without restarting NA treatment.
Secondary	
• To evaluate the safety and tolerability of the study intervention throughout the study.	• Safety and tolerability including but not limited to the proportion of participants with (S)AEs and abnormalities in clinical laboratory tests (including hematology, blood biochemistry, blood coagulation, urinalysis, urine chemistry, and renal biomarkers), 12-lead ECGs, vital signs, and physical examinations throughout the study.

Objectives	Endpoints
• To evaluate the efficacy of the study intervention at the end of treatment.	• Proportion of participants with HBsAg seroclearance at Week 48. • Proportion of participants with HBV DNA <LLOQ at Week 48.
• To evaluate the efficacy as measured by blood markers (such as HBsAg, HBV DNA, and ALT) during study intervention and follow-up.	• Proportion of participants with HBsAg seroclearance at Week 96 (ie, 48 weeks after completion of all study interventions at Week 48) without restarting NA treatment. • Proportion of participants with HBsAg seroclearance 24 weeks after stopping all study interventions without restarting NA treatment. • Proportion of participants with HBsAg seroclearance 48 weeks after stopping all study interventions without restarting NA treatment. • Proportion of participants with (sustained) reduction, suppression, and/or seroclearance considering single and multiple markers (such as HBsAg, HBV DNA and ALT). • Proportion of participants with HBsAg seroconversion. • Change from baseline over time in HBsAg and HBV DNA. • Time to achieve first HBsAg 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 participants with HBV DNA levels and/or changes from baseline below/above different cut-offs (eg, <LLOQ of the assay). • Proportion of participants with flares (virologic, biochemical, and clinical).
• To evaluate the frequency of virologic breakthrough during study intervention.	• Proportion of participants with virologic breakthrough.
• To evaluate the proportion of participants requiring NA re-treatment during follow-up.	• Proportion of participants who meet the NA re-treatment criteria.

Objectives	Endpoints
• To identify baseline and on-treatment markers associated with sustained off-treatment response.	• Correlation of baseline characteristics and baseline/on-treatment viral blood markers (such as baseline NA treatment duration, age, and baseline/on-treatment HBsAg levels) with selected off-treatment efficacy variables.
• To evaluate the PK of JNJ-3989 (JNJ-3976 and JNJ-3924), JNJ-6379, and NA, as applicable.	• Population PK parameters of JNJ-3989 (JNJ-3976 and JNJ-3924), JNJ-6379, and NA, as applicable.
Exploratory	
• To evaluate the efficacy of NA re-treatment during follow-up.	• Proportion of participants with decline in HBV DNA, ALT and/or HBsAg levels after restart of NA treatment during follow-up.
• To explore changes in the severity of liver disease.	• Changes in fibrosis (according to Fibroscan liver stiffness measurements) at end-of-study intervention (EOSI) and end of follow-up versus baseline.
• To explore the efficacy in terms of changes in HBV RNA and HBcrAg levels.	• Changes from baseline in HBV RNA and HBcrAg levels during study intervention and follow-up.
• To explore the impact of study intervention on participants' self-stigma and health-related quality of life using patient-reported outcomes (PROs) during study intervention and follow-up and to assess the psychometric properties of the HBV-specific self-stigma scale.	• Changes over time in score on the HBV-specific self-stigma scale. • Psychometric properties of the HBV-specific self-stigma scale. • Changes over time in the 5-Level EuroQol 5-Dimension (EQ-5D-5L) Visual Analog Scale (VAS) score and Index score.
• To explore the relationship of PK with selected pharmacodynamic (PD) parameters of efficacy and safety.	• Relationship of various PK parameters with selected efficacy and safety endpoints.
• To explore the HBV genome sequence during study intervention and follow-up.	• Assessment of intervention-associated mutations.
• To explore HBV-specific T-cell responses during study intervention and follow-up.*	• Changes from baseline in HBV-specific peripheral blood T-cell responses.

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

1.2. Trial Design

This is a Phase 2b, multicenter, randomized, double-blind, placebo-controlled, 2-arm parallel-group study to evaluate the efficacy of 48-week study intervention with a JNJ-3989+JNJ-6379+NA regimen compared to NA treatment alone, assessed by HBsAg seroclearance at Week 72 (ie, 24 weeks after completion of all study interventions at Week 48) without restarting NA treatment in HBeAg-negative virologically suppressed CHB-infected

participants who received NA treatment for at least 2 years prior to screening. All participants will stop all study interventions including NAs at Week 48 and will be followed up until Week 96. After completing this study, participants may have the option to enroll into a long-term follow-up study.

A target of 120 HBeAg-negative virologically suppressed CHB-infected male and female participants, 18-65 years (inclusive) of age, who received NA treatment for at least 2 years prior to screening will be randomized in a 2:1 ratio to one of the following intervention arms:

- Arm 1 (N=80): 200 mg JNJ-3989 + 250 mg JNJ-6379 + NA
- Arm 2 (N=40): Placebo + Placebo + NA

NA treatment refers to entecavir (ETV), or tenofovir disoproxil fumarate (TDF), or tenofovir alafenamide (TAF).

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. All participants who complete 48-week study intervention should stop all study interventions including NAs at Week 48.
- **Follow-up phase**: for 48 weeks after the end of investigational intervention.

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 efficacy and safety 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

The primary hypothesis of this study is that the combination regimen of JNJ-3989+JNJ-6379+NA is more efficacious than NA treatment alone, as measured by the primary efficacy endpoint, the proportion of participants with HBsAg seroclearance at Week 72 (ie, 24 weeks after completion of all study interventions at Week 48) without restarting NA treatment (ie, from Week 48 through Week 72).

1.4. Sample Size Justification

The total study sample size is 120 participants who will be randomly assigned to one of the two intervention arms in a 2:1 ratio (JNJ-3989+JNJ-6379+NA: placebo+placebo+NA). Statistical

power to test the primary hypothesis was assessed using the Mantel-Haenszel test with a 1-sided Type 1 error rate of 0.05, assuming the observed percentage of participants with HBsAg seroclearance at Week 72 in the placebo+placebo+NA arm to be 5%. The sample size of 80 participants in the investigational arm and 40 participants in the control arm provides >91% statistical power to detect a ≥20% difference in the primary endpoint.

1.5. Randomization and Blinding

Randomization

Central randomization is implemented in this study. Participants will be randomly assigned in a 2:1 ratio to 1 of 2 intervention arms (JNJ-3989+JNJ-6379+NA:placebo+placebo+NA). The randomization is stratified by screening HBsAg level (<1,000 IU/mL or ≥1,000 IU/mL), race (Asian versus non-Asian) and type of NA (TDF/TAF versus ETV).

Blinding

The investigators and participants will remain blinded to intervention allocation until all participants have reached Week 72 (or discontinued earlier), while the sponsor's central study team will be unblinded at the time of the Week 48 IA.

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.

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 (200 mg) + JNJ-6379 (250mg qd) + NA
  - Arm 2: 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	Maximum [Date of last study treatment (JNJ-3989/placebo or JNJ-6379/placebo) intake, Week 48] + 5 days[a] or cut-off date[b], whichever comes first

Table 1: Analysis Phases Start and End Dates

Analysis phase	*Start date*	*End date*
Follow-up	End of the double-blind study intervention phase + 1 day	The end date will be derived as trial termination date (date of last contact) or cut-off date[b], whichever comes first

[a] +5 days is only attributed to adverse events and concomitant medications.
[b] Cut-off dates will be defined to match the prespecified timepoints for IDMC safety monitoring, interim analyses, the primary analysis and the final analysis, respectively.

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.

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 is used. All efficacy and safety assessments during the double-blind phase will be assigned a 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:

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

2.1.3. 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 Point and Time Intervals by Analysis Phase

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

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

Follow-up	FU Target day	Analysis time point (Week)	Analysis time point (label)	Time interval (FU days)
	15	50	Follow-up Week 2	[1, 22]
	29	52	Follow-up Week 4	[23,43]
	57	56	Follow-up Week 8	[44, 71]
	85	60	Follow-up Week 12	[72, 99]
	113	64	Follow-up Week 16	[100, 127]
	141	68	Follow-up Week 20	[128, 155]
	169	72	Follow-up Week 24	[156, 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]
	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, +∞]
	last visit in the study	999*	EOS	

*End of treatment (EOT) visit will be the last post-baseline visit in double-blind phase, and End of study (EOS) visit (last available data during the follow-up) will be the last visit in the study.
** Visits at Follow-up Weeks 28, 32, 40, and 44 were added to the study with Protocol Amendment 3 (finalized on 30 September 2021) to allow more frequent monitoring of NA re-treatment criteria. Consequently, the time intervals for Follow-up Weeks 30 and 42 have been shortened to create space for the new visits.

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 were randomized in the study and received at least one dose of study treatment within this ISA. 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 72, 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 study treatment within this ISA. Participants will be analyzed according to the study intervention they actually received.

Per protocol analysis set (PP): All participants in the ITT analysis set who do **not** have any of the selected major protocol deviations that may affect the assessment of efficacy in terms of the primary endpoint at 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. Participants will be analyzed according to the study intervention they were randomly assigned to.

The PK analysis set*:* All participants who have received at least one dose of study treatment and have at least one 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 selected safety analyses (see Sections 6.1.2 and 6.2.2).

Due to the small sample size of the study, only subgroups with approximately 10% of the population (i.e., 12 subjects total) within the level of the subgroup across intervention arms will be reported in summary tables. Nevertheless, interpretation should be done with caution in the event of small sample sizes within a subgroup.

2.4.1. Subgroups for Efficacy Analyses

- Sex: Male, Female
- Age categories: ≤ 45 years, > 45 years
- Type of NA at study entry – stratification levels:
  - TDF/TAF
  - Entecavir (ETV)
- Type of NA at study entry – categorization levels
  - TDF
  - TAF
  - ETV
- Duration of NA (see Section 4.2.2): > 2 years to ≤ 4 years, > 4 years to ≤ 8 years, > 8 years
- Race: Asian, non-Asian

- HBsAg level at baseline – stratification levels:
  - <1,000 IU/mL
  - ≥1,000 IU/mL
- HBsAg level at baseline – categorization levels:
  - <1,000 IU/mL
  - ≥1,000 IU/mL-<10,000 IU/mL
  - ≥10,000 IU/mL
- HBV DNA level at baseline:
  - <LLOQ TND
  - < LLOQ TD
  - <LLOQ
  - ≥LLOQ
- HBV RNA level at baseline:
  - Negative
  - < 1,000 copies /mL
  - ≥1,000 copies /mL
- HBcrAg level at baseline:
  - <3 log U/mL
  - ≥3 log U/mL-<4 log U/mL
  - ≥4 log U/mL
- HBsAg Antibody (Anti-HBs) level at baseline:
  - <LLOQ
  - ≥LLOQ
  - <10 mIU/mL
  - ≥10 mIU/mL
- Alanine Transferase (ALT) at baseline: ≤ 1.0 ULN, > 1.0 ULN - <2.5 ULN, ≥ 2.5 ULN
- Anti-HBe antibody at baseline: Positive, Negative

2.4.2. Subgroups for Safety Analyses

- Age categories: ≤ 45 years, > 45 years
- Sex: Male, Female
- Type of NA at study entry:
  - TDF

  - TAF
  - ETV
- Duration of NA (see Section 4.2.2): > 2 years to ≤ 4 years, > 4 years to ≤ 8 years, > 8 years

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), 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 Dates

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. Prior and Concomitant Medication Dates

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

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

If the medication was taken prior to study start (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.

Generally, participants should only be taking one NA medication at a time. Therefore, the imputed dates will need further adjustment as to not overlap with the next adjacent NA taken.

2.5.4. Alcohol Dates

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

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

- if end date is completely missing and marked as Ongoing then impute with randomization date. Otherwise, no imputation if completely missing.

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. 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 IDMC will also review the results of the interim analysis (IA) comprising cumulative safety and selected efficacy endpoints for providing the sponsor with further insight and interpretation of the data and the primary analysis. 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.

3.1. Interim Analysis

The one interim analysis will be conducted to monitor safety and evaluate the time course of different disease markers to support the sponsor's interactions with health authorities, as well as inform decisions about additional studies and/or investigation of other treatment combinations. This IA is planned when all participants have completed Week 48 or discontinued earlier.

Up to two additional IAs may be performed at the sponsor's discretion between Week 48 and Week 72 to support interactions with health authorities. Both primary and interim analysis 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 primary analysis will be conducted at the time when all participants have completed Week 72 or discontinued earlier.

The final analysis will be performed when all participants have completed the last study visit (Week 96) or discontinued earlier.

This SAP covers the definitions of analysis sets, derived variables and statistical methods for the primary, 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 5.3.1.1.6.

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 both the ITT and safety sets (only for 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, and 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 IA or primary analysis cut-off (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 re-treatment will also be included.

4.2. Demographics and Baseline Characteristics

Tabulations of demographic and baseline characteristics will be presented by intervention arm and overall for the ITT and PP analysis sets. Continuous variables will be summarized by descriptive statistics including the number of participants, mean, standard deviation, standard error, median, range and interquartile range. Categorical/binary variables will be summarized by counts and percentages.

Additional summaries will be presented by the 3 randomization stratification factors (HBsAg level, race and type of NA). 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. If the eCRF data is missing, then the IWRS data will be used.

4.2.1. Demographic Characteristics

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

- Sex: Male, Female, Unknown, Undifferentiated
- Age (years)
- Age categories: ≤30 years, >30-≤ 45years, > 45 years-≤60 years, >60 years
- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Not reported, Unknown
  - In case the participant is Asian provide subgroup: Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, Other Asian
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown
- Country
- 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
- Type of Substance (Beer, Wine, Distilled Spirits): Current/Former/Never
- Type of Substance (Beer, Wine, Distilled Spirits) Duration (Months) = (stop date – start date +1)/30.4375; rounded to 1 decimal
- Standard drinks containing alcohol (weekly period)

4.2.2. Baseline Characteristics

For the viral activity parameters (e.g. HBsAg, HBV DNA), 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
- For HBeAg negative participants only: Time since HBeAg seroconversion (Years) = (date of randomization – date of HBeAg seroconversion+1)/365.25; rounded to 1 decimal.

- Prior treatment for HBV infection: Lamivudine, Telbivudine, Adefovir, Tenofovir Disoproxil Fumarate (TDF), Tenofovir Alafenamide Fumarate (TAF), Entecavir, IFN, Other
- Duration of NA (Years) = (Sum of all NA treatment duration [prior and current])/365.25; rounded to 1 decimal; calculated as: end date – start date +1. If the end date is missing for latest NA treatment, then the randomization date is used.
- Type of NA at study entry: TDF, TAF, ETV
- HBsAg at baseline (quantitative: IU/mL and log10 IU/mL)
- HBsAg level at baseline (quantitative: IU/mL):
  - Participants with HBsAg <100 IU/mL
  - Participants with HBsAg <500 IU/mL
  - Participants with HBsAg <1,000 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: 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) and target not detected (TND)
  - Participants with HBV DNA < LLOQ (20 IU/mL) TD
  - Participants with HBV DNA < LLOQ (20 IU/mL) TND
  - Participants with HBV DNA ≥LLOQ - < 60 IU/mL
  - Participants with HBV DNA ≥ 60 IU/mL
- HBV RNA (quantitative: 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: 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 (Anti-HBs) status at baseline (qualitative): Positive/Negative
- HBsAg Antibody (Anti-HBs) at baseline (quantitative: 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
- 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, and F2
- HBV genotype (using historical information or sequence based HBV genotyping data): Genotype A, B, C, D, E, F, G, H, I, J, and Unknown;
- Hemoglobin at baseline (quantitative: g/L)
- Platelets at baseline (quantitative: 10^{9}/L)
- GFR from Creatinine Adjusted for BSA at baseline (quantitative: mL/sec/m^2)

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.

Major 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 the primary database lock to define the Per-Protocol population (Section 2.3). The number and percentage of ITT participants who are included in the PP analysis set will be summarized by intervention arm, accompanied by number and percentage of ITT participants who are excluded from the PP analysis set with the incidence of the major protocol deviations.

4.6. Extent of Exposure

Extent of exposure to study treatments will be summarized and presented based on the safety analysis set. The total duration of exposure during the 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 oral dosing) 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 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 cut-off) - first drug administration date in the given phase + 1)/ 7

Cut-off dates will be defined to match the prespecified timepoints for IDMC periodical data reviews, interim analysis 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 phase. For FU, the total duration will add up the weeks from the start of FU for those participants who met the requirement to re-start NA treatment. Those participants who stopped NA treatment at 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 100 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), two-sided 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 will be provided by stratification factors (i.e. screening HBsAg level [<1,000 IU/mL or ≥1,000 IU/mL], race [Asian versus non-Asian] and type of NA [TDF/TAF versus ETV]) for secondary efficacy endpoints. Graphic displays will also be used to summarize the data.

5.1.1. Level of Significance

All statistical hypothesis tests will be based on one-sided alpha level of 0.05, and 90% confidence interval (CI) will be presented, 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 in Table 3.

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

HBV parameter	LLOQ	ULOQ	Imputed Values	
			If value< LLOQ	If value> ULOQ
HBsAg	0.05 IU/mL	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 $\log_{10}$ U/mL	7.0 $\log_{10}$ U/mLw/o dilution 9.0 $\log_{10}$ U/mL with dilution	2.7 $\log_{10}$ U/mL	7.7 $\log_{10}$ U/mL[(b)(c)] w/o dilution 9.9 $\log_{10}$ U/mL [(b)] with dilution
HBV DNA	20 IU/mL	170,000,000 IU/mL w/o dilution	If target detected: 15 IU/mL If target not detected: 5 IU/mL	187,000,000[(b)(c)] w/o dilution

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

HBV parameter	LLOQ	ULOQ	Imputed Values	
			If value< LLOQ	If value> ULOQ
HBV RNA*	LLOQ = 4.04 log_{10} cp/mL LOD = 2.49 log_{10} cp/mL	NAP	If <LOD or target not detected then 2.19 log_{10} 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 > ULOQ, then take the re-test value (i.e. diluted result). If the diluted result is not available, use the imputed value indicated in this table

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

5.2. Primary Efficacy Endpoint

5.2.1. Definition

The primary endpoint, also known as "functional cure", is the proportion of participants who achieved HBsAg seroclearance at Week 72 (24 weeks after completion of 48 weeks of treatment with all study interventions) without restarting NA treatment.

5.2.2. Main Estimand for the Primary Endpoint

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

Scientific Question: in HBeAg negative, virologically suppressed adult population with chronic HBV infection, what is the benefit of JNJ-3989 200 mg+JNJ-6379+NA (Arm 1) for 48 weeks in terms of functional cure 24 weeks after stopping all study interventions compared with NA alone (Arm 2)?

A) Study Intervention:

- Arm 1: JNJ-3989 (200 mg) + JNJ-6379 (250 mg qd) + NA
- Arm 2: Placebo + Placebo + NA

B) Study Population: HBeAg-negative chronic HBV-infected patients who 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 5.2.1

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. 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**.**

5.2.2.1. Main Estimator

5.2.2.1.1. Analysis Methods

The main estimator is constructed using a Mantel-Haenszel (Mantel N., et al. 1959) test controlling for stratification factors, i.e., screening HBsAg level (<1,000 IU/mL or ≥1,000 IU/mL), race (Asian versus non-Asian) and type of NA (TDF/TAF versus ETV) for the difference in proportions between the intervention arms (Arm 1 minus Arm 2). A 2 sided 90% CI of the difference in proportions will be provided.

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

5.2.2.1.4. 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 (race [Asian versus non-Asian] and type of NA [TDF/TAF versus ETV]) 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 primary endpoint response status (binary variable) will be derived using both imputed and observed HBsAg values at Week 72.

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 four sensitivity estimators for the main estimand as defined in Section 5.2.2. One estimator will test the assumption of homogeneous treatment effect across the 3 randomization stratification factors, and the three 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 the comparison vs control arm. For this sensitivity estimator 1, the same included data, missing data assumption (MAR), and missing data handling rule (multiple imputation) 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 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 3 randomization stratification factors and interaction terms. The model will include intervention arm, screening HBsAg level (<1,000 IU/mL or ≥1,000 IU/mL), race (Asian versus non-Asian) and type of NA (TDF/TAF versus ETV) 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 (stratum-adjusted MH test), and data included 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 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 72 will be considered as non-responders. After taking into account all the intercurrent events and applying the intercurrent event strategies specified in Section 5.2.2, if a subject who did not experience any ICEs has missing response status for the primary endpoint then the LOCF approach will be used as follows.

If the HBsAg value 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 to Week 72 or no later than 12 weeks after Week 72. If 2 non-missing laboratory values are equidistant, the later observation will be preferred. If a subject who did not experience any ICE and does not have HBsAg data within ± 12 weeks of Week 72, then the subject will be considered as a non-responder.

5.2.2.2.3. Sensitivity Estimator 3 For the Main Estimand (Missing as Non-response)

For this sensitivity estimator 3, the same statistical model (stratum-adjusted MH test), and data included 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 HBsAg are Missing Not at Random
- The treatment effect is homogeneous across strata

5.2.2.2.3.2. Missing Data Handling Rule

For sensitivity estimator 3, 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 5.2.2, if a subject who did not experience any ICEs has missing response status for the primary endpoint then the primary endpoint status will be imputed as non-responders.

5.2.2.2.4. Sensitivity Estimator 4 For the Main Estimand (Tipping Point)

For this sensitivity estimator 4, the same statistical model (stratum-adjusted MH test), and data included 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.

5.2.2.2.4.1. Assumptions

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

5.2.2.2.4.2. Missing Data Handling Rule

For sensitivity estimator 4, after taking into account all the intercurrent events and applying the intercurrent event strategies specified in Section 5.2.2, the tipping point approach with the exhaustive scenario's analysis will be applied.

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 JNJ-3989+JNJ-6379+NA 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 JNJ-3989+JNJ-6379+NA arm 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 (stratum-adjusted MH test), will be used as for the

main estimator of the comparisons vs control (Section 5.2.2.1.1). A graphical display of the p-value significance will summarize the results across all scenarios for the tipping point analysis.

5.2.2.3. Supplementary Estimators of the Main Estimand

Supplementary analyses to better interpret the 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 on the functional cure at Week 72, the following supplementary estimators 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 (stratum-adjusted MH test), and assumptions will be used as for the main estimator (Section 5.2.2.1).

The missing data approach will follow the MI approach as described in (Section 5.2.2.1.4).

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.

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

For this supplementary estimator, the same estimand defined in Section 5.2.2, statistical model (stratum-adjusted MH test), and assumptions will be used as for the main estimator (Section 5.2.2.1).

The missing data approach will follow the LOCF approach as described in Section 5.2.2.2.2.2.

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.

5.2.2.3.3. Supplementary Estimator 3 (ITT Analysis Set + Missing as Non-Response)

For this supplementary estimator, the same estimand defined in Section 5.2.2, statistical model (stratum-adjusted MH test), and assumptions will be used as for the main estimator (Section 5.2.2.1).

The missing data approach will follow the missing as non-response approach as described in Section 5.2.2.2.3.2.

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.

5.2.2.3.4. Supplementary Estimator 4 (ITT Analysis Set + Tipping Point)

For this supplementary estimator, the same estimand defined in Section 5.2.2, statistical model (stratum-adjusted MH test), and assumptions 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 5.2.2.2.4.2.

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.

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

A) Study Intervention:

- Arm 1: JNJ-3989 (200 mg) + JNJ-6379 (250 mg qd) + NA
- Arm 2: Placebo + Placebo + NA

B) Study Population: HBeAg-negative chronic HBV-infected patients who are virologically suppressed by being treated with NA 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 in Section 5.2.1

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**.**

5.2.3.1. Main Estimator

5.2.3.1.1. Analysis Methods

Similar stratum-adjusted MH test on the difference of proportions as described for the main estimator of the main estimand will be used (see section 5.2.2.1.1).

5.2.3.1.2. Data Included

All available data from randomized participants that are included in the PP analysis set will be used, after taking into account the intercurrent events and applying the intercurrent event strategies specified in Section 5.2.3.

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

5.2.3.1.3. Assumptions

- 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 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, but HBsAg values missing at Week 72, then the primary method to handle missing data will be the imputation to non-responder.

5.2.4. Subgroup Analyses of the Primary Endpoint

The potential association between the functional cure rate and the randomization stratification factors will be explored by a logistic regression model and exploration of the interaction terms using observed case data. The model will include intervention arm, screening HBsAg level, race and type of NA, as factors, and the intervention arm-by-HBsAg level, intervention arm-by-race, and intervention arm-by-type of NA interaction terms. The functional cure rate 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 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, screening HBsAg level, race, type of NA 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.

Tabulations of the primary endpoint by intervention arm and predefined subgroups will be used to summarize the data descriptively.

5.3. Major Secondary Endpoints

See Section 1.1 for a list of the secondary endpoints. All major secondary endpoints will be analyzed using observed case data. Additional analyses with specific imputation methods for missing data are added for selected endpoints.

5.3.1. Definitions

5.3.1.1. Binary Endpoints

Analyses described below as being with emphasis are for endpoints at selected time points. These analyses will utilize imputation methods for handling missing data and will be compared between study intervention arms (see Section 5.3.2.1).

5.3.1.1.1. HBsAg Seroclearance

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

HBsAg seroclearance will be evaluated over all time points when assessed, 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,
- 24 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

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.

For the analyses of seroclearance 24 and 48 weeks after stopping all study intervention respectively, participants with HBsAg seroclearance at the respective time points, and without restarting NA treatment will be considered as having achieved this endpoint. If HBsAg values are missing, then LOCF in conjunction with the next available observation (if available for 48 weeks after stopping all study interventions) imputation approach will be used. The available non-missing HBsAg value closest to the time point which is no earlier/later than 12 weeks prior/after to the respective time point will be used.

For the analyses of seroclearance at Week 96 participants with HBsAg seroclearance at the respective time points, and without restarting NA treatment will be considered as having achieved this endpoint. If HBsAg values are missing, then LOCF approach will be used. The available non-missing HBsAg value closest to the time point which is no earlier than 12 weeks prior to the respective time point will be used.

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

5.3.1.1.2. Suppressed HBV DNA

HBV DNA < LLOQ and HBV DNA TND will be evaluated over time.

5.3.1.1.3. Thresholds Based on HBsAg and HBV DNA

The following blood marker reduction/seroclearance thresholds over time on treatment, and at 12, 24, 36 and 48 weeks, respectively, after stopping all study interventions (including NA) and not having NA re-treated will be evaluated.

- **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 5.4.1.1.1)
- **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 TD, TND and overall.

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

5.3.1.1.4. HBsAg Seroconversion

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

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

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

5.3.1.1.5. HBsAg and HBV DNA cut-offs

The cut-offs for HBsAg level are as follows:

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

The cut-offs for HBsAg change from baseline are as follows:

- decrease by ≥ 0.3 log10 IU/mL
- decrease by ≥ 0.5 log10 IU/mL
- decrease by ≥ 1 log10 IU/mL
- decrease by ≥ 2 log10 IU/mL
- decrease by ≥ 3 log10 IU/mL
- decrease by ≥ 4 log10 IU/mL

The cut-offs for HBV DNA are as follows:

- <LLOQ
- <LLOQ TND
- <LLOQ TD
- <60 IU/mL
- <200 IU/mL
- <2000 IU/mL
- <20000 IU/mL
- <100000 IU/mL

HBV DNA change from time of NA re-start

- decrease by ≥ 1 log10 IU/mL
- decrease by ≥ 2 log10 IU/mL
- decrease by ≥ 3 log10 IU/mL
- decrease by ≥ 4 log10 IU/mL
- decrease by ≥ 5 log10 IU/mL

5.3.1.1.6. Flares

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

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

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

The start date of a virologic flare is defined as the first date of two consecutive visits with HBV DNA > 200 IU/mL. The end date of the same 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 four thresholds within the start and end date of that flare as follows: 100,000 IU/mL, 20,000 IU/mL, 2,000 IU/mL and 200 IU/mL.

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

The start date of a virologic flare is defined as the first date of two consecutive visits with HBV DNA $\log_{10}$ increase from end of treatment >1 $\log_{10}$. The end date of the same virologic flare is defined as the first date when HBV DNA $\log_{10}$ increase from end of treatment returns to ≤ 1 $\log_{10}$ or the date of 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: 1 $\log_{10}$, 2 $\log_{10}$ and 3 $\log_{10}$.

- 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 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 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, i.e., the later date of HBV DNA ≤200 IU/mL (or ≤1 $\log_{10}$) and 50% reduction from the peak ALT and/or AST level.

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

The virologic and clinical flares will be assessed only off-treatment, while biochemical flares will be identified on treatment and off treatment, respectively. On-treatment virologic flares are described as virologic breakthrough in Section 5.3.1.1.7. On-treatment will be defined as the time period in which the participant receives any of the study interventions. Off-treatment will be defined as the period after stopping all study interventions (including NA).

5.3.1.1.7. Virologic Breakthrough

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

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

5.3.1.1.8. NA Re-Treatment Criteria During Follow-Up

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

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

5.3.1.1.9. ALT Normalization

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

Participants who achieve ALT normalization on treatment and off treatment but without restarting NA treatment will be evaluated over time.

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

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

5.3.1.2. Continuous Endpoints

Actual values (original unit and $\log_{10}$ transformed values) and changes from baseline ($\log_{10}$ transformed values) over time in HBsAg, HBV DNA and ALT (original unit) will be evaluated. Change from baseline is defined as follows: value at a given time point minus baseline value.

Changes in HBsAg ($\log_{10}$ transformed values) from both EOT and Week 48 will be evaluated for the follow-up period.

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

5.3.1.3. Time to Event Endpoints

5.3.1.3.1. First HBsAg Seroclearance

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

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

- HBsAg <10 IU/mL
- HBsAg <100 IU/mL
- HBsAg decline ≥ 1.0 log10 IU/mL
- HBsAg decline ≥ 2.0 log10 IU/mL
- HBsAg decline ≥ 3.0 log10 IU/mL

These endpoints will also be analyzed considering participants who were re-treated with NA before achieving the endpoint as censored at the date of NA re-treatment.

5.3.1.3.2. Time to Flare

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

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 [the first of the two confirmation visits] of each type- the date of first study intervention intake+1). The participants who withdrew early from the study before experiencing on-treatment flare or who did not experience on-treatment flare will be censored at the last available blood markers or liver enzymes assessment at or before EOT.

Time to 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[the first of the two confirmation visits] 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.

5.3.1.3.3. 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 first of the two confirmation visits] - the date of first study intervention intake +1). The participants who withdrew early from the study before experiencing virologic breakthrough or who did not experience virologic breakthrough will be censored at the last available HBV DNA assessment at or before EOT.

5.3.1.4. Endpoints for Correlation

Correlations between baseline characteristics, and on-treatment HBV blood markers and/or their change from baseline at Week 24 and 48 with off-treatment endpoints will be evaluated. The list of HBV blood markers, including but not limited to, are defined below:

Off treatment HBV marker	Baseline Characteristics/On treatment HBV marker
HBsAg change from baseline at FU Week 12	• Age • Baseline NA treatment duration • HBsAg value at baseline • HBsAg change from baseline at Week 24 • HBsAg change from baseline at Week 48
HBsAg change from baseline at FU Week 24	• Age • Baseline NA treatment duration • HBsAg value at baseline • HBsAg change from baseline at Week 24 • HBsAg change from baseline at Week 48
HBsAg change from baseline at FU Week 48	• Age

Off treatment HBV marker	Baseline Characteristics/On treatment HBV marker
	• Baseline NA treatment duration • HBsAg value at baseline • HBsAg change from baseline at Week 24 • HBsAg change from baseline at Week 48
HBsAg seroclearance at FU week 24 (Yes;No)	• Age • Baseline NA treatment duration • HBsAg value at baseline • HBsAg change from baseline at Week 48 • HBsAg value at Week 48 • HBsAg seroclearance at week 24 (Yes;No) • HBsAg seroclearance at week 48 (Yes;No) • Anti-HBe antibodies status at week 48 (Positive:Negative)
HBsAg seroclearance at FU week 48 (Yes;No)	• Age • Baseline NA treatment duration • HBsAg value at baseline • HBsAg change from baseline at Week 48 • HBsAg value at Week 48 • HBsAg seroclearance at week 24 (Yes;No) • HBsAg seroclearance at week 48 (Yes;No) • Anti-HBe antibodies status at week 48 (Positive:Negative)
Partial cure (Yes;No) at FU Week 24 (Yes;No)	• Age • Baseline NA treatment duration • HBsAg value at baseline • HBsAg value at Week 48 • HBsAg seroclearance at week 24 (Yes;No) • HBsAg seroclearance at week 48 (Yes;No) • Anti-HBe antibodies status at week 48 (Positive:Negative)
Partial cure (Yes;No) at FU Week 48 (Yes;No)	• Age • Baseline NA treatment duration • HBsAg value at baseline • HBsAg value at Week 48 • HBsAg seroclearance at week 24 (Yes;No) • HBsAg seroclearance at week 48 (Yes;No) • Anti-HBe antibodies status at week 48 (Positive:Negative)
Treatment failure at FU Week 24 (Yes;No)	• Age • Baseline NA treatment duration • HBsAg value at baseline • HBsAg value at Week 48 • HBsAg seroclearance at week 24 (Yes;No) • HBsAg seroclearance at week 48 (Yes;No) • Anti-HBe antibodies status at week 48 (Positive:Negative)
Treatment failure at FU Week 48 (Yes;No)	• Age • Baseline NA treatment duration • HBsAg value at baseline • HBsAg value at Week 48 • HBsAg seroclearance at week 24 (Yes;No) • HBsAg seroclearance at week 48 (Yes;No) • Anti-HBe antibodies status at week 48 (Positive:Negative)

5.3.2. Analysis Methods

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

5.3.2.1. Binary Endpoints

The number and proportion (%) of participants achieving the endpoints defined in Section 5.3.1.1 will be summarized. The associated 90% CI may also be included.

The following binary endpoints will be compared between treatment arms using a 2-sided 90% CI of the difference in proportions between the treatment groups (Arm 1 minus Arm 2) that will be constructed using a Mantel-Haenszel test controlling for stratification factors, i.e., HBsAg level (<1,000 IU/mL or ≥1,000 IU/mL), race (Asian versus non-Asian) and type of NA (TDF/TAF versus ETV):

- HBsAg seroclearance:
  - at Week 48
  - at Week 96 (ie, 48 weeks after completion of all study interventions at Week 48) without restarting NA treatment,
  - 24 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

Bar charts will be provided for selected endpoints for proportions (%) in each intervention arm.

Cumulative percentage of participants achieving any given decrease from baseline at Week 72 and Week 96 in HBsAg and HBV DNA (Section 5.3.1.1.5) will be presented graphically.

Subsections below describe the additional analyses planned for only those specific other secondary binary endpoints that require further evaluations.

5.3.2.1.1. Suppressed HBV DNA

The number of occurrences each subject has HBV DNA <LLOQ will be determined and summarized by intervention arm using frequency distributions and descriptive statistics. Additionally, the number of occurrences will be displayed graphically.

5.3.2.1.2. HBsAg Seroconversion

For all 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 and without seroclearance of HBsAg will also be summarized by intervention arm and analysis phase.

5.3.2.1.3. Flares

The incidence rate will be calculated and summarized for each type of on-treatment or off-treatment flares (virologic, biochemical and clinical) separately, as well as the overall incidence of participants experiencing at least one flare, regardless of type, by study intervention arm. Additionally, for each participant the total number of flares the participant experienced will be counted by type. Such counts will be used to summarize the distribution of the total number of flares by type and 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.

For off-treatment virologic, biochemical and clinical flares, the count and percentage of participants who experienced a flare will be summarized by intervention arm and selected subgroups (i.e. by NA type at study entry, by HBsAg levels at EOT, by HBcrAg levels at EOT). Biochemical flares will also be summarized in the follow-up after NA re-treatment. The cut-offs for HBsAg and HBcrAg levels at EOT are provided in Sections 5.3.1.1.5 and 5.4.1.1.2.

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

5.3.2.1.4. NA Re-Treatment Criteria During Follow-Up

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.

5.3.2.2. Continuous Endpoints

Descriptive statistics on actual values (original unit and $\log_{10}$ transformed values) and changes from baseline ($\log_{10}$ transformed values) over time in HBsAg, HBV DNA, and ALT (original unit) will be summarized by intervention arm. Mean (+/- SE) plots of the actual values and the change from baseline ($\log_{10}$ transformed) will be presented over time per endpoint by intervention arm.

Subsections below describe the additional analyses planned for only those specific secondary endpoints that require further evaluations.

5.3.2.2.1. HBsAg and HBV DNA

The change from baseline value to the nadirs (i.e. maximum decrease for each participant) in HBsAg and HBV DNA will be summarized descriptively by intervention arm. Box plots of the changes to nadirs in HBsAg and HBV DNA will display the distribution by intervention arm.

Change from baseline based on log_{10} transform for quantitative HBsAg and HBV DNA will be analyzed using mixed effects model for repeated measures [MMRM]) including intervention arm, analysis time point (week), their interaction, and 3 randomization stratification factors (screening HBsAg level [<1,000 IU/mL or ≥1,000 IU/mL], race [Asian versus non-Asian] and type of NA [TDF/TAF versus ETV]) and baseline blood marker categorical variable as fixed effects. In addition, the above model will be augmented with an intervention arm-by-analysis week interaction term (i.e. treatment-by-time interaction term) to evaluate the change of treatment effect over time and the intervention arm-by-baseline interaction term. The covariance structure will include a random intercept at the level of the participant to capture between-participant variability, while within-participant variability will be captured with an unstructured (type=UN) covariance matrix. In case of convergence problems, simpler variance-covariance structures such as Toeplitz or AR (1) will be considered. The selection of any of these structures will be determined after exploration of the observed correlation structure. The LS mean of change from baseline, standard error (SE), 90% confidence interval (CI) and p-values will be provided.

Descriptive statistics on actual values (original unit and log_{10} transformed values) and changes from baseline (log_{10} transformed values) at end of treatment in HBsAg and HBV DNA will be summarized by study intervention arm by outcome response (i.e. by functional cure status at Week 72, and by partial cure status at Week 72).

Spaghetti plots for both absolute values and changes from baseline of HBsAg and HBV DNA will be presented over time per blood marker by intervention arm and by selected subgroups (e.g. HBV Genotype) and by outcome response (i.e. by functional cure status at Week 72, and by partial cure status at Week 72).

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

Shift tables in HBV DNA categories from baseline will also be summarized by study intervention arm.

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

5.3.2.3. Time to Event Endpoints

The Kaplan-Meier method will be used to estimate and plot the cumulative incidence by each intervention arm. The log-rank test will be performed to compare between the intervention arms. The median time with 90% CI will be estimated using Kaplan-Meier method. To explore the impact of selected baseline factors in addition of study intervention, the survival probabilities will be estimated based on a stratified Cox regression model including study intervention arm, and each baseline factor at a time with the intervention arm-by-baseline factor interaction term. The strata in the stratified Cox model are the 3 randomization stratification factors to allow for a separate baseline hazard for each level of those factors. The interaction between study intervention arm and baseline/disease characteristic will be explored graphically.

5.3.2.4. Endpoints for Correlation

Correlations will be evaluated graphically with scatter plots and heat maps displaying such potential associations by intervention arm and/or selected subgroups (baseline NA treatment duration, age, and baseline HBsAg).

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

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

5.4. Exploratory Endpoints

5.4.1. Definitions

5.4.1.1. Binary Endpoints

5.4.1.1.1. 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.

If the HBV DNA or HBsAg 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 a subject does not have data within 12 and 36 weeks after stopping all study interventions then the subject will be considered as a non-responder.

If the HBV DNA or 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. If a subject does not have data 36 weeks after stopping all study interventions then the subject will be considered as a non-responder.

5.4.1.1.2. HBV RNA and HBcrAg

The cut-offs for HBV RNA level are as follows:

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

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

- decrease by ≥ 1 log_{10} copies/mL
- decrease by ≥ 2 log_{10} copies/mL
- decrease by ≥ 3 log_{10} copies/mL

The cut-offs for HBcrAg level are as follows:

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

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

- decrease by ≥ 1 log U/mL
- decrease by ≥ 2 log U/mL
- decrease by ≥ 3 log U/mL
- decrease by ≥ 4 log U/mL

5.4.1.1.3. Anti-HBe Antibodies

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

5.4.1.1.4. Impact of Finite Treatment Duration on Functional Cure

The following exploratory analysis will be performed to have a better understanding of the impact of finite treatment duration and of the below criteria to stop NA treatment after 48 weeks of treatment on the outcome of HBsAg seroclearance 24 weeks off treatment.(functional cure).

For this finite treatment duration analysis, a participant will be defined as having functional cure at Week 72 (responder) if he/she has:

- completed 48 weeks of treatment, and
- met the following criteria at Week 44:
  - The participant has ALT <3x ULN, AND
  - The participant has HBV DNA <LLOQ, AND
  - The participant is HBeAg-negative, AND
  - The participant has HBsAg <10 IU/mL.
- had HBsAg seroclearance at Week 72 (i.e. 24 weeks after end of study intervention), and

- not required NA re-treatment between Weeks 48 and 72.

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 status will be imputed as non-responders.

5.4.1.1.5. Treatment Failure

Treatment failure and the reasons will be evaluated based on observed case data. A participant will be defined as a treatment failure at Week 72 if he/she never achieves functional cure (see Section 5.2.1) at Week 72.

The reasons for not achieving functional cure are as follows:

- HBsAg ≥LLOQ at Week 72
- required NA re-treatment between Week 48 and 72

Similarly, a participant will be defined as having treatment failure at Week 96 for either of the following reasons:

- HBsAg ≥LLOQ at Week 96
- required NA re-treatment between Week 48 and 96

5.4.1.2. Continuous Endpoints

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

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

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

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

5.4.1.2.1. Decline in HBsAg and HBV DNA Levels

Participants achieving the maximum decline (change from peak level in follow-up to the lowest level achieved during the remainder of follow-up) in the magnitude of the cut-offs as described in Section 5.3.1.1.5 will be evaluated by intervention arm and over time in the follow-up phase only for those participants who restarted NA treatment during the follow-up.

5.4.1.3. Time to Event Endpoints

5.4.1.3.1. HBV RNA <LOD

Time to HBV RNA <LOD is defined as the duration from the date of first study intervention intake to the date of the first occurrence of HBV RNA <LOD (i.e. the date of the first occurrence of HBV RNA <LOD – the date of first study intervention intake + 1). The participant who did not achieve

HBV RNA <LOD or who early withdrew from the study before achieving HBV RNA <LOD will be censored at the last HBV RNA assessment before the date of withdrawal. Only the participants with HBV RNA values ≥LOD+ 0.5 $\log_{10}$ cp/mL (i.e. ≥2.99 $\log_{10}$ cp/mL) at baseline will be included in this analysis. Similarly, additional analyses only for participants with HBV RNA values ≥LOD+ 1.0 $\log_{10}$ cp/mL and ≥LOD+ 2.0 $\log_{10}$ cp/mL, respectively, will be summarized.

This endpoint will also be analyzed considering participants who were re-treated with NA before achieving the endpoint as censored at the date of NA re-treatment.

5.4.1.3.2. HBcrAg Undetectability

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 $\log_{10}$ U/mL (i.e. ≥3.5 $\log_{10}$ U/mL) at baseline will be included in this analysis.

This endpoint will also be analyzed considering participants who were re-treated with NA before achieving the endpoint as censored at the date of NA re-treatment.

5.4.1.3.3. Time to Appearance of Anti-HBs Antibodies

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

Time to appearance of anti-HBs antibodies is defined as the time (days) from the date of first study intervention intake to the date of the first occurrence of anti-HBs antibodies appearance + 1. The 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.

This endpoint will also be analyzed considering participants who were re-treated with NA before achieving the endpoint as censored at the date of NA re-treatment.

5.4.1.3.4. Time to Appearance of Anti-HBe Antibodies

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

Time to appearance of anti-HBe antibodies is defined as the time (days) from the date of first study intervention intake to the date of the first occurrence of anti-HBe antibodies appearance + 1. The 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.

This endpoint will also be analyzed considering participants who were re-treated with NA before achieving the endpoint as censored at the date of NA re-treatment.

5.4.2. Analysis Methods

Statistical comparisons of all exploratory endpoints between intervention arms will be done with no adjustment for multiplicity.

5.4.2.1. Binary Endpoints

The number and proportion (%) of participants achieving the endpoints defined in Section 5.4.1.1 will be summarized. The associated 90% CI may also be included.

Participants who achieve partial cure at 24 weeks and 48 weeks after stopping all study interventions will be compared between treatment interventions using the Mantel-Haenszel test and 90% CIs adjusted for the stratification factors. Similar analysis for the impact of finite treatment duration on functional cure will also be done.

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

5.4.2.2. Continuous Endpoints

The values of and changes from baseline in anti-HBs antibodies will be summarized only descriptively in a similar manner as described for values and changes from baseline over time in other blood disease markers in Section 5.3.2.2.

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

Subsections below describe the additional analyses planned for only those specific exploratory endpoints that require further evaluations.

5.4.2.2.1. Fibrosis

The changes from baseline at end of study intervention and follow-up will be summarized using descriptive statistics (for example, may include n, mean, SD, 90% CI, median, minimum, maximum) by intervention arm. The comparison between 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.

5.4.2.2.2. HBV RNA and HBcrAg

The changes from baseline value to nadirs (i.e. maximum decrease for each participant) in HBV RNA and HBcrAg, respectively, and the various graphical displays will be presented.

5.4.2.2.3. Anti-HBs

For participants with positive anti-HBs antibodies at baseline who will reach HBsAg seroclearance (as defined in Section 5.2.1), 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.

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

5.4.2.3. Time to Event Endpoints

The time-to-event analyses will be analyzed in a similar manner as for the time to event endpoints described in the Section 5.3.2.3.

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 adverse events of special interest (AESIs) will be listed separately. Listings will include all information collected on the Adverse Event CRF pages (e.g. information on time of onset, duration of events, time of resolution, concomitant therapies and relationship to study treatment).

For participants reporting rash, a listing with specific grade will be provided 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 from the central laboratory will be summarized by category of laboratory test. The different categories and laboratory tests used in the analysis are listed in Table 4. The tests will be allocated to the categories in the table.

Table 4: Laboratory Parameters to Be Summarized

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 % Reticulocytes	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 Section 10.9, Appendix 9, DAIDS Table) or in accordance with the normal ranges of the clinical laboratory if no gradings are available.

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

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

Change from baseline will be evaluated for all time points when assessed and is defined as follows: value at a given time point minus baseline value.

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, time point and per 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 selected laboratory parameters will be presented by intervention arm.

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

Spaghetti-plots for selected laboratory parameters may be presented by intervention arm over time (with Week shown on x-axis).

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 $\geq$ 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).

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

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 criteria (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 percentage and number 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 Section 10.7, Appendix 7).

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

For each parameter, a "worst-case" analysis will be performed by using the worst abnormality and time point per participant. Worst-case will be derived within each phase, including unscheduled assessments. In case the same subject has both abnormalities (low and high) for the same test within the same phase, the participant will be counted in the analysis for both abnormality directions (abnormally high and low).

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

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

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

Viral genome sequence analysis will be performed to evaluate the presence of genetic variations (including substitutions) associated with JNJ-56136379, JNJ-3989, and/or ETV or TDF/TAF treatment on both nucleotide and/or amino acid level.

Sequencing of the HBV genome will be performed to monitor HBV variants present at the time points indicated in Section 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 Virologic Breakthrough: time point with sequence data available closest to the time point of virologic breakthrough (FTPT) (see Section 5.3.1.1.7 for virologic breakthrough definition)
- Time Point of Sequence at Virologic Flare: time point with sequence data available closest to the time point of Virologic flare (see Section 5.3.1.1.6 for virologic flare definition)
- Time Point of Sequence at Re-treatment during Post-treatment Follow-up: time point with sequence data available closest to time point where re-treatment criteria is met (see Section 5.3.1.1.8)
- Aggregated Post-Baseline Study Period (ASSEQ): entire post-baseline study period, aggregate of all available time points in the study with sequence data available
- Aggregated Post-Baseline Treatment Period (ATSEQ): entire post-baseline treatment period, aggregate of all available post-baseline time points during the treatment phase with sequence data available

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

7.2. Definitions

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

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

- 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.

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

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

In the sequence analysis, sequences will be mapped to the respective genotype specific reference sequences after which 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 nt changes and/or aa substitutions in terms of frequency of variant, a read frequency cut-off of ≥0.15 will be used. The persistence of nt changes and aa substitutions will be evaluated using a cut-off of ≥0.15 and ≥0.01.

The applicability of the sequencing approach described here (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 (ECo numbering will be used)

In the precore region:

- 1896 (ECo 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=48): 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, 121, 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 48 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, 133, 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=29): 23, 24, 25, 29, 30, 33, 37, 38, 102, 105, 106, 109, 110, 118, 121, 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 29 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, 133, 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
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.

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

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

7.5.1. Post-Baseline

- Time of Virologic Breakthrough (if applicable)

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

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

- Time of Virologic /Clinical Flare (if applicable)

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

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

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

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

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

- Other Post-Baseline

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

7.5.2. Over the Study Period

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

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

7.6. HBV genotype

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

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, JNJ-3924 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 HBV treatment on participants will be assessed using PROs at predefined time points. The following PRO instruments will be used: HBV-specific self-stigma scale and EQ-5D-5L questionnaire. All PRO analyses will be performed using the ITT analysis set.

9.1. HBV-specific Self-stigma PRO Scale

9.1.1. Definition

The HBV-specific self-stigma scale is a 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").

9.1.2. Analysis Methods

Descriptive statistics of the actual values and change from baseline values at each timepoint (including baseline and available analysis time point) for the scores will be displayed for each aspect 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 as appropriate for different subgroups: 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 3 randomization stratification factors, as main effect in the model, and the three 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. 5-Level EuroQol 5-Dimension Questionnaire

9.2.1. Definition

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

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

- EQ-5D descriptive system scores (5 scores reflecting each of the 5 dimensions see Attachment 3 for a representative example of the EQ-5D-5L).

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

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

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

- EQ-5D Valuation Index The information of the 5 dimensions of the descriptive system summarized intone index. (a weighted scoring of the 5 dimensions scores with a possible range from 0 to 1);

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

a. Assign the level code 1, 2, 3, 4 and 5 to each level of the 5 dimensions (see above)
b. Create a health state for each patient-time point combination. A health state is a combination of 5 level codes; one level code for each dimension. The dimensions are ordered as described in the attachment.

   E.g. health state 12543 indicates 'no problems in walking about, slight problems washing or dressing myself, unable to do my usual activities, severe pain or discomfort, moderately anxious or depressed'.
c. Assign an index value (valuation index) to each observed health state using the UK crosswalk value set as defined in Attachment 3. Based on the origin of the subjects, another method can be used.

Missing Data:

- If – for a questionnaire – one (or more) dimensions of the descriptive system are missing, then
  - The EQ-5D VAS will be tabulated if not missing
  - The valuation index will not be tabulated
  - The non-missing dimensions of EQ-5D descriptive system will be summarized
- If – for a questionnaire – the EQ-5D VAS is missing then the EQ-5D descriptive system and validation index will be tabulated if complete.

9.2.2. Analysis Methods

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

For the EQ-5D VAS and for the Valuation index, descriptive statistics for the actual and change from baseline values at each time point will be displayed. In addition, mean changes from baseline will be explored per subgroup: participants with versus participants without HBsAg seroclearance 24 weeks and 48 weeks after completion of all study intervention at Week 48. The clinically

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

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

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

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

REFERENCES

Barnes A., Mallinckrodt C. et al. The impact of missing data and how it is handled on the rate of false-positive results in drug development. Pharmaceut. Statist. 2008; 7: 215–225

Bourne, C. R., Finn, M. G., & Zlotnick, A. (2006). Global structural changes in hepatitis B virus capsids induced by the assembly effector HAP1. Journal of virology, 80(22), 11055-11061.

Brooks ST, Whitely E, Egger M, Smith GD, Mulheran PA, Peters TJ. Subgroup analyses in randomized trials: risks of subgroup-specific analyses; power and sample size for the interaction test. J Clin Epidemiol. 2004;229-236

Graham JW, Olchowski A E, Gilreath T D, How Many Imputations are Really Needed? Some Practical Clarifications of Multiple Imputation Theory, Prev Sci . 2007 Sep;8(3):206-13

Honaker J, King G et al.. Amelia II: A Program for Missing Data. Journal of Statistical Software, 45, 7, Pp. 1-47.

Katen, S. P., Tan, Z., Chirapu, S. R., Finn, M. G., & Zlotnick, A. (2013). Assembly-directed antivirals differentially bind quasiequivalent pockets to modify hepatitis B virus capsid tertiary and quaternary structure. Structure, 21(8), 1406-1416.

King G., Honaker J., Joseph A., et al. Analyzing Incomplete Political Science Data: An Alternative Algorithm for Multiple Imputation. American Political Science Review, Vol. 95:49-69.

Klumpp, K., Lam, A. M., Lukacs, C., Vogel, R., Ren, S., Espiritu, C., ... & Efimov, A. (2015). High-resolution crystal structure of a hepatitis B virus replication inhibitor bound to the viral core protein. Proceedings of the National Academy of Sciences, 112(49), 15196-15201.

Lui K.J., Kelly C. A Revisit on Tests for Homogeneity of the Risk Difference, Biometrics, 2000; 56:309-315.

Mantel N and Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959;22:719-748.

Qiu, Z., Lin, X., Zhou, M., Liu, Y., Zhu, W., Chen, W., ... & Huang, M. (2016). Design and synthesis of orally bioavailable 4-methyl heteroaryldihydropyrimidine based hepatitis B virus (HBV) capsid inhibitors. Journal of medicinal chemistry, 59(16), 7651-7666.

Ratitch B., Lipkovitch I., O'Kelly M. (2013), Combining Analysis Results from Multiply Imputed Categorical Data, PhasrmaSUG, Paper SP03.

Tu, J., Li, J. J., Shan, Z. J., & Zhai, H. L. (2017). Exploring the binding mechanism of Heteroaryldihydropyrimidines and Hepatitis B Virus capsid combined 3D-QSAR and molecular dynamics. Antiviral research, 137, 151-164.

Zhou, Z., Hu, T., Zhou, X., Wildum, S., Garcia-Alcalde, F., Xu, Z., ... & Shen, F. (2017). Heteroaryldihydropyrimidine (HAP) and sulfamoylbenzamide (SBA) inhibit hepatitis B virus replication by different molecular mechanisms. Scientific reports, 7, 42374.

ATTACHMENTS

Attachment 1. Selected Major Protocol Deviations For Analysis Purposes

The major protocol deviations (MPD) that may affect the assessment of efficacy will be finalized prior to the primary analysis database lock. The major deviations that are selected to exclude participants from the PP set are listed below. The flag of Intercurrent Event is added to each deviation for facilitating the implementation of the estimands for the primary endpoint.

Sequence No.	Protocol Deviation Description (DVTERM)	Protocol Deviation Coded Term (DVDECOD)	Exclude from PP	Intercurrent Event
1	Inclusion criterion M03/A02. not met: Subject did not meet the following: o Be HBeAg-negative, o Be on stable HBV treatment, defined as currently receiving NA treatment (ETV, TDF, or TAF) for at least 24 months prior to screening and having been on the same NA treatment regimen (at the same dose) as used in this study (see Section 6.1) for at least 3 months at the time of screening, AND o Have serum HBV DNA <60 IU/mL on 2 sequential measurements at least 6 months apart (one of which is at screening), AND o Have documented ALT values <2.0x ULN on 2 sequential measurements at least 6 months apart (one of which is at screening).	Entered but did not satisfy criteria	Yes	No
2	Inclusion Criterion A05. not met: Participants have HBsAg ≤100 IU/mL at screening.	Entered but did not satisfy criteria	Yes	No
3	Exclusion criterion M01/A01. met: Participants has evidence of hepatitis A virus infection (hepatitis A antibody IgM), hepatitis C virus (HCV) infection (HCV antibody and detectable HCV RNA), hepatitis D virus (HDV) infection (HDV antibody), 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
4	Exclusion criterion M02. met: Participant at any time point prior to or at the time of screening has: a. Direct bilirubin >1.2xULN (unless there is documentation of a benign cause such as Gilbert's disease), OR b. Prothrombin time >1.3xULN (unless caused by anticoagulation therapy or vitamin K deficiency), OR c. Serum albumin <3.2 g/dL, OR d. History of clinical symptoms of hepatic decompensation (eg, ascites, jaundice, hepatic encephalopathy or coagulopathy, especially if resulting in a Child-Pugh classification B or C at the time clinical symptoms present or at screening).	Entered but did not satisfy criteria	Yes	No
5	Participants with evidence of hepatic decompensation at any time point prior to or at the time of screening: a. Total bilirubin >1.5xULN, b. . Direct bilirubin >1.2xULN OR c. Prothrombin time >1.3xULN (unless caused by anticoagulation therapy or vitamin K deficiency), OR d. . Serum albumin <3.2 g/dL, OR e. . History of clinical symptoms of hepatic decompensation (eg, ascites, jaundice, hepatic encephalopathy or coagulopathy, especially if resulting in a Child-Pugh classification B or C at the time clinical symptoms present or at screening).	Entered but did not satisfy criteria	Yes	No
6	Exclusion criterion M03. met: Participant has a history or evidence of hepatic decompensation ((eg, ascites, jaundice, hepatic encephalopathy or coagulopathy,)	Entered but did not satisfy criteria	Yes	No
7	Exclusion criterion M04. met: Participant has evidence of liver disease of non HBV etiology	Entered but did not satisfy criteria	Yes	No

Sequence No.	Protocol Deviation Description (DVTERM)	Protocol Deviation Coded Term (DVDECOD)	Exclude from PP	Intercurrent Event
8	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	Yes, if classified as MPD (reviewed case by case)	Yes
9	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	Yes, if classified as MPD (reviewed case by case)	Yes
10	Received wrong treatment of study drug JNJ-6379 for at least 1 week period: was randomized to receive JNJ-6379 but received placebo or vice versa.<*specify study drug administration detailed information, such as study drug dose, start date and time, end time etc.* >.	Received wrong treatment or incorrect dose	Yes, if classified as MPD (reviewed case by case)	Yes
11	Received wrong treatment of study drug JNJ-3989 for at least 2 or more times: was randomized to receive JNJ 3989 but received placebo or vice versa <*specify study drug administration*>	Received wrong treatment or incorrect dose	Yes, if classified as MPD (reviewed case by case)	Yes
12	Subject did not receive dose of study drug JNJ-3989 within window: *Within three weeks of the planned administration JNJ-3989 should be administered, If realized later than three weeks the dose should be skipped and administration of the next planned dose as per visit schedule should be awaited.* <*Specify duration*>	Received wrong treatment or incorrect dose	Yes, if classified as MPD (reviewed case by case)	Yes
13	Subject missed more than 5 JNJ-6379/Placebo doses within a four week period.	Received wrong treatment or incorrect dose	Yes, if classified as MPD (reviewed case by case)	Yes
14	Subject missed NA treatment for more than 5 doses within a four week period.	Received wrong treatment or incorrect dose	Yes, if classified as MPD (reviewed case by case)	Yes
15	Subject received expired study medication <*JNJ-3989, JNJ-6379, NA or placebo*>.	Received wrong treatment or incorrect dose	Yes, if classified as MPD (reviewed case by case)	Yes
16	Subject continue NAs despite no relevant change in participant baseline status with regards to ALT, HBV DNA levels and/or HBeAg status or without any discussion with the sponsor regarding event that could prevent stopping NA	Received wrong treatment	Yes, if classified as MPD (reviewed case by case)	Yes
17	Subject has event of signs of decreasing liver function based on laboratory findings or clinical findings, but did not start NA treatment	Received wrong treatment or incorrect dose	Yes, if classified as MPD (reviewed case by case)	Yes
18	Subject has confirmed HBeAg seroreversion, but did not start NA treatment.	Received wrong treatment or incorrect dose	Yes, if classified as MPD (reviewed case by case)	Yes
19	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	Yes, if classified as MPD (reviewed case by case)	Yes
20	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	Yes, if classified as MPD (reviewed case by case)	Yes
21	Subject has confirmed signs of hepatic decompensation <*specify*> but subject continued study treatment	Developed withdrawal criteria but not withdrawn	Yes	Yes
22	The subject has confirmed HBV virological breakthrough but continued study treatment.	Developed withdrawal criteria but not withdrawn	Yes	Yes
23	Accidental unblinding of treatment group of a subject or a blinded staff member prior to planned unblinding at <*specify visit*>.	Other	Yes, if classified as MPD (reviewed case by case)	No
24	Study <specify the visit which> procedure not done at scheduled Visits.	Other	Yes, if classified as MPD (reviewed case by case)	No
25	Efficacy evaluation not done at Week 72*	Other	Yes, if classified as MPD (reviewed case by case)	No

* The algorithm to determine if a subject has the major protocol deviation "Efficacy evaluation not done at Week 72" will not only check DV.DVCRIT records, but will also check the central lab data. If a subject is continuing in the trial at Week 72, i.e., not withdraw from the study prior to Week 72, but HBsAg assessment results are not available at analysis visit Week 72 based on the central lab data (LB), the subject will be considered as having the major protocol deviation and will be excluded from the PP set.

Attachment 2. Adverse Events of Special Interest List of Preferred Terms

Adverse Event of Special Interest	Source	Preferred Term
ALT/AST elevation	(Modified) Liver related investigations, signs and symptoms (SMQ) narrow, (MedDRA 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

Adverse Event of Special Interest	Source	Preferred Term
		Very low density lipoprotein decreased
		Very low density lipoprotein increased
Hematologic abnormalities	(Modified) Haematopoietic cytopenias affecting more than one type of blood cell (SMQ), (MedDRA 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

Adverse Event of Special Interest	Source	Preferred Term
		Microcytic anaemia
		Proerythroblast count decreased
		Red blood cell count decreased
		Reticulocyte count decreased
		Reticulocytopenia
		Anaemia
		Erythroblast count abnormal
		Erythropoiesis abnormal
		Haematocrit abnormal
		Haematocrit decreased
		Haemoglobin abnormal
		Haemoglobin decreased
		Leukoerythroblastic anaemia
		Normochromic anaemia
		Normochromic normocytic anaemia
		Normocytic anaemia
		Proerythroblast count abnormal
		Red blood cell count abnormal
		Reticulocyte count abnormal
		Reticulocyte percentage decreased
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

Adverse Event of Special Interest	Source	Preferred Term
		Metamyelocyte count decreased
		Monoblast count decreased
		Monocyte count decreased
		Monocytopenia
		Myeloblast count decreased
		Myelocyte count decreased
		Neutropenia
		Neutropenic infection
		Neutropenic sepsis
		Neutrophil count decreased
		Promyelocyte count decreased
		Pure white cell aplasia
		T-lymphocyte count decreased
		White blood cell count decreased
		Basophil count abnormal
		Basophil percentage decreased
		B-lymphocyte abnormalities
		B-lymphocyte count abnormal
		Differential white blood cell count abnormal
		Eosinophil count abnormal
		Eosinophil percentage decreased
		Full blood count abnormal
		Granulocytes abnormal
		Leukopenia neonatal
		Lymphocyte count abnormal
		Lymphocyte percentage abnormal
		Lymphocyte percentage decreased
		Monocyte count abnormal
		Monocyte percentage decreased
		Mononuclear cell count decreased
		Myeloblast percentage decreased
		Myelocyte percentage decreased
		Myeloid maturation arrest
		Neutrophil count abnormal
		Neutrophil percentage decreased
		Plasma cell disorder
		Plasma cells absent
		White blood cell analysis abnormal

Adverse Event of Special Interest	Source	Preferred Term
		White blood cell count abnormal
		White blood cell disorder
Hematologic abnormalities	(Modified) Haematopoietic thrombocytopenia (SMQ), (MedDRA v23.1)	
		Acquired amegakaryocytic thrombocytopenia
		Megakaryocytes decreased
		Platelet count decreased
		Platelet maturation arrest
		Platelet production decreased
		Platelet toxicity
		Thrombocytopenia
		Megakaryocytes abnormal
		Platelet count abnormal
		Platelet disorder
		Plateletcrit abnormal
		Plateletcrit decreased

Attachment 3. EQ-5D-5L Crosswalk Value Sets

Crosswalk value sets, (obtained from https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/crosswalk-index-value-calculator/) are located in the DPS.