Janssen Research & Development

Statistical Analysis Plan

A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Study with Deferred Active Treatment to Investigate the Efficacy, Safety, and Pharmacokinetics of JNJ-73763989+ Nucleos(t)ide Analog in Participants Co-infected with Hepatitis B and Hepatitis D Virus

The REEF-D Study

Protocol 73763989HPB2004; Phase 2
AMENDMENT 5

JNJ-73763989

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

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AMENDMENT HISTORY

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Document	**Date**
Amendment 6	04 August 2023
Amendment 5	15 June 2023
Amendment 4	15 March 2022
Amendment 3	08 July 2021
Amendment 2	24 February 2021
Amendment 1	12 August 2020
Original SAP	27 May 2020

Amendment 6

Overall rationale for the Amendments: This is an administrative amendment to add in Sections 5.6.1.6 and 5.6.1.7 that were inadvertently removed during last amendment as well as to fix the date of approval in the footer.

Amendment 5

Overall rationale for the Amendments: Based on the observation that in Part 2 of the REEF-D study significant ALT elevations were more frequently observed in participants with HBsAg levels >10,000 IU/mL at screening or at baseline (irrespective of HDV RNA levels), a temporary halt of new enrollment into the study was implemented in December 2022. Since there was no immediate risk to the safety of participants already enrolled in the trial, treatment and monitoring of ongoing participants was continued as per current protocol.

This amendment aligns the Statistical Analysis Plan (SAP) with Protocol Amendment #4 issued on April 7, 2023 which was submitted in context of the Sponsor's strategic decision to discontinue further investment in its hepatitis B and D discovery and development programs. In light of this decision, which was not driven by safety concerns with JNJ-73763989 (JNJ-3989), enrollment of new participants into the REFF-D study will not be reopened.

The overall reason for this amendment is to continue the study in a modified way for participants already enrolled and to describe the reduced sample size in the study. The hypothesis test is no longer going to be performed and the analyses in the study will be descriptive. Per IDMC recommendation, it was added that in Part 2, participants with HBsAg values >10.000 IU/mL at screening or baseline, who were assigned to Arm 1 (placebo), will not roll-over to the open-label phase and will enter the follow-up phase. In addition, the stopping criteria for nucleos(t)ide analog (NA) treatment at Week 144/148 have been updated upon HA request.

Main Changes		
Section Number and Name	**Description of Change**	**Rationale**
Throughout the SAP	Sample size for Part 2 was reduced from 145 to 30 patients	The enrollment in the study was stopped so the final Part 2 sample size is 30.
Throughout the SAP	Interim Analysis for Sample Size Re-Estimation has been removed from the SAP.	Due to stopped enrollment, the sample size re-estimation is no longer relevant.
Throughout the SAP	Removed sections on Type I error rate.	The study is now a descriptive study so no Type I error control is required.
Throughout the SAP	Removed wording on multiplicity adjustment	Due to stopped enrollment, the study will only have descriptive analyses
5.5.1.1.12 ALT/AST Elevations 5.5.1.1.11 HBV Flares	Updated Flare definitions	Clarification
5.3. Primary Efficacy Endpoint 5.4. Key Secondary Endpoints	Removed sensitivity estimators and per protocol analyses.	Due to stopped enrollment, the study will only have descriptive analyses.
2.4. Definition of Subgroups 5.3.3. Subgroup Analyses	Removed some of the subgroup analyses.	Due to stopped enrollment and smaller sample size, some of the subgroup analyses are no longer needed.
5.6.1.6. Relationship Between On-Treatment ALT Elevations, Efficacy and Safety Endpoints, and Baseline Characteristics	Added analyses on the relationship between On-Treatment ALT elevations and Efficacy and Safety Endpoints, and Baseline Characteristics	Due to safety concern and ALT Flares, new analyses were included
5.1.1. Virology Data Handling Rules	Changed Imputation Rules for laboratory values and LLOQ Values	The focus of the analyses for HBV DNA are on < LLOQ. New assay with lower LLOQ value is used for HBV DNA from Jne 2023 and therefore LLOQ value was updated.
Throughout the SAP	Other changes, clarifications, and corrections made throughout the document.	To be aligned with other SAPs within the Hepatitis B project

Amendment 4

Overall rationale for the Amendment: This amendment aims to align the Statistical Analysis Plan (SAP) to the Protocol Amendment #3 issued on December 6, 2021 which was submitted in the context of data supporting start of Part 2. Protocol amendment #3 introduces updated inclusion criteria for the population enrolled in Part 2: cirrhotic participants will no longer be enrolled and adapted inclusion criteria for HBsAg and HDV RNA are provided. In addition, guidance to continue NA treatment until the last study visit and the discontinuation criteria of prolonged ALT elevation (as recommended by FDA) is introduced.

Protocol Amendment #3 also includes optional liver biopsies for Part 2 participants to allow a better understanding of the impact of JNJ-3989 treatment on viral and immune markers in the liver in these HBV/HDV co-infected participants, described as new exploratory endpoints. This amendment provides details on the analyses for those endpoints.

Additional changes are implemented for the simulations related to the sample re-estimation IA planned during the double-blind phase of Part 2 as the enrollment rate has been updated for Part 2 from 0.23 to 0.27 patient/site/month.

Main Changes		
Section Number and Name	**Description of Change**	**Rationale**
Section 1.2 Trial Design Section 1.5 Randomization and Blinding Section 5.3 Primary Efficacy Endpoint Section 5.4 Key Secondary Endpoints (KSE)	Stratification factor "Presence of compensated cirrhosis" removed from the statistical models for both primary and key secondary endpoints.	This stratification factor is no longer relevant to be included into the statistical models since all Part 2 participant randomized in the study are non-cirrhotic.
Section 5.4.3 KSE3: HBsAg Seroclearance at Week 48 Section 5.4.4 KSE4 : Reduction in LSM From baseline to Week 48	Positions are switched for the last two key secondary endpoints - 3rd KSE is Proportion of participants with HBsAg seroclearance at Week 48 - 4th KSE is Proportion of participants with ≥2 kPa reduction from baseline in LSM at Week 48.	Since all Part 2 participants are non-cirrhotic, it will be more difficult to reach significance for the proportion of participants with ≥2 kPa reduction from baseline in LSM. Consequently, this endpoint is now ranked at the last position as per fixed sequence approach.
Section 5.5 Other Secondary Endpoints	on / off treatment and nadir definitions are moved into this section and additional definitions are included:	The naming convention for on/off treatment should remain consistent across the program. Consequently, for HDV endpoints (whose on-treatment period refers to the period

Main Changes		
Section Number and Name	**Description of Change**	**Rationale**
	- JNJ3989 on-treatment - JNJ-3989 off-treatment - JNJ-3989 on-treatment nadir - JNJ-3989 off-treatment nadir	when the participant receives JNJ-3989 regardless of continuing NA treatment), a JNJ-3989-specific convention should be used to differentiate those terms from the standard HBV convention.
Section 5.5.1.1.12 ALT/AST Elevations	Section added	The treatment discontinuation criteria required by the FDA as prolonged 3xULN and 2xnadir is defined as "ALT elevation".
Section 5.6.1.6 Liver Immune Response Section 5.6.1.7 Liver Immune Response Section **Error! Reference source not found. Error! Reference source not found.** Section 5.6.2.6 Liver Immune Response Section 5.6.2.7 Liver Immune Response Section **Error! Reference source not found. Error! Reference source not found.**	Sections added	Align with the additional intrahepatic exploratory endpoints described in the protocol amendment 3.
Error! Reference source not found. : **Error! Reference source not found.**	Simulation results updated as per the current recruitment rate of 0.27 patients/site/month.	Clarification
Throughout the SAP	Minor grammatical, formatting or spelling changes were made	Minor errors were noted

Amendment 3

Overall rationale for the Amendment: This amendment aims to align the Statistical Analysis Plan (SAP) to the protocol Amendment #2 issued on June 18, 2021 which introduced two interim analyses (IA) during the Part 1 of the study. The first IA (Part 1 IA1) will occur after all participants of Part 1 have completed at least Week 16 (or discontinued earlier) and the second one (Part 1 IA2) when all participants of Part 1 have completed at least Week 48 (or discontinued earlier). In addition, the unblinding of the sponsor, including the Sponsor Committee, for conducting and reviewing of results of the Part 1 IA1 and IA2 was introduced in this amendment.

During the conduct of Part 1 of this study, a higher than-expected proportion of participants (approximately 50% of 22 participants enrolled in Part 1 at the time of this amendment) experienced elevations of alanine aminotransferase (ALT) on treatment. Management of these acute elevations has been following the protocol defined criteria but some of the cases showed a prolonged pattern of ALT elevation for which no management criteria were provided in the protocol. To better characterize these observed ALT elevations and to protect participants from a potential risk, the Sponsor, after consultation with the Independent Data Monitoring Committee (IDMC), decided to implement the following changes:

1. Introduction of new treatment discontinuation criteria

2. Sponsor unblinding for review of antiviral activity parameters to interpret the ALT flares

3. Addition of two interim analyses (IA) of study Part 1 data

The first IA (Part 1 IA1) is planned after all participants of Part 1 have completed at least Week 16 (or discontinued earlier). This timepoint was chosen based on the observed pattern of ALT elevations occurring at or before treatment Week 16.

Part 2 of this study will only be initiated after the conduct of Part 1 IA1 and conditional upon the IA1 results. The knowledge of a more complete characterization of ALT elevations in Part 1 will be critical to decide on the start of Part 2 while ensuring the protection of the participants' safety, and to guide management of potential ALT elevations in Part 2 by the investigators.

A second IA during the double-blind phase of Part 1 (Part 1 IA2), after all participants of Part 1 have completed at least Week 48 (or discontinued earlier), was introduced to continue the comprehensive assessment of the benefit-risk ratio of the investigational regimen in hepatitis D virus (HDV) infected participants with longer term data on participants of Part 1.

Additional changes are implemented to correct and/or clarify technical details for the sample re-estimation IA planned during the double-blind phase of Part 2.

Main Changes		
Section Number and Name	**Description of Change**	**Rationale**
Section 1.2 Trial Design Section 3.1 Independent Data Monitoring Committee and Sponsor Committee Section 3.2 Independent Flares Expert Panel Section 3.3 Data Reviews and Interim Analyses	Added the two IAs during the double-blinded treatment phase of Part 1 and modified the wording accordingly across the relevant sections.	Align the data review and interim analyses processes to assess and characterize ALT elevations observed in approximately 50% of the randomized HDV-infected participants of Part 1.
Section 1.2 Trial Design Section 1.5 Randomization and Blinding Section **Error! Reference source not found. Error! Reference source not found.**	Clarification of the randomization ratio of 4:1 (JNJ-3989+NA : placebo+NA) to remain the same regardless of a potential sample size increase in Part 2, and of the exact fixed weights used to adjust the efficacy analyses for the sample size re-estimation will be made prior to the IA in Part 2. Correction in the formula for the sample-size re-estimation.	Clarification on the fixed randomization ratio and technical details of the statistical method for sample size re-estimation.
Section 5.1.1 Virology Data Handling Rules	Updated ULOQ for HBsAg and HBeAg	Correction
Section 5.5.1.1.3 Virologic HDV RNA Breakthrough Section 5.5.1.1.9 Virologic HBV Breakthrough	Updated definition of both HDV RNA and HBV DNA virologic breakthroughs	Correction
Throughout the SAP	Minor grammatical, formatting or spelling changes were made	Minor errors were noted

Amendment 2

Overall rationale for the Amendment: This amendment addresses the expansion of the estimand framework for all analyses of the primary endpoint and key secondary endpoints following the ICH E9-R1 guidance including the per-protocol analysis. In addition, improved alignment with other clinical trials SAP within the JNJ-3989 development program is made with regards to clarification of endpoints (eg. definition of flares), addition of subgroup variables and safety analyses, as well as inclusion of sensitivity estimators based on additional missing data handling rules.

Main Changes		
Section Number and Name	**Description of Change**	**Rationale**
Section 2.3 Analysis Sets 0 attachments Attachment 1: Selected Major Protocol Deviations for Analysis Purposes	Added definition of 4 Per Protocol analyses sets: PP1, PP2, PP3 and PP4. Exclusion criteria and definition of intercurrent events for each PPs added in 0.	Clarify the appropriate intercurrent events within the corresponding estimand to conduct a per-protocol analysis of primary and key secondary endpoints.
Section 5.3 Primary Efficacy Endpoint and 5.4 Key Secondary Endpoints	Expanded text in the estimand section. Updated intercurrent events and added missing data handling rules. Added supplementary estimands and sensitivity estimators.	Improve the structure of the efficacy analyses of the primary endpoint and key secondary endpoints in alignment with the estimand framework following the ICH E9-R1 guidance. Correction of some intercurrent events.

Clarifications, Additions, Corrections		
Section Number and Name	**Description of Change**	**Rationale**
Section 2.1.1 Analysis Phase	Updated the definition of start and end dates for each analysis phase.	Correction.
Section 2.1.2 Relative Day by Study Phase	Removed Open Label Relative Day.	Alignment of open-label analysis windows with the week/day labels in the protocol Time & Events Schedule as defined relative to Double Blind Day 1.
Section 2.4.1 Subgroups for Efficacy Analyses	Added new subgroup variables and categories.	For completeness and alignment with other clinical trials SAP within the JNJ-3989 development program.
Section 3.3.1 Data Reviews	Updated Table 3 by limiting the output for the IA for sample size re-estimation to the primary efficacy endpoint analysis.	Correction.
Section 3.3.3 Rule to Start Part 2 of the Study or Determine Futility	Added the qualification “On-treatment” to the lab values used in the criteria defining antiviral activity.	Clarification
Section 4.6 Extent of Exposure	Updated derivation of durations of exposure.	Clarification and consistency with the wording used in Section 2.1.1 Analysis Phase
Section 5.1.1 Virology Data Handling Rules	LLOQ and imputed values updated for HDV RNA and HBV RNA.	Updates from external vendors on assay properties on RNA quantification.

Clarifications, Additions, Corrections		
Section Number and Name	**Description of Change**	**Rationale**
Section 5.5.1.1.4 JNJ-3989 Off-Treatment HDV RNA Relapses	Updated with additional definitions of off-treatment HDV RNA relapses	Clarification of approach to define different off-treatment HDV relapses based on HDV RNA value at End of Treatment visit.
Section 5.5.1.1.11 HBV Flares	Updated definition of virologic, biochemical and clinical flares by adding start and end dates for each type of flares.	Clarification of approach to identify distinct flare events over time.
Section 5.5.1.3.1 Time to Event Endpoints Based on Parameters Used in Key Secondary Endpoints	Analyses of time to event endpoints changed to overall during the study instead of by analysis phase.	Clarification.
Section 5.5.1.4 Additional Efficacy Endpoints Relative to The Actual Duration of JNJ-3989 Treatment and Section 5.6.1.3 Time to Event Endpoints	Added Table 5: Correspondence between timepoints for Arm 1 and Open Label timepoints for Arm **2** for the analysis based on actual duration of treatment exposure.	Alignment of time points to match the exposure to JNJ-3989+NA between the 2 arms, given the deferred active treatment design.
Section 5.6 Exploratory Endpoints	Added exploratory analyses for HDV RNA, HBV DNA and HBsAg	Added for accounting
Section 6.2.1 Definitions	Added imputation rules for laboratory data in the event of "<", ">", "≥" and "≤" being contained in the character result value.	Clarification
Section **Error! Reference source not found. Error! Reference source not found.**	Added definitions of HBV genetic and viral variations as well as parameters of interest with accompanying analyses.	Added for completeness
Section **Error! Reference source not found. Error! Reference source not found.**	Updated the calculation of the HBQOL total and subitems scores.	Correction
0 attachments Attachment 1: Selected Major Protocol Deviations for Analysis Purposes	Updated the list of major protocol deviations for the purpose of the efficacy analyses.	Alignment of the major deviations to the detailed estimands definition and expanded list of intercurrent events.
0 attachment 2: Adverse events of special interest list of preferred terms.	Added attachment 2 to identify the preferred terms for the identification of adverse events of special interest.	Added for completeness

Clarifications, Additions, Corrections		
Section Number and Name	**Description of Change**	**Rationale**
Throughout the document	Clarification of text.	Typographical corrections or improved language for clarity and precision

Amendment 1

Overall rationale for the Amendment: Following the FDA's response to the protocol and SAP submission, the study team agreed to amend the SAP to align with FDA recommendations, mainly Furthermore, clarifications, additions and corrections were made throughout the SAP.

Main Changes		
Section Number and Name	**Description of Change**	**Rationale**
Section 5.3.2.2 Supplementary Estimator	Supplementary estimator added for the primary estimand where all subjects with missing HDV RNA and ALT values in the analysis window of Week 48 are imputed as non-responders	To evaluate the robustness of the assumption of MAR and the type of missing data.
Sections 0 Supplementary Estimand (Per-protocol analysis)	Supplementary estimand for the Per-Protocol analysis set	To define the PP analyses according to the estimand framework
Sections 1.2 Trial Design, 3 Interim Analysis, 4 Subject Information, **Error! Reference source not found.** Level of significance, 5.3 Primary Efficacy Endpoint, 5.4 Key Secondary Endpoints, 5.5 Other Secondary Endpoints, 5.6 Exploratory Endpoints, 6 Safety	Removed the inferentially seamless feature of the study; stated a clear separation of efficacy analyses by study parts, with use of Part 2 data only as the pivotal part of the study.	To protect the study integrity and allow the involvement of the Sponsor Committee in making the decision to initiate Part 2 based on the assessment of antiviral activity criteria in Part 1.
Sections 5.3 Primary Efficacy Endpoint, 5.4 Key Secondary Endpoints,	Clarification of intercurrent events in the main estimand definition for the primary efficacy endpoint regarding the major protocol deviations, and update of the missing data handling rule in presence of intercurrent events.	Alignment of the missing data handling rule with the treatment policy strategy proposed for selected intercurrent events defined in the primary estimand in accordance with the ICH-E9-R1 guidance.

Clarifications, Additions, Corrections		
Section Number and Name	**Description of Change**	**Rationale**
Section 1.4 Sample Size Justification	The text on sample size calculation was clarified by adding the type of statistical test used, and the justification for the assumptions made in the power calculations and sample size re-estimation. Changed the planned sample size of Part 2 to 145 participants with a potential increase to a maximum of 170.	Clarification of assumptions for the sample size calculation and update of the sample size increase for Part 2 due to the inferential separation of Part 1 from Part 2.
Section 2.1.1 Analysis Phase	Updated the definition for end of Double Blind Study Intervention Phase	Correction
Section 2.4.1 Subgroups for Efficacy Analyses Section 5.3.3	Subgroup analysis based on prior exposure to PegIFN-α added Pooling of Part 1 and Part 2 data for explorations of subgroups	To align with EUnetHTA recommendation to account for prior use of PegIFN-α as potential subgroup of interest for primary and key secondary endpoints. To leverage the whole study data.
Section 2.4.2 Subgroups for Safety Analyses	Comment “To team: do we also need duration?]” removed	Correction
Section **Error! Reference source not found.** Level of Significance	References for the use of median-unbiased estimate were updated	To correct a typo and to include an additional relevant reference
Section 5.1.1 Virology Data Handling Rules	ULOQ for HBsAg updated to 124,925 IU/mL without dilution	To align rules with other clinical trials within Hepatitis B therapeutic area.

ABBREVIATIONS

ADY	analysis relative day
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomic and therapeutic class
BMI	body mass index
CHB	chronic hepatitis B
CI	confidence interval
CKD	Chronic Kidney Disease
CRF	case report form
DAIDS	division of acquired immunodeficiency syndrome
DB	double-blind
DR	data review
DRC	data review committee
ECG	electrocardiogram
EOS	end of study
EOT	end of treatment
eCRF	electronic case report form
ETV	entecavir
FU	follow-up
HBQOL	hepatitis B Quality of Life
HBcrAg	hepatitis B core-related antigen
HBe	hepatitis B envelope
HBs	hepatitis B surface
HBeAg	hepatitis B envelope antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HBV DNA	hepatitis B virus deoxyribonucleic acid
HBV RNA	hepatitis B virus ribonucleic acid
HIV-1(-2)	human immunodeficiency virus type 1 (type 2)
HDV RNA	hepatitis D virus ribonucleic acid
HRQoL	Heart-Related Quality of Life
ICS	intracellular cytokine staining
IDMC	independent data monitoring committee
iFLEP	independent flares expert panel
IA	interim analysis
IFN	interferon
IQR	interquartile range
IRT	item response theory
ISR	injection site reaction
ITT	Intent-to-treat
IU/mL	international units per milliliter
IWRS	interactive website response system
KSE	Key Secondary Endpoint
LiPA	line probe assay
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LSM	liver stiffness measurement
MAR	missing at random
MCAR	missing completely at random
MCS	mental component summary
MCT	multiple contrast test
MedDRA	medical dictionary for regulatory activities
MH	Mantel-Haenszel

MI	multiple imputation
mITT	modified intent-to-treat
MNAR	missing not at random
MSE	missing score estimation
NA	nucleos(t)ide analog
NGS	next generation sequencing
OL	open-label
PBMC	peripheral blood mononuclear cell
PC	precore
PCS	physical component summary
pegIFN	peginterferon
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PRO	patient-reported outcomes
Q4W	every 4 weeks
qd	once daily
QTcF	QT interval corrected for heart rate according to Fridericia
RR	Interval between R wave of one heartbeat and R wave of preceding heartbeat
RT	reference timepoint
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SC	sponsor committee
TEAE	treatment-emergent adverse event
TAF	tenofovir alafenamide
TD	target detected
TeD	tenofovir disoproxil
TND	target not detected
TNF	tumor necrosis factor
ULN	upper limit of normal
VCTE	vibration-controlled transient elastography
WBC	white blood cell

1. INTRODUCTION

This statistical analysis plan (SAP) for the 73763989HPB2004 phase 2 trial describes the statistical analyses and definitions to assess the efficacy and safety of the study intervention with JNJ-73763989 (100 mg every 4 weeks [Q4W]) and Nucleos(t)ide analogs (NA) in participants co-infected with hepatitis B virus (HBV) and hepatitis D virus (HDV). In this document the abbreviation JNJ-3989 is used to refer to the treatments JNJ-73763989. This SAP to be interpreted in conjunction with the clinical protocol amendment 4 finalized on 07 April 2023.

This is a 2-part, Phase 2, randomized, double-blind, placebo-controlled deferred active treatment, parallel, multicenter, interventional study comprising a proof-of-concept Part 1 followed by Part 2.

Part 1 will provide the data to evaluate the safety, tolerability, and HDV anti-viral activity signal of JNJ-3989+NA in a small number of participants (N=20), prior to enrolling a further number of participants in Part 2. The Part 2 of the study was originally planned with N = 145, however, as of protocol Amendment 4, sample size was reduced to 30 participants due to stopped enrollment. Monitoring of the safety and efficacy in terms of HDV RNA and HBsAg data in the JNJ-3989+NA arm aims to exclude futility of the regimen and initiate Part 2.

Part 2 will provide additional evidence of safety and efficacy of the JNJ-3989 regimen in the treatment of HBV/HDV co-infection.

An independent data monitoring committee (IDMC) will be commissioned for this study to monitor data on a regular basis to ensure the continuing safety, efficacy and well-being of the participants enrolled in this study (see Section 3.1).

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 on-treatment efficacy against HDV of JNJ-3989 + NA regimen compared to NA alone.	• Proportion of participants with HDV RNA ≥2 $\log_{10}$ IU/mL decline from baseline or HDV RNA TND in combination with normal ALT at Week 48.
Key Secondary	
To evaluate on-treatment efficacy of the JNJ-3989 + NA regimen in suppressing HDV replication as measured by HDV RNA.	• Proportion of participants with HDV RNA ≥2 $\log_{10}$ IU/mL decline from baseline or HDV RNA TND at Week 48.
To evaluate efficacy of the JNJ-3989 + NA regimen on liver inflammation during study intervention phase.	• Proportion of participants with normal ALT at Week 48.

Objectives	Endpoints
To evaluate the efficacy of the JNJ-3989 + NA regimen in terms of HBsAg response.	• Proportion of participants with HBsAg seroclearance at Week 48.
To evaluate the efficacy of the JNJ-3989 + NA regimen on liver fibrosis.	• Proportion of participants with ≥2 kPa reduction from baseline in liver stiffness measurement (LSM) assessed by vibration-controlled transient elastography (VCTE) (FibroScan) at Week 48.
Other Secondary	
To evaluate the efficacy of the JNJ-3989 + NA regimen during study intervention phase and follow-up phase.	• Proportion of participants with HDV RNA ≥2 $\log_{10}$ IU/mL decline from baseline or HDV RNA TND in combination with normal ALT. • Proportion of participants with HDV RNA ≥2 $\log_{10}$ IU/mL decline from baseline in combination with normal ALT. • Proportion of participants with HDV RNA TND in combination with normal ALT. • Proportion of participants with HDV RNA ≥2 $\log_{10}$ IU/mL decline from baseline or HDV RNA TND. • Proportion of participants with HDV RNA ≥2 $\log_{10}$ IU/mL decline from baseline. • Proportion of participants with HDV RNA TND. • Proportion of participants with normal ALT. • Time to reach HDV RNA ≥2 $\log_{10}$ IU/mL decline or HDV RNA TND. • Changes from baseline in HDV RNA. • Changes from baseline in ALT.
To evaluate the safety and tolerability of the study intervention throughout the study.	• Proportion of participants with incidences of (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 examination.
To evaluate the efficacy of the JNJ-3989 + NA regimen as measured by HBV blood markers (such as HBsAg, HBeAg*, HBV DNA) during study intervention and follow-up.	• Proportion of participants with HBsAg seroclearance and/or seroconversion. • Change from baseline over time in HBsAg, HBeAg*, HBV DNA. • Proportion of participants with HBsAg, HBeAg*, and/or HBV DNA levels or changes from baseline below/above different cut-offs. • Time to reach efficacy thresholds such as HBsAg <1 IU/mL.

Objectives	Endpoints
To evaluate the frequency of HBV virologic breakthrough throughout the study.	• Proportion of participants with HBV DNA virologic breakthrough.
To evaluate the PK of JNJ-3989 throughout the study.	• PK parameters of JNJ-3989 (JNJ-73763924 and JNJ-73763976).
To evaluate changes in liver fibrosis during study intervention and follow-up.	• Proportion of participants with ≥2 kPa reduction from baseline in Liver Stiffness Measurement (LSM) assessed by VCTE (FibroScan). • Change from baseline in LSM over time assessed by VCTE (FibroScan).
To evaluate the anti-HDV efficacy during the follow-up phase.	• Proportions of participants with sustained HDV response off-treatment post end of JNJ-3989 treatment. • Proportions of participants with HDV relapse post end of JNJ-3989 treatment.
To evaluate the anti-HBV efficacy during the follow-up phase.	• Proportions of participants with sustained HBV response off-treatment post end of JNJ-3989 treatment. • Proportions of participants with HBV flare (virologic, biochemical, and clinical) post end of treatment.
Exploratory	
To explore the relationship between PK parameters (JNJ-3989) and selected pharmacodynamic (PD) parameters of efficacy and/or safety, as applicable.	• Relationship between various PK parameters (JNJ-3989) and selected efficacy and/or safety endpoints, as applicable.
To explore the relationship between HBsAg and HDV RNA.	• Correlation between HBsAg decline and HDV RNA levels/changes.
To explore the impact of the viral and host baseline characteristics on safety and efficacy.	• Correlation of viral and host baseline characteristics (such as HBV/HDV genotype, baseline HBV DNA levels, baseline HDV RNA levels, age, sex, body mass index [BMI]) with selected efficacy and safety variables.
To explore the effect of any baseline variation in the HBV and HDV (if feasible) genome on efficacy.	• Correlation of HBV and HDV genome sequence with selected efficacy parameters.
To explore changes in the HBV and HDV (if feasible) genome sequence during study intervention and follow-up.	• Emergence of intervention-associated mutations.

Objectives	Endpoints
To explore efficacy as measured by HBV RNA and HbcrAg during study intervention and follow-up.	• Changes from baseline in HBV RNA and HBcrAg levels. • Time to reach undetectability of HBV RNA and HBcrAg.
To explore HBV-specific T-cell responses during study intervention. **	• Changes from baseline in peripheral blood T-cell responses.
To explore medical resource utilization (MRU) to manage participants during study intervention and follow-up.	• Number and type of medical visits. • Number (proportion) of participants requiring hospitalization and duration of hospitalization (total days length of stay, including duration by wards; eg, intensive care unit (ICU). • Number and character of diagnostic and therapeutic tests and procedures.
To explore liver viral responses during study intervention.***	• Changes from baseline in intrahepatic viral parameters (such as HDV RNA, HDAg, cccDNA, pgRNA, intrahepatic RNA, or HBsAg in terms of copy number, or number of positive cells). • Changes from baseline in intrahepatic cccDNA. • Levels and transcriptional activity (pgRNA/cccDNA ratio).
To explore liver immune responses during study intervention.***	• Changes between baseline and on-treatment liver biopsy in intrahepatic immune response (eg, CD45+ T-cells, CD4+ T-cells, CD8+ T-cells, Natural Killer cells, and dendritic cells) in terms of proportion of cells, cell types, and spatial redistribution
To explore the relationship of intrahepatic markers with blood markers (immune and viral).	• Association between levels and changes in intrahepatic and blood markers.

*: in HBeAg-positive participants only

** Peripheral blood mononuclear cell (PBMC) samples for immune analyses will be collected at selected sites only and as operationally feasible

*** If sufficient number of participants contribute to the liver biopsy collection

1.2. Trial Design

Prior Protocol Amendment #4 the study was planned to include 2 parts, Part 1 (approximately N=20) with proof of concept objectives and Part 2 (approximately N=145) with confirmatory objectives. As of Protocol Amendment #4, Part 2 sample size was reduced to 30 participants which triggered modifications of objectives of Part 2 from confirmatory to exploratory.

Part 2 of the study will only be initiated once the antiviral activity criteria in Part 1 have been met and after evaluation of the results of the first IA during the double-blind phase of Part 1. Cirrhotic participants will be excluded from participation in Part 2 of the study.

Each part includes 3 phases: a 4-week screening phase (may be extended up to a maximum of 6 weeks), 144-weeks study intervention phase (Arm 1) and 148-weeks study intervention phase (Arm 2), 48-week follow-up phase. The first 52 weeks of the intervention phase are double-blind followed by 96 weeks of open-label (OL) treatment.

In each part the participants will be randomized in a 4:1 ratio to Arms 1:2.

- Arm 1: 100 mg JNJ-3989 (subcutaneous [SC] injection every 4 weeks [Q4W]) + NA qd for 144 weeks;
- Arm 2: placebo for JNJ-3989 (SC injection Q4W) + NA qd for 52 weeks, followed by 100 mg JNJ-3989 (SC injection Q4W) + NA qd for 96 weeks (control deferred active treatment arm).

Randomization will be stratified by presence of compensated cirrhosis at screening (yes or no) (Part 1 only), HDV RNA testing laboratory location (China versus outside China) (all sites in China will utilize the laboratory testing in China and all sites in other countries will utilize the laboratory outside of China), and HBeAg status at screening (positive versus negative).

Prior Protocol Amendment #4, if safety was confirmed and futility excluded in Part 1, the total number of participants in this study was planned to be approximately 165 participants (specifically with a target of approximately 20 participants in Part 1, and 145 participants [up to a maximum of 170 participants] in Part 2), aged ⩾18 to 65 years of age, co-infected with HDV and HBV. An interim analysis (IA) during DB study intervention phase was planned to re-assess the sample size in Part 2 and potentially increase it to maintain the statistical power at minimum at 80%. The maximum total sample size allowed for Part 2 of this study was 170. A reduction in sample size was not allowed, hence the minimum sample size for Part 2 was the planned number of 145 participants (see Section 1.4). The confirmatory conclusions of the study would be based on data from Part 2 only (145 participants, or, if recommended by IDMC, up to 170 participants). As Per Protocol Amendment #4, the total sample size of the study is 52, with 22 participants in Part 1 and 30 participants in Part 2. Data from Part 1 and Part 2 will be reported both separately and together to contribute to the overall benefit/risk ratio assessment of the regimen.

1.3. Statistical Hypotheses for Trial Objectives

The original protocol had as primary hypothesis of this study that the combination regimen of JNJ-3989 + NA has superior efficacy compared to NA treatment alone in reducing HDV replication and improving the associated liver inflammation, as measured by the primary efficacy endpoint at Week 48 (the proportion of participants with HDV RNA decline ≥2 log10 IU/mL from baseline or HDV RNA TND in combination with normal ALT at Week 48). Due to the decision to stop enrollment at 30 participants in Part 2 of the study (see Section 1.2), the primary study hypothesis can no longer be tested with sufficient power, and hence the statistical analyses will be descriptive.

1.4. Sample Size Justification

A total sample size of 130 participants for Part 2 in the original protocol would have yielded a statistical power >90% to detect a between-arm difference of ≥26% in the primary efficacy endpoint at Week 48, at a 1-sided Type 1 error rate of 0.025, based on the test for the between-arm difference in proportions with the normal approximation. Per Protocol Amendment 4, the sample size in Part 2 was reduced to 30 participants. In the original protocol, sample size re-estimation was planned at the single IA during Part 2 to allow for an increase to a maximum of 170 participants in Part 2 for the conditional power at the end of the study to be at least 80% in case the assumed 0.04 response rate for placebo was too conservative. Due to reduction in sample size per Protocol Amendment 4, the single IA with sample size re-estimation was removed. In the original protocol, the number of participants included in this study was planned to be a minimum of approximately N=20 (if Part 2 is not initiated) or between a minimum of N=165 and a maximum of N=190 if Part 2 is initiated. Per Protocol Amendment 4, the planned number of participants included in the study will be N=20 in Part 1 and N=30 in Part 2.

1.5. Randomization and Blinding

Randomization and Stratification

Randomization will be performed using a 4:1 ratio (Active regimen from the start Arm1 : Placebo/ deferred treatment Arm 2), regardless of the study part, to minimize bias in the assignment of participants to intervention arms, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment arms, and to enhance the validity of statistical comparisons across intervention arms.

Randomization will be stratified by presence of compensated cirrhosis at screening (yes or no) (Part 1 only), HDV RNA testing laboratory location (China versus outside China), and HBeAg status at baseline (positive versus negative) in order to provide an evenly balanced representation across the 2 arms.

Blinding

Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

The investigators, participants and all site personnel will remain blinded to study intervention allocation until Week 52 (Part 1) and Week 48 (Part 2). After Week 52 (Part 1) and Week 48 (Part 2), it will be communicated to the investigators whether the participants were allocated to either the investigational arm (Arm 1) or the control arm (Arm 2) to allow the correct open-label and follow-up visits schedule to be followed (see Schedules of Activities). For each participant, all HDV RNA, HBsAg, HBeAg, HBcrAg, anti-HBs, and anti-HBe antibody testing individual results will be provided to the investigator and the sponsor for managing the participant's safety.

After Week 52 and up and until Week 144, study intervention will be administered in open-label fashion to all participants (except Part 2 participants allocated to Placebo+NA who had HBsAg >10,000 IU/mL at screening or baseline).

Prior to Part 1 IA1 (see Section 3.3.2.1.1), the Sponsor Committee will review unblinded aggregated interim data of HDV RNA, HBsAg, ALT, AST, total and direct bilirubin, HBV DNA and individual patient profiles for the values/changes from baseline over time for all participants in Part 1 including those randomized to the placebo+NA arm.

Part 1 IA1 will include the review of all unblinded efficacy and safety results by the Sponsor Committee and the decision whether the Part 2 can be initiated based on the review of the antiviral activity criteria in conjunction with ALT elevations and other safety data, taking into consideration the IDMC recommendations. From the moment of unblinding for this IA onwards, the Sponsor Committee will remain unblinded to Part 1 data.

The Study Team will become unblinded at the time of the IA1 of Part 1, throughout IA2 of Part 1 until completion of Part 1, but will remain blinded to all data of Part 2 until the end of double-blind phase (each individual participant will be unblinded after they reach Week 48 or discontinue earlier).

2. GENERAL ANALYSIS DEFINITIONS

The SAP will use throughout the document the following definitions:

- Study treatment refers to: JNJ-3989, placebo, or NA [entecavir (ETV), tenofovir disoproxil (TD), or tenofovir alafenamide fumarate (TAF)]
- Study agent refers to: JNJ-3989 or placebo
- Study intervention arm refers to:
  - Arm 1: JNJ-3989 (100 mg) + NA
  - Arm 2: 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 (DB) Study Intervention	Date of first study agent intake	**If participant did not withdraw from the study and did not discontinue treatment early prior to the projected/actual Week 52 Visit date**: Min(Date of Week 52 study agent intake – 1 day, cut-off date*) **Otherwise:** [Min (Early study withdrawal visit date, study agent discontinuation date) + 5 days[a]] or cut-off date*, whichever occurs first
Open-Label (OL) Study Intervention	**If participant has a projected/actual Week 52 Visit date**: – End date of DB study intervention phase + 1 day **Otherwise**: – Missing	**If participant did not withdraw from the study prior to the projected/actual Week 144 (Arm 1)/Week 148 (Arm 2) Visit date and did not discontinue treatment early prior to the projected/actual Week 140 (Arm 1)/Week 144 (Arm 2) Visit date**: [Min (Date of Week 144 Visit (for Arm 1) or / Date of Week 148 Visit (for Arm 2))+ 5 days[a]] or cut-off date*, whichever occurs first **if participant withdrew from the study or discontinued treatment between projected/actual Week 52 Visit date + 1 day and projected/actual Week 144 (Arm 1)/Week 148 (Arm 2) Visit date**: [Min (Early study withdrawal visit date, study agent discontinuation date)+ 5 days[a]] or cut-off date*, whichever occurs first
Follow-up	**If participant did not withdraw informed consent during DB or OL study intervention phases** Max (End date of DB study intervention phase, End date of OL study intervention phase) + 1 day **Otherwise**: Missing	**If participant entered the Follow-up phase:** Max [early study withdrawal visit date, study completion date] or cut-off date, whichever occurs first. **Otherwise**: Missing

*Cut-off dates will be defined to match the prespecified timepoints for IDMC safety monitoring, interim analysis, the primary analysis and the final analysis, respectively.

[a]: Addition of 5 days is only applicable for Adverse Events and Concomitant Medications

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 Study Intervention Relative Day

The Double-Blind (DB) Study intervention start date (DB Day 1) is defined as the date of first study agent intake. All efficacy and safety assessments during the DB study intervention phase will be assigned a day relative to this date.

The study day in the Double-Blind intervention phase (DB ADY) is defined as:

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

for visits on or after Day 1, and

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

for visits before DB Day 1 (Screening phase).

There is no '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 days 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

Phase	Target day	Analysis time point (Week)	Analysis time point (label)	Time interval (days) for Arm 1	Time interval (days) for Arm 2[(a)]
Screening	-28 to -1	-1	Screening	<0	
Double-Blind (DB) 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	[324,351]	
Open-Label (OL) Study Intervention	365	52	Week 52	[352, 372]	
	379	54	Week 54	[373, 386]	
	393	56	Week 56	[386, 407]	
	421	60	Week 60	[408, 435]	
	449	64	Week 64	[436, 463]	
	477	68	Week 68	[464, 491]	
	505	72	Week 72	[492, 519]	
	533	76	Week 76	[520, 547]	
	561	80	Week 80	[548, 575]	
	589	84	Week 84	[576, 603]	
	617	88	Week 88	[604, 631]	
	645	92	Week 92	[632, 659]	
	673	96	Week 96	[660, 687]	
	701	100	Week 100	[688, 715]	
	729	104	Week 104	[716, 743]	
	757	108	Week 108	[744, 771]	
	785	112	Week 112	[772, 799]	
	813	116	Week 116	[800, 827]	
	841	120	Week 120	[828, 855]	
	869	124	Week 124	[856, 883]	
	897	128	Week 128	[884, 911]	
	925	132	Week 132	[912, 939]	
	953	136	Week 136	[940, 967]	
	981	140	Week 140	[968, 995]	
	1009	144	Week 144 [(b)]	Not Applicable	[996, 1023]

Phase	Target day	Analysis time point (Week)	Analysis time point (label)	Time interval (days) for Arm 1	Time interval (days) for Arm 2[a]
	last visit during the intervention phase	149*	EOT[b]		
Follow-Up (FU)	15	150	Follow-up Week 2	[1, 22]	
	29	152	Follow-up Week 4	[23,36]	
	43	154	Follow-up Week 6	[37, 50]	
	57	156	Follow-up Week 8	[51, 71]	
	85	160	Follow-up Week 12	[72, 99]	
	113	164	Follow-up Week 16	[100, 127]	
	141	168	Follow-up Week 20	[128, 155]	
	169	172	Follow-up Week 24	[156, 190]	
	211	178	Follow-up Week 30	[191, 232]	
	253	184	Follow-up Week 36	[233, 274]	
	295	190	Follow-up Week 42	[275, 316]	
	337	196	Follow-up Week 48	[317, +∞]	
	last visit in the study	999*	EOS		

(a) Participants randomized to Arm 2 (placebo + NA) will have additional assessments during the OL phase at Week 54 and Week 144. See Protocol Section 1.3.2 for more details

(b) For participants who completed the OL phase (see Table 1), EOT corresponds to Week 144 Visit Date for Arm 1 and Week 148 for Arm 2

*End of treatment (EOT) visit will be the last post-baseline visit in double-blind or open-label phase, and End of study (EOS) visit (last available data during the follow-up) will be the last visit in the study.

2.2. Baseline

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

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

An additional reference timepoint (RT) will be used for an additional analysis of selected efficacy endpoints for Part 2 relative to the actual duration of treatment with JNJ-3989 as motivated by the deferred treatment design. This is described in Section 5.5.1.4.

2.3. Analysis Sets

Due to the issues caused by the pandemic Coronavirus Disease (COVID-19), the study team had decided to add the Modified Intent-to-treat analysis set (mITT) as defined below. It will be used for the efficacy analyses instead of the ITT in case of significant impact of future pandemics on the conduct and data collection for this study. The assessment of the impact will be made beforethe primary analysis of Part 2, however, the mITT is tentatively planned to be used if 6 or more participants are affected.

All randomized analysis set: All participants who were randomly assigned to an intervention arm 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 randomly assigned to an intervention arm and who received at least 1 dose of study intervention. 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 48, 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 take at least 1 dose of study intervention. Participants will be analyzed according to the study intervention they actually received.

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

2.4. Definition of Subgroups

Subgroup analyses will be performed if at least 5 participants fall into the category.

2.4.1. Subgroups for Efficacy Analyses

- Sex: Male, Female
- Age categories: 18 years - ≤ 30 years, > 30 years -≤ 45 years, > 45 years-≤ 60 years, > 60 years
- Duration of NA at Baseline: ≤ 2 years, > 2 years Race: Asian, non-Asian
- NA Treatment history at screening
  - Yes
  - No

- Presence of compensated cirrhosis at screening (yes or no) (Part 1 only)
- HDV RNA level at baseline:
  - < 1000 IU/mL vs ≥ 1000 IU/mL
  - < 10,000 IU/mL vs ≥ 10,000 IU/mL
  - < 100,000 IU/mL vs ≥ 100,000 IU/mL
- HBeAg status at screening (positive vs negative)
- HBV DNA level at baseline:
  - <LLOQ
  - ≥ LLOQ
  - < 200 IU/mL vs ≥ 200 IU/mL
  - < 2,000 IU/mL vs ≥ 2,000 IU/mL
- HBV RNA level at baseline:
  - TND
  - Detectable
- HBsAg level at baseline:
  - <1,000 IU/mL
- ≥1,000 IU/mL-<10,000 IU/mL
  - ≥10,000 IU/mL
- HBcrAg level at baseline:
  - <3 $\log_{10}$ U/mL
  - ≥3 $\log_{10}$ U/mL-<4 $\log_{10}$ U/mL
  - ≥4 $\log_{10}$ U/mL
- HBsAg Antibody (Anti-HBs) level at baseline:
  - <LLOQ
  - <10 mIU/mL
  - ≥10 mIU/mL
- Alanine transferase (ALT) at baseline: ≤ 1.0xULN, > 1.0xULN - <2.5xULN, ≥ 2.5xULN
- Combination of HDV RNA and HBsAg at screening**:**
  - < 100,000 IU/mL/< 10,000 IU/mL
  - ≥ 100,000 IU/mL/< 10,000 IU/mL
  - < 100,000 IU/mL/ ≥ 10,000 IU/mL
  - ≥ 100,000 IU/mL/≥10,000 IU/mL

2.4.2. Subgroups for Safety Analyses

- Age categories: 18 years - ≤30 years, > 30 years - ≤ 45 years, > 45 years - ≤ 60 years, > 60 years
- Presence of compensated cirrhosis at screening (yes or no) (Part 1 only)
- Type of NA at baseline
  - TeD
  - TAF
  - ETV
  - None
- Duration of NA at screening: ≤ 2 years, > 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) and NA/IFN prior to baseline/study entry dates will be imputed according to the rules in the following subsections. The original, non-imputed, dates will be used only in listings.

2.5.1. Adverse Event Onset Date and Resolution Date

Partial AE onset dates will be imputed as follows:

- If the AE onset date is missing the day only, it will be set to:
  - The first day of the month when the AE occurred, if month and year of the AE onset date is different than the month and year of the first administration of study treatment date.
  - The day of the first study treatment administration, if the month and year of the AE onset date is the same as the month and 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 and 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 and HDV 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. NA and IFN Treatment Dates Prior to Study Entry

In case of partially missing NA and IFN start/end dates recorded as medical history (i.e prior to study entry), 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 NA end date, further adjustment of the imputed start date is required. It will be imputed as the NA end date

No imputation if completely missing

2.5.4. 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 (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 (Day 1) based on eCRF question, and the imputed start date is prior to first dosing date, the imputed start date will be further adjusted to be the first

study treatment dosing date. The partially missing medication end date will be imputed following the rule described at the beginning of this section to ensure it is on or after first dosing date, and after its start date.

In case of a completely missing start date, the concomitant therapy will be considered as having started before the trial, unless the eCRF indicates that the medication was taken after study start.

In case of a completely missing end date, the concomitant therapy will be considered as ongoing at the end of the trial, unless the eCRF indicates as not ongoing.

2.5.5. Dates of Alcohol Consumptions

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

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

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

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

3.1. Independent Data Monitoring Committee and Sponsor Committee

An IDMC will monitor data on a regular basis to ensure the continuing safety, efficacy and well-being of the participants enrolled in this study. The IDMC will review the 2 interim analyses data of Part 1.

The IDMC members will be appointed before the start of the study to review unblinded interim data for both safety and efficacy and formulate recommendation(s) to the SC, who will make the final decision(s). Possible recommendations of the IDMC include, but are not limited to, continuing the study unchanged, stopping the study for safety concerns, or for futility or make a study amendment.

The IDMC will consist of at least one medical expert in the relevant therapeutic area and at least

one statistician. The IDMC role and responsibilities, communication flow with other stakeholders (such as SC and Statistical Support Group), and procedures will be documented in its charter.

The SC includes representatives from the sponsor's Clinical, Biostatistics, Global Medical Safety and Virology departments who are not involved in the study conduct.

The Sponsor Committee will be unblinded in the initial evaluation of the antiviral activity criteria in up to all the participants randomized in Part 1 of the study based on aggregate interim data of HDV RNA and HBsAg and/or individual HDV RNA and HBsAg profiles.

Prior to Part 1 IA1 (see Section 3.3.2.1.1), the Sponsor Committee will review unblinded aggregated interim data of HDV RNA, HBsAg, ALT, AST, total and direct bilirubin, HBV DNA and individual patient profiles for the values/changes from baseline over time for all participants in Part 1 including those randomized to the placebo+NA arm.

Part 1 IA1 will include the review of all unblinded efficacy and safety results by the Sponsor Committee and decision whether the Part 2 can be initiated based on the review of the antiviral activity criteria (Section 3.3.3) in conjunction with ALT elevations and other safety data, and the recommendations from the IDMC. From the moment of unblinding for this IA onwards, the Sponsor Committee will remain unblinded to Part 1 data.

After Part 2 has commenced, all Sponsor personnel, including the Sponsor Committee, will remain blinded to all Part 2 data and any subsequent IDMC data reviews concerning Part 2 until the end of the double-blind phase of Part 2 of the study. Only the IDMC will remain unblinded for Part 2 data during the double-blind phase of each individual patient.

After enrolment has been expanded beyond the participants in Part 1, the efficacy monitoring will be conducted by the IDMC using all the data available at that time to protect the well-being of the participants against unexpected absence of further HDV RNA decline and/or HDV RNA rebound/breakthrough contrary to the initial antiviral activity signal.

The criteria to assess the antiviral activity or to declare futility will be based on predefined thresholds for HDV RNA and HBsAg reductions from baseline. Details are provided in Section 3.3.3.

3.1.1. Internal Data Review Committee

The Members of the Sponsor Committee will form a newly established Internal Data Review Committee (DRC) which replaces the IDMC once all patients have completed the double-blind phase. The DRC will monitor SAEs, AEs leading to discontinuation, and ALT flares during the open-label and follow-up phases of the study. The committee will meet periodically to review data of the efficacy parameters measured by different HBV and HDV disease blood markers (eg, HDV RNA, HBV DNA, HBeAg, HBsAg, etc). DRC members will not be involved in the study conduct.

3.2. Independent Flares Expert Panel

An independent flare expert panel (IFLEP) will be appointed. The IFLEP is composed of 3 independent medical experts with experience and expertise in HBV/HDV. The responsibilities of the IFLEP include: conduct regular review of all relevant and available individual participant blinded study data related to ALT flares; determine and adjudicate each ALT flare; and provide documentation of the final decision to IDMC. Adjudication review cycles will match IDMC schedule and will be set up ideally 2 weeks before IDMC.

In order to allow for an unbiased assessment, members of the committee will not serve as study investigators or as members of the IDMC. They will be unblinded to treatment assignment for all Part 1 participants from the time of Part1 IA1 and will remain blinded to the treatment assigned to

each participant of Part 2. Further details on the IFLEP process will be included in the IFLEP charter.

HBV Flares are defined in Section 5.5.1.1.11**.**

3.3. Data Reviews and Interim Analyses

The IDMC will conduct unblinded periodic safety data reviews to ensure the continuing safety of the study participants during the entire course of the study.

The primary aim of Part 1 is to assess if the antiviral activity criteria to start Part 2 are met and to exclude futility of the regimen JNJ-3989+NA. As introduced in Section 3.1, the IDMC will also periodically review unblinded efficacy parameters measured by different HDV and HBV disease blood markers (e.g., HDV RNA, HBV DNA, HBsAg, and HBeAg) to support the detection of anti-HDV viral activity and to protect the well-being of the participants against the eventuality of lack of sufficient efficacy after Part 2 of the study has started enrolling.

3.3.1. Data Reviews

The IDMC will periodically review unblinded cumulative safety and efficacy data at the following timepoints:

Reviews by the IDMC before Part 2 has started (up to approximately 20 participants randomized into the study)

- The first data review (DR) will be performed after approximately 8 participants completed 8 weeks of treatment.
- Thereafter, data reviews will occur approximately every 4 weeks.

Reviews by the Sponsor Committee and selected Study Team members before Part 2 has started

It is worth noting that during this period, the SC will perform every 2 weeks an unblinded review of accruing HDV RNA and HBsAg data to assess the antiviral activity based on criteria defined in Section 3.3.3.

Due to the higher than expected rate of ALT elevations observed among several participants randomized in Part 1, even if the antiviral activity criteria are met, the Sponsor Committee will not initiate Part 2 yet, and continue to review the Part 1 data (see Section 3.3.2.1.1). The Sponsor Committee will make the decision to start Part 2 based on data from or after Part 1 IA1, jointly with the IDMC and unblinded Study team members, based on the preliminary evaluation of the benefit/risk ratio of the investigational treatment regimen.

For safety-related decisions and participant's safety management, selected unblinded data (e.g. HDV RNA and hepatitis B surface antigen [HBsAg]) and treatment assignment will be available to selected team members to instruct the sites to discontinue study treatment in patients receiving active treatment and meeting the additional discontinuation criteria defined in the Protocol Amendment #2.

Reviews by the IDMC after Part 2 has started (enrollment extended beyond the first approximately 20 participants)

- The first data review will be performed after approximately 12 weeks since the start of Part 2 (enrollment expanded to >20 participants).
- Data reviews will occur approximately every 8 weeks up until decision in Protocol Amendment #4 to stop the enrollment.
- Thereafter, data reviews will occur approximately quarterly.

It is worth noting that after the decision is made (either to start Part 2 or declare futility), the SC and selected study team members will not review any Part 2 data any longer, and will remain blinded to all Part 2 data (Section 1.5) for the rest of the study up to the end of the double-blind phase for each individual patient (see Section 5.2).Safety data comprising AEs, SAEs, AEs of special interest, laboratory data, and any other data applicable for the study, will be summarized, plotted and provided as appropriate.

HDV RNA, HBV DNA, HBsAg, and HBeAg values and changes from baseline will be summarized by intervention arm over time. Count and proportions of participants achieving given cutoffs in absolute values and/or reductions from baseline will be summarized descriptively.

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

Table 3: Overview of Times of Unblinding and Data Summaries and Analyses at Planned Data Review Milestones and IAs

	DR's Before Part 2 starts	**IA1 Part1**[(1)]	**IA2 Part1** [(2)]	**DR's After Part 2 has started and quarterly**		**Primary Analysis**	**Open Label IAs**
UNBLINDING							
IDMC	X	X	X	X	X	X	X
Sponsor Committee/DRC[(3)]	X	X	X			X	X
Study Team		X[(4)]	X[(4)]			X	X
DATA DOMAINS FOR ANALYSIS							
Subject Information							
Baseline & Demographic characteristics	X	X	X	X		X	X
Disposition and Study Populations	X	X	X	X	X	X	X
Extent of Exposure	X	X	X	X		X	X
Safety							
TEAEs, SAEs, AE of interest, fatal AEs, AEs causing treatment discontinuation	X	X	X	X		X	X
Laboratory Tests	X	X	X	X		X	X

	DR's Before Part 2 starts	IA1 Part1[(1)]	IA2 Part1 [(2)]	DR's After Part 2 has started and quarterly		Primary Analysis	Open Label IAs
ECG	X	X	X	X		X	X
Vital signs	X	X	X	X		X	X
Efficacy							
Primary efficacy endpoint	X		X	X	X	X	X
Key secondary efficacy endpoints			X	X		X	X
Values and changes over time in HDV RNA, HBV DNA, HBsAg and HBeAg	X	X	X	X		X	X
Proportion of participants with HDV RNA reduction ≥ 0.5 log_{10} IU/mL, ≥1 log_{10} IU/mL, ≥ 2 log_{10} IU/mL	X	X	X	X		X	X
Proportion of participants with HDV RNA <LLOQ and TND	X	X	X	X		X	X
Proportion of participants with HBsAg reduction ≥0.5 log_{10} IU/mL, ≥1 log_{10} IU/mL and ≥2 log_{10} IU/mL	X	X	X	X		X	X
Values and changes over time ALT	X	X	X	X		X	X
Proportion of participants with normal ALT	X	X	X	X		X	X
Virologic breakthrough HDV	X	X	X	X		X	X
Virologic breakthrough HBV	X	X	X	X		X	X
Flares: Viral, Biochemical, Clinical	X	X	X	X		X	X

(1) Part 1 IA1 will be performed when all participants will have completed at least Week 16 or discontinued earlier
(2) Part 1 IA2 will be performed when all participants will have completed at least Week 48 or discontinued earlier
(3) Prior to Part 1 IA1, the Sponsor Committee will review unblinded aggregated interim data of HDV RNA, HBsAg, ALT, AST, total and direct bilirubin, HBV DNA and individual patient profiles for the values/changes from baseline over time for all participants in Part 1 including those randomized to the placebo+NA arm. At time of Part 1 IA1, the Sponsor Committee will review all unblinded efficacy and safety results from Part 1 IA1.
(4) Operational Study team members involved with and at the sites will remain blinded together with investigators and participants.

3.3.2. Interim, Primary and Final Analyses

During the Double-Blind Treatment Phase:

Part 1 :

Part 1 IA1: One IA will be conducted after all participants of Part 1 have completed at least Week 16 (or discontinued earlier), to enable initiation of Part 2. At the time of this first IA in Part 1, members of the Study team [as described in Table 3, footnote 5)] will be unblinded to the Part 1 clinical data.

Part 1 IA2: This IA will be conducted by the Sponsor after all participants of Part 1 have completed at least Week 48 visit (or discontinued earlier) to continue a comprehensive assessment of the benefit-risk ratio of the investigational regimen in HDV-infected participants with longer term data

on participants in Part 1. All Sponsor personnel unblinded for Part 1 IA1 will also be unblinded for Part 1 IA2.

Part 2 :

During the Open-label follow-up phase:

One IA will be conducted after all participants have finished open-label phase or discontinued earlier to assess safety and evaluate the time course of different disease markers to support the sponsor's interactions with health authorities.

The primary analysis of this study will be performed when the last participant in the study has reached study visit Week 48 or has discontinued earlier.

The final analysis will be performed when all participants in the study (both parts if Part 2 of the study has started) have reached the final study visit FU Week 48 or have discontinued earlier.

3.3.2.1. IAs During the Double-Blind Treatment Phase

3.3.2.1.1. Part 1 IA1

This IA will be conducted by the Sponsor and will provide unblinded aggregated summaries and individual profiles for selected unblinded safety and virology activity parameters (including, but not limited to, HDV RNA and HBsAg data) after all participants in Part 1 have completed at least Week 16 or discontinued earlier. It will allow a more in-depth assessment of the benefit-risk ratio of the investigational regimen by the Sponsor and the IDMC to better characterize the observed ALT elevations and to decide whether or not Part 2 can be initiated. This decision may be also based on data available after the Part 1 IA1 cut-off. The Sponsor will be unblinded to the Part 1 clinical data although the investigators, participants, site personnel, and operational Sponsor team members involved with the sites will remain blinded. Following this IA, the Sponsor (as defined above, i.e excluding the operational team) will be unblinded to the rest of Part 1 data.

3.3.2.1.2. Part 1 IA2

After all participants in Part 1 have completed at least Week 48 (or discontinued earlier), a second IA of Part 1 data will be performed by the Sponsor to evaluate additional safety and efficacy data for the participants in Part 1 to monitor the benefit/risk ratio of the investigated regimen, regardless whether or not Part 2 has been initiated. While the Study Team, Sponsor Committee and IDMC will be unblinded to Part1 IA2, the investigators, participants, site personnel, and operational Sponsor team members involved with the sites will remain blinded. For safety-related decisions and participant's safety management, selected unblinded virology activity data (e.g. HDV RNA and hepatitis B surface antigen [HBsAg]) may be discussed with investigators on a case by case basis).

In case Part 2 has started prior to the timing of this IA of Part 1, there is no impact on keeping the blind of Part 2. All Sponsor personnel, including the Sponsor Committee, will remain blinded to

all Part 2 data, any subsequent IDMC data reviews concerning Part 2 until the end of the double-blind phase for each individual patient.

3.3.2.2. IA at the end of Open-label Phase

The IA at the end of the open-label phase of the study is planned when all participants have reached:

- Week 144 (Arm 1) and Week 148 (Arm 2), that is, end of treatment [EOT], or discontinued earlier.

Additional IAs may be performed by the sponsor in the open-label phase, given the long duration of the study and the uncertainty of the exact timing of future interactions with health authorities relative to the actual completion of enrollment and time of execution of the primary efficacy analysis.

3.3.3. Rule to Start Part 2 of the Study or Determine Futility

The SC will be unblinded to treatment allocation in the exploration of antiviral activity criteria in Part 1 based on aggregate interim data of HDV RNA and HBsAg, as well as individual HDV RNA and HBsAg profiles. This is to assess whether the initial and early evaluation of antiviral activity warrants the enrollment of participants beyond the subjects in Part 1.

Due to the higher than expected rate of ALT elevations observed during the double-blind treatment phase among several participants in Part 1, the Sponsor has amended the protocol to introduce Part 1 IAs to allow a better characterization of the acute ALT elevations. Hence, the SC decision to initiate Part 2 will not be made before the review of the results of Part 1 IA1, which will include unblinded safety and virology activity data.

However, as soon as Part 2 commences, the SC and Sponsor personnel will be blinded to all Part 2 data. Study site personnel, investigators and participants will have no access to any of the HDV RNA and HBsAg evaluations performed by the IDMC at any time during Part 2.

The SC will use the rule described below to decide whether antiviral activity can be declared, as well as to declare futility if Step 4 is reached. The decision outcome will depend on the timing when the rule is met or not, and after the evaluation of the results of Part 1 IA1.

Antiviral activity criteria to start Part 2

At least 8 participants in Arm 1 have:

a On-treatment HDV RNA reduction from baseline at any time $\geq 0.5 \log_{10}$ **and**

b On-treatment HBsAg reduction from baseline at any time $\geq 0.5 \log_{10}$ **and**

c ($\geq$ 4 participants have on-treatment HDV RNA reduction from baseline at any time $\geq 1 \log_{10}$) **or** ($\geq$4 participants have on-treatment HDV RNA continuous decline at least at the last 2 timepoints)

Step 1 – When the first 8 participants randomized to Arm 1 have at least 8 weeks of data assess the antiviral activity criteria a) **and** b) **and** c). If criteria a) **and** b) **and** c) are met, start Part 2. Otherwise, go to Step 2.

Step 2- If the criteria a) **and** b) **and** c) are not met at Step 1, repeat the review of HDV RNA and HBsAg incremental data available every 2 weeks and make a decision as described in Step 1. If Part 2 has not started by the time 16 participants in Arm 1 have reached Week 36, go to Step 3.

Step 3 – If criteria a) **and** b) **and** c) have not been met when all 16 participants randomized to active Arm 1 have at least 36 weeks of data, the decision to start Part 2 of the study will be based on the following more detailed rule:

- If 4 or fewer participants out of 16 meet the two criteria a) and b) described above, then Part 2 will not start
- If 5-7 out of 16 participants meet the 2 criteria a) and b) described above, then Part 2 might be started depending on a further review of the individual longitudinal profiles of HDV RNA and HBsAg of all participants. The totality of the HDV RNA and HBsAg data for the participants so far in the study will be taken into account to properly evaluate the magnitude of change and variability over time of the blood markers for each individual.

Step 4 – If Part 2 has not started based on data at Step 3, repeat the review of HDV RNA and HBsAg incremental data available every 2 weeks and make a decision following the rule described in Step 3. If the detailed rule described in Step 3 has not been met by the time when 16 participants randomized to active Arm 1 have at least 44 weeks of data, the study will be stopped for futility.

The antiviral activity criteria become the futility criteria if the antiviral activity is not observed by Week 44 in the 16 participants randomized to JNJ-3989+NA in Part 1. It is worth noting that if the treatment appears ineffective, the futility is declared to avoid that up to 20 participants will be treated for much longer than 1 year.

Since the data for Part 1 and Part 2 are analyzed separately there will be no penalty on the alpha level of one-sided 0.025, used in the efficacy comparisons as described in the rest of this document.

If Part 2 of the study begins, the SC will stop reviewing any Part 2 data and remain blinded to any Part 2 data for the rest of the study up to the time of the primary analysis (see Section 5.2). However, the IDMC will continue monitoring the efficacy data, as well as safety, for both the first 20 subjects randomized in Part 1 and the accruing participants in Part 2. The IDMC will start their review of the HDV and HBV markers 12 weeks after opening of Part 2. This is to ensure the well-being of all participants and avoid HDV RNA rebound/ or unexpected absence/insufficient efficacy trends in terms of HDV RNA/HBsAg declines after Part 2 has been opened and more data will be available. The primary efficacy endpoint will not be reviewed by the IDMC.

Details on the operating characteristics of the antiviral activity criteria to start Part 2 and futility rule are presented in 0.

4. SUBJECT INFORMATION

All the summaries will be done on the ITT analysis set unless specified otherwise. Subject information analyses will be reported by study Parts 1 and 2, as well as for the whole study overall.

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, and mITT sets, respectively, will be summarized by intervention arm. Summaries will be repeated also by DB, OL and FU study phase.

Completion/withdrawal information, study disposition and treatment disposition will be summarized for the ITT, mITT and safety sets (only for ITT and mITT sets 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/ open-label study intervention phase, 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 data reviews or IAs cutoff (except the final analysis) will be presented by treatment and intervention arm and phase. The incidences of treatment discontinuation reasons will also be summarized by study intervention arm for each treatment and overall and by phase.

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

4.2. Demographic and Baseline Characteristics

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

Additional summaries will be presented by the 3 randomization stratification factors (by presence of compensated cirrhosis at screening, and HDV RNA testing laboratory location, and HBeAg status at screening. 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. Baseline Characteristics

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

- Duration of HBV infection (Years) = (date of randomization – date of HBV infection +1)/365.25; rounded to 1 decimal
- Time since HBV diagnosis (Years) = (date of randomization – date of HBV diagnosis+1)/365.25; rounded to 1 decimal
- Mode of HBV infection: Sexual transmission, intravenously injectable drug use, blood transfusion, hemophilia-associated injection, occupational exposure, mother to child transmission, unknown and other.
- Duration of HDV infection (Years) = (date of randomization – date of HDV infection +1)/365.25; rounded to 1 decimal
- Time since HDV diagnosis (Years) = (date of randomization – date of HDV diagnosis+1)/365.25; rounded to 1 decimal
- Mode of HDV infection: co-infection, super-infection, Other, Unknown.
- Presence of compensated cirrhosis at screening: Yes, No
- Has never received HBV treatment (only for currently not treated participants): Yes, No
- Type of NA at baseline: TeD, TAF, ETV, None
- NA Treatment history at screening:
  - Yes
  - No
- Duration of NA at baseline (Years) = (Sum of all NA treatment duration [prior to randomization])/365.25; rounded to 1 decimal; calculated as: end date – start date +1. If for the latest NA treatment an end date is missing, randomization date is used.
- HDV RNA at baseline (quantitative: IU/mL and $\log_{10}$ IU/mL)
- HDV RNA category at baseline:
  - Participants with HDV RNA < LLOQ
    - Participants with HDV RNA < LLOQ TND
    - Participants with HDV RNA < LLOQ TD
  - Participants with HDV RNA < 500 IU /mL
  - Participants with HDV RNA ≥ 500 IU /mL
  - Participants with HDV RNA < 10000 IU/mL

- Participants with HDV RNA > 10000 IU/mL and <100000 IU/mL
- Participants with HDV RNA ≥ 100000 IU/mL

- Liver Stiffness Measurement (LSM) at baseline (quantitative)
- LSM category at baseline: 2 kPa - < 7.1 kPa, ≥ 7.1 kPa - < 9.5 kPa, ≥ 9.5 kPa - < 12.5 kPa, ≥ 12.5 kPa
- HBeAg status at screening: positive, negative
- HBeAg at baseline (quantitative): values in IU/mL and log_{10} IU/mL (for HBeAg positive participants only)
- HBsAg at baseline (quantitative): values in IU/mL and log_{10} IU/mL
- HBsAg category at baseline (quantitative: IU/mL):
  - Participants with HBsAg <500 IU/mL
  - Participants with HBsAg <1,000 IU/mL
  - Participants with HBsAg <10,000 IU/mL
  - Participants with HBsAg ≥10,000 IU/mL
- HBV DNA at baseline (quantitative): values in IU/mL and log_{10} IU/mL
- HBV DNA category at baseline (quantitative: IU/mL):
  - Participants with HBV DNA < LLOQ (20 IU/mL or 10 IU/mL for the new assay)
  - Participants with HBV DNA < 60 IU/mL
  - Participants with HBV DNA < 2,000 IU/mL
  - Participants with HBV DNA < 20,000 IU/mL
  - Participants with HBV DNA ≥ 20,000 IU/mL
- HBV RNA (quantitative): values in copies/mL and log_{10} copies/mL
- HBV RNA category at baseline (quantitative: copies/mL):
  - Participants with HBV RNA < LOD
  - Participants with HBV RNA < LLOQ
  - Participants with HBV RNA ≥ LLOQ
- Hepatitis B core related antigen (HBcrAg) at baseline (quantitative): values in log U/mL
- HBcrAg category at baseline (quantitative: log_{10} U/mL):
  - Participants with HBcrAg <3 log_{10} U/mL
  - Participants with HBcrAg≥3 log_{10} U/mL-<4 log_{10} U/mL
  - Participants with HBcrAg≥4 log_{10} U/mL
- HBsAg Antibody (Anti-HBs) category at baseline (quantitative: mIU/mL):
  - Participants with Anti-HBs<10 mIU/mL

  - Participants with Anti-HBs≥10 mIU/mL
- HBeAg Antibody (Anti-HBe) status at baseline (qualitative): Positive, Negative, Borderline
- Anti-HDV status at baseline: Positive, Negative
- Alanine aminotransferase (ALT) at baseline:
  - Baseline ALT values (U/L)
  - Baseline ALT toxicity grade according to DAIDS
  - Baseline ALT categorization (≤ 1.0xULN, > 1.0xULN to <2.5xULN, ≥ 2.5xULN)
- Stage of liver fibrosis: F0, F1, F3 or F4
- HBV genotype (using the INNO-LiPA or sequence based HBV genotying data): Genotype A, B, C, D, E, F, G, H, I, J and Unknown

4.2.2. Demographic Characteristics

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

- Sex: Male, Female
- Age (years)
- Age categories: 18 years - ≤ 30 years, > 30 years -≤ 45 years, > 45 years-≤ 60 years, > 60 years
- Race: American Indian or Alaska Native, Asian (Japanese, Other Asian), Black or African American, Native Hawaiian or Other Pacific Islander, White, Not reported, 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
- Region: Asia (China, Japan, and Other Asian Country), Europe, North America, South America
- Height at baseline (cm)
- Weight at baseline (kg)
- Body mass index (BMI) at baseline (kg/m^2) = weight at baseline (kg) / (height at baseline $(m))^2$ (rounded to 1 decimal)
- Body mass index group: Underweight <18.5, Normal ≥18.5-<25, Overweight ≥25-<30 and Obese ≥30
- History of Tobacco use: Yes/No
- 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

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 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 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.

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 will be summarized by analysis phase. A listing of prior medications and concomitant medications respectively, will be also provided.

4.5. Protocol Deviations

Major protocol deviations will be based on clinical review, but not limited to, the following criteria: (1) entered but did not satisfy inclusion/exclusion criteria, (2) received wrong treatment or incorrect dose, (3) received a disallowed concomitant treatment, (4) 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.

In addition, the use of the mITT analysis set in the efficacy analyses will be determined based on the impact of the COVID-19 or similar pandemics prior to database lock for the first IA (i.e. IA during the DB intervention phase for sample size re-estimation). The number and percentage of participants in ITT vs mITT will be summarized by intervention arm.

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 and OL study intervention phases will

be calculated by each study treatment (JNJ-3989/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 for participants with presence of compensated cirrhosis at screening by intervention arm.

Because of the different route and frequency of treatment administration across the 2 study treatments (for JNJ-3989/placebo one subcutaneous injection once every 4 weeks, and for NA once daily tablet), the total duration of exposure (weeks) will be calculated by analysis phase for each agent as follows:

- For the DB study intervention phase:
    - JNJ-3989/placebo: [Min ((Date of last injection in the DB intervention phase +27 days), Early study withdrawal visit date, cut-off date) – date of first injection in the DB phase + 1] / 7
    - NA: [Min (Date of the last NA administration in the DB phase, Date of discontinuation from NA, Early study withdrawal visit date, cut-off date) - first drug administration date in the DB phase + 1] / 7
- For the OL study intervention phase (only for participants with non-missing OL phase start date, as defined in Section 2.1.1):
    - JNJ-3989: [Min ((Date of last injection in the OL phase +27 days), Early study withdrawal visit date, cut-off date) – Week 52 study agent intake date + 1] / 7
    - NA: [Min (Date of the last NA administration in the OL phase, Date of discontinuation from NA, Early study withdrawal visit date, cut-off date) - Week 52 NA intake date + 1] / 7

Cutoff dates will be defined to match the prespecified timepoints for IDMC periodical data reviews, interim analyses and the primary and final analyses, respectively (see Section 3.3).

The number and percentage of participants who skipped any dose of JNJ-3989/placebo or NA will be summarized separately for each study treatment by intervention arm during the DB and OL study intervention phases, separately. Additionally, the number and percentage of participants who missed 2 or more consecutive JNJ-3989/placebo injections, or who missed more than 5 doses of NA within a four-week period will be presented.

For NA treatment, the total duration of exposure will be calculated separately for the DB, OL and FU study phases.

- For the FU study phase:
    - NA: [Min (Date of the last NA administration in the FU study phase, Date of discontinuation from NA, Date of trial disposition, Date of clinical cut-off) - first drug administration date in the FU phase + 1] / 7

Those participants who stopped NA treatment at Week 144/Week 148 and never restarted NA treatment thereafter will be counted as having zero weeks of NA exposure during the FU study phase.

4.7. Treatment Compliance

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

DB Treatment compliance (%) is defined as follows.

For JNJ-3989/placebo: (Total number of injections received/ 13) * 100%

OL Treatment compliance (%) is defined as follows.

For JNJ-3989 in Arm 1: (Total number of injections received/ 23) * 100%

For JNJ-3989 in Arm 2: (Total number of injections received/ 24) * 100%

5. EFFICACY

The primary analysis set will be the ITT analysis set (see definition in Section 2.3), unless specified otherwise. Efficacy assessments over time will be performed at the analysis time points defined in Section 2.1.3. However, the use of the mITT analysis set (instead of ITT) in the efficacy analyses will be determined based on the impact of the COVID-19 or similar pandemics and assessed prior to the database lock for the first IA during DB study intervention phase.

All efficacy data will be summarized by study Parts 1 and 2, as well as for the whole study data overall:

- For DB study intervention phase: by study intervention arm over time (when applicable), as well as by study part (1 and 2).

- For OL study intervention and Follow-up phases: by study intervention arm over time and by study part 1 and 2. Additional selected efficacy analyses will be conducted to compare the OL study intervention data from Week 52 to Week 148 in Arm 2 with data from the first 96 weeks of DB study intervention in Arm 1 (i.e same duration of exposure toJNJ-3989+NA in both arms). See Section 5.5.1.4 for more details.

Subgroup analyses will be conducted on Part 2 data alone as well as combined data (Part 1 and Part 2) to leverage the total sample size of the entire study. Subgroup analyses will be performed if their size is at least 10% of the total sample size. All analyses will be presented only in a descriptive fashion.

For OL intervention and FU study phases, all efficacy data will be presented only descriptively, and no formal testing will be performed.

5.1. Analysis Specifications

In general, continuous variables will be summarized using descriptive statistics including the number of participants, mean, standard deviation (SD), two-sided 95% 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 presence of compensated cirrhosis at screening (yes or no) (Part 1 only), HDV RNA testing laboratory location (China versus outside China), and HBeAg status at screening (positive vs negative). Graphic displays will also be used to summarize the data.

5.1.1. Virology Data Handling Rules

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

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

HDV parameter	**LLOQ**	**ULOQ**	**Imputed Values** **If value< LLOQ**	**If value> ULOQ**
HDV RNA	**For outside of China :** LLOQ = 63 IU/mL LOD = 14 IU/mL	NA	**For outside of China :** **Main imputation:** If <LLOQ 31.5 IU/mL **Exploratory Imputation:** If LLOQ TD: 31.5 IU/ml If LLOQ TND: 15.75 IU/ml[(a)]	NA
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)]	137,417.5 IU/mL[(b)(c)] w/o dilution 274,725.00 IU/mL [(c)] 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) (c)] w/o dilution 7,700.00 IU/mL [(c)] 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 For Roche CAP/CTM Assay 10IU/mL for Roche COBAS 6800 assay	170,000,000 IU/mL w/o dilution	If < LLOQ: 5 IU/mL	187,000,000[(b)(c)] w/o dilution
HBV RNA	LLOQ = 2.939 $\log_{10}$ cp/mL (i.e 869 cp/mL) LOD = 1.398 $\log_{10}$ cp/mL (i.e 25 cp/mL)	NA	If < LOD or target not detected then 1.114 $\log_{10}$ cp/mL (13 cp/mL)	NA
Anti-HBs	5mIU/mL	10000.0 mIU/mL	2.5 mIU/mL[(a)]	11000.0 mIU/mL [(b)]

Key: NA=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 and Final Analyses

The primary analysis of this study will be performed when the last participant in the study has reached study visit Week 48 or has discontinued earlier.

The final analysis will be performed when all participants in the study (both parts if Part 2 of the study has started) have reached the final study visit FU Week 48 or have discontinued earlier.

5.3. Primary Efficacy Endpoint

5.3.1. Definition

The primary efficacy endpoint is defined as the proportion of participants with normal ALT (defined as ALT < ULN with ULN = 34 U/L for female and 43 U/L for male) in combination with HDV RNA ≥ 2 $\log_{10}$ IU/mL decline from baseline and/or HDV RNA TND at Week 48.

5.3.2. Main Estimand for the Primary Endpoint

Primary Study Objective: To evaluate the efficacy of JNJ-3989 + NA regimen versus Placebo + NA in reducing HDV replication and associated liver inflammation.

Scientific question: in the adult non-cirrhotic population co-infected with HBV and HDV, what is the benefit of JNJ-3989 (100mg Q4W) in combination with NA compared with Placebo + NA for 48 weeks in reducing HDV replication measured by HDV RNA and liver inflammation measured by ALT?

The main estimand for the primary endpoint is characterized by the following attributes:

A) Study Intervention:

- Arm 1: JNJ-3989 + NA
- Arm 2: Placebo + NA

B) Study population: Non-cirrhotic patients 18 to 65 years of age, inclusive, with HBV/HDV co-infection

C) Variable: Response status defined as having HDV RNA decline ≥ 2 $\log_{10}$ IU/mL from baseline or HDV RNA TND in combination with normal ALT at Week 48

D) Intercurrent events (ICEs):

- Treatment discontinuation prior to Week 48: if the participant discontinued treatment prior to Week 48 then the participant will be considered as non-responder (composite strategy).
- Selected major protocol deviations affecting efficacy: 0 identifies deviations considered ICE. Participants with such deviations and who have missing ALT and/or HDV RNA data for the primary endpoint at Week 48 will be considered as non-responders (composite strategy).
- Deaths prior to Week 48 are handled in a composite strategy as participants who die prior to Week 48 will be considered as non-responders.

E) Population level summary: Difference in proportion of responders defined by the primary endpoint between the two intervention arms (Arm 1 – Arm 2).

5.3.2.1. Main Estimator of the Main Estimand for the Primary Endpoint

5.3.2.1.1. Analysis Methods

Statistical Model

The proportion of responders will be compared between the 2 arms using the stratum-adjusted Mantel-Haenszel (MH) test on the difference of proportions, with the following stratification factors: HDV RNA testing laboratory location (China versus outside China) and HBeAg status at screening (positive vs negative).

5.3.2.1.2. Data Included

All available data from randomized participants that have received at least one dose are included (ITT analysis set in Part 2), after taking into account all the ICEs and applying the ICE strategies in Section 5.3.2.

5.3.2.1.3. Assumptions

- Missing Data for HDV RNA and ALT are Missing At Random (MAR)
- The treatment effect is homogeneous across strata

5.3.2.1.4. Missing Data Handling Rule

- Participants who withdraw from the study prior to Week 48 will be considered as non-responders.
- For participants who remain in the study at Week 48 after experiencing a major protocol deviation defined for the purpose of efficacy analyses, which is an ICE, and have missing HDV RNA and/or ALT values at Week 48, then the imputation to non-response will be applied. If the value for the primary endpoint at Week 48 is available, then such data will be used to determine their response status.
- For participants who remain the study at Week 48 and have had no major protocol deviations defined as ICE and have the values of HDV RNA and ALT available, such data will be used to determine their response status.
- For participants who remain in the study at Week 48 and who have not experienced any major protocol deviations defined for the purpose of efficacy analyses as ICE, and has missing HDV RNA and/or ALT values missing at Week 48, then the primary method to handle missing data will be the Multiple Imputation (MI) approach[3] under the assumption of MAR, applied in a joint fashion to leverage the correlation between HDV RNA and ALT values over time.

The multiple imputation (MI) model will use all available data and be applied to the continuous HDV RNA and ALT 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 3 randomization factors, the available non-missing log-transformed HDV RNA data (values < LLOQ, < LOD TND or < LOD TD will be first substituted following the main rules described in Table 4, ALT values for each scheduled time point (Week) and the following demographic and baseline characteristics[4,6]: age, gender, and baseline value for HDV RNA level, ALT level, HBsAg level, and HBV DNA level.

Depending on the amount of missing data, the number of imputed datasets to be generated will be 10 and will be adjusted appropriately to ensure robustness in the results [5].

5.3.2.2. Sensitivity Estimators of the Main Estimand for the Primary Endpoint

Sensitivity analyses will be conducted by constructing a different sensitivity estimator for the primary estimand as defined in Section 5.3.2. The estimator will use Missing as Non-Responsedata imputation rule.

5.3.2.2.1. Sensitivity Estimator of the Main Estimand (Missing as Non-Response) for the Primary Endpoint

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

5.3.2.2.1.1. Assumptions

- Missing Data for HDV RNA and ALT are Missing Not At Random (MNAR)
- The treatment effect is homogeneous across strata

5.3.2.2.1.2. Missing Data Handling Rule

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

5.3.2.3. Supplementary Estimators of the Main Estimand for the Primary Endpoint

Supplementary analysis to better interpret the primary analysis results will be conducted by constructing additional estimator for the main estimand of the primary endpoint as defined in Section 5.3.2. This estimator will be based on the mITT set (instead of ITT) for participants in Part 2. To provide a comprehensive interpretation of the study results and the impact of COVID-19 pandemic, the following supplementary estimator will utilize the mITT analysis set for participants in Part 2. The supplementary estimator analysis will only be performed if there is a difference of more than 5% from ITT to mITT.

5.3.2.3.1. Supplementary Estimator (mITT + Missing as Non-Response) of the Main Estimand for the Primary Endpoint

For this supplementary estimator, the same estimand defined in Section 5.3.2, statistical model (stratum-adjusted MH test) and assumptions will be used as for the main estimator (Section 5.3.2.1).

5.3.2.3.2. Data Included

All available data from mITT analysis set in Part 2, after taking into account all the ICEs and applying the ICE strategies specified in the previous Section 5.3.2, will be included.

5.3.2.3.3. Assumptions

- Missing Data for HDV RNA and ALT are Missing Not At Random (MNAR)
- The treatment effect is homogeneous across strata

5.3.2.3.4. Missing Data Handling Rule

The missing data approach will follow the missing as non-response approach as described in Section 5.3.2.2.1.2.

5.3.3. Subgroup analyses

Subgroup analyses will be performed on the primary endpoint by the subgroups defined in Section 2.4.1. Subgroup analyses, as exploratory, will be conducted on Part 2 data alone as well as combined data (Part 1 and Part 2) to leverage the total sample size of the entire study. They will only be performed if their size is more than 10% of the total sample size.

The potential association between the primary efficacy endpoint and the selected demographic and baseline characteristics (in Section 2.4.1) will be explored using a logistic regression model which will be estimated for each subgroup variable, one at a time. The factors in each model will be treatment arm, the randomization stratification factors, the subgroup variable, and the treatment-by-stage and treatment-by-subgroup variable as the interaction-terms. The Firth's penalized likelihood method9,10 (as implemented in SAS PROC LOGISTIC) will be used in the logistic regression to reduce possible bias which could arise in the presence of a zero-response rate in one or more subgroup levels and/or intervention arms.

Corresponding 95% CIs will be also calculated. A forest plot will present graphically the endpoint estimates resulting from the models described above, by treatment arm and the prespecified subgroup levels, with the corresponding 95% CIs.

5.4. Key Secondary Endpoints (KSE)

All key secondary endpoints will be summarized individually by intervention arm, stage and study parts (Parts 1 and 2, as well as for the whole study data overall). The statistical analysis will follow the estimand and estimators framework as described in the following sections. Testing will be performed by providing adjusted p-values as per Section **Error! Reference source not found.**.

5.4.1. KSE1: HDV RNA Decline from Baseline ≥2 log_{10} IU/mL or HDV RNA TND at Week 48

5.4.1.1. Definition

The first key secondary efficacy endpoint (KSE 1) is defined as the proportion of participants with HDV RNA decline ≥ 2 log_{10} IU/mL from baseline or HDV RNA TND at Week 48.

5.4.1.2. Main Estimand for the KSE1

Study Objective: To evaluate the efficacy of JNJ-3989 + NA regimen versus Placebo + NA in reducing HDV replication.

Scientific question: in the adult population co-infected with HBV and HDV, what is the benefit of JNJ-3989 (100mg Q4W) in combination with NA compared with Placebo + NA for 48 weeks in reducing HDV replication?

The main analysis of this endpoint will be addressed by using the following estimand attributes:

A) Study Intervention:

- Arm 1: JNJ-3989+NA
- Arm 2: NA alone

B) Study population: Non-cirrhotic patients 18 to 65 years of age, inclusive, with HBV/HDV co-infection.

C) Variable: Response status defined as having HDV RNA decline ≥ 2 log_{10} IU/mL from baseline or HDV RNA TND at Week 48

D) Intercurrent events:

- Treatment discontinuation prior to Week 48: if the participant discontinued treatment prior to Week 48 then the participant will be considered as non-responder (composite strategy).
- Selected major protocol deviations affecting efficacy: 0 identifies deviations considered as ICEs. Participants with such deviations and who have missing data for HDV RNA at Week 48 will be considered as non-responders (composite strategy).
- Deaths prior to Week 48 are handled in a composite strategy as participants who die prior to Week 48 will be considered as non-responders.

E) Population level summary: Difference in proportion of responders defined by KSE 1 between the two intervention arms.

5.4.1.2.1. Main Estimator of the Main Estimand for the KSE1

5.4.1.2.1.1. Analysis Methods

Statistical Model

The same stratum-adjusted MH test on the difference of proportions as described for the main estimator of the main estimand for the primary endpoint will be used (see Section 5.3.2.1).

5.4.1.2.1.2. Data Included

All available data from ITT analysis set in Part 2, after taking into account all the ICEs and applying the ICE strategies specified in the previous Section 5.4.1.2, will be included.

5.4.1.2.1.3. Assumptions

- Missing Data for HDV RNA are Missing At Random (MAR)
- The treatment effect is homogeneous across strata

5.4.1.2.1.4. Missing Data Handling Rule

- Participants who withdraw from the study prior to Week 48 will be considered as non-responders.
- For participants who remain in the study at Week 48 after experiencing a major protocol deviation defined for the purpose of efficacy analyses, which is an ICE, and have missing HDV RNA at Week 48, then the imputation to non-response will be applied. If the value for the primary endpoint at Week 48 is available, then such data will be used to determine their response status.
- For participants who remain the study at Week 48 and have had no major protocol deviations defined as ICE and have the values of HDV RNA available, such data will be used to determine their response status.
- For the participants who remain in the study at Week 48 and who have not experienced any major protocol deviations defined for the purpose of efficacy analyses as ICE, and has missing HDV RNA values missing at Week 48, then missing data will be imputed by the values obtained from the MI model performed for the main estimator of the primary efficacy endpoint to leverage the correlations between HDV RNA and ALT values (see Section 5.3.2.1.4). Once the HDV RNA values at Week 48 are obtained, the binary key secondary endpoint will be derived and analyzed as described in Section 5.3.2.1.

5.4.1.2.2. Sensitivity Estimators of the Main Estimand for the KSE1

Sensitivity analyses will be conducted by constructing a sensitivity estimator for the main estimand of KSE1 as defined in Section 5.4.1.2. This sensitivity estimator will be similar to the one defined for the main estimand of the primary endpoint, i.e it will use Missing as Non-Response data imputation rule.

5.4.1.2.2.1. Sensitivity Estimator of the Main Estimand (Missing as Non-Response) for the KSE1

For this sensitivity estimator, the same statistical model (stratum-adjusted MH test) and data included will be used as for the main estimator (Section 5.4.1.2.1). The assumption for missing data and the rule to handle missing data have changed.

5.4.1.2.2.1.1. Assumptions

- Missing Data for HDV RNA are Missing Not At Random (MNAR)
- The treatment effect is homogeneous across strata

5.4.1.2.2.1.2. Missing Data Handling Rule

Participants who withdraw from the study prior to Week 48 will be considered as non-responders. All participants with missing HDV RNA data for the determination of the KSE1 will be imputed as non-responders.

5.4.1.2.3. Supplementary Estimators of the Main Estimand for the KSE1

Supplementary analyses to better interpret the results will be conducted by constructing additional estimator for the main estimand of the KSE1 as defined in Section 5.4.1.2. This supplementary estimators will be similar to the sensitivity estimator of the main estimand (Section 5.4.1.2.2) but based on the mITT set (instead of ITT) for participants in Part 2: mITT + Missing as Non-Response (Supplementary Estimator). The supplementary estimator analysis will only be performed if there is a difference of more than 5% from ITT to mITT.

5.4.2. KSE2: Normal ALT at Week 48

5.4.2.1. Definition

The second key secondary efficacy endpoint is defined as the proportion of participants with normal ALT at Week 48.

5.4.2.2. Main Estimand for the KSE2

Study Objective: To evaluate the efficacy of JNJ-3989 + NA regimen versus Placebo + NA in reducing liver inflammation.

Scientific question: in the adult population co-infected with HBV and HDV, what is the benefit of JNJ-3989 (100mg Q4W) in combination with NA for 48 weeks in reducing liver inflammation?

The main analysis of this endpoint will be addressed by using the following estimand attributes:

A) Study Intervention:

- Arm 1: JNJ-3989+NA
- Arm 2: NA alone

B) Study population: Non-cirrhotic patients 18 to 65 years of age, inclusive, with HBV/HDV co-infection.

C) Variable: Response status defined as having normal ALT at Week 48

D) Intercurrent events:

- Treatment discontinuation prior to Week 48 if the participant discontinued treatment prior to Week 48 then the participant will be considered as non-responder (composite strategy).
- Selected major protocol deviations affecting efficacy: 0 identifies deviations considered as ICEs. Participants with such deviations and who have missing data for ALT at Week 48 will be considered as non-responders (composite strategy).
- Deaths prior to Week 48 are handled in a composite strategy as participants who die prior to Week 48 will be considered as non-responders.

E) Population level summary: Difference in proportion of responders defined by KSE2 between the two intervention arms.

5.4.2.2.1. Main Estimator of the Main Estimand for the KSE2

5.4.2.2.1.1. Analysis Methods

Statistical Model

The same stratum-adjusted MH test on the difference of proportions as described for the main estimator of the main estimand for the primary endpoint will be used (see Section 5.3.2.1).

5.4.2.2.1.2. Data Included

All available data from ITT analysis set in Part 2, after taking into account all the ICEs and applying the ICE strategies specified in the previous Section 5.4.2.2, will be included.

5.4.2.2.1.3. Assumptions

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

5.4.2.2.1.4. Missing Data Handling Rule

- Participants who withdraw from the study prior to Week 48 will be considered as non-responders.
- For participants who remain in the study at Week 48 after experiencing a major protocol deviation defined for the purpose of efficacy analyses, which is an ICE, and have missing ALT at Week 48, then the imputation to non-response will be applied. If the ALT value for the KSE2 at Week 48 is available, then such data will be used to determine their response status.

- For participants who remain the study at Week 48, have had no major protocol deviations defined as ICE and have the values of ALT available, such data will be used to determine their response status.
- For the participants who remain in the study at Week 48 and who have not experienced any major protocol deviations defined for the purpose of efficacy analyses as ICE, and has missing ALT values missing at Week 48, then missing data will be imputed by the values obtained from the MI model performed for the main estimator of the primary efficacy endpoint to leverage the correlations between HDV RNA and ALT values (see Section 5.3.2.1.4). Once the ALT values at Week 48 are obtained, the binary key secondary endpoint will be derived and analyzed as described in Section 5.3.2.1.

5.4.2.2.2. Sensitivity Estimators of the Main Estimand for the KSE2

Sensitivity analyses will be conducted by constructing a sensitivity estimator for the main estimand of KSE2 as defined in Section 5.4.2.2. This sensitivity estimator will be similar to the one defined for the main estimand of the primary endpoint, i.e it will use different Missing as Non-Response data imputation .

5.4.2.2.2.1. Sensitivity Estimatorof the Main Estimand (Missing as Non-Response) for the KSE2

For this sensitivity estimator, the same statistical model (stratum-adjusted MH test) and data included will be used as for the main estimator (Section 5.4.2.2.1). The assumption for missing data and the rule to handle missing data have changed.

5.4.2.2.2.1.1. Assumptions

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

5.4.2.2.2.1.2. Missing Data Handling Rule

Participants who withdraw from the study prior to Week48 will be considered as non-responders. All participants with missing ALT data for the determination of the KSE2 will be imputed as non-responders.

5.4.2.2.3. Supplementary Estimators of the Main Estimand for the KSE2

Supplementary analysis to better interpret the results will be conducted by constructing additional estimator for the main estimand of the KSE2 as defined in Section 5.4.2.2. This supplementary estimator will be similar to the sensitivity estimator of the main estimand (5.4.2.2.2) but based on the mITT set (instead of ITT) for participants in Part 2 : mITT + Missing as Non-Response (Supplementary Estimator). The supplementary estimator analysis will only be performed if there is a difference of more than 5% from ITT to mITT.

5.4.2.2.4. Main Estimator of the Supplementary Estimand for the KSE2

5.4.2.2.4.1. Analysis Methods

Statistical Model
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 5.4.1.2.1).

5.4.2.2.4.2. Data Included

All available data from randomized participants in Part 2 that are included in the mITT analysis set will be used, after taking into account the ICEs and applying the ICE strategies specified in Section 5.4.2.2.

5.4.2.2.4.3. Assumptions

- The treatment effect is homogeneous across strata

5.4.2.2.4.4. Missing Data Handling Rule

Participants who withdraw from the study prior to Week 48 will be considered non-responders. For the participants who remain in the study at Week 48 and who have not experienced an ICE as listed in 0, but with ALT values missing at Week 48, then the method to handle missing data will be the imputation to non-responder.

5.4.3. KSE3: HBsAg Seroclearance at Week 48

5.4.3.1. Definition

The third key secondary efficacy endpoint is defined as the proportion of participants with HBsAg seroclearance i.e. with HBsAg (quantitative) < LLOQ (see Table 4) at Week 48.

5.4.3.2. Main Estimand for the KSE3

Study Objective: To evaluate the efficacy of JNJ-3989 + NA regimen versus Placebo + NA in reducing HBsAg levels.

Scientific question: in the adult population co-infected with HBV and HDV, what is the benefit of JNJ-3989 (100mg Q4W) in combination with NA compared with Placebo + NA for 48 weeks in reducing HBsAg levels?

The main analysis of this endpoint will be addressed by using the following estimand attributes:

A) Study Intervention:

- Arm 1: JNJ-3989+NA
- Arm 2: NA alone

B) Study population: Non-cirrhotic patients 18 to 65 years of age, inclusive, with HBV/HDV co-infection.

C) Variable: HBsAg level at Week 48

D) Intercurrent events:

- Treatment discontinuation prior to Week 48: if the participant discontinued treatment prior to Week 48 then the participant will be considered as non-responder (composite strategy).
- Selected major protocol deviations affecting efficacy: 0 identifies deviations considered as ICEs. Participants with such deviations and who have missing data for HBsAg at Week 48 will be considered as non-responders (composite strategy).
- Deaths prior to Week 48 are handled in a composite strategy as participants who die prior to Week 48 will be considered as non-responders.

E) Population level summary: Difference in proportion of participants with HBsAg seroclearance at Week 48 between the two intervention arms.

5.4.3.2.1. Main Estimator of the Main Estimand for the KSE3

5.4.3.2.1.1. Analysis Methods

Statistical Model

The same stratum-adjusted MH test on the difference of proportions as described for the main estimator of the main estimand for the primary endpoint will be used (see Section 5.3.2.1).

5.4.3.2.1.2. Data Included

All available data from ITT analysis set in Part 2, after taking into account all the ICEs and applying the ICE strategies specified in the previous Section 5.4.3.2, will be included.

5.4.3.2.1.3. Assumptions

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

5.4.3.2.1.4. Missing Data Handling Rule

- Participants who withdraw from the study prior to Week 48 will be considered as non-responders.
- For participants who remain in the study at Week 48 after experiencing a major protocol deviation defined for the purpose of efficacy analyses, which is an ICE, and have missing HBsAg at Week 48, then the imputation to non-response will be applied. If the HBsAg value for the KSE4 at Week 48 is available, then such data will be used to determine their response status.
- For participants who remain the study at Week 48, have had no major protocol deviations defined as ICE and have the values of HBsAg available, such data will be used to determine their response status.

- For the participants who remain in the study at Week 48 and who have not experienced any major protocol deviations defined for the purpose of efficacy analyses as ICE, and have missing HBsAg values missing at Week 48, missing data will be imputed using a MI model.

The MI model will use all available data and be applied to the continuous 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 MI model will include treatment, the 3 randomization factors, the available non-missing log-transformed HBsAg (values < LLOQ will be first substituted following rules described in Table 4) for each scheduled time point (Week) and the following demographic and baseline characteristics4,6: age, gender, and baseline value for HDV RNA level, ALT level, HBsAg level, and HBV DNA level.

The details on the implementation of this MI model will follow the same steps as described in Section 5.3.2.1.4.

5.4.4. KSE4 : Reduction in LSM From baseline to Week 48

5.4.4.1. Definition

The fourth key secondary efficacy endpoint is defined as the proportion of participants with LSM reduction ≥2kPa from baseline to Week 48 as assessed by vibration-controlled transient elastography (VCTE) (FibroScan).

5.4.4.2. Main Estimand for the KSE4

Study Objective: To evaluate the efficacy of JNJ-3989 + NA regimen versus Placebo + NA in reducing liver fibrosis.

Scientific question: in the adult population co-infected with HBV and HDV, what is the benefit of JNJ-3989 (100mg Q4W) in combination with NA compared with Placebo + NA for 48 weeks in reducing liver fibrosis determined using LSM?

The main analysis of this endpoint will be addressed by using the following estimand attributes:

A) Study Intervention:

- Arm 1: JNJ-3989+NA
- Arm 2: NA alone

B) Study population: Non-cirrhotic patients 18 to 65 years of age, inclusive, with HBV/HDV co-infection

C) Variable: Response status defined as having reduction in LSM from baseline ≥ 2 kPa at Week 48 as assessed by VCTE (Fibroscan)

D) Intercurrent events:

- Treatment discontinuation prior to Week 48: if the participant discontinued treatment prior to Week 48 then the participant will be considered as non-responder (composite strategy).
- Selected major protocol deviations affecting efficacy: 0 identifies deviations considered as ICEs. Participants with such deviations and who have missing data for LSM at Week 48 will be considered as non-responders (composite strategy).
- Deaths prior to Week 48 are handled in a composite strategy as participants who die prior to Week 48 will be considered as non-responders.

E) Population level summary: Difference in proportion of responders defined by KSE3 between the two intervention arms.

5.4.4.2.1. Main Estimator of the Main Estimand for the KSE4

5.4.4.2.1.1. Analysis Methods

Statistical Model

The same stratum-adjusted MH test on the difference of proportions as described for the main estimator of the main estimand for the primary endpoint will be used (see Section 5.3.2.1).

5.4.4.2.1.2. Data Included

All available data from ITT analysis set in Part 2, after taking into account all the ICEs and applying the ICE strategies specified in the previous Section 5.4.4.2, will be included.

5.4.4.2.1.3. Assumptions

- Missing Data for LSM are Missing At Random (MAR)[12]
- The treatment effect is homogeneous across strata.

5.4.4.2.1.4. Missing Data Handling Rule

- Participants who withdraw from the study prior to Week 48 will be considered as non-responders.
- For participants who remain in the study at Week 48 after experiencing a major protocol deviation defined for the purpose of efficacy analyses, which is an ICE, and have missing LSM at Week 48, then the imputation to non-response will be applied. If the LSM value for the KSE3 at Week 48 is available, then such data will be used to determine their response status.
- For participants who remain the study at Week 48 and have had no major protocol deviations defined as ICE and have the values of LSM available, such data will be used to determine their response status.
- For the participants who remain in the study at Week 48 and who have not experienced any major protocol deviations defined for the purpose of efficacy analyses as ICE, and has missing LSM values at Week 48, then they will be considered as non-responder (composite strategy).

5.4.5. Subgroup analyses

Subgroup analyses will be performed on the key secondary endpoints by the subgroup variables listed in Section 2.4.1. The same analysis as defined in Section 5.3.3 will be performed.

5.5. Other Secondary Endpoints

Other secondary endpoints will be summarized descriptively by intervention arm, by study phase (unless specified otherwise), timepoint and study part. No imputation rule will be used in case of missing data and the analysis will be based on observed cases. Statistical analyses of selected other secondary endpoints will be done with no adjustment for multiplicity.

The following on and off-treatment periods will be used for all secondary efficacy endpoints:

- For all HBV endpoints:
    - **On-treatment** will be defined as the time periods in which the participant receives any of the study interventions (JNJ-3989/placebo and/or NA).
    - **Off-treatment** will be defined as the periods when the participants do not receive any of the study interventions (JNJ-3989/placebo and NA).
- For all HDV endpoints:
    - **JNJ-3989 on-treatment** will be defined as the time period in which the participant receives JNJ-3989/placebo (regardless of continuing NA treatment).
    - **JNJ-3989 off-treatment** will be defined as the time period in which the participant is not receiving JNJ-3989 (regardless of continuing NA treatment).

The following on and off-treatment nadirs will be used for all secondary efficacy endpoints:

- **On-treatment nadir** will be defined as the lowest value during the on-treatment period up to the time of assessment.
- **JNJ-3989 on-treatment nadir** will be defined as the lowest value during the JNJ-3989 on-treatment period up to the time of assessment.
- **Off-treatment nadir** will be defined as the lowest value during the off-treatment period up to the time of assessment.
- **JNJ-3989 off-treatment nadir** will be defined as the lowest value during the JNJ-3989 off-treatment period up to the time of assessment.
- **Overall nadir** will be defined as the lowest value collected during the study up to the time of assessment.

A confirmed criteria means that the criteria should be fulfilled at 2 or more consecutive time points or at the last observed time point.

5.5.1. Definition

5.5.1.1. Binary Endpoints

The number and proportion of participants experiencing the endpoints defined in the following subsections will be calculated and summarized as specified in Section 5.5.2.1.

5.5.1.1.1. HDV RNA Decline and Normal ALT

The following individual and combined endpoints related to HDV RNA decline and normal ALT will be evaluated over time during the study intervention and follow-up phases:

- HDV RNA ≥ 2 $\log_{10}$ IU/mL decline from baseline or TND in combination with normal ALT.
- HDV RNA ≥ 2 $\log_{10}$ IU/mL decline from baseline or HDV RNA TND.
- HDV RNA ≥ 2 $\log_{10}$ IU/mL decline from baseline in combination with normal ALT.
- HDV RNA ≥ 2 $\log_{10}$ IU/mL decline from baseline or < LLOQ in combination with normal ALT.
- HDV RNA ≥ 2 $\log_{10}$ IU/mL decline from baseline or < LLOQ
- HDV RNA TND in combination with normal ALT.
- HDV RNA < LLOQ in combination with normal ALT.
- HDV RNA ≥ 2 $\log_{10}$ IU/mL decline from baseline.
- HDV RNA TND.
- HDV RNA < LLOQ
- ALT categorization ($\leq$ 1.0xULN, > 1.0xULN to <2.5xULN, $\geq$ 2.5xULN)

Those endpoints will be analyzed as observed case without imputation (for combined endpoints, in case one of the two individual parameters is missing for a specific timepoint, the endpoint will be considered missing for that timepoint).

5.5.1.1.2. HDV RNA Cut-offs

HDV RNA will be analyzed over time using binary endpoints on both absolute values and reductions from baseline

The cutoffs for HDV RNA absolute values are as follows:

- <LLOQ
  - <LLOQ TND
  - <LLOQ TD
- > LLOQ
- < 2,000 IU/mL
- < 10,000 IU/mL

- The cutoffs for HDV RNA reductions from baseline are as follows:
  - ≥ 1 log10 IU/mL
  - ≥ 2 log10 IU/mL
  - ≥ 3 log10 IU/mL
  - ≥ 4 log10 IU/mL

5.5.1.1.3. Virologic HDV RNA Breakthrough

Two types of HDV RNA breakthroughs will be defined using 2 distinct thresholds:

Confirmed JNJ-3989 on-treatment increase in HDV RNA of >1$\log_{10}$ IU/mL from JNJ-3989 on-treatment nadir in participants who did not have HDV RNA JNJ-3989 on-treatment nadir < LLOQ or confirmed >1$\log_{10}$ IU/mL (i.e., 630 IU/ml) above LLOQ of the HDV RNA assay in participants who had HDV RNA JNJ-3989 on-treatment nadir <LLOQ.

Confirmed JNJ-3989 on-treatment increase in HDV RNA of >2$\log_{10}$ IU/mL from JNJ-3989 on-treatment nadir in participants who did not have HDV RNA JNJ-3989 on-treatment nadir < LLOQ or confirmed >2$\log_{10}$ IU/mL above LLOQ of the HDV RNA assay in participants who had HDV RNA JNJ-3989 on-treatment nadir <LLOQ.

5.5.1.1.4. JNJ-3989 Off-Treatment HDV RNA Relapses

JNJ-3989 off-treatment HDV RNA relapse will be defined using 2 distinct rules:

1) In participants with HDV RNA <LLOQ (i.e., 630 IU/ml) at EOT: Confirmed increase in HDV RNA of > 1 $\log_{10}$ IU/mL above the LLOQ JNJ-3989 off-treatment.

2) In participants with HDV RNA >LLOQ at EOT: Confirmed increase in HDV RNA of > 1 $\log_{10}$ IU/mL from EOT HDV RNA value JNJ-3989 off-treatment.

5.5.1.1.5. JNJ-3989 Off-treatment HDV Clinical Flares

An JNJ-3989 off-treatment HDV clinical flare is defined as a confirmed increase in HDV RNA of > 1 $\log_{10}$ IU/mL above the LLOQ JNJ-3989 off-treatment and confirmed ALT and/or AST >=3x ULN and >=3x JNJ-3989 off-treatment nadir during the follow-up phase**.**

The start date of an JNJ-3989 off-treatment HDV clinical flare is defined as the minimum date between the date when the confirmed HDV RNA criterion is met and start date of the JNJ-3989 off-treatment biochemical flare.

The end date of a JNJ-3989 off-treatment HDV clinical flare is defined as either:

- The maximum date between HDV RNA increase returns to ≤ 1 $\log_{10}$ IU/mL and the date when a 50% reduction from the peak ALT and/or AST level is reached.
- Or the date of JNJ-3989 treatment restart, whichever comes first.
  - 1 (Yes)= confirmed HDV RNA of > 1 $\log_{10}$ IU/mL above the LLOQ JNJ-3989 off-treatment and confirmed ALT and/or AST≥3x ULN and ≥3x JNJ-3989 off-treatment nadir

- 0 (No) = otherwise
- 2 (Not applicable) = no JNJ-3989 off-treatment HDV RNA and/or ALT/AST quantitative measurements available.

5.5.1.1.6. JNJ-3989 Off-treatment Sustained HDV Response

A JNJ-3989 off-treatment sustained HDV response is defined by having HDV RNA TND during the FU phase after stopping JNJ-3989 regardless of continuing NA treatment.

Alternative JNJ-3989 off-treatment sustained HDV responses will be evaluated using the following definitions:

- Having HDV RNA < LLOQ during the FU phase
- Having HDV RNA TND with normal ALT during the FU phase
- Having HDV RNA < LLOQ and normal ALT during the FU phase
- HDV RNA > 2 $\log_{10}$ IU/mL decline from baseline and normal ALT during the FU phase.

Participants with missing HDV RNA at a specific timepoint will be considered as non-responders for that timepoint. No imputation rule will be used in case of missing data.

5.5.1.1.7. HBsAg Seroclearance

HBsAg seroclearance (i.e quantitative HBsAg < LLOQ) will be evaluated at all time points when assessed, and analyzed as observed case without imputation, with emphasis at the following time points:

- At Week 48 (Also defined as KSE 4, see section 5.4.3)
- Week 96
- Week 144/EOT
- FU Week 24
- FU Week 48

Of note, HBsAg seroclearance may be achieved prior to the FU Week 12, 24, 36, or 48, respectively, but must be observed at the given week of interest.

Note that HBsAg seroclearance at Week 48 is used for one of the key secondary endpoints and specific imputation rules applied. However, for this analysis over time, HBsAg data at Week 48 will be treated similarly to the other timepoints, i.e no imputation will be done in case of missing value.

5.5.1.1.8. 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.

5.5.1.1.9. Virologic HBV Breakthrough

Virologic HBV breakthrough is defined as having a confirmed on-treatment HBV DNA increase by >1 $\log_{10}$ from on-treatment nadir level in participants who did not have on-treatment HBV DNA <LLOQ or a confirmed on-treatment HBV DNA level >200 IU/mL in participants who had on-treatment HBV DNA <LLOQ.

In addition, participants who experience a virologic breakthrough followed by on-treatment biochemical flare (see Section 5.5.1.1.11) will be evaluated.

5.5.1.1.10. HBsAg, HBeAg and HBV DNA Cut-offs

HBsAg, HBeAg (only for participants HBeAg-positive at screening) and HBV DNA will be analyzed over time using binary endpoints on both absolute values, change ($\log_{10}$ transformed) and reductions ($\log_{10}$ transformed) on from baseline.

The cutoffs for HBsAg absolute values are as follows:

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

The cutoffs for HBsAg reductions from baseline are as follows:

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

The cutoffs for HBeAg **absolute** values are as follows:

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

The cutoffs for HBeAg **reductions** from baseline are as follows:

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

The cutoffs for HBV DNA **absolute** values are as follows:

- <LLOQ
- < 2000 IU/mL
- > 2000 IU/mL

- The cutoffs for HBV DNA **reduction** from baseline are as follows:
- ≥ 1 $\log_{10}$ IU/mL
- ≥ 2 $\log_{10}$ IU/mL
- ≥ 3 $\log_{10}$ IU/mL
- ≥ 4 $\log_{10}$ IU/mL

5.5.1.1.11. HBV Flares

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

a) HBV Virologic flare is defined as follows:

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

The start date of a confirmed virologic flare is defined as the first date of two consecutive visits with HBV DNA > 200 IU/mL. The end date of the same confirmed virologic flare is defined as the first date when HBV DNA value returns to ≤200 IU/mL or the date of treatment restart (ie JNJ-3989 and/or NA), whichever comes first. Each virologic flare will be categorized based on the confirmed (ie two consecutive values) peak HBV DNA above any of the three thresholds within the start and end date of that flare as follows: 20,000 IU/mL 2,000 IU/mL and 200 IU/mL.

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

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

The start date of a confirmed virologic flare is defined as the first date of two consecutive visits with HBV DNA log10 increase > 1 log10 from EOT. The end date of the same confirmed virologic flare is defined as the first date when HBV DNA log10 increase from EOT returns to ≤1 log10 or the date of treatment restart (ie JNJ-3989 and/or NA), whichever comes first. Each virologic flare will be categorized based on the confirmed (ie, two consecutive values) peak HBV DNA increase above any of the three thresholds within the start and end date of that flare as follows: 1 log10, 2log10, 3 log10.

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

b) Off-treatment HBV biochemical flare is defined as follows:

The start date of a confirmed off-treatment biochemical flare is defined as the first date of two consecutive visits with ALT and/or AST ≥3x ULN and ≥3x nadir (ie, lowest value observed up to the start of the flare). The end date of the same off-treatment biochemical flare is defined as the first date when there is a 50% reduction from the peak ALT and/or AST level or the date of treatment restart (ie JNJ-3989 and/or NA), whichever comes first.

- 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

c) On-treatment HBV biochemical flare is defined as follows:

The start date of a confirmed on-treatment biochemical flare is defined as the first date of two consecutive visits with ALT and/or AST ≥3x ULN and ≥3x nadir (ie, lowest value observed up to the start of the flare). The end date of the same on-treatment biochemical flare is defined as the first date when there is a 50% reduction from the peak ALT and/or AST level, regardless of stopping JNJ-3989 and/or NA.

- 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

d) HBV Clinical flare is defined as follows:

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

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

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

The HBV virologic and clinical flares will be assessed only off-treatment, while biochemical flares will be identified on-treatment and off-treatment, respectively. On-treatment virologic flares are described as virologic HBV breakthrough in Section 5.5.1.1.9.

5.5.1.1.12. ALT/AST Elevations

ALT/AST elevation is defined as follows:

The start date of a confirmed ALT/AST elevation is defined as the first date of two consecutive visits with ALT and/or AST ≥3x ULN and ≥2x nadir (ie, lowest value observed up to the start of the flare). The end date of the same ALT/AST elevation is defined as the first date when ALT (and/or AST) < 3xULN or ALT (and/or AST) < 2x nadir (ie, lowest value observed up to the start of the flare) whichever comes first.

- 1 (Yes) = confirmed ALT and/or AST ≥3x ULN and ≥2x nadir (ie, lowest value observed up to the start of the flare)
- 0 (No) = otherwise

5.5.1.1.13. Liver Stiffness Measurement

The proportion of participants with the following LSM changes from baseline (both in terms of reductions and increases) will be evaluated over time:

- ≥ 1 kPa
- ≥ 2 kPa
- ≥ 4 kPa
- ≥ 6 kPa

Only participants from sites with available VCTE (Fibroscan) will be included in the analysis. Within these participants, missing LSM (in kPa) at a specific timepoint will be considered as non-responders for that timepoint.

5.5.1.2. Values and Changes Over Time

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

Actual values (original unit and log_{10} transformed values, where applicable) and changes from baseline (log_{10} transformed values, where applicable) will be derived for the following parameters:

HDV virology:
- HDV RNA (original unit and log_{10} transformed values)

Liver inflammation
- ALT

Liver Fibrosis:
- Liver stiffness measurement assessed by vibration-controlled transient elastography (FibroScan)

HBV virology and serology:
- HBsAg (original unit and log_{10} transformed values)
- HBeAg (only for participants HBeAg-positive at screening; original unit and log_{10} transformed values)
- HBV RNA (original unit and log_{10} transformed values)
- HBV DNA (original unit and log_{10} transformed values)

5.5.1.3. Time to Event Endpoints

5.5.1.3.1. Time to Event Endpoints Based on Parameters Used in Key Secondary Endpoints

All time to event endpoints will analyzed throughout the entire study (and not by study phase) using DB day 1 as reference timepoint by study part.

5.5.1.3.1.1. Time to HDV RNA ≥ 2 log_{10} IU/mL Decline or HDV RNA TND or <LLOQ

Time to reach HDV RNA ≥ $2log_{10}$ IU/mL decline or HDV RNA TND is defined as the number of days between the date of first study intervention intake and the date of the first occurrence of HDV RNA ≥ $2log_{10}$ IU/mL decline or HDV RNA TND, whichever event is first (i.e. min [the date of the first HDV RNA ≥ $2log_{10}$ IU/mL decline, date of the first time HDV RNA is TND] – the date of first study intervention intake + 1). The participants who withdrew early from the study before achieving such event, or who did not achieve it at the time of the cut-off date for the analysis will

be censored at the last available HDV RNA assessment during the study or the cut-off date, whichever comes first.

5.5.1.3.1.2. Time to HDV RNA ≥ 2 log_{10} IU/mL Decline

The same derivation and censoring rules as in Section 5.5.1.3.1.1 apply for the time to reach HDV RNA decline≥ 2log_{10} IU/mL, which will be calculated using the date of first HDV RNA decline≥ 2log_{10} IU/mL.

5.5.1.3.1.3. Time to HDV RNA TND or <LLOQ

The same derivation and censoring rules as in Section 5.5.1.3.1.1 apply for the time to reach HDV RNA TND and time to reach HDV RNA < LLOQ, which will be calculated using the date of first HDV RNA TND and date of first HDV RNA < LLOQ respectively.

5.5.1.3.1.4. Time to Normal ALT Levels

The same derivation and censoring rules as in Section 5.5.1.3.1.1 apply for the time to reach normal ALT (i.e. ALT value ≤ULN), which will be calculated using the first date of normal ALT value.

5.5.1.3.1.5. Time to HBsAg Thresholds

The following thresholds will be evaluated:

- HBsAg < LLOQ (i.e seroclearance)
- HBsAg < 1 IU/mL
- HBsAg < 10 IU/mL
- HBsAg < 100 IU/mL
- HBsAg decline ≥ 2 log_{10}IU/mL

The same derivation and censoring rules as in Section 5.5.1.3.1.1 apply for the time to reach HBsAg thresholds, which will be calculated using the date of first occurrence of the given HBsAg threshold.

5.5.1.3.2. Time to Event Endpoints Based on Other Parameters

5.5.1.3.2.1. Time to JNJ-3989 Off-Treatment HDV Relapse

It is defined as the number of days between the date of EOT and the date of the first occurrence of JNJ-3989 off-treatment HDV relapse as defined in Section 5.5.1.1.4. The participants who withdrew during the FU phase before the end of the study and before achieving the event or without achieving it will be censored at the last available HDV RNA assessment during the FU phase.

5.5.1.4. Additional Efficacy Endpoints Relative to The Actual Duration of JNJ-3989 Treatment

This section intends to evaluate some selected efficacy endpoints over time conditional upon the same treatment duration with JNJ-3989 across the 2 arms based on Part 2 data. For example, DB

Week 24 for Arm 1 corresponds to Week 76 for Arm 2 (Week 52+24, See Table 2), as participants in Arm 2 start treatment with JNJ-3989 at Week 52 when they switch over to the active regimen. For each DB Week X for Arm 1 data, the corresponding Week 52+X for Arm 2 data will be considered, as described in Table 5:

Table 5: Correspondence between timepoints for Arm 1 and Open Label timepoints for Arm 2

Analysis Time point for Arm 1 (label)	Matching Analysis OL Timepoint for Arm 2 (label)
Baseline	Week 52
Week 2	Week 54
Week 4	Week 56
Week 8	Week 60
Week 12	Week 64
Week 16	Week 68
Week 20	Week 72
Week 24	Week 76
Week 28	Week 80
Week 32	Week 84
Week 36	Week 88
Week 40	Week 92
Week 44	Week 96
Week 48	Week 100
Week 52	Week 104
Week 56	Week 108
Week 60	Week 112
Week 64	Week 116
Week 68	Week 120
Week 72	Week 124
Week 76	Week 128
Week 80	Week 132
Week 84	Week 136
Week 88	Week 140
Week 92	Week 144
Week 96	EOT (only for OL completers)

When applicable, the reference timepoint (RT) for those analyses will be baseline (DB Day 1) for Arm 1 and Week 52 for Arm 2.

The following endpoints will be presented for those time points during the open-label phase in Arm 2 that match the treatment duration in Arm 1 during the double-blind phase, because of the deferred active trial design, as per Table 5.

The selected endpoints are:

- Proportion of participants with HDV RNA ≥ 2 $\log_{10}$ IU/mL decline from RT or HDV RNA TND in combination with normal ALT
- Proportion of participants with HDV RNA ≥ 2 $\log_{10}$ IU/mL decline from RT or HDV RNA < LLOQ in combination with normal ALT

- Proportion of participants with HDV RNA ≥ 2 $\log_{10}$ IU/mL decline from RT or HDV RNA TND
- Proportion of participants with HDV RNA TND
- Proportion of participants with HDV RNA <LLOQ
- Proportion of participants with normal ALT
- Proportion of participants with LSM reduction ≥ 2 kPa from RT
- Proportion of participants with HBsAg seroclearance i.e. with HBsAg < LLOQ, with HBsAg < 1 IU/mL and < 10 IU/mL
- Change from RT in HDV RNA
- Change from RT in ALT
- Change from RT in HBsAg
- Change from RT in LSM

5.5.2. Analysis Methods

All secondary efficacy data will be summarized by study Parts 1 and 2, as well as for the whole study data overall.

All other secondary endpoints at Week 48 will be analyzed and summarized as described in Section 5. No adjustment for multiple endpoints will be made.

All secondary endpoints evaluated at all other time points different than Week 48 during the study will be summarized descriptively by intervention arm, by phase and time point. No imputation rule will be used in case of missing data and the analysis will be based on observed cases.

5.5.2.1. Binary Endpoints

The binary endpoints will be analyzed using the stratum-adjusted MH test similar to the primary efficacy endpoint with corresponding 95% CIs on the difference of proportions.

The number and proportion of participants achieving the endpoints defined in Section 5.5.1.1 will be summarized over time with associated 95% CI. Between-arm difference in proportions with 95% CI will also be provided for all timepoints.

Bar charts will be provided for proportions in each intervention arm.

Cumulative percentage of participants achieving any given decrease from baseline at Week 48 in selected virology markers (e.g. HBsAg, HBV DNA etc.) will be presented graphically.

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

5.5.2.1.1. HDV RNA

In addition to the summaries described in Section 5.5.2.1, shift tables in HDV RNA categories from baseline will be provided.

In an additional summary, the proportions will be calculated based on the number of participants who have achieved HBsAg seroclearance at the FU weeks of interest after stopping JNJ-3989. regardless of continuing NA.

5.5.2.1.2. HBsAg Seroclearance

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

5.5.2.1.3. 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 will be summarized over time for the subset of the participants achieving HBsAg seroconversion at any time before or at that given timepoint by intervention arm.

Furthermore, the number and proportion of participants with appearance of anti-HBs antibodies and without HBsAg seroclearance will also be summarized.

5.5.2.1.4. HBV Flares

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

For on-treatment biochemical flares, the incidence of flares causing treatment discontinuation will be summarized. Further, for off-treatment flares, the count and percentage of participants who experienced a flare followed by NA re-treatment will be summarized by flare type. Similarly, the incidence of flares followed by the achievement of HBsAg seroclearance (at any time) will be summarized by flare type. Flares that are associated with signs of liver decompensation will be provided in a listing.

5.5.2.1.5. HBV DNA Cut-offs

The proportion of participants achieving HBV DNA cutoffs described in Section 5.5.1.1.10 will be summarized over time for all time points.

In an additional summary, the proportions will be calculated based on the number of participants who have achieved HBV DNA cutoffs at the FU weeks of interest after stopping all study interventions including NA.

5.5.2.2. Values and Change Over Time

Continuous variables will be summarized using descriptive statistics including the number of participants in the analysis, mean, standard deviation (SD), two-sided 95% CIs, median, and range. Descriptive statistics on actual values (original unit and log_{10} transformed values, when appropriate) and changes from baseline (log_{10} transformed values when appropriate) will be summarized over time. Mean (+/- SE) plots of the actual values and the change from baseline (log_{10} transformed when appropriate) will be presented over time.

Spaghetti plots for both absolute values and changes from baseline will be presented over time and by selected subgroups for efficacy (see Section 2.4.1).

Subsections below describe the additional analyses planned for specific continuous endpoints.

5.5.2.2.1. HDV RNA

5.5.2.2.1.1. Change from Baseline to Nadirs

The following change from baseline value to nadir values (defined in Section 5.5) in HDV RNA will be summarized descriptively and displayed graphically via box plots by intervention arm.

- Change from baseline to JNJ-3989 on-treatment nadir

- Change from baseline to overall nadir.

5.5.2.2.1.2. Change from Baseline Over Time

Change from baseline based on log_{10} transformed values for quantitative HDV RNA to leverage the longitudinal data during the DB study intervention phase will be analyzed using mixed effects model for repeated measures [MMRM]) including intervention arm, analysis time point (week), 3 randomization stratification factors (presence of compensated cirrhosis at screening [yes or no], HDV RNA testing laboratory location (China versus outside China), and HBeAg status at screening [positive vs negative]) as fixed effects and baseline HDV RNA (continuous) as covariate. 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. 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), 95% CI and p-values will be provided.

5.5.2.2.2. ALT

Change from baseline in ALT over time will be analyzed using similar MMRM as described in Section 5.5.2.2.1 using baseline ALT (continuous) as covariate. The LS mean of change from baseline, standard error (SE), 95% CI and p-values will be provided.

5.5.2.2.3. HBsAg, HBeAg and HBV DNA

5.5.2.2.3.1. Change from Baseline to Nadir

The following change from baseline value to nadir values (JNJ3989 on-treatment and overall, respectively, as described in Section 5.5) in HBsAg, HBeAg (only for HBeAg-positive participants at screening) and HBV DNA will be summarized descriptively and box plots of the changes to nadirs in each blood marker will display the distribution.

5.5.2.2.3.2. Change from Baseline Over Time

Descriptive statistics on actual values (original unit and log_{10} transformed values) and changes from baseline (log_{10} transformed values) over time in each HBV blood marker will be summarized.

For HBsAg and HBV DNA, respectively, the comparison between intervention arms to leverage the longitudinal data during the DB study intervention phase will be done using similar MMRM as described in Section 5.5.2.2.1 using baseline value (quantitative) as covariate.

Waterfall plots for changes from baseline of HBsAg, HBeAg, and HBV DNA will also be presented by intervention arm at selected timepoints: Week 48, 72, 96, 120 and 144 (for Study Part 2).

5.5.2.2.3.3. Qualitative versus Quantitative Values

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

5.5.2.2.4. Liver Stiffness Measurement

The change from baseline in LSM will be compared between intervention arms at Week 48 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. A graphical display will also illustrate the findings. In addition, a waterfall plot will be produced to display the individual changes from baseline in LSM.

5.5.2.3. 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 the intervention arms. The median time with 95% CI will be estimated using Kaplan-Meier method. This analysis method will apply to all time-to-events variables defined in Section 5.5.1.3.

5.6. Exploratory Endpoints

All exploratory endpoints will be summarized descriptively by intervention arm, phase, time point and study part. No imputation rule will be used in case of missing data and the analysis will be based on observed cases.

5.6.1. Definitions

5.6.1.1. Binary Endpoints

5.6.1.1.1. HDV RNA Decline and Normal ALT

All endpoints described in Section 5.5.1.1.1 which include HDV RNA TND will be evaluated by replacing TND by < LLOQ for assay sensitivity purpose:

- HDV RNA ≥ 2 $\log_{10}$ IU/mL decline from baseline or < LLOQ in combination with normal ALT.
- HDV RNA ≥ 2 $\log_{10}$ IU/mL decline from baseline or HDV RNA < LLOQ.
- HDV RNA < LLOQ in combination with Normal ALT.
- HDV RNA < LLOQ.

Additionally, some of the HDV RNA endpoints above may also be evaluated using the exploratory imputation rules defined in Table 4.

Those endpoints will be analyzed as observed case without imputation (for combined endpoints, in case one of the two individual parameters is missing for a specific timepoint, the endpoint will be considered missing for this timepoint).

5.6.1.1.2. HDV RNA Cutoffs

HDV RNA will be evaluated when assessed at the following time points:

- 12 weeks after stopping JNJ-3989 (regardless of continuing NA treatment and when JNJ-3989 was stopped) without restarting JNJ-3989 treatment,
- 24 weeks after stopping JNJ-3989 (regardless of continuing NA treatment and when JNJ-3989 was stopped)) without restarting JNJ-3989 treatment,
- 36 weeks after stopping JNJ-3989 (regardless of continuing NA treatment and when JNJ-3989 was stopped)) without restarting JNJ-3989 treatment,
- 48 weeks after stopping JNJ-3989 (regardless of continuing NA treatment and when JNJ-3989 was stopped)) without restarting JNJ-3989 treatment,

For each timepoint, the following cutoffs on actual values will be evaluated:

- LLOQ
  - <LLOQ TND
  - <LLOQ TD
- > LLOQ
- < 100 IU/mL
- < 2,000 IU/mL

5.6.1.1.3. HBV RNA and HBcrAg

The cutoffs for HBV RNA level are as follows:

- < LOD
- < LLOQ

The cutoffs for HBV RNA change from baseline are as follows:

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

The cutoffs for HBcrAg level are as follows:

- <3.0 Log_{10} U/mL
- <4.0 Log_{10} U/mL

The cutoffs for HBcrAg change from baseline are as follows:

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

5.6.1.1.4. HBV DNA Cutoffs

HBV DNA <LLOQ will be also evaluated when assessed at the following time points:

- 12 weeks after stopping JNJ-3989 (regardless of continuing NA treatment and when JNJ-3989 was stopped) without restarting JNJ-3989 treatment,24 weeks after stopping JNJ-3989 (regardless of continuing NA treatment and when JNJ-3989 was stopped) without restarting JNJ-3989 treatment,
- 36 weeks after stopping JNJ-3989 (regardless of continuing NA treatment and when JNJ-3989 was stopped) without restarting JNJ-3989 treatment, 48 weeks after stopping JNJ-3989 (regardless of continuing NA treatment and when JNJ-3989 was stopped) without restarting JNJ-3989 treatment

5.6.1.1.5. HBsAg Seroclearance

Participants achieving HBsAg seroclearance (HBsAg <LLOQ) will be evaluated when HBsAg assessed at the following time points:

- 12 weeks after stopping JNJ-3989 (regardless of continuing NA treatment and when JNJ-3989 was stopped) without restarting JNJ-3989 treatment,24 weeks after stopping JNJ-3989 (regardless of continuing NA treatment and when JNJ-3989 was stopped) without restarting JNJ-3989 treatment,36 weeks after stopping JNJ-3989 (regardless of continuing NA treatment and when JNJ-3989 was stopped) without restarting JNJ-3989 treatment,48 weeks after

stopping JNJ-3989 (regardless of continuing NA treatment and when JNJ-3989 was stopped) without restarting JNJ-3989 treatment,

5.6.1.2. Value and Change Over Time

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

Actual values (original unit and log_{10} transformed values, where applicable) and changes from baseline (log_{10} transformed values, where applicable) over time will be summarized by intervention arm and phase for the following variable:

- HBV RNA (original unit and log_{10} transformed)
- HBcrAg (original unit and log_{10} transformed)
- Anti-HBs antibodies

5.6.1.3. Time to Event Endpoints

The analyses will be performed if at least 10% of the participants experience the events.

5.6.1.3.1. Time to Undetectability of HBcrAg

The same derivation and censoring rules as in Section 5.5.1.3.1.1 apply for the time to undetectability of HBcrAg, which will be calculated using the date of first HBcrAg TND.

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

5.6.1.3.2. Time to Appearance of Anti-HBs Antibodies

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

The same derivation and censoring rules as in Section 5.5.1.3.1.1 apply for the time to appearance of anti-HBs antibodies, which will be calculated using the date of first appearance as defined above.

5.6.1.3.3. 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.

The same derivation and censoring rules as in Section 5.5.1.3.1.1 apply for the time to appearance of anti-HBe antibodies, which will be calculated using the date of first appearance as defined above.

5.6.1.4. Relationship between HBsAg and HDV RNA

HBsAg levels and decline from baseline (in log_{10} transformed values) and HDV RNA levels and change from baseline (in log_{10} transformed values) during study intervention and follow-up will be used to analyze a potential relationship between the two markers.

In case either HBsAg or HDV RNA is missing at a specific timepoint, no imputation will be performed.

Correlations between HBsAg and HDV RNA markers may be evaluated. The list of HBsAg and HDV RNA endpoints, including but not limited to, are defined below. Note, that these analyses may be performed if sufficient data are collected on patients and will only be performed at a later time point in a post hoc nature.

Off-Treatment Clinical HDV Flares (Yes/No)	• HBsAg value and change from baseline (absolute and log_{10} values) at End of Treatment of JNJ-3989. • HBsAg seroclearance at End of Treatment of JNJ-3989- . (Yes/No)

5.6.1.5. Relationship Between Baseline characteristics and Efficacy Endpoints

The relationship between efficacy endpoints at Week 48 and selected baseline characteristics defined in the list of subgroup variables for efficacy (see Section 2.4.1) will be evaluated as part of the subgroup analyses in Sections 5.3.3 and 5.4.5. In addition, an analysis of correlation at Week 48 will be performed to evaluate the relationship between endpoints at Week 48 (HDV RNA decline from baseline, change from baseline in ALT, change in HBsAg, change in LSM) and selected baseline characteristics. This analysis will use continuous variables only. More details are provided in Section 5.6.2.5.

In addition, the relationship between efficacy endpoints and on-treatment predictive outcomes at early visits (such as HDV RNA reduction ≥ 2 log10 from baseline, normal ALT, LSM reduction, HBsAg seroclearance etc) will also be explored.

5.6.1.6. Liver Viral Response

In case a sufficient number of participants agrees to undergo the optional liver biopsy at baseline and/or Week 24, the following endpoints will be evaluated:

- Change from baseline at Week 24 in intrahepatic HDV RNA (semi-quantitative: negative, low, middle, high expression)
- Change from baseline at Week 24 in intrahepatic HDAg (semi-quantitative: negative, low, middle, high expression)
- Change from baseline at Week 24 in number and proportion of pgRNA-positive hepatocytes
- Change from baseline at Week 24 in number and proportion of HBsAg-positive hepatocytes
- Change from baseline at Week 24 in number and proportion of silent hepatocytes
- Change from baseline at Week 24 in pgRNA levels (copies/cell)
- Change from baseline at Week 24 in intrahepatic HBsAg (semi-quantitative: negative, low, middle, high expression)

- Change from baseline at Week 24 in intrahepatic HBV RNA (semi-quantitative: negative, low, middle, high expression)

Additional endpoints may be added if sufficient biopsy data are available for the analysis.

5.6.1.7. Liver Immune Response

In case a sufficient number of participants agrees to undergo the optional liver biopsy at baseline and/or Week 24, the following immune cells may be evaluated:

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

5.6.1.8. Relationship Between On-Treatment ALT Elevations, Efficacy and Safety Endpoints, and Baseline Characteristics

The relationship between On-Treatment ALT elevations will be evaluated. The following relationships will be evaluated:

- Efficacy outcomes by ALT Elevation Status: HBsAg, HBeAg, HDV RNA, HBV DNA, HBcrAg, Liver stiffness measurement
- Safety outcomes by ALT/AST Elevation Status: Direct Bilirubin, Total Bilirubin, Individual GFR, Platelets, Cholesterol, INR (ratio), Hemoglobin, Eosinophils, Albumin, LDH, Prothrombin time, Alkaline Phosphatase, GGT, Alpha Fetoprotein,
- Tables of ALT elevation status by HBsAg, HBeAg, HDV RNA, HBV DNA, HBV RNA, type of NA, race, BMI, age, anti-HDV IgM, Fibroscan at Baseline
- ALT values over time by HBsAg, HBeAg, HDV RNA, HBV DNA, HBV RNA, type of NA or none, race, BMI, age, anti-HDV IgM, Fibroscan at Baseline (Cut-offs or Categories)

5.6.2. Analysis Methods

5.6.2.1. Binary Endpoints

Descriptive summaries including 95% CI and graphical displays will be provided for the exploratory binary endpoints.

5.6.2.1.1. HDV RNA Cutoffs

The proportion of participants with HDV RNA $< \text{or} \geq$ cutoffs defined in Section 5.6.1.1.2 will be evaluated at each of the following off-treatment time points: 12, 24, 36 and 48 weeks, respectively, after stopping JNJ-3989.

In an additional summary, these proportions will be calculated with the denominator including only those participants who have reached the off-treatment time points (week 12, 24, 36 or 48) and have stopped JNJ-3989 and have not restarted JNJ-3989, regardless of continuing NA treatment prior to the time point of interest

5.6.2.1.2. HBsAg Seroclearance

The proportion of participants achieving HBsAg seroclearance will be evaluated at each of the following off-treatment time points: 12, 24, 36 and 48 weeks, respectively, after stopping all study interventions and without restarting JNJ-3989.

In an additional summary, these proportions will be calculated with the denominator including only those participants who have reached the off-treatment time points (week 12, 24, 36 or 48) and have stopped JNJ-3989 and have not restarted JNJ-3989 , regardless of continuing NA treatment prior to the time point of interest.

5.6.2.2. Value and Change Over Time

Similar summaries and graphical displays as described in Section 5.5.2.2 will be provided for the exploratory continuous endpoints.

Subsections below describe the additional analyses specific to individual continuous exploratory endpoints.

5.6.2.2.1. HBV RNA and HBcrAg

HBcrAg will be summarized by NA treatment history (Yes/No) and overall, while HBV RNA will only be summarized by NA treatment history.

The values of and changes from baseline in HBV RNA and HBcrAg, respectively, will be summarized only descriptively over time in a similar manner as for values and changes from baseline over time in HBsAg, HBeAg, and HBV DNA as described in Section 5.5.2.2.3, including the change from baseline value to nadir values (both on and off treatment) and the various graphical displays.

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

5.6.2.2.2. Anti-HBs Antibodies

For participants with positive anti-HBs antibodies at baseline who will reach HBsAg seroclearance (as defined in Section 5.4.3.1), descriptive statistics will be calculated for the change (increase) 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 Week 48 will be summarized descriptively for the subset of the participants achieving HBsAg seroclearance at any time before or at that given timepoint by intervention arm.

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

5.6.2.2.3. Anti-HBe Antibodies

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

Shift tables from baseline will also be provided over time.

5.6.2.3. Time to Event Endpoints

The time to event endpoints defined in Section 5.6.1.3 will be analyzed using the Kaplan Meier method and Log-Rank test similarly to the time to event endpoints described in the Section 5.5.2.3. No Cox model will be provided for the time to event exploratory endpoints.

5.6.2.4. Relationship between HBsAg and HDV RNA

The relationship between HBsAg and HDV RNA will be explored over time during the intervention and FU phases by providing the following scatterplots and heat maps :

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.

Potential relationship on the selected subgroups defined in Section 2.4.1 will also be explored using the same graphical approach. Graphical display combining individual profiles for HDV RNA and HBsAg over time (and mean by intervention arm) will also be provided.

5.6.2.5. Relationship Between Baseline Characteristics and Efficacy Endpoints

The analysis of correlation between each secondary endpoint at Week 48 and selected subgroup variables for efficacy (see Section 2.4.1 for the list of variables) will be performed using the correlation coefficients described in Section 5.6.2.4 , scatter plots and heat plots.

Analysis of correlation and graphical displays will also be used to explore the relationship between efficacy endpoints and predictive outcomes at early visits.

5.6.2.6. Liver Viral Response

Descriptive statistics on actual values at baseline and Week 24 and changes from baseline at Week 24 may be summarized for the list of parameters described in Section 5.6.1.6 if sufficient biopsy data on Part 2 subjects are collected.

Number of cells may be expressed in original unit and proportions, or ratios may be provided in both original and $\log_{10}$ transformed scales. Change from baseline may be provided in $\log_{10}$ transformed unit. In addition, graphical displays e.g spaghetti plots, scatter plot, box plots may be provided.

5.6.2.7. Liver Immune Response

Descriptive statistics on actual values at baseline and Week 24 and changes from baseline at Week 24 will be summarized for the list of parameters described in Section 5.6.1.7 if sufficient biopsy data on Part 2 subjects are collected.

In addition, graphical displays e.g spaghetti plots, scatter plot, box plots may be provided.

Additional immune cells may be evaluated depending on data availability and clinical interest. Spatial distribution for each cell type at baseline and Week 40 may be graphically evaluated.

6. SAFETY

The Safety Analysis Set will be used for all safety analyses based on pooled data from Part 1 and Part 2 of the study. In addition, selected safety analyses may be reported by study part.

All assessments will be presented by analysis phase and study intervention, 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 periodic safety data 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, COVID-19 AEs (serious and non-serious) and fatal AEs by presenting by intervention arm the number and percentage of participants who experienced at least one of such AE. The overview AEs table will be also presented stratified by the subgroup of interests identified in Section 2.4.2.

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

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

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

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

For participants reporting rash, a listing with specific grade will be provided and Rash questionnaire will be tabulated by study intervention arm and overall.

6.1.3. Adverse Events of Special Interest

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

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

The list of all preferred terms belonging to ALT/AST elevations, renal complications, cholesterol increase, and hematologic abnormalities is provided in 0. Injection site reactions will be identified using the eCRF Injection Site Reaction form.

6.2. Clinical Laboratory Tests

6.2.1. Definitions

Laboratory data will be summarized by category of laboratory test. The different categories and laboratory tests used in the analysis are listed in Table 6.

Table 6: Laboratory Parameters

Laboratory Category	Parameters		
Hematology	Platelet count RBC count Hemoglobin Hematocrit Reticulocyte count Reticulocyte index	<u>RBC Indices:</u> Mean corpuscular volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration	<u>WBC count with Differential:</u> Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Blood Coagulation	Activated partial thromboplastin time International normalized ratio Prothrombin time		
Clinical Chemistry	Sodium Potassium Chloride Bicarbonate Blood urea nitrogen Creatinine 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	<u>Dipstick</u> Specific gravity pH Glucose Protein Blood Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase	<u>Sediment (if dipstick result is abnormal)</u> RBCs WBCs Epithelial cells Crystals Casts Bacteria	
Urine Chemistry (quantitative measurement)	Creatinine Sodium Phosphate	Glucose Protein Albumin	
Renal Biomarkers	Retinol binding protein Beta-2-microglobulin		

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

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

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

Imputation rules:

In case continuous laboratory results are not numerically expressed, but as a character (e.g. 'less than 2', '>25'), these results will be numerically imputed as follows:

- If the analysis result contains '<' then the result will be multiplied by 0.999 (e.g. <6.1 becomes 6.0939).
- If analysis result contains '>' then the result will be multiplied by 1.001 (e.g. >6.1 becomes 6.1061).
- If analysis result contains '≤' or '≥' then only the numeric portion of the result will be used.

This also applies to normal limits expressed as such.

6.2.2. Analysis Methods

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

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

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

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

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

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

6.3. Renal Safety

6.3.1. 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. Stage of Chronic Kidney Disease (CKD) are defined as follows: 1 (Normal): eGFR ≥ 90; 2 (Mild): eGFR 60-89; 3 (Moderate): eGFR 30-59; 4 (Severe): eGFR <30.

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

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

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

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

Phosphate excretion

Other renal biomarkers include FEPO4 that will be summarized by 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).

6.4. Electrocardiogram

6.4.1. Definitions

Evaluation of the triplicate 12-lead ECGs will be based on the mean value of the triplicate parameters and the abnormalities will be defined on the triplicate means.

The following ECG parameters measurements will be analyzed:

- PR interval (ms)
- Heart Rate (bpm)
- QT interval (ms)
- QRS duration (ms)
- QTc Corrected (Fridericia's formula QTcF)

The abnormalities in ECG parameters will be determined according to the criteria specified in the Cardiovascular Safety – Abnormalities Table (see Clinical Protocol Appendix 6, Cardiovascular Safety- Abnormalities Table). Abnormalities on actual values are provided for HR, PR, QRS and QTcF. Additional abnormalities on change from baseline will be provided for QTcF. No abnormalities will be defined for actual uncorrected QT values. Uncorrected QT ≥ 500 ms will be flagged and only shown in listings.

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

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

6.4.2. Analysis Methods

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

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

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

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

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

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

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

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

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

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

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

6.5. Vital Signs and Body Temperature

6.5.1. Definitions

The following parameters measurements will be analyzed:

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

The abnormalities in vital signs (not applicable for body temperature) will be determined according to the criteria specified in the Cardiovascular Safety – Abnormalities Table (see Clinical Protocol Appendix 7).

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

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

6.5.2. 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.

6.6. Physical Examination

The physical examination findings and abnormalities will be listed.

7. VIRAL GENOME SEQUENCE ANALYSIS AND GENOTYPING

Viral genome sequence analysis may be performed to identify pre-existing baseline polymorphisms and to evaluate emergence of genetic variations (including substitutions) associated with JNJ-3989, and/or ETV, TDF or TAF treatment on both nucleotide and/or amino acid level. The sequencing of samples may be triggered by the sponsor virologist based on changes in HBV DNA or HDV RNA levels observed in each individual participant and the limits of the sequencing assay. Virology results will be presented by specified timepoints and genetic region and position of interest. A separate virology report may be prepared.

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ATTACHMENTS

Attachment 1: Selected Major Protocol Deviations for Analysis Purposes

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

Sequence No.	Protocol Deviation Description (DVTERM)	Protocol Deviation Coded Term (DVDECOD)	Intercurrent Event
1	Inclusion criterion 4 not met: Chronic HBV infection was not documented by serum HBsAg positivity at screening and/or chronicity was not documented by serum HBsAg positivity at least 6 months prior to screening, or by alternative markers of chronicity. Or Chronic HDV infection was not documented by positive HDV antibodies or HDV RNA at screening and/or chronicity was not documented by positive HDV antibodies or HDV RNA at least 3 months prior to screening.	Entered but did not satisfy criteria	No
2	Inclusion Criterion 6 not met: Participant has HDV RNA < 1,000 IU/mL at screening.	Entered but did not satisfy criteria	No
3	Inclusion Criterion 7 not met: Participant has ALT levels ≥ 10xULN at screening.	Entered but did not satisfy criteria	No
4	Exclusion Criterion 1 met: Participant has evidence of hepatitis A virus infection (hepatitis A antibody IgM), HCV infection (HCV antibody), HDV infection (HDV antibody), or hepatitis E virus infection (hepatitis E antibody IgM), or HIV-1 or HIV 2 infection (confirmed by antibodies) at screening.	Entered but did not satisfy criteria	No
5	Exclusion Criterion 2 met Participant has Total bilirubin >1.7x ULN or Direct bilirubin >1.4x ULN or Prothrombin time >1.3x ULN or Serum albumin <3.2 g/dL within 12 months prior to screening.	Entered but did not satisfy criteria	No
6	Exclusion Criterion 3 met: Participant has a history or evidence of hepatic decompensation <*Specify*>.	Entered but did not satisfy criteria	No
7	Exclusion Criterion 4 met: Participant has a Child-Pugh score B or C at Screening <*Specify*>.	Entered but did not satisfy criteria	No
8	Exclusion Criterion 5 met: Participant has evidence of liver disease of non-HDV or non-HBV etiology. <*specify liver disease of non-HBV or non-HDV etiology*>.	Entered but did not satisfy criteria	No
9	Subject used disallowed medication as specified in the concomitant medication protocol Section:<*specify treatment, dose, unit, frequency, reason administered*>.	Received a disallowed concomitant treatment	Yes
10	Received wrong treatment of study drug JNJ-3989: *incorrect dose or placebo when randomized to active (and vice versa)*	Received wrong treatment or incorrect dose	Yes
11	Subject did not receive dose of study drug JNJ-3989/placebo within window: Subject missed two consecutive injections or missed more than 2 injections.	Received wrong treatment or incorrect dose	Yes
12	Subject missed NA treatment for more than 5 doses within a four week period.	Received wrong treatment or incorrect dose	Yes
13	Subject received expired study medication <*JNJ-3989, NA or placebo*>.	Received wrong treatment or incorrect dose	Yes
14	Subject has event of signs of decreasing liver function based on laboratory or	Received wrong treatment or incorrect	Yes

Sequence No.	Protocol Deviation Description (DVTERM)	Protocol Deviation Coded Term (DVDECOD)	Intercurrent Event
	clinical findings, but did not start NA treatment.	dose	
15	Subject has confirmed signs of hepatic decompensation <*specify*> but subject continued study treatment.	Developed withdrawal criteria but not withdrawn	Yes
16	The subject has confirmed HBV virological breakthrough but continued study treatment.	Developed withdrawal criteria but not withdrawn	Yes
17	Accidental unblinding of treatment group of a subject or a blinded staff member prior to planned unblinding at <*specify visit*>.	Other	No
18	Study < specify the visit which >procedure not done at scheduled Visits.	Other	No
19	Efficacy evaluation of HDV RNA not done at Week 48 Visit	Other	No
20	Efficacy evaluation of ALT not done at Week 48 Visit	Other	No
21	Efficacy evaluation of LSM not done at Week 48 Visit	Other	No
22	Efficacy evaluation of HBsAg not done at Week 48 Visit	Other	No
23	Study Visits not performed per protocol.	Other	No

attachment 2: Adverse events of special interest list of preferred terms.

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

Adverse Event of Special Interest	Source	Preferred Term
		Urine output decreased
		Nephropathy
		Nephropathy toxic
		Glomerulonephropathy
		Nephrolithiasis
Cholesterol increase	Dyslipidaemia (SMQ), (as per MedDRA version used for the analysis)	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), (as per MedDRA version used for the analysis)	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), (as per MedDRA version used for the analysis)	Aplasia pure red cell
		Aplastic anaemia
		Erythroblast count decreased
		Erythroid maturation arrest

Adverse Event of Special Interest	Source	Preferred Term
		Erythropenia
		Hypoplastic anaemia
		Microcytic anaemia
		Proerythroblast count decreased
		Red blood cell count decreased
		Reticulocyte count decreased
		Reticulocytopenia
		Anaemia
		Erythroblast count abnormal
		Erythropoiesis abnormal
		Haematocrit abnormal
		Haematocrit decreased
		Haemoglobin abnormal
		Haemoglobin decreased
		Leukoerythroblastic anaemia
		Normochromic anaemia
		Normochromic normocytic anaemia
		Normocytic anaemia
		Proerythroblast count abnormal
		Red blood cell count abnormal
		Reticulocyte count abnormal
		Reticulocyte percentage decreased
Hematologic abnormalities	(Modified) Haematopoietic leukopenia (SMQ), (as per MedDRA version used for the analysis)	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

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

Adverse Event of Special Interest	Source	Preferred Term
		White blood cell disorder
Hematologic abnormalities	(Modified) Haematopoietic thrombocytopenia (SMQ), (as per MedDRA version used for the analysis)	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: Justification of the Decision Rule to start Part 2

The antiviral activity criteria to decide if /when to trigger Part 2 (Section 3.3.3) are based on the expectation that early declines of HBsAg and HDV RNA will eventually lead to achieve response in terms of the primary endpoint at Week 48 (defined in Section 5.3.1) with JNJ-3989+NA treatment. However, the magnitude of the correlation between the early changes (at Week 8, 12, 24, etc.) and the Week 48 primary time point is currently not known for the investigational treatment regimen in this study. This correlation will primarily depend on the positive predictive probability of the early declines of HDV RNA and HBsAg for the primary endpoint response status, i.e. the probability that a participant who meets the antiviral activity criteria will eventually achieve responder status for the primary endpoint. In addition, it is assumed that all participants who do not meet the antiviral activity criteria will be non-responders for the primary endpoint. Initially, the positive predictive probability is assumed to be 0.75. As the study targets a response rate of 30% in Arm 1, this translates into a target value of 40% for the percentage of participants meeting the antiviral activity criteria.

The performance of the proposed decision rule was evaluated by two different metrics:

- Lower bound and upper bound of an asymmetric credible interval (20%, 90%) of the posterior distribution of the proportion of participants who meet the criteria for each potential outcome after which the decision rule is applied (using a non-informative prior distribution, beta[0.5,0.5]).
- The probability of the each of the 3 different decisions (decide to start Part 2 in Step 1 or Step 2; consider starting Part 2 in Step 3 or decide not to start Part 2 in Step 3) as a function of the true percentage of participants meeting the criteria varying from 0% to 100%. This was obtained through simulation (10,000 replicates for each scenario).

The decision to start Part 2 can be taken as early as after the first 8 participants randomized to Arm 1 (JNJ-3989+NA) have data for at least 8 weeks and all of them meet the antiviral activity criteria. At the other extreme, it can also happen that the threshold of 8 participants is only reached after the total number of 16 participants on the investigational regimen in Part 1 have completed at least 36 weeks. In all possible scenarios where Part 2 would be triggered, the lower bound of the credible interval exceeds 40% (Figure 1, panel A). This implies that in each case where the decision rule will lead to the start of Part 2, the available data from Part 1 indicate that the probability that the proportion of participants meeting the criteria is in the region of interest (>40%) is at least 80%. On the other hand, if the number of participants meeting criteria a) and b) is ≤4 out of 16, the upper bound of the credible interval excludes the region of interest (<40%) and therefore it is not warranted to start Part 2 (Figure 1, panel B). Otherwise, the evidence of the data in Part 1 is considered inconclusive. In such case, the decision to start of Part 2 may then be based on a further exploration of the individual longitudinal profiles of HDV RNA and HBsAg of all participants up to at least Week 36.

The operational characteristics of the decision rule in relation to the true, but unknown, proportion of participants meeting the criteria is shown in Figure 2. The probability to start Part 2 exceeds

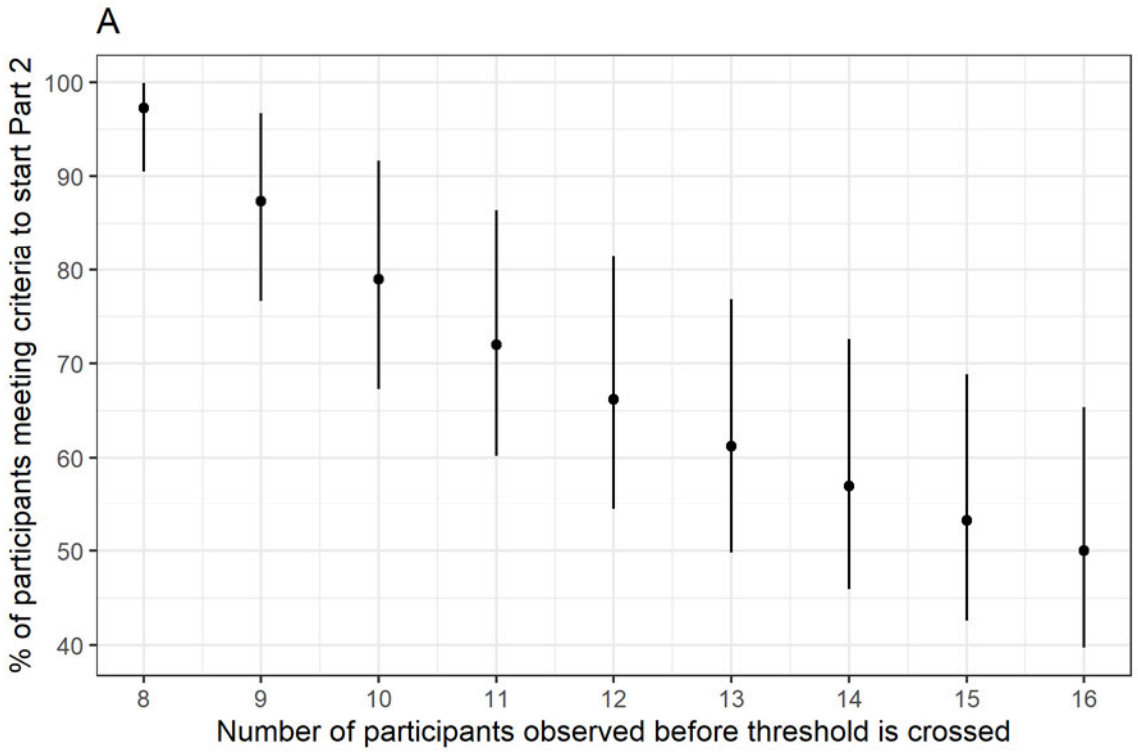
80% when the true proportion of participants meeting the criteria is higher than 57%. Conversely, if the true proportion is less than 20%, the probability not to start Part 2 exceeds 80%.

As the predictive probability of the early HDV RNA and HBsAg declines is not known, a sensitivity analysis was performed by assuming different values for the positive predictive probability of the early reductions in HDV RNA and HBsAg. The results are shown in (Figure 2). Here the probability for the different decisions are now plotted against the response rate (i.e. the percentage of participants achieving the primary endpoint). When the positive predictive probability is less than 0.75, the assumption made above, each value of the response rate now maps to a higher value of the percentage of participants meeting the antiviral activity criteria. Consequently, the curves shift to the left in comparison to Figure 2. When the positive predictive probability is less than 0.5, there is now a high chance of starting Part 2 when the response rate is in the region of 10% to 30%. However, the likelihood to start Part 2 is strongly reduced when the response rate is less than 10%, even with a predictive value as low as 0.3

In conclusion, the proposed decision rule has acceptable operational characteristics in terms of the probability to start Part 2 over a broad range of the unknown predictive value of the early declines in HDV RNA and HBsAg and the uncertainty around the primary efficacy endpoint response rate.

Figure 1: Median and [20%, 90%] credible interval of the posterior distribution of the proportion of participants meeting the antiviral activity criteria to start Part 2.

Panel A



Panel B

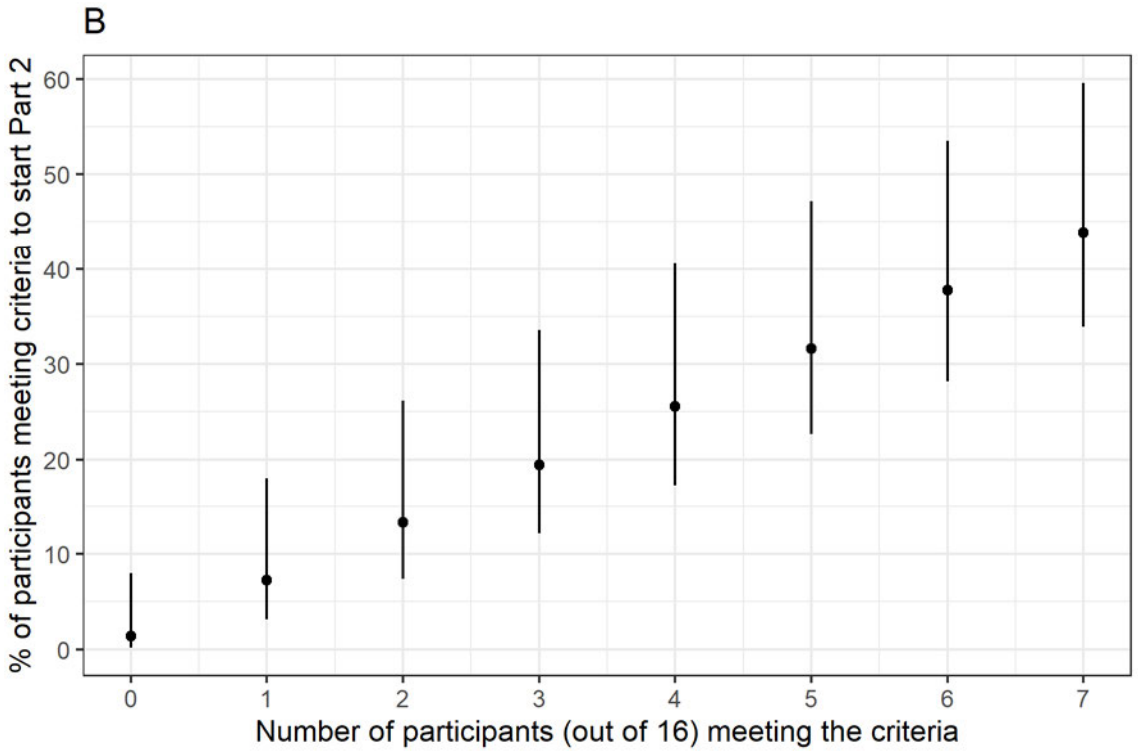


Figure 2: Probability of the outcome of the decision rule as a function of the percentage of participants meeting the criteria to start Part 2

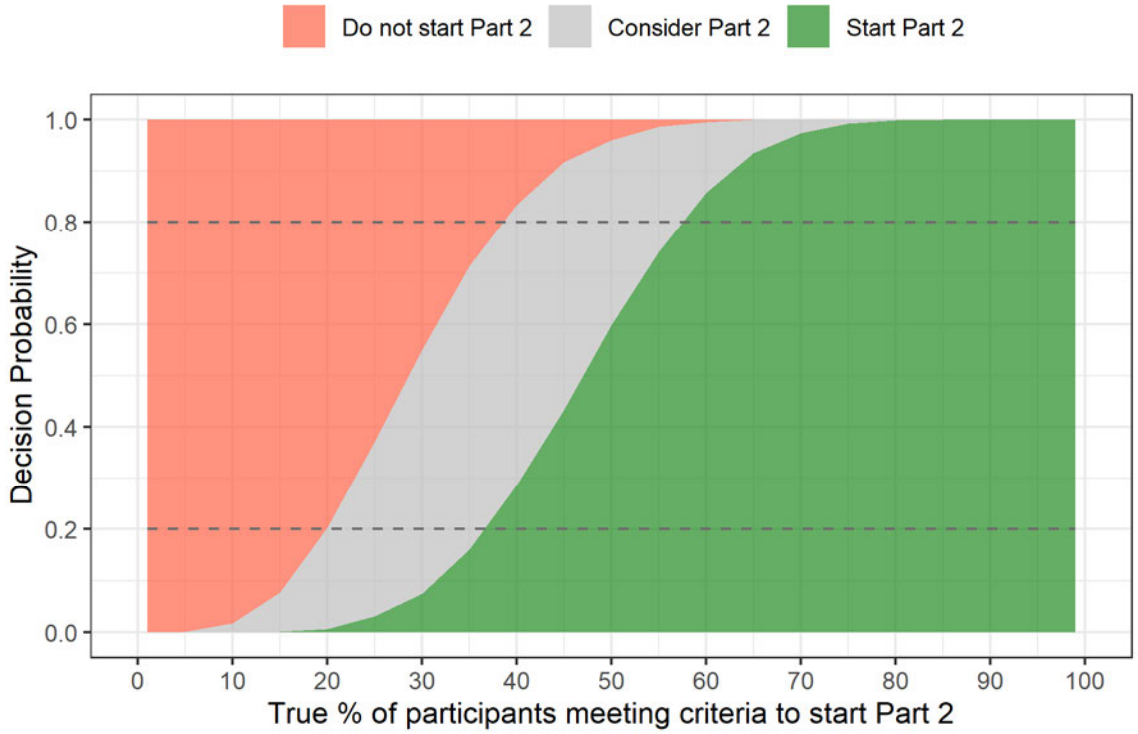


Figure 3: Probability of the outcome of the decision rule as a function of the percentage of participants meeting the primary endpoint for different values of the probability that a participant who meets the antiviral activity criteria will attain the primary endpoint.