Statistical Analysis Plan

A Phase 2a, Randomized, Partially-blind, Placebo-controlled Study to Assess the Efficacy, Safety, and Pharmacokinetics of Treatment With Multiple Doses of JNJ-56136379 as Monotherapy and in Combination With a Nucleos(t)ide Analog in Subjects With Chronic Hepatitis B Virus Infection

Protocol 56136379HPB2001: Phase 2a

JNJ-56136379

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

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AMENDMENT HISTORY

Updated to reflect the most recent protocol version, EDMS-ERI-148527695, 15.0

SAP version 2.0 was created to reflect some minor corrections from the submission team.

SAP version 3.0 was created to reflect the changes in study design, described in protocol amendments 1 to 2.

SAP version 4.0 was created to add analysis period of the study. The treatment phase includes an initial 24 week treatment period and a treatment extension period of 24 weeks, described in protocol amendments 3 to 4.

SAP version 5.0 was created to finalize as no further comments received.

Protocol Version	Issue Date
Original Protocol	20 October 2017
Amendment 1	18 December 2017
Amendment 2	06 Mars 2018
Amendment 3	18 June 2018
Amendment 4	21 February 2019
Amendment 5	2 August 2019

Amendment 1 (18 December 2017)

The overall reason for the amendment: Health Authority feedback regarding follow-up treatment and safety monitoring after the 24-week treatment period, and hormonal contraceptive treatment have been incorporated (detailed below).

- Clarification that, after the 24-week JNJ-56136379 treatment period, NA treatment (ETV [entecavir] or TDF [tenofovir disoproxil fumarate]) will be continued or started based on local treatment guidelines, ensuring subjects qualifying for Hepatitis B Virus (HBV) treatment are treated adequately.

- Recommendation that subjects not continuing or starting NA treatment should be followed up by their primary care physician, outside of the study, for an additional 24 weeks after the 24-week follow-up phase in the study (as per local treatment guidelines). This should ensure adequate safety monitoring for subjects not on HBV treatment.

- As oral contraceptive (OC) treatment is associated with potential risks, such as venous thrombosis, and these risks have been reported to be highest during the first 3 months of treatment, female subjects on OC treatment, can only be included in the study if at time of screening they have been on a stable OC treatment regimen for at least 3 months, without any safety concerns. Furthermore, given the observed

increase in EE exposure in combination with JNJ-56136379, stable OC treatment regimens including EE are only allowed at the lowest commercially available EE dose, i.e. 20 µg, to minimize any potential safety risks. If female subjects start OC treatment during the study, OC treatment regimens should not include EE, to minimize any potential safety risks due to the observed increase in EE exposure in combination with JNJ-56136379.

- Severity of AEs will be assessed based on the standardized DAIDS Toxicity Grading Scale, in line with laboratory abnormalities assessment.

- The response criterion for continuation in the treatment extension study has been reworded; subjects who have completed 24 weeks of treatment and who have HBV DNA levels <LLOQ at Week 20, with or without evidence of HBsAg decline will participate in the treatment extension study.

- Addition that choice of ETV or TDF by investigator is per local practice, ensuring consistency throughout the protocol.

- As the age of legal consent in certain countries is > 18 years, the inclusion criterion regarding minimum age in the study is updated to clarify this.

- Clarification on instructions in case of missed dose

- Removal of verapamil and felodipine from list of concomitant therapy to be used with caution as these are on the list of disallowed concomitant medication.

- Corrections to assessments during the follow-up phase ensuring consistency with treatment phase:

- Fibroscan assessment as part of efficacy evaluations to be performed only in subjects in the PK substudy.

- Triplicate ECGs to be performed.

- Clarification that ECGs will be read centrally. However, on Day 1, pre-dose ECG assessment will also be done locally on-site to determine eligibility.

- Correction of recommendations in case of specific toxicities, ensuring consistency with the treatment discontinuation and study withdrawal criteria.

- Clarification added that returned NA treatment can be re-dispensed to the same subject.

- Replacement of incorrect version of EQ-5D-5L (tablet version rather than paper version)

- Replacement of incorrect version of SF-36v2 (2010 version rather than 2000 version)
- Minor updates of abbreviation for entecavir corrected (ETV rather than ETF)
- Minor updates of IB addendum reference updated with final date

Amendment 2 (06 March 2018)

The overall reason for the amendment: Considering Health Authority recommendation to evaluate the effect of extended treatment on hepatitis B surface antigen (HBsAg) decline, the treatment duration will be extended to 48 weeks in subjects with virologic response who did not experience any safety concerns during the first 24 weeks of treatment that preclude continued study drug treatment as determined by the investigator.

Amendment 3 (18 June 2018)

The overall reasons for the current amendment are the selection of the high dose to be administered in Part B of the study, and an update of the available clinical data on JNJ-56136379.

Amendment 3 /JPN-1 (28 June 2018)

The overall reason for the current amendment was that HBcrAg is an important marker used for patient management in Japan and thus, as recommended by Japanese treatment guidelines for chronic hepatitis B, HBcrAg results at Week 40 may also be used to support the decision to stop all treatment after completion of 48 weeks of treatment.

Amendment 4 (18 June 2018)

The Sponsor has decided to stop further dosing of subjects with JNJ-56136379 in the open-label 75 mg monotherapy arm, upon recommendation from the Data Review Committee (DRC).

In addition, the Sponsor has limited the duration of JNJ-56136379 250 mg monotherapy to 24 weeks. Subjects in the 250 mg monotherapy arm eligible for treatment extension, will receive JNJ-56136379 in combination with nucleos(t)ide analog (NA) treatment from Week 24 to Week 48, limiting the duration of JNJ-56136379 monotherapy.

ABBREVIATIONS

ADaM	Analysis Data Model
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
Anti-HBe	Hepatitis B e Antibody
Anti-HBs	Hepatitis B surface Antibody
ATC	Anatomical Therapeutic Chemical
BCP	Basal Core Promoter
BMI	Body Mass Index
CHB	Chronic Hepatitis B
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
CTP	Clinical Trial Protocol
DAIDS	Division of AIDS
DBP	Diastolic Blood Pressure
DPS	Data Presentation Specifications
DRC	Data Review Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of study
EOT	End of treatment
ESI	Event of special interest
ETV	Entecavir
HBcrAg	Hepatitis B core related Antigen
HBeAg	Hepatitis B e Antigen
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HIV	Human Immunodeficiency Virus
HR	Heart Rate
ICH	International Conference on Harmonization
ITT	Intent-to-Treat
IU	International Unit
LLOQ	Lower Limit of Quantification
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed effects Model for Repeated Measures
NA	Nucleos(t)ide Analogue
NAP	Not applicable
NAV	Not available
NUC	Nucleos(t)ide
PC	Precore

PD	Pharmacodynamic
PK	Pharmacokinetic(s)
PR/PQ	Interval between onset of P wave and onset of QRS complex
QRS	Begins at the onset of Q wave and ends at endpoint of S wave
QT	Begins at the onset of QRS complex and ends at endpoint of T wave
QTc	Corrected QT interval
QTcB	QT corrected by Bazett's formula
QTcF	QT corrected by Fridericia's formula
RR	Interval between R wave of one heartbeat and R wave of preceding heartbeat
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
TDF	Tenofovir Disoproxil Fumarate
TEAE	Treatment emergent-adverse events
DPS	Data Presentation Specification
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) for the 56136379HPB2001 phase 2 trial (both part A and B) describes the statistical analysis to assess the efficacy and safety of JNJ-56136379 as Monotherapy and in Combination with a Nucleos(t)ide Analog (NA) in subjects with Chronic Hepatitis B Virus Infection. This SAP will also be used for the interim analyses that may be performed in this study when at least 80% of subjects have completed visits at Week 12, Week 24, Week 48 and when all subjects have completed the Follow-up Week 12. The interim analyses will present a subset of the output meant for the final analysis. The SAP specifies the analysis displays to be presented and describes the methods and procedures in a more elaborated way than in the statistical methods section of the protocol.

The pharmacokinetics analysis of this study will be described and reported in the PK/PD report.

The statistical analysis will be performed using SAS® (version 9.2 or higher) and for dose response modeling also the Proc MCPMod from Citel for SAS will be used for which the versions will be clearly described.

The statistical principles applied in the design and planned analyses of this study are consistent with International Conference on Harmonization (ICH) E9 guidelines.

No adjustments for multiplicity will be performed.

Minor modifications may be necessary to the planned design of tables, figures, and listings to accommodate data collected during the actual study conduct. Any major deviations from the final approved SAP or additional unplanned analyses will be documented (with justification) in a revised version of the plan approved prior to the primary analysis or will documented in the Clinical Study Report (CSR).

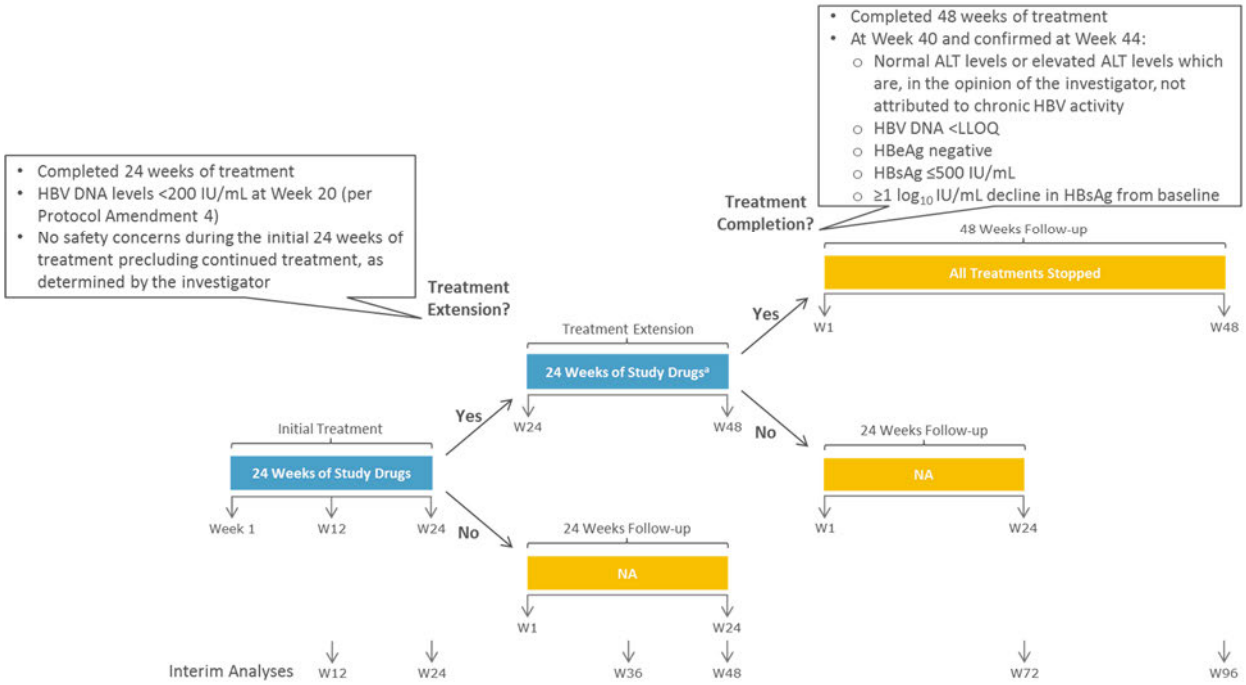
1.1. Trial Objectives and Endpoints

See Clinical Trial Protocol (CTP), Section 2.1.

1.2. Trial Design

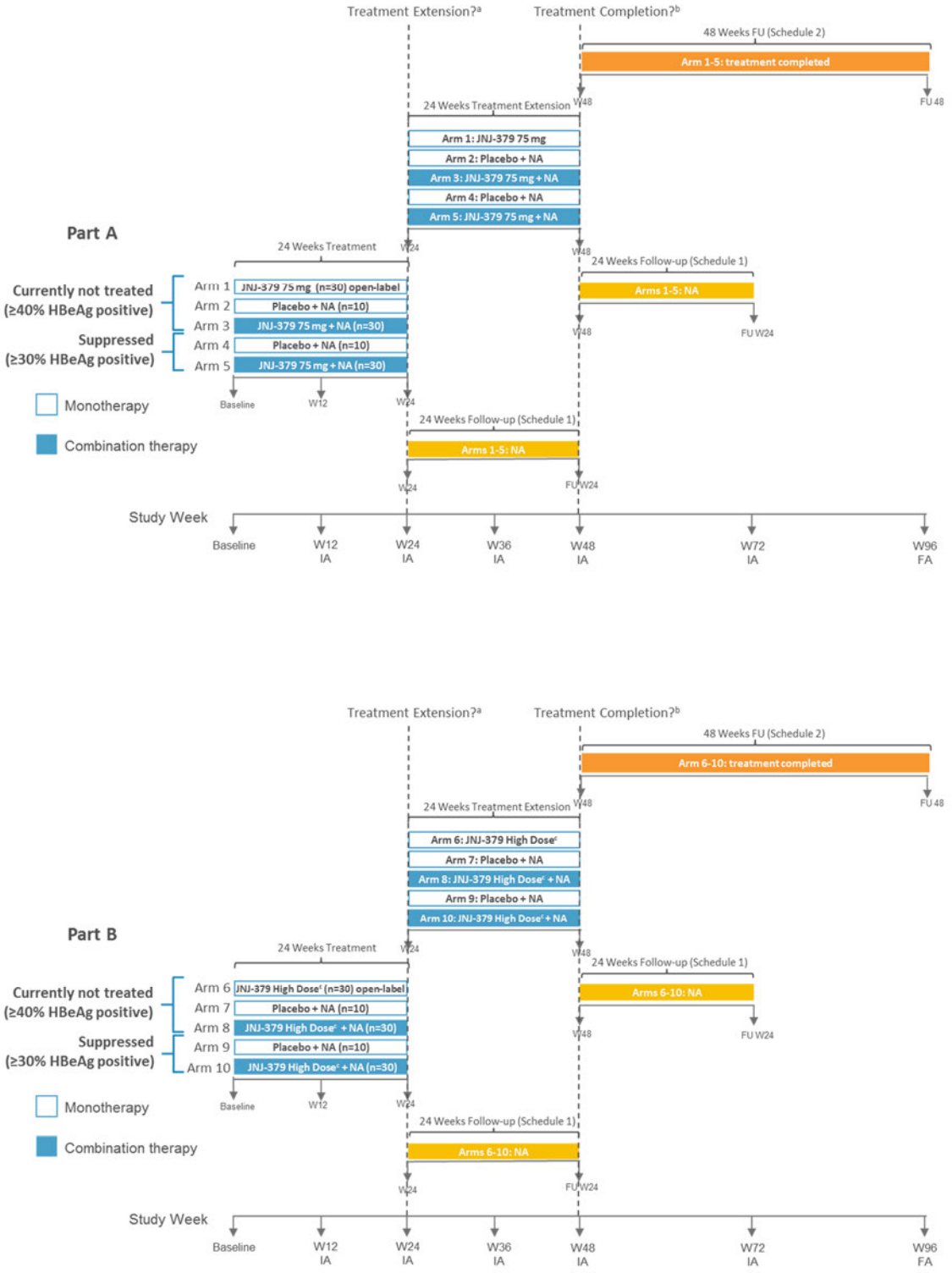
See CTP, Section 3.1. The schematic overview of the study design provided in the protocol is reproduced below.

Figure 1: High-level Overview of the Study Design



[a] Per Protocol Amendment 4, subjects in the JNJ-56136379 250 mg monotherapy arm (Treatment Arm 6) who are eligible for treatment extension, based on the treatment extension criteria assessed at Week 20, will receive JNJ-56136379 in combination with NA treatment from Week 24 to Week 48.

Figure 2: Schematic Overview of the Study



Abbreviations: FA: final analysis; IA: interim analysis; JNJ-379: JNJ-56136379; NA: nucleos(t)ide analog.

[a] , Subjects who have successfully completed 24 weeks of treatment, have HBV DNA levels <LLOQ by Week 20and who did not experience any safety concern that would preclude continued study drug treatment will receive another 24 weeks of study treatment in the extension phase. For all other subjects, NA treatment (either ETV or TDF as per local practice) should be continued or, in case of JNJ-56136379 monotherapy during the 24-week treatment phase, started at Week 24 as per local treatment guidelines. An additional 24-week follow-up (as per local treatment guidelines), by their primary care physician outside of the study, is recommended after the 24-week follow-up phase in the study (FU Schedule 1), for subjects who do not continue or start NA treatment at Week 24.

[b] After completion of 48 weeks of study treatment, a subject will complete all treatment if all of the Individual Subject Treatment Completion Criteria (see Section 6.2) are met. For these subjects, follow-up assessments will be obtained until 48 weeks after EOT (FU Schedule 2). A Subject should re-start NA treatment (ETV or TDF) during the 48 weeks of post-treatment follow-up (FU Schedule 2) if he/she meets one of the criteria described in Section 6.3. Subjects who do not meet the Individual Subject Treatment Completion Criteria after 48 weeks of study treatment, should continue or, in case of JNJ-56136379 monotherapy, start NA treatment as per local treatment guidelines. For these subjects, follow-up assessments will be obtained until 24 weeks after EOT (FU Schedule 1). For subjects who do not continue or start NA treatment at Week 48, an additional 24-week follow-up (as per local treatment guidelines), by their primary care physician outside of the study, is recommended after the 24-week follow-up phase in the study.

[c] The sponsor, in agreement with the DRC, will select the dose for Part B which will be based on all available clinical safety data of JNJ-56136379 following the completion of the dose evaluation in the Phase 1b study 56136379HPB1001. This dose will not exceed the highest dose evaluated in study 56136379HPB1001, i.e., 250 mg once daily.

1.3. Protocol Amendments

This SAP was prepared based on the trial protocol number EDMS-ERI-148527695, 13.0

1.4. Statistical Hypotheses for Trial Objectives

As this is an exploratory, hypothesis-generating study, no formal statistical hypothesis testing will be performed.

1.5. Sample Size Justification

See CTP, Section 11.2.

1.6. Randomization and Blinding

See CTP, Section 5.

2. GENERAL ANALYSIS DEFINITIONS

The SAP will use throughout the document the following definitions:

- *Treatment* includes JNJ-56136379, placebo and NA (ETV or TDF)
- *Study agent* includes JNJ-56136379 and placebo
- *NA* includes NA (ETV or TDF)

2.1. Analysis Sets

Screened Population or all subjects consists of all subjects, i.e. screening failures and (not) randomized subjects.

Safety population consists of all subjects who received at least one dose of the study agent and all safety endpoints will be analyzed by the treatment arm as treated.

Intent-to-Treat Population (ITT): all subjects who are randomized and received at least one dose of any study agent. If a subject receives a study agent other than their randomly assigned study agent, subjects will be shown in the treatment arm as randomized.

The analysis population will be indicated in the title of each table and listing.

2.2. Definition of Baseline

The last observed measurement before the date and time of the first administration of the study agent will be considered the baseline measurement.

In case the first administration time and/or the measurement time is missing,
the day 1 measurement will be considered as baseline measurement. The underlying assumption is that the protocol is followed which states that day 1 samples are to be collected before the first dose of study drugs.

2.3. Definition of Analysis Phases, Periods, Types of Follow-up, Time Points and Visit Windows

Analysis phase allocation will be included for all part of the analysis if applicable. The analysis periods and follow-up types will be presented in the efficacy part and the safety part (except for adverse events) of the analysis and in the general output if mentioned.
The analysis phase and periods and analysis time points are presented in the table 1 and table 2 below.
The procedures to be performed throughout the study at each time point are outlined in the time and events schedule in appendix 4, appendix 5 and appendix 6 of this document.

Table 1: Construction of phases

Analysis phase	***Analysis Period***	***Start date***	***End date***
Screening (phase 1)		The date of signing the informed consent	1 day before the first study agent intake
Treatment (phase 2)	Initial Treatment	Date of first study agent intake	- If <u>not</u> included in the treatment extension°: Date of last study agent intake + 5 days*

Analysis phase	*Analysis Period*	*Start date*	*End date*
	(period 1)		- If included in the treatment extension°: Date of Week 24 study agent intake+5 days[#]
	Treatment Extension (period 2)	End of the initial treatment period + 1 day	Date of last study agent intake + 5 days*
Follow-up (phase 3)		End of the treatment phase +1 day	Trial termination date (date of last contact) or cut-off date for an interim analysis, whichever comes first

° depending on the answer in the FA dataset: FAOBJ =" WILL THE SUBJECT CONTINUE TREATMENT IN TREATMENT EXTENSION PHASE?" and whether actually treatment was extended in the EX dataset.
* or study termination date (date of last contact) or cut-off date for an interim analysis, whichever comes first.
# Date of the Week 24 visit included the EX dataset.

Note: The last phase, whichever it is for a subject, always ends on the day of trial termination (last contact) or the cut-off date in case the data are analysed for an interim or DRC analysis (whichever comes first).

There are two types of follow-up in this study defined (FAOBJ = 'DID THE SUBJECT MEET ALL THE TREATMENT COMPLETION CRITERIA AS PER PROTOCOL?'):

- Treatment free: subjects meeting the criteria mentioned in CTP section 6.3 and therefore subject will start follow-up phase without NA treatment.
- NA follow-up: subjects not meeting the criteria mentioned in CTP section 6.3 and therefore subject will start/continue follow-up phase with NA treatment.

For analyses that require a particular visit, the Time Point Window and Visit Window are defined in the table 2 as below.

Table 2: Construction of Analysis Time point and Visit Window

Analysis phase	**Analysis period**	**Target day[a]**	**Analysis time point (numeric version)**	**Analysis time point**	**Time interval (days)[b]**
Screening		-∞	-1	Screening	<0
Treatment	Initial Treatment	1	0	Baseline	Pre-dose
		7	1	Week 1	[2,11]
		14	2	Week 2	[12,21]
		28	4	Week 4	[22,42]
		56	8	Week 8	[43,70]
		84	12	Week 12	[71, 98]
		112	16	Week 16	[99, 126]
		140	20	Week 20	[127, 154]
		168	24	Week 24	[155, 182]
	Treatment Extension	196	28	Week 28	[183, 210]
		224	32	Week 32	[211, 238]

		252	36	Week 36	[239, 266]
		280	40	Week 40	[267, 294]
		308	44	Week 44	[295, 322]
		336	48	Week 48	[323, +∞]
		last visit in treatment phase	49*	EOT	
Follow-up		9	50	Follow-up Week 2	[1,16]
		23	52	Follow-up Week 4	[17,30]
		37	54	Follow-up Week 6	[31,44]
		51	56	Follow-up Week 8	[45,65]
		79	60	Follow-up Week 12	[66,93]
		107	64	Follow-up Week 16	[94,121]
		135	68	Follow-up Week 20	[122,149]
		163	72	Follow-up Week 24	[150,191]
		219	80	Follow-up Week 32	[192,247]
		275	88	Follow-up Week 40	[248,303]
		331	96	Follow-up Week 48	[304, +∞]
Overall		last visit in the study	999*	EOS	

[a] Target day in follow-up phase equals target day in the protocol minus 5 days.
[b] The reference day of the Treatment and Screening phase is the day of the first study agent intake (= day 1 in Treatment phase). The reference day of the Follow-up phase is the first day of the follow-up phase.
*End of treatment and End of study visit (last available data at the end of the study) will be derived

The number of days in the treatment phase (ADY) will be defined as:

ADY = visit date – date of first study drug intake +1 for visits on or after the day of first study drug intake

ADY = visit date – date of first study drug intake for visits before the day of first study drug intake

The number of days in the follow-up phase (ADY) will be defined as:

ADY = visit date – start date of the follow-up phase + 1

All visits (regardless the investigated parameter) will be allocated within each phase/period to analysis time points based on the number of days in phase (ADY)
If two visits fall within the same interval only one measurement will be selected for the descriptive statistics/tabulations per time point and graphics in order to have only one evaluation per subject per analysis time point. Following rules will be applied:

- The measurement closest to the target day will be used.
- If the measurements fall equidistant from the target day, the last measurement in time within the interval will be used

- If there are two measurements on the same day and time, then the measurement with the highest sequence number or group ID (e.g. ECG measurements) will be used.

The listings will include all measurements.

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

Note: For the selection of the 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 (i.e., not mixing answers from different questionnaires)

2.4. Missing and Partial data

In general, missing data and partial dates will not be imputed and will treated as missing. Only partially missing diagnosis and infection dates will be temporarily imputed to calculation the duration of infection and the time since diagnosis (see section 4.2.3). The original, non-imputed, dates will be listed.

To calculate the duration of infection or duration of diagnosis, if the reported date is partially missing, the imputation rules below is to be considered:

- Impute with the first day of the month if only day is missing
- Impute with January 1st if only the year is available
- Leave missing if completely missing

2.5. Definition of Subgroups

The parameters below will be used as subgroup variable in the analysis where appropriate. Derivation will be described in section 4.2.2.

- Hepatitis B e Antigen (HBeAg) status at baseline
    - All
    - Positive
    - Negative
- Subject population
    - Currently not being treated

- Virologically suppressed by current NA treatment

Note: this should also be determined for all screened subjects.

- Hepatitis B Surface Antigen (HBsAg) level at baseline
  - For treatment naïve HBeAg positive (HBsAg ≥10,000 IU/mL versus HBsAg <10,000 IU/mL)
  - For all other (HBsAg ≥1,000 IU/mL versus HBsAg <1,000 IU/mL)
- Hepatitis B virus infection genotypes (coalesce)
  - Genotype A
  - Genotype B
  - Genotype C
  - Genotype D
  - Genotype E
  - Genotype F
  - Genotype G
  - Genotype H
  - Etc..
  - Unknown

2.6. Presentation of results

Continuous parameters will be summarized using the following statistics: number of observations, mean, 95% confidence interval (CI) for mean, standard deviation (SD), standard error (SE), minimum, median and maximum, unless specified otherwise. The minimum and maximum will be presented to the same number of decimal places as the original data. The mean and median should be expressed with 1 decimal place more than the original values. The standard deviation, standard error and 95% confidence limits with be shown with 2 decimal place more than the original values.

Frequencies and percentages will be used for summarizing categorical (discrete) data. If a count is 0, the 0 count will be displayed, but the corresponding percentage should be omitted. If the corresponding denominator for the count is also 0, a hyphen (-) should be displayed rather than a 0 count or NAP [not applicable], and the corresponding percentage should be omitted.

All tables and graphs will be evaluated by subject population (i.e., subjects currently not being treated, virologically suppressed by current NA treatment or all population), by hepatitis B e antigen (HBeAg) status and overall, by treatment group (i.e., JNJ-56136379 [at two dose levels] and NA [entecavir {ETV} or tenofovir disoproxil fumarate {TDF}] as monotherapy or coadministered), unless otherwise specified. Data will be presented in listings by subject population, HBeAg status, treatment group and subject number.

The main layout for the tables, unless specified otherwise, will be as followed:

Layout 1	Pooled Placebo + NA	JNJ6379 75 mg	JNJ6379 75 mg + NA	All JNJ6379 75mg	JNJ6379 250 mg	JNJ6379 250 mg + NA	All JNJ6379 250 mg	All JNJ6379 Doses

Layout 2	Pooled Placebo + NA	Placebo + NA Part A	Placebo + NA Part B

3. INTERIM ANALYSIS AND DATA REVIEW COMMITTEE

3.1. Interim Analysis

At week 12 an interim analysis will be performed. The sponsor will remain blinded to the randomization codes (unless the Data Review Committe [DRC] recommends unblinded analyses) and data will be analyzed using dummy identification. Aggregated efficacy summary statistics (subsequent analyses) will be available to the sponsor at the blinded Week 12 interim analyses and the randomization codes will be available to the sponsor at the unblinded Week 24 interim analyses. The subjects and investigators will remain blinded to randomization codes until the end of the study. Note that blinding does not apply to the JNJ-56136379 monotherapy arms (open label).

The interim analyses, encompassing efficacy and safety, and pharmacokinetics, may be conducted for both **Parts A and B** when:

- at least 80% of subjects have completed visits at Week 12 or have discontinued earlier;
- at least 80% of subjects have completed visits at Week 24 or have discontinued earlier.
- at least 80% of subjects have completed visits at Week 48 or have discontinued earlier.

These interim analyses may also be performed separately by subject population (currently not being treated versus virologically suppressed) in case recruitment rates differ between the subject populations. Additional interim analyses (e.g., when subjects completed the Follow-up Week 12) may be performed at the sponsor's discretion to support decision making for further development of JNJ-56136379 and to support interactions with health authorities.

A final analysis will be performed when all subjects in the study have completed the Follow-up Week 24 visit or have discontinued earlier.

The selection of the required analyses output for the different types of interim analysis (e.g. Week 12, Week 24, Week 48, Final analysis) to be performed are indicated in the Data Presentation Specifications (DPS).

3.2. Independent Data Review Committee

An independent data review committee (DRC) independent from the study team, will be established to monitor safety and efficacy data in an unblinded manner on a regular basis throughout the study and will make recommendations on treatment continuation for longer treatment durations to safeguard the health and the well-being of the study participants.

The details will be provided in a separate DRC charter and the selection of the required analysis outputs are indicated in a separated the DPS. The DRC output is a subset of the output included in the DPS of the final analyses.

4. SUBJECT INFORMATION

All general analyses will be done on the ITT population unless specified otherwise for a specific display.

4.1. Disposition Information

The following subject data will be tabulated:

- The number and percentage of subjects who are screened, screening failure and reason of that screening failure, as also the (not) randomized and (not) treated subjects. Only an all subjects group will be provided. This table does not have to be presented by

subject population and HBeAg status. The information on screening failures and not treated subjects is also listed for all subjects meeting the previous criteria.

- The number and percentage of subjects who completed or discontinued (or were ongoing for [only for interim analyses]) the study as documented on the study termination page and the number and percentage of subjects for each study discontinuation reason.
- The number and percentage of subjects who overall completed or discontinued (or were ongoing for [only for interim analyses]) the study agent as documented on the study drug termination page and the number and percentage of subjects for each study agent discontinuation reason. Further, the number and percentage of subjects who completed the initial 24 weeks treatment and treatment extension and information on participation in a treatment extension is included.
- The number and percentage of subjects randomized and treated for each analysis time point with information of the status of study participation at that particular analysis time point (i.e. ongoing, terminated study participation with the reason or completed).
- A listing including information (i.e. the date of last study visit, the last treatment period analysis time point, the date of discontinuation and the reason) on subjects which prematurely terminated the study and/or study agent is included.
- The overall date of first signed informed consent, first visit, last visit and last contact will be provided.

4.2. Demographics and Baseline Characteristics

Tabulations of demographics, baseline characteristics and stratification factors will be presented for all subjects and by treatment group in the intent-to-treat population.

4.2.1 Demographic characteristics

- Gender: Male, Female, Unknown, Undifferentiated
- Age (years)
    - Age (years) will use age at informed consent, if missing, age will be calculated as (date of informed consent – date of birth +1) / 365.25

- Age categories: ≤ 45 years, > 45 years
- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other and Unknown
- In case the subject is Asian provide subgroup: Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, Other, Multiple and Unknown
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not Reported
- Country
- Region: Asia /Non- Asia (Based on country according to UN classification of Geographic regions: https://www.un.org/en/development/desa/policy/wesp/wesp_current/2014wesp_country_classification.pdf)
- 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
- Current smoker: Yes/No (Former smokers are included in the 'No' category)
- Subject population: Currently not being treated or virologically suppressed by current NA treatment: (SUPPDM.QNAM = 'SBVIRSUP')
- Hormonal contraceptive in females: Yes/No (only include for female subjects: SUPPDM.QNAM = 'FHORCONT')
- Type of Tobacco, Cigarettes, Cigars, Pipes, E-cigarette, Smokeless tobacco (listed only)
- Date of signing the Informed Consent (listed only)
- Date of birth (listed only)
- Childbearing potential (only listed)
- Alcohol test results (only listed)
- Drug testing results (only listed)

4.2.2 Baseline characteristics

For the viral activity parameters (e.g. HBeAg, HBsAg, HBV DNA), non-historical results are used unless specified differently.

- Mode of Infection: MSM, Heterosexual Contact, Intravenously Injectable Drug Use, Blood Transfusion, Hemophilia-associated Injection, Occupational Exposure, Mother to Child Transmission, Other, Unknown
- Last NA treatment before baseline: Lamivudine, Telbivudine, Adefovir, Tenofovir, Entecavir, IFN, Other:
    - The last historical NA treatment with indication in the FA dataset that the NA treatment is still used.
- Duration of infection (Years) = (date of baseline – date of HBV infection +1)/365.25; rounded to 1 decimal
    - Imputation rules for partially missing dates to calculate the duration are included in section 2.4.
- Time since diagnosis (Years) = (date of baseline – date of diagnosis+1)/365.25; rounded to 1 decimal
    - Imputation rules for partially missing dates to calculate the duration are included in section 2.4.
- Chronic Hepatitis B at screening: Chronic Hepatitis B as confirmed by a positive historical HBsAg status and a negative Hepatitis B IgM Antibody at screening.
    - Use the last available historical measurement for HBsAg: the qualitative result or the quantitative result. The quantitative result is positive when the result is higher than the quantification limit available in the dataset. If both are available at the same date use the quantitative result.
    - Use the last available measurement for Hepatitis B IgM Antibody before first study agent administration.
- Historical HBeAg status in virologically currently being suppressed subjects not being on NA treatment (LBHISTRT = 'N'). In case of multiple records available the latest prior to baseline should be used.
- HBeAg status at baseline (qualitative): Positive / Negative
    - Borderline is included as Negative
- HBeAg at baseline (quantitative: IU/mL and log10 IU/mL, for HBeAg positive qualitative results only): all samples are used, not only the quantitative counterpart of the qualitative result which is the same sample.
- HBsAg status at baseline (qualitative: IU/mL and log10 IU/mL): Positive / Negative
    - Borderline is included as Negative
- HBsAg at baseline (quantitative: IU/mL and log10 IU/mL): all samples are used, not only the quantitative counterpart of the qualitative result which is the same sample.
- HBsAg group at baseline
    - HBeAg positive currently not treated subjects
        - Subjects with HBsAg <10000 IU/mL

        - Subjects with HBsAg ≥10000 IU/mL
    - All other
        - Subjects with HBsAg <1000 IU/mL
        - Subjects with HBsAg ≥1000 IU/mL
- Historical HBV DNA at baseline (qualitative, based on historical data)
- HBV DNA at baseline (quantitative: IU/mL and log10 IU/mL)
- HBV DNA category at baseline (quantitative)
    - Subjects with HBV DNA < 20 IU/mL
    - Subjects with HBV DNA < 60 IU/mL
    - Subjects with HBV DNA < 2000 IU/mL
    - Subjects with HBV DNA < 20000 IU/mL
    - Subjects with HBV DNA ≥ 20000 IU/mL
    - Subjects with HBV DNA >=100 000 IU/mL
    - Subjects with HBV DNA < 100 000 IU/mL

- HBV RNA (quantitative: copies/mL and log10 copies/mL)
- Hepatitis B core related antigen (HbcrAg) at baseline (quantitative: log10 IU/mL)
- HBV Surface Antibody (Anti-HBs) status at baseline (qualitative): Positive/Negative
- HBV Surface Antibody at baseline (quantitative: mIU/mL and log10 mIU/mL): all samples are used, not only the quantitative counterpart of the qualitative result which is the same sample.
- HBV e Antibody (Anti-HBe) status (Positive/Negative)
    - Borderline is included as Negative
- Alanine Transferase (ALT) at baseline (only Covance results)
    - Baseline ALT values (U/L))
    - Baseline ALT toxicity grade according to DAIDS
    - Baseline ALT categorization (≤ 1.0 ULN, > 1.0 ULN - <2.5 ULN, ≥ 2.5 ULN)
    - Baseline ALT categorization (≤ 1.0 ULN, > 1.0 ULN)
    - Baseline ALT categorization (<2.5 ULN, ≥ 2.5 ULN)
- HIV-1/2 AB / HIV-1 P24 AG Combo test (qualitative)

- Fibrosis Stage: F0, F1, F2, F3 and F4
    - Use the last available liver disease staging assessments performed by liver biopsy or fibroscan before first study agent administration should be used. If both results of liver biopsy and fibroscan at the same date, use the fibroscan result
- Method of liver staging assessment (Fibroscan / Biopsy) (listed only)
- HBV infection genotype/subtype (Coalesce): Genotype A, B, C, D, E, F, G, H, .., Unknown and Other
    - Use results from DDL Next generation Sequencing. If not available, use results from Covance Innogenetics Line Probe Assay method (Use for derivation of genotype
- HBV infection genotype/subtype (Covance Innogenetics Line Probe Assay): Genotype A, B, C, D, E, F, G, H,…, Unknown and Other
- HBV infection genotype/subtype (DDL Next generation Sequencing): Genotype A, B, C, D, E, F, G, H,…, Unknown and Other
- HBV infection genotype/subtype (historical from FA domain): Genotype A, B, C, D, E, F, G, H,…, Unknown and Other
- HBV genotype (Coalesce) method: DDL Next generation Sequencing, Covance Innogenetics Line Probe Assay, Historical + method specified in dataset. (Use this genotype at baseline and listings only)

An additional listing will be provided representing any NA treatment prior to screening including drug type, start date of treatment, end date of treatment, an indication whether the drug is currently being used and reason for treatment discontinuation (FATESTCD = “REASDSC”).

4.2.3 Randomization and stratification factors

The stratification factors found in IWRS are also found in the Electronic Case Report Form (eCRF):

- HBeAg status at screening (positive versus negative)
- HBsAg level at screening
    - HBeAg positive currently not treated subjects
        - Subjects with HBsAg <10000 IU/mL
        - Subjects with HBsAg ≥10000 IU/mL
    - All other
        - Subjects with HBsAg <1000 IU/mL
        - Subjects with HBsAg ≥1000 IU/mL
- Chronic Hepatitis B (CHB)-infected subject population
    - Currently not being treated
    - Virologically suppressed by current NA treatment (ETV or TDF)

The following randomization and stratification factor data will be tabulated:

- A cross–tabulation of the stratification factor HBeAg status and the HBeAg status at baseline/screening by treatment group. The number of subjects and percentages are shown. A totals column and row are included. This table does not have to be presented by subject population and HBeAg status.
- A cross–tabulation of the stratification factor HBsAg status and the HBsAg status at baseline/screening by treatment group. The number of subjects and percentages are shown. A totals column and row are included. This table does not have to be presented by subject population and HBeAg status.
- A tabulation of the stratification factors in the IWRS by treatment group. This table does not have to be presented by subject population and HBeAg status.
- A listing with randomization data (e.g. randomization date, number), stratification factors and randomized / actual treatment will be provided.

4.2.4 Genotype/Subtype

Different methods of genotyping is used in the study. The following methods can be found:

- Covance Innogenetics Line Probe Assay (Inno LiPA)
- DDL Next generation Sequencing

The following tabulation about the different methods concerning genotypes will be provided:

- A cross-tabulation of the genotype (DDL Next generation Sequencing) and the genotype (Covance Inno LiPA) by treatment group will be provided. A total and missing, if applicable, column/row will be provided. This table does not have to be presented by subject population and HBeAg status.

4.3. Protocol Deviations and Inclusion/Exclusion Criteria

- Only major protocol deviations will be defined in this study. All major protocol deviations will be tabulated per coded term by treatment group.
- All inclusion criteria which were not met and exclusion criteria which were met are tabulated represented as inclusion/exclusion number.
- A listing of the major protocol deviation will be presented
- A listing of the deviations to the inclusion/exclusion criteria will be included
- A listing of the major protocol deviation coded as 'Received wrong treatment of incorrect dose' will be provided.

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:

- Prior medications are defined as medications with a start date occurring before date of first dose of study agent regardless of when dosing of the medication ended.
- Concomitant medications are defined as medications received at or after the first dose of the study agent, medication that was received before initial dosing and continued after initial dosing of the study agent, or medication with missing stop date.
- Medication that started before the first dose of study agent and continued after the first dose of study agent will be summarized as prior medication and separately as concomitant medication.
- In case of a completely missing start date, the concomitant therapy will be considered as having started before the trial or use all available information in the eCRF indicating if before or after or ongoing.
- In case of a completely missing end date, the concomitant therapy will be considered as ongoing at the end of the trial or use all available information in the eCRF indicating if before or after or ongoing.

All medication will be allocated to analysis phases taking into account their start date and end date as also the eCRF indication before or after or ongoing.

Concomitant medications of interest will be provided in this analysis. These will be determined by medical review of a distinct list of all coded concomitant medications and its Anatomical Therapeutic Chemical (ATC) class levels. The following categories will be included:

- Anti-HBV NA rescue medication (Nucleoside and nucleotide reverse transcriptase inhibitors)
- Any other types of rescue medication
- Oral contraceptives (hormonal contraceptive of systemic use)
- Medications that impact immune system (e.g. corticosteroids, cyclosporin, interferon)
- Medication that can be subject to CYP3A4 induction

The following tabulations and listings will be provided:

- Tabulation of the ATC level 2, ATC level 4 and preferred terms of the concomitant medications per treatment group and by analysis phase.
- Tabulation of the ATC level 2, ATC level 4 and preferred terms of the prior medications per treatment group and by analysis phase during which they were applied.
- Tabulation of the ATC level 2, ATC level 4 and preferred terms of the anti-HBV NA rescue medication (i.e. concomitant medications of interest) per treatment group and by analysis phase during which they were applied.
- Tabulation of the ATC level 2, ATC level 4 and preferred terms of any other types of rescue medication (i.e. concomitant medications of interest) per treatment group and by analysis phase during which they were applied.
- Tabulation of the category of the concomitant medications of interest and preferred terms of the concomitant medications of interest per treatment group and by analysis phase during which they were applied.
- A listing including all prior and concomitant medication (i.e. verbatim and coded term) with indication of prior/concomitant will be provided. All available data will be included as also ATC levels 2 and 4.
- A listing including the anti-HBV NA rescue medication and the any other types of rescue medication (i.e. concomitant medications of interests) will be provided. This listing will be similarly to the listing for prior and concomitant medication.
- A listing including all concomitant medications of interests will be provided similarly to the listing for prior and concomitant medication. This listing will be similarly to the listing for prior and concomitant medication except for an additional column for the concomitant medications of interest categories.

4.5. Medical History

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

Listings including the general medical history, surgical medical history and family medical history will be included.

4.6. Exposure

The total duration of exposure of the study agent in weeks is calculated as follows:

(last drug intake date – first drug intake date + 1)/7

The following categories of total duration of exposure of the study agent are used in the analysis:

- < 1 week
- ≥ 1 - ≤24 weeks
- > 24 weeks

The following categories of cumulative total duration of exposure of the study agent are used in the analysis:

- ≥ 1 week (i.e. also including all subjects included in the '≥ 24 weeks' cumulative duration of exposure category)
- ≥ 24 weeks

The following categories of adjustments of the study agent are used in the analysis:

- As study planned: No adjustments reported throughout the complete study
- At least one dose missed, reduced or increased: if any adjustments reported throughout the complete study.

The following tabulation and listings will be included:

- Descriptive statistics of the total duration of exposure of the study agent will be provided, as also the tabulation of total duration of exposure categories and cumulative total duration of exposure categories for all subjects, not by subject population and HBeAg status and using the safety population. Additionally, the descriptive statistics of the total duration of exposure for non-completed subjects (i.e. discontinued subjects and ongoing subjects [only for interim analyses]) and completed subjects will be presented separately.

- A cross-tabulation of the randomized and actual treatment arms are included. This table will not be presented by treatment group, subject population and HBeAg status.
- A tabulation of categories of adjustments of the study agent will be included. This table will not be presented by subject population and HBeAg status using the safety population.
- For every treated subject, the trial medications (i.e. study agent and NA treatment), their times of administration, as well as the corresponding doses and an indication whether a dose adjustment was present and the reason will be shown in a listing. Treatment administration on site and at home will be shown in chronological order.

4.7. Drug Accountability and Compliance

The compliance in this study is defined as the correct amount of tablets taken as there is no distinction made between the different doses of tables (i.e. 25mg or 100mg).

The percentage of compliance will be defined by the number of tablets that patients have taken during their duration of the study, assuming n tablets per day.

$$Compliance\ (\%) = \frac{Number\ of\ tablets\ dispensed - Number\ of\ tablets\ returned}{n * number\ of\ day\ during\ the\ study} * 100$$

Where n = 3 for part A (3*25 mg=75mg) and n=4 for part B (2*100mg + 2*25mg=250mg)

Percentage of compliance will be summarized descriptively in the treatment phase and by discontinuing the trial during the treatment period

The treatment exposure and compliance will be summarized using the safety population by treatment group and for the treatment phase (including the extension follow-up phase) and for overall.

4.8. Comments

All comments will be listed in one listing, indicating each domain.

5. EFFICACY EVALUATIONS

Efficacy assessments will be performed at the planned time points indicated in section 2.3 above (see Appendix 4, 5 and 6) using the ITT population. All HBV virology (i.e. HBV DNA and RNA) and serology (i.e. HBsAG, HBeAg, HbcrAg, Anti-HBs, Anti-HBe) available data will be analyzed by subject population, hepatitis B e antigen (HBeAg) status

and overall, treatment group, analysis phase, analysis period and follow-up type and at each analysis time point (when applicable). Placebo treatments can be pooled as 'placebo' over Parts A and B. The sections below describe the data handling rules used in the primary, secondary and exploratory analysis.

5.1. Data handling rules

Units as provided in the SAP will be used in the analyses if these are deviated from the units provided in the Study Data Tabulation Model (SDTM) data. The viral activity parameters (i.e. virology and serology parameters) will be analyzed using log10 transformation rounded to 2 decimal places.

Historical as actual data for viral activity parameters will be used in the analysis. In the case a diluted and a non-diluted sample are present for a parameter at any time point, only the diluted sample will be included in the analysis. Historical viral activity measurements will not be imputed. The actual measurements will be imputed as follows:

- **HBsAg** values were tested with an upper limit of quantification of 124925.00 IU/mL and a lower limit of quantification of 0.05 IU/mL. Samples for the determination of HBsAg were processed in real-time using an assay such as the ARCHITECT platform (Abbott Laboratories).
- Values above the upper limit of quantification (124925.00 IU/mL), will be imputed by the value of round (ULOQ+(ULOQ/10)) IU/mL in the analysis.
- Values below the lower limit of quantification (0.05 IU/mL) will be imputed by a rounded value of (LLOQ/2) IU/mL in the analysis.

- **HBeAg** values were tested with an upper limit of quantification of 1400.00 IU/mL and a lower limit of quantification of 0.11 IU/mL.
- Values above the upper limit of quantification (1400.00 IU/mL), will be imputed by a value of round (ULOQ+(ULOQ/10)) IU/mL in the analysis.
- Values below the lower limit of quantification (0.11 IU/mL) will be imputed by a rounded value of (LLOQ/2) IU/mL in the analysis.

- **HBcrAg** values were tested within a measurement range of 3.0 LogU/mL - 9.0 LogU/mL

    - Values below lower limit of quantification (<3.0 LogU/mL) will be imputed by 2.7 log U/mL
    - Values above the upper limit of quantification (official ULOQ = 7 Log U/ml but with dilution ULOQ= 9.0 Log U/ml) will be imputed by value of round (ULOQ+(ULOQ/10)) log10U/mL with or without dilution method

- **Plasma HBV DNA** values were measured by the HBV COBAS AmpliPrep – COBAS TaqMan, V. 2.0 test (lower limit of quantification 20 IU/mL). Values below the lower limit of quantification (20 IU/mL) will be imputed as follows:
    - Values below the lower limit of quantification (20 IU/mL), but target detected will be imputed by a value of 15 IU/mL in the analysis.
    - Values below the lower limit of quantification (20 IU/mL, target not detected) will be imputed by a value of 5 IU/mL in the analysis.
    - Values above the upper limit of quantification (>170000000 IU/mL), will be imputed by the value of round (ULOQ+(ULOQ/10)) IU/mL in the analysis

- **HBV RNA** values were tested with an upper limit of quantification (ULOQ) and a lower limit of quantification (LLOQ), all values, even below LLOQ (4.0 log10 cp/mL) or LOD (2.49 log10 cp/mL) will be reported and all numeric values will be used in the analysis.

    - Negative or Not Detected ("TND") values will be imputed by a value of 5 copies/mL (log10 (5) = 0.69897 log10 cp/mL) in the analysis.
    - Values above the upper limit of quantification (>ULOQ), will be imputed by the value of round (ULOQ+(ULOQ/10)) $\log_{10}$ cp/mL in the analysis

- **Anti-HBs** values were tested with an upper limit of quantification (ULOQ) and lower limit of quantification (LLOQ), all values, even below LLOQ (< 5.0 mIU/mL) will be reported and all numeric values will be used in the analysis.

- Values below LLOQ (<5mIU/mL) will be imputed by value of round (LLOQ/2) mIU/mL
- Values ">10000.00 mIU/mL" (with annotation "diluted for quantitation") will be imputed by value of round (ULOQ+(ULOQ/10)) mIU/mL

Additionally, all other viral activity data with values below a LLOQ and not included in the impuation rules above will be imputed by the absolute value divided by 2 and rounded to the amount of decimal place provided in the dataset.

5.2. Primary efficacy analysis

The primary efficacy endpoint is the qualitative measurement of the viral activity parameter hepatitis B surface antigen (HBsAg) determined using standard serologic assays in a central laboratory.

Descriptive statistics (specified in section 2.6) and the comparison of the efficacy of 24 weeks treatment (i.e. combinations of JNJ-56136379 monotherapy, JNJ-56136379+NA and placebo+NA) is mainly of interest. These comparisons will be done overall, by subject population (i.e., subjects currently not being treated or virologically suppressed by current NA treatment), and by HBeAg status (Positive or Negative).

5.2.1 Analysis of the primary endpoint

The following tabulation will be included:

- Descriptive statistics of the actual values (original unit and log10 transformed values) and the change from baseline (log10 transformed values) over time according to the specification described in section 2.6 will be included.
- Least Square (LS) means (SE) of change from baseline (and 95% confidence interval) per time point and overall based on log10 transformed values will be analyzed by subject population and part using mixed effects model for repeated measures. Also P-values for treatment, time, their interaction and overall will be added.
- LS means (SE) of change from baseline (and 95% confidence interval) per time point and overall based on log10 transformed values will be analyzed by subject population, part and by HBeAg status using mixed effects model for repeated measures. Also, P-values for treatment, time, their interaction and overall will be added.

5.2.1.1 Mixed effects model for repeated measures

The main comparisons of interest in the efficacy analyses are:

- to evaluate the efficacy of 24 weeks of JNJ-56136379 monotherapy versus placebo+NA;
- to evaluate the efficacy of 24 weeks of JNJ-56136379+NA versus placebo+NA;
- to evaluate the efficacy of 24 weeks of JNJ-56136379 monotherapy versus JNJ-56136379+NA.

The primary endpoint, Week 24 HBsAg change from baseline, will be analyzed by a comparison of each dose of JNJ-56136379 added to the background NA therapy with the concurrent control arm (placebo + NA), within each of the 4 categories defined by subject population and HBeAg status:

- Low dose (75 mg) of JNJ-56136379+NA with placebo+NA (Part A) in currently not treated HBeAg positive subjects
- Low dose (75 mg) of JNJ-56136379+NA with placebo+NA (Part A) in currently not treated HBeAg negative subjects
- Low dose (75 mg) of JNJ-56136379+NA with placebo+NA (Part A) in virologically suppressed HBeAg positive subjects
- Low dose (75 mg) of JNJ-56136379+NA with placebo+NA (Part A) in virologically suppressed HBeAg negative subjects
- High dose (TBD) of JNJ-56136379+NA with placebo+NA (Part B) in currently not treated HBeAg positive subjects
- High dose (TBD) of JNJ-56136379+NA with placebo+NA (Part B) in currently not treated HBeAg negative subjects
- High (TBD) of JNJ-56136379+NA with placebo+NA (Part B) in virologically suppressed HBeAg positive subjects

- High (TBD) of JNJ-56136379+NA with placebo+NA (Part B) in virologically suppressed HBeAg negative subjects

The same comparisons versus placebo+NA as above will also be conducted with JNJ-56136379 monotherapy.

Change from baseline based on log10 transform for quantitative HBsAg, will be analyzed by subject population using mixed effects model for repeated measures [MMRM]) including treatment group, analysis time point (treated as discrete/categorical), their interaction, HBeAg status (in the pooled analysis only), as fixed effects. The covariance structure will include a random intercept at the level of the subject to capture between-subject variability, while within-subject variability will be captured with an unstructured (type=UN) covariance matrix. In case the latter leads to convergence issues, alternative within-subject covariance structures will be considered, in the following hierarchy:

i) First-order ante-dependence structure (type=ANTE(1)),

ii) Heterogeneous first-order autoregressive structure (type=ARH(1))

iii) First-order autoregressive structure (type=AR(1)).

The mean difference, SE adjusted means, p-values and 95% confidence interval (CI) will be constructed around the difference between the LS means of each JNJ-56136379 (open label), JNJ-56136379+NA and placebo +NA at each time point and each factor where appropriate.

In addition, the effect of the subgroups (by subject population and by HBeAg status) on the efficacy parameters will be explored descriptively. A subgroup analysis by subject population and by HBeAg status will be performed using mixed effects model for repeated measures [MMRM]) including treatment group, analysis time point (treated as discrete/categorical) and their interaction as fixed effects. The covariance structure will include a random intercept at the level of the subject to capture between-subject variability, while within-subject variability will be captured with an

unstructured (type=UN) covariance matrix. In case the latter leads to convergence issues, alternative within-subject covariance structures will be considered, in the following hierarchy:

i) First-order ante-dependence structure (type=ANTE(1)),

ii) Heterogeneous first-order autoregressive structure (type=ARH(1))

iii) First-order autoregressive structure (type=AR(1)).

Subgroup levels may be combined, or subgroups omitted, if not enough data is available within the subgroup levels.

Data will also be presented graphically by treatment group and by subgroups at all different analysis timepoints (X-axis) and by individual subject.

Graphs for the mean (SE) of the transformed log10 values will be also presented by subgroups at all different analysis timepoints.

5.2.1.2 Bayesian Efficacy Analysis

For each of the comparisons listed above, a Bayesian approach will be employed. Non-informative priors will be used for the JNJ-56136379 arms. The prior for the mean of the placebo+NA treatment arms, on the other hand, will consist of a meta-analytic predictive (MAP) prior, derived from historical data. For the residual variance, a non-informative prior will be used for all treatments. To explore the robustness of the Bayesian analysis to a potential prior-data conflict, the analysis will be conducted with both full and no borrowing and the results compared.

A systematic review of published data on the HBsAg change from baseline at Week 24 in treatment of subject populations with NA (tenofovir, entecavir) has been carried out by Clinical Virology and Statistics & Decision Sciences. The respective MAP distributions for the different subject populations have been derived based on a pre-final version of this database. Since the MAP distributions are not of standard form, they are each approximated

as a mixture of normal distributions. The resulting normal mixtures, with corresponding component means and variances, are summarized in **Table 3.**

Table 3: Components of the normal mixtures (mean and variance) of the MAP by sub-population.

Mixture Component	Currently Not Being Treated		Virologically Suppressed (applies to both HbeAg Negative /Positive)
	HBeAg Positive	HBeAg Negative	
1	0.7447 N(-0.3059, 0.01892)	0.0177 N(-0.01450, 0.1045)	0.3809 N(-0.06528, 0.01440)
2	0.2553 N(-0.3122, 0.05255)	0.5728 N(-0.00925,0.005850)	0.6191 N(-0.05667, 0.004036)
3		0.4095 N(-0.01308, 0.01988)	

To facilitate description of the methodology, for the remainder of this section, the treatment arm containing JNJ-56136379 will be referred to as the experimental (E) arm, to be compared with the active comparator or standard of care (S) arm (i.e. placebo+NA arm).

The efficacy analysis of JNJ-56136379HPB2001 aims to demonstrate superiority of JNJ-56136379 in combination with NA therapy over NA therapy alone. Within a Bayesian framework, declaring superiority is based on the posterior probability

$$\boldsymbol{P}\left(\boldsymbol{\theta_E^* - \theta_S^* < 0} \middle| \boldsymbol{Y_E^*, Y_S^*, \mu_{E_{prior}}, \mu_{S_{prior_i}}, \tau^2_{E_{prior}}, \tau^2_{S_{prior_i}}}\right), \quad (1)$$

where:

Y_E^* and θ_E^* respectively denote the observed and true mean change in serum HBsAg levels for the experimental arm in the current trial, JNJ-56136379HPB2001,

Y_S^* and θ_S^* respectively denote the observed and true mean change in serum HBsAg levels for the Control arm in the current trial, JNJ-56136379HPB2001,

$(\theta_E^* - \theta_S^*) \equiv \Delta$ denotes the treatment effect of JNJ-56136379 in combination with NA therapy over NA therapy alone for the current trial, JNJ-56136379HPB2001,

$\mu_{E_{prior}}$ and $\tau^2_{E_{prior}}$ respectively denote the prior mean and prior variance for θ^*_E, and

$\mu_{S_{prior_i}}$ and $\tau^2_{S_{prior_i}}$ respectively denote the mean and variance of the i[th] component of the mixture prior for θ^*_S.

Since no historical efficacy data is available for the experimental arm, a non-informative normal prior distribution will be specified for θ^*_E, that is $\mu_{E_{prior}} = 0$ and $\tau^2_{E_{prior}} = 100$. For the Control arm, $\mu_{S_{prior_i}}$ and $\tau^2_{S_{prior_i}}$ are the means and variances enumerated in **Table 3** for the corresponding subject population.

Using Markov chain Monte Carlo (MCMC) methods, the posterior distribution for the treatment effect, $(\theta^*_E - \theta^*_S) \equiv \Delta$, of JNJ-56136379 in combination with NA therapy over NA therapy alone, will be derived using the MCMC procedure in SAS© (see Appendix for sample implementation). The posterior probability in (1) will be obtained from this posterior distribution of $(\theta^*_E - \theta^*_S) \equiv \Delta$.

The MCMC sampling will be initially run with 10,000,000 iterations (excluding 100,000 burn-in iterations) and thinning parameter of 100, specifying the seed as 123. Assessment of the convergence of the chain will be done using the built-in diagnostic tools of the MCMC procedure in SAS© (**See APPENDIX 1 for the SAS code**) Depending on the results of the diagnostic approaches, some of the MCMC settings may be modified to improve convergence.

- Summary of the posterior distribution

The posterior distribution of $(\theta^*_E - \theta^*_S) \equiv \Delta$ will be summarized using: mean, median, standard deviation, 5[th],10[th], 20[th], 50[th], 80[th], 90[th], 95[th] percentiles, posterior probability that the Week 24 change is smaller than 0, smaller than -0.5 and smaller than -1.

A density function of the posterior distribution will also be plotted.

5.2.1.3 Sensitivity Analysis

In addition, a similar analysis but without historical data in a frequentist approach will also be conducted as a sensitivity analysis for both part A and B using all population in ITT population at week 24 and will be conducted to compare:

- The mean of HBsAg change from baseline in log 10 transformed at week 24 of JNJ-56136379 monotherapy (open label) versus placebo+NA
- The mean of HBsAg change from baseline in log 10 transformed at week 24 of JNJ-56136379+NA versus placebo+NA
- The mean of HBsAg change from baseline in log 10 transformed at week 24 of JNJ-56136379 as monotherapy (open label) versus JNJ-56136379+NA

5.3. Secondary efficacy endpoints

The viral activity parameters HBsAg (qualitative), HBeAg (quantitative / qualitative), Anti-HBs (quantitative / qualitative), Anti-HBe (qualitative), HBcrAg (quantitative), HBV DNA (quantitative), HBV RNA (quantitative) and derivation from these paramters (also including HBsAg [qualtitative] derivations) will be assessed as secondary efficacy objectives.

5.2.1 Parameter Definitions

The following parameters will be derived as follows:

Viral breakthrough during 24 weeks of treatment (all subjects), during 48 weeks of treatment (subject with treatment extension) and during NA follow up for all subject who switch to NA-treatment during follow-up:

HBV virological breakthrough is defined as having a confirmed on-treatment HBV DNA increase by >1 log10 from nadir level (lowest level reached during 24/48 weeks treatment) or a confirmed on-treatment HBV DNA level >200 IU/mL in subjects who had HBV DNA level below the lower limit of quantification (LLOQ) of the HBV DNA assay.

The proportion of subjects with a viral breakthrough is defined as follows:

- 0 (No) = subject has not had a viral breakthrough (see definition above) up to the considered time point
- 1 (Yes) = subject has a viral breakthrough at the considered time point or has had a viral breakthrough before (regardless of the HBV DNA result at the considered time point)
- 2 (No: ongoing): subject has not had a viral breakthrough (see definition above) up to the last time point but is still ongoing (only for interim analysis)

Confirmed means that the criterion should be fulfilled at 2 or more consecutive time points or at the last observed time point on-treatment. On-treatment means in the treatment phase, except for the baseline record.

The proportion of subjects with a viral breakthrough during initial 24- or 48-weeks treatment but still on NA Treatment (Yes / No)

Note: For Viral breakthrough during NA follow up, only subject on NA treatment will be include in the denominator.

Viral relapse is defined in the follow-up phase as follows:
- 1 (Yes) = viral relapse: confirmed ≥ 2000 IU/mL quantifiable.
- 0 (No) = no viral relapse: at least one post-treatment measurement available and not a viral relapse
- 2 (Not applicable) = no post-treatment HBV DNA measurements available
- 3 (No: ongoing) = no viral relapse: at least one post-treatment measurement available and not a viral relapse but still ongoing (only for interim analysis)

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

Note: viral relapse will only be assessed for those subjects who at the actual end of treatment have HBV DNA < 20 IU/ml detectable/ undetectable.

Biochemical relapse is defined in the follow-up phase as follows:
- 1 (Yes) = biochemical relapse: confirmed ALT>2*ULN.
- 0 (No) = no biochemical relapse: at least one post-treatment measurement available and not a viral relapse
- 2 (Not applicable) = no post-treatment ALT measurements available

- 3 (No: ongoing) = no biochemical relapse: at least one post-treatment measurement available and not a biochemical relapse but still ongoing (only for interim analysis)

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

Note: biochemical relapse will only be assessed for those subjects who at the actual end of treatment have ALT ≤ ULN.

Clinical viral relapse is defined as follow:

- 1 (Yes) = if both viral and biochemical relapse
- 0 (No) = otherwise and not ongoing
- 2 (Not applicable) = no post-treatment measurements available
- 3 (No: ongoing) not both viral and biochemical relapse but still ongoing (only for interim analysis)

Note: clinical viral relapse will only be assessed for those subjects who at the actual end of treatment have HBV DNA < 20 IU/ml detectable/ undetectable and ALT ≤ ULN.*Seroclearance of HBsAg (all subjects) / HBeAg (positive subjects) at week 24 of the treatment* and *at week 48 of the treatment (only subjects with treatment extension)* is defined as a confirmed loss of HBsAg/HBeAg at week 24/48 of the treatment. Loss is defined as a baseline HBeAg /HBsAg (qualitative) with a "REPEAT REACTIVE, CONFIRMED" or "POSITIVE" result and a post-baseline assessment with a "NEGATIVE" result.

Seroconversion of HBsAg (all subjects) /HBeAg (positive subjects) at week 24 of the treatment and *at week 48 of the treatment (only subjects with treatment extension)* is defined as:

- Use the selected time point for the week 24 or 48 visit as described in 2.3.
- A confirmed loss of HBsAg/HBeAg at week 24/48-of the treatment (i.e. seroclearance)
- and an appearance of Anti-HBs/Anti-HBe.

Loss is defined as a baseline HBeAg /HBsAg (qualitative) with a "REPEAT REACTIVE, CONFIRMED" or "POSITIVE" result and a post-baseline assessment with a

"NEGATIVE" result. Appearance is defined as a baseline Anti-HBs/ Anti-HBe (qualitative) with a "NEGATIVE" result and a post-baseline assessment with a "POSITIVE" result. Both criteria should be fulfilled.

Status changes from baseline at week 24 and *at week 48 (only subjects with treatment extension)* for HBsAg, HBeAg, anti-HBs and anti-HBe status. Only the qualitative result will be considered. Use the selected time point for the week 24 or 48 visit as described in 2.3. The following categories were defined. The categories can be extended when missing values are present. A borderline result will be mapped as negative.

- Positive to Positive
- Negative to Negative
- Negative to Positive
- Positive to Negative

Maximum decrease from baseline is defined as the minimum value for change of baseline for the viral activity parameters HBeAg, HBsAg, HBVRNA, HBVDNA and HBcrAg)

Biochemical response or alanine aminotransferase (ALT) normalization from baseline per post-baseline time point is defined for subjects with elevated ALT (ALT>ULN) at baseline as:

- 0 (No) = ALT>ULN
- 1 (Yes) = ALT≤ULN

On-treatment failure during week 24 period is defined as:

- Subject who has at week 4 HBVDNA < 1log10 IU/mL decline from baseline and confirmed by retesting at week 8 visit (apply only for the naïve treatment population)
- Or for subject who experienced viral breakthrough as defined above

On-treatment failure during week 48 period is defined as:

- Subject whom after completed week 24 treatment and still on JNJ-56136379 experienced viral breakthrough as defined above

- Subject who did not meet the treatment extension criteria at week 24 as defined in the protocol (this should be derived using the criteria below)
    - Completed 24 weeks of treatment
    - HBVDNA levels < 200 IU/mL at week 20
    - No safety concerns during the initial 24 weeks of treatment
- Subject who did not meet the week 40/44 treatment completion criteria as defined in the protocol (this should be derived using the criteria below)
    - Completed 48 weeks of treatment
    - At week 40 and confirmed at week 44
        - Normal ALT levels or elevated ALT levels by investigator opinion
        - HBV DNA <LLOQ
        - HBeAg negative
        - HBsAg < 500 IU/mL
        - >=1 log10 IU/mL decline in HBsAg from baseline

Post-treatment failure during follow-up with NA treatment is defined as:

Subject who completed study treatment at week 24 and did not met the treatment extension criteria or subject who did not met treatment completion criteria at week 48 as defined above or subjects who discontinued study treatment earlier and experienced viral breakthrough as defined above (NA treatment)

Post-treatment failure during follow-up free treatment is defined as:

Subject who completed 48 weeks of treatment (treatment extension phase) and met the treatment completion criteria and experienced viral relapse as defined below

- HBV DNA <20 IU/mL at week 40/44 (requirements of the treatment completion criteria)
- Confirmed post-treatment (follow-up free treatment) increase of HBV DNA > 2000 IU/mL

Response categories of the viral activity parameters will be tabulated per analysis phase and period and analysis timepoint if more than one records in the interval is available

Table 4: response categories for viral activity parameters

	Category criteria	Additional info
HBsAg Response	Subject who has achieved a HbsAg level <1000 IU/mL per time point	These proportions will also be included per analysis phase and analysis period. A subject will be included in the numerator if the response category is at least once met within the analysis phase/period.
	Subject who has achieved a HbsAg level <100 IU/mL per time point	
	Subject who has achieved a HbsAg level <10 IU/mL per time point	
	Subject who has achieved a HbsAg level <0.05 IU/mL per time point	
HBV DNA Response	Subject who has achieved a HBV DNA level <1 log10 IU/mL per time point	These proportions will also be included per analysis phase and analysis period. A subject will be included in the numerator if the response category is at least once met within the analysis phase/period.
	Subject who has achieved a HBV DNA level <2 log10 IU/mL per time point	
	Subject who has achieved a HBV DNA level <3 log10 IU/mL per time point	
	Subject who has achieved a HBV DNA level <20 IU/mL per time point	
	Subject who has achieved a HBV DNA level <60 IU/mL per time point	
	Subject who has achieved a HBV DNA level <100 IU/mL per time point	
	Subject who has achieved a HBV DNA level <1000 IU/mL per time point	
	Subject who has achieved a HBV DNA level <2000 IU/mL per time point	
	Subject who has achieved a HBV DNA level <20000 IU/mL per time point	
	Subject who has achieved a HBV DNA level < LLQ for target detected and not detected per time point	
	Subject who has achieved a HBV DNA level < LLQ for target not detected per time point	
	Subject who has achieved a HBV DNA level < LLQ for target detected per time point	
HBV RNA Response	Subject who has achieved a HBV RNA level <100 cp/mL per time point	These proportions will also be included per analysis phase and analysis period. A subject will be included in the numerator if the response category is at least once met within the analysis phase/period.
	Subject who has achieved a HBV RNA level <1000 cp/mL per time point	
	Subject who has achieved a HBV RNA level <2000 cp/mL per time point	
	Subject who has achieved a HBV RNA level <20000 cp/mL per time point	
	Subject who has achieved HBV RNA target not detected per time point	
	Subject who has achieved HBV RNA < LLOQ per time point	
	Subject who has achieved a HBV RNA level <250 cp/mL at week 24	
HbcrAg Response	Subject who has achieved a HBV DNA level <2 log10 IU/mL per time point	These proportions will also be included per analysis phase and analysis period. A subject will be included in the numerator if the response category is at least once met within the analysis phase/period.
	Subject who has achieved a HBV DNA level <3 log10 IU/mL per time point	
	Subject who has achieved a HBV DNA level ≥2 - <3 log10 IU/mL per time point	
HbsAg Reduction	Subject who has HbsAg reduced by > 0.3 log10 IU/mL from baseline per time point	These proportions will also be included per analysis phase and analysis period. A subject will be included in the numerator if the response category is at least once met within the analysis phase/period.
	Subject who has HbsAg reduced by > 0.5 log10 IU/mL from baseline per time point	
	Subject who has HbsAg reduced by > 1 log10 IU/mL from baseline per time point	
	Subject who has HbsAg reduced by > 2 log10 IU/mL from baseline per time point	
	Subject who has HbsAg reduced by > 3 log10 IU/mL from baseline per time point	
HbeAg Reduction	Subject who has HbeAg reduced by > 0.5 log10 IU/mL from baseline per time point	These proportions will also be included per analysis phase and analysis period. A subject will be included in the numerator if the response category is at least once met within the analysis phase/period.
	Subject who has HbeAg reduced by > 1 log10 IU/mL from baseline per time point	
	Subject who has HbeAg reduced by > 2 log10 IU/mL from baseline per time point	
HBV DNA Reduction	Subject who has HBV DNA reduced by > 1 log10 IU/mL from baseline per time point	These proportions will also be included per analysis phase and analysis period.

	Subject who has HBV DNA reduced by > 2 log10 IU/mL from baseline per time point	A subject will be included in the numerator if the response category is at least once met within the analysis phase/period.
	Subject who has HBV DNA reduced by > 3 log10 IU/mL from baseline per time point	
	Subject who has HBV DNA reduced by > 1 log10 IU/mL from baseline at week 4 and confirmation at week 8.	
HBV RNA Reduction	Subject who has HBV RNA reduced by > 1 log10 cp/mL from baseline per time point	These proportions will also be included per analysis phase and analysis period. A subject will be included in the numerator if the response category is at least once met within the analysis phase/period.
	Subject who has HBV RNA reduced by > 2 log10 cp/mL from baseline per time point	
	Subject who has HBV RNA reduced by > 3 log10 cp/mL from baseline per time point	
HbcrAg Reduction	Subject who has HBV DNA reduced by > 0.5 log10 IU/mL from baseline	These proportions will also be included per analysis phase and analysis period. A subject will be included in the numerator if the response category is at least once met within the analysis phase/period.

5.2.1 Time to events definition

All the time-to-event variables listed and defined below will be calculated for each subject. Subject who do not achieve the corresponding event will be censored. Details of the censored data are listed in the table 5 below.

Table 5: Time to event definitions and censored data

Variables	Definition	Censored data
HBsAg Response	Time to a HBsAg level of <1000 IU/mL	Subjects who did not achieve "HBsAg <xxx IU/mL" will be censored at the last HBsAg assessment
	Time to a HBsAg level <100 IU/mL	
	Time to a HBsAg level <10 IU/mL	
	Time to a HBsAg level <0.05 IU/mL	
HBsAg Reduction	Time to a HBsAg reduction of > 0.3 log10 IU/mL	Subjects who did not reduce HBsAg by ">xxx log 10 IU/mL" from baseline will be censored at the last HBsAg assessment
	Time to a HBsAg reduction of > 0.5 log10 IU/mL	
	Time to a HBsAg reduction of > 1 log10 IU/mL	
	Time to a HBsAg reduction of > 2 log10 IU/mL	
	Time to a HBsAg reduction of > 3 log10 IU/mL	
HBsAg Seroclearance (in all subjects)	Time to HBsAg seroclearance as defined in section 5.3.1	Subjects who did not achieve HBsAg seroclearance will be censored at the last HBsAg assessment
HBeAg Seroclearance (in HBeAg-positive subjects only)	Time to HBeAg seroclearance as defined in section 5.3.1	Subjects who did not achieve HBeAg seroclearance will be censored at the last HBeAg assessment
HBeAg Reduction	Time to a HBeAg reduction of > 0.5 log10 IU/mL from baseline	Subjects who did not achieve "HBeAg <xxx IU/mL" from baseline will be censored at the last HBeAg assessment
	Time to a HBeAg reduction of > 1 log10 IU/mL from baseline	
	Time to a HBeAg reduction of > 2 log10 IU/mL from baseline	
HBV virological breakthrough	Time to HBV virological breakthrough as defined in section 5.3.1	Subjects who did not achieve HBV virological breakthrough will be censored at the last HBV DNA assessment during the defined time frame

HBV DNA Response	Time to a HBV DNA level <1 log10 IU/mL	Subjects who did not achieve "HBV DNA <xx log 10" will be censored at the last HBV DNA assessment
	Time to a HBV DNA level <2 log10 IU/mL	
	Time to a HBV DNA level <3 log10 IU/mL	
	Time to a HBV DNA level <100 IU/mL	Subjects who did not achieve "HBV DNA<xxxx IU/mL" will be censored at the last HBV DNA assessment
	Time to a HBV DNA level <1000 IU/mL	
	Time to a HBV DNA level <2000 IU/mL	
	Time to a HBV DNA level <20000 IU/mL	
	Time to HBV DNA < LLQ for target detected and not detected	Subjects who did not achieve HBV DNA<LLQ for both target will be censored at the last HBV DNA assessment
	Time to HBV DNA < LLQ for target not detected	Subjects who did not achieve HBV DNA<LLQ for target not detected will be censored at the last HBV DNA assessment
	Time to HBV DNA < LLQ for target detected	Subjects who did not achieve HBV DNA<LLQ for target detected will be censored at the last HBV DNA assessment
HBV DNA Reduction	Time to a HBV DNA reduction of > 1 log10 IU/mL from baseline	Subjects who did not reduce "HBV DNA by >x log 10 IU/mL" from baseline will be censored at the last HBV DNA assessment
	Time to a HBV DNA reduction of > 2 log10 IU/mL from baseline	
	Time to a HBV DNA reduction of > 3 log10 IU/mL from baseline	
HBV RNA Response	Time to a HBV RNA level <100 cp/mL	Subjects who did not achieve "HBV RNA<xxxx cp/mL" will be censored at the last HBV RNA assessment
	Time to a HBV RNA level <1000 cp/mL	
	Time to a HBV RNA level <2000 cp/mL	
	Time to a HBV RNA level <20000 cp/mL	
	Time to HBV RNA target not detected	Subjects who did not achieve HBV RNA target not detected will be censored at the last HBV RNA assessment
	Time to HBV RNA < LLOQ	Subjects who did not achieve HBV RNA <LLOQ will be censored at the last HBV RNA assessment
	Time to a HBV RNA level <250 cp/mL	Subjects who did not achieve HBV RNA <250IU/ml will be censored at the last HBV RNA assessment
HBV RNA Reduction	Time to a HBV RNA reduction of > 1 log10 cp/mL from baseline	Subjects who did not reduce HBV RNA by ">xx log 10 cp/mL" from baseline will be censored at the last HBV RNA assessment
	Time to a HBV RNA reduction of > 2 log10 cp/mL from baseline	
	Time to a HBV RNA reduction of > 3 log10 cp/mL from baseline	

5.2.1 Secondary Analysis

- Descriptive statistics of the actual values (original unit and log10 transformed values) and the change from baseline (log10 transformed values) over time for qualitative viral activity parameters according to the specification described in section 2.6 will be included.
- LS means (SE) of change from baseline (and 95% confidence interval) for qualitative viral activity parameters per time point and overall based on log10 transformed values will be analyzed by subject population and part using mixed effects model for repeated measures similar as described in section 5.2.1.1.. Also P-values for treatment, time, their interaction and overall will be added.
- LS means (SE) of change from baseline (and 95% confidence interval) for qualitative viral activity parameters (except for HBeAg) per time point and overall based on log10

transformed values will be analyzed by subject population, part and by HBeAg status using mixed effects model for repeated measures similar as described in section 5.2.1.1. Also P-values for treatment, time, their interaction and overall will be added.

- A tabulation of the proportion of subjects with virological breakthrough during 24 week treatment and during 48 week treatment (only subjects with treatment extension) will be included.
- A tabulation of the proportion of subjects with viral relapse will be provided. For the purpose of the analysis, the denominator will only include those subjects with values Yes and No.
- Descriptive statistics of the maximum decrease from baseline (log10 transformed values) over time for qualitative viral activity parameters according to the specification described in section 2.6 will be included.
- A tabulation of the status change from baseline at week 24 and at week 48 (only subjects with treatment extension) will be displayed by viral activity parameter.
- A tabulation of the proportion of subjects who meet the criteria of response categories per time point defined in section 5.3.1 will be displayed by viral activity parameter.
- A tabulation of the proportion of subjects who meet the criteria of response categories per period defined in section 5.3.1 (additional information in the table) will be displayed by viral activity parameter.
- A tabulation of the qualitative result of HBeAg and HBsAg per timepoint (week 24 and week 48) will be included.
- A tabulation of the biochemical response per time point will be included.
- All individual values will be presented in subject listings: (1) including all subjects, (2) including subjects with viral breakthrough during 24 weeks or 48 weeks treatment (only subjects with treatment extension) and (3) including subjects with viral relapse.
- Mean (+/- SE) plots of the actual (log10 transformed) values for all viral activity parameters will be presented by parameter.
- Mean (+/- SE) plots of the change from baseline for all viral activity parameters will be presented by parameter.
- A plot representing all actual (log10 transformed) values of all viral activity parameters for each subject will be included. One graph per subject.
- The actual (log10 transformed) values over time are plotted per the viral activity parameter. Each line will represent one subject.
- The change from baseline (log10 transformed values) over time are plotted per the viral activity parameter. Each line will represent one subject.

The proportion of subjects for the secondary categorical endpoints below will be categorized by treatment group, HBeAg status and overall (pool HBeAg status) during study treatment and follow-up and where appropriate the difference between proportions and Clopper-Pearson 95%CIs may be calculated using a chi-square test of equal proportions.

- The proportion of subjects with a viral breakthrough
- The proportion of subjects with HBsAg seroclearance
- The proportion of subjects with HBsAg seroconversion
- The proportion of subject with viral relapse
- The proportion of subjects with HBsAg reduction
- The proportion of subjects with HBeAg reduction
- The proportion of subjects with HBVDNA reduction
- The proportion of subjects with HBVRNA reduction
- The proportion of subjects with biochemical relapse
- The proportion of subjects with clinical viral relapse

5.4. Dose response Analysis

The dose-response of the effect of JNJ-56136379 in an NA background regimen on the Week 24 HBsAg change from baseline will be studied using the combined data of Part A and Part B. The data will consist of three dose groups:

- Placebo: pooled control arms of Part A and Part B
- Low Dose (75 mg): JNJ-56136379+NA arm of Part A
- High Dose (to be determined): JNJ-56136379+NA arm of Part B

The dose-response analysis will be carried out by subject population (currently not treated or virologically suppressed by current NA treatment), irrespective of HBeAg status, and also by HBeAg status within each population.

The presence of a dose-response signal will be assessed using a multiple contrast test, following the MCP-Mod methodology (REF: Bjornkamp et al. 2009). In this approach, a candidate set of plausible dose-response shapes need to be defined. As only 2 JNJ-

56136379 doses (and placebo) are studied in the current trial, possible dose-response shapes to consider are determined by the relative effect of the low dose compared to the high dose and the spacing of the dose. Three monotone dose-response shapes are included in the candidate model set:

- Linear
- Emax: the effect of the low dose is higher than expected from a linear relationship
- Exponential: the effect of the low dose is less than expected from a linear relationship

These models are parametrized as follows (using notation as in Bornkamp et al., 2009):

- Linear model (no parameters)
- Emax (ED_{50}=0.20)
- Exponential (δ=0.18)

The three dose response shapes are illustrated in Figure 1.

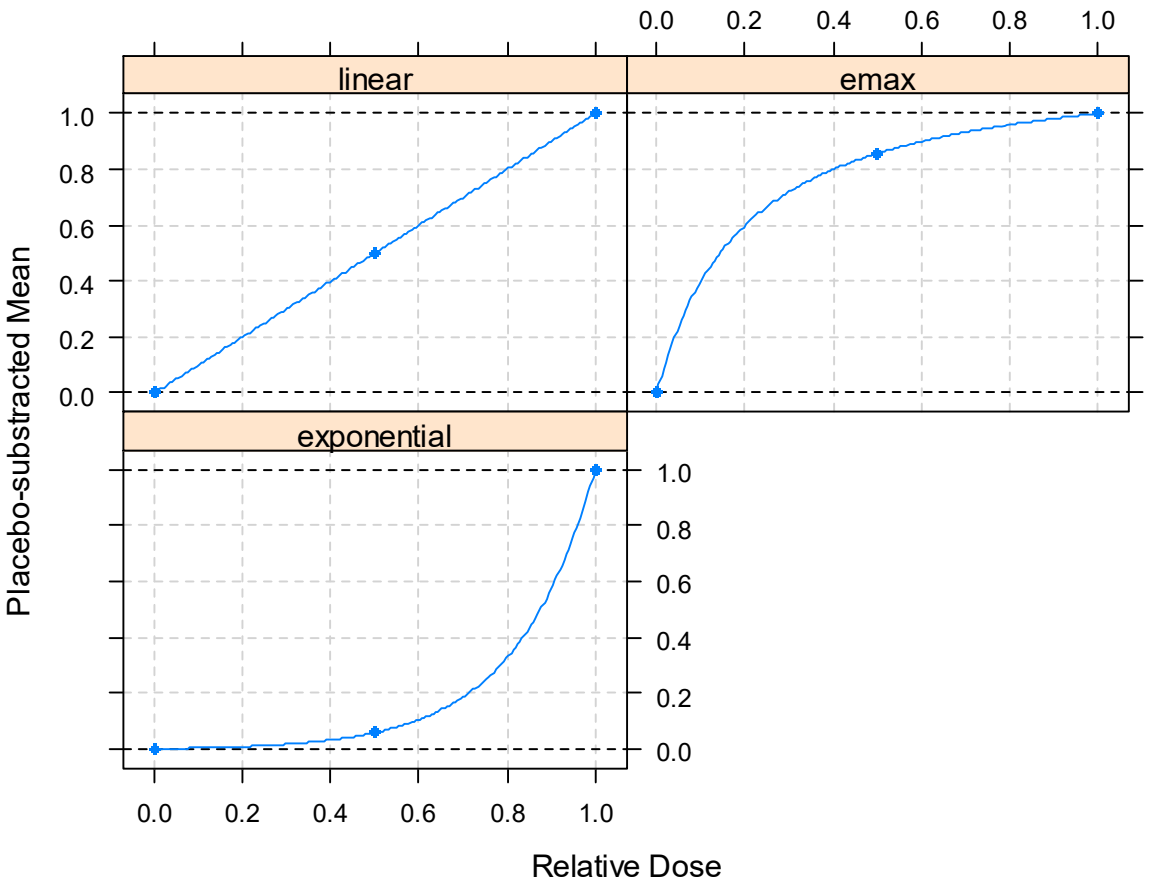


Figure X2: Multiple Contrast Test Candidate Model Set

The significance of the dose-response signal associated with each candidate model will be determined using trend tests with model-specific optimal contrast coefficients. The maximum of the candidate model trend test statistics will be used to evaluate the presence of a dose-response signal, properly accounting for multiplicity at an overall level of 5% (1-sided) using MCP-Mod methodology.

Calculation of the optimal contrasts

The optimal contrasts for each model depend on the dose spacing and hence can only be determined when the high dose (Part B) has been selected. The optimal contrasts will be calculated using the Dose Finding R-package (See **APPENDIX 2**). In this code, the low dose is expressed relative to the high dose. At the time of

execution, the scalar "dose.rat" will be replaced by ratio of the low dose over the high dose (R code in Appendix)

Multiple Contrast Test

The MCT will executed using the MCTtest-function of the R-package DoseFinding (version 0.9-16) using the R code (See **APPENDIX 2**). In this code, the low dose is expressed relative to the high dose. At the time of execution, the scalar "dose.rat" will be replaced by ratio of the low dose over the high dose.

Input:

1. mean.placebo = mean Week 24 HBsAg change from baseline in the placebo-group (arms pooled over Part A and Part B).
2. mean.low.dose = mean Week 24 HBsAg change from baseline in the JNJ379+NA group of |Part A
3. mean.high.dose = mean Week 24 HBsAg change from baseline in the JNJ379+NA group of |Part B
4. se.mean.placebo = standard error of the mean Week 24 HBsAg change from baseline in the placebo-group (arms pooled over Part A and Part B
5. se.low.dose = standard error of the mean Week 24 HBsAg change from baseline in the JNJ379+NA group of Part A
6. se.high.dose = standard error of the mean Week 24 HBsAg change from baseline in the JNJ379+NA group of Part B

5.5. Exploratory Endpoints

5.2.1 Parameters Definition

The key exploratory endpoints for this study are

- Changes in the severity of liver disease.
    - Changes in fibrosis at week 24 (according to Fibroscan liver stiffness measurements) at end-of-treatment (EOT) and end of follow-up versus baseline will be analyzed.
- Explore HBV RNA and HBcrAg levels during study treatment and follow-up.

- Changes from baseline in HBV RNA and HBcrAg levels during study treatment and follow-up will be calculated

- Impact of viral and host baseline factors on different efficacy and safety parameters

5.2.1 Analysis Methods

For continuous variables defined above, descriptive statistics (n, mean, SE, 95%CI, median, minimum, maximum) will be calculated; mean difference and CIs may be calculated where appropriate and a general linear mixed model will be used to compare the different study treatments. For categorical variables, frequency tables will be presented. Difference in proportions and 95%CIs may be calculated using a chi-square test of equal proportions where appropriate

In addition, changes from baseline to assess the severity of liver disease (changes in fibrosis according to Fibroscan liver stiffness measurements) at end-of-treatment (EOT) and end of follow-up versus baseline will be analyzed using a ANCOVA with treatment group, subject population (ie, subjects currently not being treated or virologically suppressed by current NA treatment), HBeAg status (positive/negative) as main effect in the model and baseline as covariate.

6. SAFETY EVALUATIONS

All safety analyses will be performed using the Safety population. All assessments will be analyzed as described in section 2.6. Additionally, the displays will also be presented by analysis phase, analysis period and follow-up type except for the adverse event displays which will be displayed by analysis phase and follow-up type. The planned time points will be considered for time point analysis if applicable.

Safety and tolerability will be assessed by the incidence of treatment emergent-adverse events (TEAEs), physical examinations, vital signs measurements, changes in clinical laboratory parameters (including hematology, blood biochemistry, blood coagulation, and urinalysis), and 12-lead ECGs.

6.1. Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 20.1).

Allocation of adverse events into analysis phases:

Adverse events are allocated to phases according to the start date (time). Treatment-emergent AEs (TEAE) are all AEs with a start date (no time) on or after the first administration of study agent or any ongoing event on the date of the first dose of study treatment that worsens in severity, intensity or frequency after the date of the first administration of study agent.

For the purpose of calculating treatment emergence and inclusion in summary tables, (incomplete) adverse event onset date will be allocated to a phase and overlapping AEs will be combined as below:

Step 1: allocation of events to the phases:

Adverse events present in the SDTM database are 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 phase, the AE is attributed to that phase (treatment-emergent principle). In case an AE has a start date and time, the date time of the first administration will also be taken into account.

Incomplete dates (i.e. time and/or day and/or month and/or year missing):

- In case of partial start or stop dates, the events are allocated to the phases using the available partial information on start and end date; no imputation will be done. If, for instance, for the AE start date only month and year are available, these data are compared to the month and year information of the phases. This rule may lead to multiplication of the event as a consequence of its assignment to multiple phases.

- In case of a completely missing start date, the event is allocated to the first active treatment phase, except if the end date of the AE falls before the start of the first active treatment phase.
- In case of a completely missing end date, the following decision rules apply:
  - in case the date is identified as unknown the date will remain missing
  - in case the date is not flagged as unknown the date is imputed by the cut-off date of the analysis for subjects still ongoing in the study, and by the end date of the last phase for subjects who discontinue.

Examples:

- Screening phase: start date: 02JAN2007 - stop date: 28JAN2007
- Treatment phase: start date: 29JAN2007 - stop date: 12AUG2007

1) Adverse event: start date: JAN2007- stop date: 15JUL2007

As the start date only has information about month and year, only this information will be used from the phases and therefore the AE will be assigned to the screening phase as well as to the treatment phase.

2) Adverse event: start date: JAN2007- stop date 27JAN2007

As the AE stops before or at the start of the treatment phase, it is only assigned to the Screening phase.

Step 2: combination of events:

Overlapping/consecutive events are defined as events of the same subject with the same preferred term who have at least 1 day in overlap or for which the start date of an event is 1 day after the end date of the preceding event. Overlapping/consecutive events may be combined into one AE or not, according to the following rules:

- In case a non-active phase (e.g. Screening) is followed by an active phase, and the overlapping/consecutive events start in both phases, they are allocated to their respective phase and are considered as separate events.
- In case overlapping/consecutive events start within a single phase, they are considered as one and the same AE. The individual events who contribute to this AE are retained as individual records in the Analysis Data Model (AdaM) database but are assigned the same onset, phase, and total duration.
- In case an active phase is followed by a non-active phase and the overlapping/consecutive events start in both phases, they are allocated to the active phase only and are considered as one and the same AE. The individual events who contribute to this AE are retained as individual records in the ADaM database but are assigned the same onset, treatment phase, and total duration.
- In case an active phase is followed by another active phase, and the overlapping/consecutive events start in both phases, they are allocated to their respective phase and are considered as separate AEs. The same rule applies for 2 non-active phases.

Remarks:

- Events can only be combined into one and the same AE if their start and stop dates are complete.
- In case the completely missing end date is imputed, this date is also considered as a complete date.
- Time is not considered when determining overlap of events.
- Adverse events will be reported from the informed consent date on (i.e. in screening phase until trial termination.

Related AEs / Fatal AEs / events of special interest:

AEs are defined as related or not related to the study agent or NA treatment. Related is defined as possible, probable, very likely relationship with the study agent or NA treatment, missing for the study agent. Not related is the categories not related and doubtful.

A subject has an AE leading to death if the outcome is defined as 'Fatal'. An AE leading to discontinuation is defined as an AE with 'Drug Withdrawn' as action taken in the dataset.

Events of special interest (ESIs) will be included in the analysis. These events indicated in the dataset with AECAT='SPECIAL INTEREST ADVERSE EVENTS'.

Analyses:

An overview table will show the number and percentage of subjects with at least one TEAE for several categories (e.g. AEs, serious AEs, and fatal AEs).

For each particular TEAE, the percentage and frequency of subjects who experience at least 1 occurrence of the given event will be tabulated. All adverse events will be sorted by incidence based on all subjects (column not provided). The following TEAEs tables will be included in the analysis:

- All TEAEs
- Serious TEAEs
- At least grade 3 TEAEs
- Ate least grade 2 TEAEs and related
- TEAEs leading to discontinuation
- Related TEAEs
- TEAEs in at least 2 subjects in total
- Events of special interest

All AEs, any serious TEAE, related TEAE, TEAE leading to death, TEAE leading to discontinuation, TEAE of at least grade 3, or ESI will be separately listed. 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 subjects reporting rash a listing with specific grade will be provided (see rash specific grade in **APPENDIX**) and Rash Questionnaire will be tabulated by study treatment group and overall.

6.2. Clinical Laboratory Tests

Laboratory data from the central laboratory will be summarized by type of laboratory test. The different categories and tests used in the analysis are listed in table 6. The tests will be allocated to the categories in the table. The analysis of laboratory data will be analyzed on Standard International converted values only (LBSTREN/LBSTRESU) except lab parameter 'GFR from Creatinine Adjusted for BSA" should be reported in Original Units (mL/min/1.73m2).

Table 6: Laboratory Parameters to Be Summarized

Category	Abnormality	SDTM LBTESTCD	Grading system
General biochemistry	Alpha-1 Acid Glycoprotein	A1AGLP	Abnormalities
	Alpha Fetoprotein	AFP	Abnormalities
	Albumin	ALB	DAIDS
	Amylase	AMYLASE	DAIDS
	Amylase, Pancreatic	AMYLASEP	DAIDS
	Bicarbonate	BICARB	DAIDS
	Calcium	CA	DAIDS
	Creatine Kinase	CK	DAIDS
	Chloride	CL	Abnormalities
	Creatinine	CREAT	DAIDS
	C Reactive Protein	CRP	Abnormalities
	Follicle Stimulating Hormone	FSH	NAP
	GFR from Creatinine Adjusted for BSA	GFRBSCRT	DAIDS
	Choriogonadotropin Beta	HCG	NAP
	Potassium	K	DAIDS
	Lipase	LIPASET	DAIDS
	Magnesium	MG	DAIDS
	Phosphate	PHOS	DAIDS
	Protein	PROT	Abnormalities
	Sodium	SODIUM	DAIDS
	Urate	URATE	DAIDS
	Urea Nitrogen	UREAN	Abnormalities
General hematology	Hematocrit	HCT	Abnormalities

	Hemoglobin	HGB	DAIDS
	Hypochromic RBC (RBC)	HPORBC	Abnormalities
	Mean Corpuscular hemoglobin	MCH	Abnormalities
	MCH concentration	MCHC	Abnormalities
	Mean Corpuscular volume	MCV	Abnormalities
	Platelet count	PLAT	DAIDS
	Erythrocytes	RBC	Abnormalities
	Leukocytes	WBC	DAIDS
Hematology coagulation	Activated Partial Thromboplastin Time	APTT	DAIDS
	Fibrinogen	FIBRINO	DAIDS
	Prothrombin Intl. Normalized Ratio	INR	NAP
	Prothrombin Time	PT	DAIDS
Hematology different counts	Basophils	BASO	Abnormalities
	Basophils/Leukocytes	BASOLE	Abnormalities
	Eosinophils	EOS	Abnormalities
	Eosinophils/Leukocytes	EOSLE	Abnormalities
	Lymphocytes	LYM	Abnormalities
	Lymphocytes/Leukocytes	LYMLE	Abnormalities
	Monocytes	MONO	Abnormalities
	Monocytes/Leukocytes	MONOLE	Abnormalities
	Neutrophils and Precursors	NEUTPR	DAIDS
	Neutrophils, Segmented	NEUTSG	Abnormalities
	Neutrophils, Segmented/Leukocytes	NEUTSGLE	Abnormalities
Hepatic parameters	Alkaline phosphokinase	ALP	DAIDS
	Alanine Aminotransferase	ALT	DAIDS
	Aspartate Aminotransferase	AST	DAIDS
	Direct Bilirubin	BILDIR	Abnormalities
	Bilirubin	BILI	DAIDS
	Indirect Bilirubin	BILIND	Abnormalities
	Gamma glutamyl transferase	GGT	Abnormalities
	Lactate Dehydrogenase	LDH	Abnormalities
Lipids and glucose	Cholesterol	CHOL	DAIDS
	Glucose	GLUC	DAIDS
	HDL Cholesterol	HDL	Abnormalities
	LDL Cholesterol	LDL	DAIDS
	Triglycerides	TRIG	DAIDS
Urinalysis	Urine Pregnancy	HCG	NAP
	Protein	PROT	DAIDS
	Glucose	GLUC	DAIDS
	Bilirubin	BILI	Abnormalities
	pH	PH	Abnormalities

	Specific Gravity	SPGRAV	Abnormalities
	Ketones	KETONES	Abnormalities
	Urobilinogen	UROBIL	NAP
	Nitrite	NITRITE	Abnormalities
	Leukocyte Esterase	LEUKASE	Abnormalities
Immunology	Hepatitis A, B, C, D and E		

Imputation rules:

Laboratory records with missing assessment date parts (any: day/month/year) will not be imputed.

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 –if possible– by adding or subtracting one precision unit to the provided value. This also applies to normal limits expressed as such.

Unless a parameter is clearly continuous as a whole (e.g. pH, specific gravity) no such imputations will be done for urinalysis parameters as these are usually character/categorical expressions.

Toxicity grades and abnormalities for laboratory parameters:

The laboratory abnormalities will be determined according to the criteria specified in the Division of AIDS (DAIDS) Toxicity Grading Scale[7]. In case different grades are available for fasted/non-fasted results, the results are assumed to be taken in the condition as specified in the protocol (i.e. not necessarily according to possible remarks indicating a deviation to this). In case no toxicity grades are defined for a laboratory test, then non-graded abnormalities (high/low vs. normal range) will be used. The tests with toxicity grades and abnormalities have been summarized in table 6. Toxicity grades according to DAIDS will be derived for urinary protein and urinary glucose although these are categorical test (see table 7).

Table 7: urinary protein and urinary glucose according to DAIDS

Parameter	Grade 0	Grade 1	Grade 2	Grade 3
Urinary protein	Normal, Negative, Trace	+1, 1+	+2, 2+	+3, 3+ (or higher)

Urinary glucose	Normal, Negative	Trace, +1, 1+	+2, 2+	+3, 3+ (or higher)

Treatment-emergent definition for toxicity grades and abnormalities:

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.

Worst grade/abnormality determination:

A worst-case analysis time point will be created for parameters for which abnormalities and/or toxicity grades are defined to summarise values considered as the worst-case. For abnormalities it is derived per parameter and in case both the lowest and the highest values are considered abnormal, a subject can have two worst-case analysis visits for a same parameter within each phase/period. For toxicity grades the worst-case is the value associated to the highest toxicity grade and is derived per parameter and toxicity direction (hypo / hyper). Worst-case will be derived within each phase/period, including unscheduled assessments.

Analyses:

- Descriptive statistics of the actual values and the change from baseline per parameter over time according to the specification described in section 2.6 will be included.
- A cross-tabulation of the worst toxicity grades versus baseline parameter and per analysis phase/period will be presented including also the number of subjects per worst grade, the number of subjects with treatment emergent worst grades per grade and the cumulative number of subjects.
- A cross-tabulation of the worst abnormalities versus baseline per parameter and analysis phase/period will be presented including also the number of subjects per abnormality, the number of subjects with treatment emergent abnormalities per abnormality.
- A tabulation of percentage and number of the subjects who have treatment-emergent worst toxicity grades per parameter and analysis phase/period will be included.

- A tabulation of percentage and number of the subjects who have treatment-emergent worst abnormalities per parameter and analysis phase/period will be included.
- A listing including all parameters with at least one treatment-emergent toxicity or abnormality per subject (exclusion of urinalysis) is provided.
- All results of the hepatic parameters per subject for subjects with at least one treatment-emergent abnormality/toxicity within these hepatic parameter results is included in a listing.
- A listing including all parameters with at least one grade 3 treatment-emergent toxicity per subject (exclusion of urinalysis) is presented.
- A listing with abnormal urinalysis results and a listing including all urinalysis data will be provided.
- The actual values over time are plotted per the laboratory parameter. Each line will represent one subject.
- Mean (+/- SE) plots of the actual values for alanine transferase will be presented.
- Mean (+/- SE) plots of the change from baseline for alanine transferase will be presented.

6.3. Electrocardiogram

Twelve-lead triplicate ECGs are collected throughout the trial. 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. Only data from the ERT vendor will be analyzed. All other data will be listed.

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)
- QTc corrected (Bazett's formula QTcB)

Triplicate ECG assessments:

For the time points on which triplicate ECGs apply, a rounded mean value per triplet will be calculated per time point and equal EGGRPID before any further handling. This rounded

mean value will be used through the entire analysis. In case a 'triplicate' has a missing record or additional records, an average will be taken nevertheless. The date time of the first record of the triplicate will be included for the mean value.

Any rounding will be performed after computation of the applicable parameters, and before any further handling.

Imputation rules / calculation of derived parameters:

ECG records with missing assessment date parts (any day/month/year) will not be used in analysis, except in the listings.

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.

Note: RR values (if available) will only be listed. Recalculated HR values will be flagged.

Corrected QT (Bazett's and Fridericia's formula) are not calculated as this is provided in the datasets.

Abnormalities for ECG parameters:

The abnormalities in ECG parameters will be determined according to the criteria specified in the Cardiovascular Safety – Abnormalities Table (see APPENDIX **8**). Abnormlities on actual values are provided for HR, PR, QRS, QTcF and QTcB. Additional, abnormlities on change from baseline will be provided for QTcB and QTcF.

No abnormalities will be defined for actual uncorrected QT values. Uncorrected QT ≥ 500 ms will be flagged and only shown in listings.

Note: the QTc definitions for abnormalities follow the ICH E14 guidance [2].

Treatment-emergent definition for abnormalities:

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 abnormalities (i.e. abnormally high, borderline prolonged, prolonged, pathologically prolonged) versus the abnormally low are considered equally important.

Abnormalities defined on changes from baseline are always treatment-emergent.

Worst abnormality determination:

A worst-case analysis time point will be created for parameters for which abnormalities are defined to summarize values considered as the worst-case. For abnormalities, it is derived per parameter and in case both the lowest and the highest values are considered abnormal, a subject can have two worst-case analysis visits for a same parameter within each phase/period. Worst-case will be derived within each phase/period, including unscheduled assessments.

Analyses:

- Descriptive statistics of the actual values and the change from baseline per parameter (all parameters except for RR) over time according to the specification described in section 2.6 will be included.
- A cross-tabulation of the worst abnormalities (on actual values) versus baseline per parameter (i.e. for HR, PR, QRS, QTcB and QTcF) and analysis phase/period will be presented including also the number of subjects per abnormality, the number of subjects with treatment emergent abnormalities per abnormality.
- A tabulation of percentage and number of the subjects who have treatment-emergent worst abnormalities per parameter (i.e. for HR, PR, QRS, QTcB and QTcF) and analysis phase/period will be included.
- A cross-tabulation of the worst change from baseline abnormalities (i.e. for QTcB and QTcF) versus the actual value per parameter and analysis phase/period will be presented including also the number of subjects per abnormality, the number of subjects with treatment emergent abnormalities per abnormality.

- A listing including all parameters (i.e. no findings) for subjects with at least one treatment-emergent abnormality (on actual values or change from baseline) is provided.
- A listing including all findings (e.g. interpretation, rhythm, technical findings) is provided.
- A listing including all parameters (i.e. no findings) for subjects with uncorrected QT values ≥ 500 ms is provided.
- The actual values over time are plotted per ECG parameter. Each line will represent one subject.
- A frequency tabulation of categorized corrected QT change from baseline per treatment and per timepoint will be presented. (<=30 msec, >30 – <= 60 msec, > 60 msec)
- A frequency tabulation of categorized corrected QT interval values per treatment group and per timepoint will be presented. (<=450 msec, >450 – <= 480 msec, >480 – <= 500 msec > 500 msec)

6.4. Vital Signs

The following vital signs parameters measurements will be analyzed:

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

For body temperature, only baseline and week 20 will be seen as planned time points. All locations of measurement (e.g. forehead, oral, tympanic) will be taken into account for body temperature as a single parameter. All measurements will be taken into account for the worst-case analysis time point determination.

Imputation rules:

Vital signs records with missing assessment dateparts (any day/month/year) will not be used in the anaysis but will be listed.

Abnormalities for vital signs parameters:

The abnormalities in vital signs will be determined according to the criteria specified in the Cardiovascular Safety – Abnormalities Table (**APPENDIX**).

Treatment-emergent definition for toxicity grades and abnormalities:

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 abnormalities (i.e. abnormally high, grade 1 or mild, grade 2 or moderate, grade 3 or severe) versus the abnormally low are considered equally important.

Worst abnormality determination:

A worst-case analysis time point will be created for parameters for which abnormalities are defined to summarize values considered as the worst-case. For abnormalities, it is derived per parameter and in case both the lowest and the highest values are considered abnormal, a subject can have two worst-case analysis visits for a same parameter within each phase/period. Worst-case will be derived within each phase/period, including unscheduled assessments.

Analyses:

- Descriptive statistics of the actual values and the change from baseline per parameter over time according to the specification described in section 2.6 will be included.
- A cross-tabulation of the worst abnormalities versus baseline per parameter and analysis phase/period will be presented including also the number of subjects per abnormality, the number of subjects with treatment emergent abnormalities per abnormality.
- A tabulation of percentage and number of the subjects who have treatment-emergent worst abnormalities per parameter and analysis phase/period will be included.
- A listing including all parameters for subjects with at least one treatment-emergent abnormality (on actual values or change from baseline) is provided.
- The actual values over time are plotted per vital signs parameter. Each line will represent one subject.

6.5. Physical Examination

The physical examination records and abnormalities will be listed.

7. VIRAL GENOME SEQUENCE ANALYSIS

Viral genome sequence analysis will be performed to identify pre-existing baseline polymorphisms and to evaluate emergence of mutations associated with JNJ-56136379 and/or ETV or TDF treatment.

Sequencing of the HBV genome will be performed to monitor HBV variants present at the time points indicated in section 7.1 (see **APPENDIX** 5 and **APPENDIX** 6 for details).

Virology results will be presented by specified timepoints and genetic region and position of interest. A separate virology report will be performed by the virologist.

7.1. Time Points and Samples

When analyzing virology parameters, the focus will be on genetic variants at

- Time Point of Sequence at Baseline (BLSEQ): Last available pre-dose time point in the study with virology data available
- Time Point of Sequence at end of JNJ-379 treatment (last available on-treatment time point)
- Time Point of Sequence at Viral Breakthrough: time point with virology data available closest to the time point of viral breakthrough (FTPT) See section 5.3.1 for viral breakthrough definition
- Time Point of Sequence at Viral Relapse: time point with virology data available closest to the time point of viral relapse See section 5.3.1 for viral relapse definition
- Time Point of Sequence at End of Study (ESSEQ): last available off-treatment post-baseline time point in the study with virology data available
- Aggregated Post-Baseline Study Period (ASSEQ): entire post-baseline study period, aggregate of all available time points in the study with virology data available

- Aggregated Post-Baseline Treatment Period (ATSEQ): entire post-baseline treatment period, aggregate of all available post-baseline time points during the treatment phase with virology data available

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

7.2. Definitions

- *(Baseline) Genetic variations (aka baseline polymorphisms)* are defined as changes (on the amino acid or nucleotide level) in the subject viral sequence compared to a HBV genotype specific reference viral sequence. The reference sequence to be used is provided in the database. The reference viral sequences to be used are:

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

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

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

- *Enriched genetic variations*: are exclusively defined for NGS analysis. If – at a certain position – a genetic variation has a prevalence of ≥1% but <15% at baseline and a prevalence of ≥15% at a later time point.

7.3. Parameters to Analyze

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

- Number (%) of subjects with a genetic variation at a specific position.
- Number (%) of subjects with a specific genetic variation.
- Number (%) of subjects with genetic variations on amino acid level (at positions of interest) in the HBV core protein, HBV core protein positions (47, 28, 15), HBV core protein positions in HBV genotype (A, B, C, D, E, F, G, H and I), polymerase region, precure mutation and basal core promotor region (nucleotide level for PC and BCP) mutation (Will be presented in separate report not in the CSR)
- Number (%) of subjects with substitutions on amino acid level (at positions of interest) in the HBV core protein, HBV core protein positions of interest (47, 28, 15), HBV core protein positions in HBV genotype (A, B, C, D, E, F, G, H and I), polymerase region, precure mutation and basal core promotor region (nucleotide level for PC and BCP) mutation
- Number (%) of subjects with treatment-emergent substitutions on amino acid level at end of treatment, at time of failure (in subjects with treatment failure as defined in section 5.3.1), at time of viral breakthrough (in subjects with viral breakthrough as defined in section 5.3.1), t time of viral relapse (in subjects with viral relapse as defined in section 5.3.1) by substitution profile in the HBV core protein position of interest (28, 15)
- Number (%) of subjects with treatment-enriched substitutions on amino acid level at end of treatment, at time of failure (in subjects with treatment failure as defined in section 5.3.1), at time of viral breakthrough (in subjects with viral breakthrough as defined in section 5.3.1), t time of viral relapse (in subjects with viral relapse as defined in section 5.3.1) by substitution profile in the HBV core protein position of interest (28, 15)

The focus will be on genetic variations at a time point, emerging genetic variations and reversion to wild type or baseline state.

Sequence variations will be analyzed and reported on both the nucleotide level (for example for changes in the basal core promotor and precore region) as well as on amino

acid (aa) level. In the sequence analysis, sequences will be mapped to the respective genotype specific reference sequences after which nt changes and aa substitutions will be annotated compared to the respective genotype specific reference (see Table in section 7.2). In addition, the X02763 (HBV genotype A), which is the master reference sequence of the HBV db[27], will be used as universal reference sequence.

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

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

7.4. Positions & Genetic Variations of Interest

On the nucleotide level:

In the basal core promotor region:

- 1762 and 1764 (ECoRI numbering will be used)

In the precore region

- 1896 (numbering to be confirmed by DDL)

Amino acid level:

In the HBV core protein (based on putative binding pocket described in Bourne et al, J Virol, 2006; Katen et al, Structure, 2013)

- Long list (n=47): 18, 19, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 37, 38, 102, 103, 105, 106, 107, 109, 110, 111, 114, 115, 116, 117, 118, 119, 122, 123, 124, 125, 126, 127, 128, 129, 131, 132, 133, 134, 136, 137, 138, 139, 140, 141

Based on some recent more detailed published structural data (Klumpp et al, PNAS, 2015, Qiu et al, J Med Chem, 2016; Zhou et al, Sci Rep, 2017; Tu et al, Antivir Res, 2017), and some in house structural analysis, a more shortened list of core positions of interest can be defined:

- Short list (n=28): 23, 24, 25, 29, 30, 33, 37, 38, 102, 105, 106, 109, 110, 118, 122, 124, 125, 127, 128, 129, 132, 133, 134, 137, 138, 139, 140, 141

- Short list (n=15): 23, 24, 25, 29, 30, 33, 37, 105, 106, 109, 110, 118, 124, 127, 128.

In the pol/RT protein:

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

7.5. Analysis Methods

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

Analysis may be performed by subgroup (see section 2.5) and treatment groups.

7.5.1 Baseline

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

Subgroup analysis by the presence of baseline genetic variations will be tabulated to evaluate the impact on treatment response (see Section 5 for treatment response categories).

7.5.2 Post-Baseline

- ***Time of Viral Breakthrough (if applicable)***

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

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

- ***Other Post-Baseline***

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

7.5.3 Over the Study Period

For all subjects, listings with relevant baseline disease and demographic characteristics, session info, all genetic variations at baseline, at time of viral breakthrough (if applicable), at end of JNJ-379 treatment, and at end of study will be generated.

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

7.1.1 Other analysis

Sequence variations will be analyzed and reported on both the nucleotide level (such us changes in the basal core promotor and pre-core region) as well as on amino acid level.
In the sequence analysis, sequences will be mapped to the respective genotype specific reference sequences after which nucleotide level changes and amino acid substitutions

will be annotated compared to the respective genotype specific reference (see Table in section 7.2). In addition, the X02763 (HBV genotype A), which is the master reference sequence of the HBV, will be used as universal reference sequence.

All NGS data will be collected using a nucleotide level and amino acid read frequency cut-off of ≥0.01.

For the analysis of baseline nucleotide level changes and/or amino acid substitutions in terms of prevalence and impact on treatment outcome, a read frequency cut-off of ≥0.15 will be used.

The analysis of treatment-emergent nucleotide level changes or amino acid substitutions will consider nucleotide level changes or amino acid substitutions absent at baseline (<0.01 read frequency) but present at a read frequency of ≥0.15 at later time points.

Virology analyses based on NGS data will also evaluate treatment-enriched nucleotide level changes and amino acid substitutions, defined as present at baseline with a read frequency ≥0.01 but <0.15 and with an increase in read frequency of at least 0.15 post-baseline.

A minimum increase in read frequency of 0.15 compared to baseline excludes small, potentially technical variations in the read frequency of minority nucleotide level changes and amino acid substitutions which are not expected to have clinical relevance. In addition, for subjects with treatment failure nucleotide level changes and amino acid substitutions detected with a read frequency ≥0.01 at baseline, at time of failure and at end of study will be described in a listing. The persistence of treatment-emergent nucleotide level changes and amino acid substitutions will be evaluated using a cut-off of ≥0.15 and ≥0.01.

8. PATIENT REPORTED OUTCOMES ANALYSIS

The impact of HBV treatment on subjects, including functioning and HRQoL will be assessed using PROs at predefined time points in the ITT population.

- 5-level EuroQol 5-Dimension (EQ-5D-5L) Visual Analog Scale score and Index Score;
- Hepatitis B Quality of Life Instrument (HBQOL).

- Medical Outcomes Study Cognitive Functioning Scale-Revised (MOS-CFS Cog-R);
- Short Form 36 version 2 (SF-36v2) 8 Domain Scores/Subscales, Physical Component Summary and Mental Component Summary scores

8.1. Level EuroQol 5-Dimension (EQ-5D-5L)

See **APPENDIX** for a representative of 5-level EuroQol 5-Dimension (EQ-5D-5L) Visual Analog Scale score and Index Score full questionnaire.

8.1.1 Definition

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

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

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

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

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

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

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

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

b. Create a health state for each patient-time point combination. A health state is a combination of 5 level codes; one level code for each dimension. The dimensions are ordered as described in the **APPENDIX** .

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

c. Assign an index value to each health state as defined in the appendix of Data Presentation Specifications (DPS) documents.

   EQ-5D health state is converted to a single summary index by applying a formula that essentially attaches weights to each of the levels in each dimension. The algorithm is based on the valuation of EQ-5D health states using the UK TTO (=time trade-off method) based value set. Based on the origin of the subjects, another method can also be used (UK crosswalk-based values).

8.1.2 Missing data

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

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

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

8.2. Hepatitis B Quality of Life (HBQOL)

See **APPENDIX 1** for a representative example of the HBQOL version 1 full questionnaire.

There are 31 scored items included in the HB-QOL, including 13 items regarding how HBV makes patients feel socially or mentally (F1-F13), 15 items regarding HBV-related concerns (C1-C15), and 3 items regarding HBV-related physical impacts.

For HBQOL, scores will be calculated as below:

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

Level 1 – 0 points
Level 2 – 25 points
Level 3 – 50 points
Level 4 – 75 points
Level 5 – 100 points

The items are combined to form 7 subscales, as follows:
Psychological Well-Being (8 Items), Anticipation Anxiety (6 Items), Vitality (5 Items), Stigma (6 Items), Vulnerability (3 Items), Transmission (3 Items) and Viral Response (4 Items).

The global score that reflects the results on all 31 items.
Each subscale score is simply calculated as the average score among the items included in that subscale. The global score is simply the average score among all the items in the HBQOL.
For example, consider these sample scores for items in the vulnerability scale:

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

The score on this subscale is 50 out of a possible score of 100, where higher scores denote more severe negative impact of HBV on HRQOL. The scores will be derived if at least 50% of the items or domain scores are available respectively, no imputation of missing data will be performed.

8.3. Medical Outcomes Study Cognitive Functioning Scale-Revised (MOS-CFS Cog-R)

See **APPENDIX 1** for a representative example of the MOS-CFS Cog-R full questionnaire. Scores will be derived and delivered by a vendor (OPTUM), in CSV file and added in ADAM datasets

8.3.1 Definition

The MOS CSF is 6 dimensions questionnaire with 5 different scales

Response choice for questions	Questionnaire Coded Value (scale)	Final Value use for scoring
All of the time	1	1
Most of the time	2	2
Some of the time	3	3
little of the time	4	4
None of the time	5	5

All scales can be scored (using a scoring algorithm such as **RAND or other**) so that a high score defines a more favorable health state. scales are scored in five steps:

- Data-cleaning (e.g., changing out-of-range values (values that are lower or higher than an item's minimum and maximum value) to missing),
- Transforming item scores linearly to a common metric with a possible range of 0-100 => New transformed= (old scale-lower-scale) *100/(5-1)=(old scale-1)*25
- Averaging across items in the same scale => Average (New Transformed)

The scores will be derived using OPTUM scoring software (Third party vendor)

8.3.1 Missing data

The score estimation techniques, we will use all missing data, OPTUM scoring software is able to input the missing scale scores and component scores and estimate the score even some items are missing.

8.4. Short Form 36 version 2 (SF-36v2)

See **APPENDIX 1** for a representative example of the SF-36v2 full questionnaire.
Scores will be derived and delivered by a vendor (OPTUM), in CSV file and added in ADAM datasets

8.4.1 Definition

The short form of SF-36 is a 11-item questionnaire that measures eight multi-item dimensions of health (HRQoL), where participants self-report on item in a domain scale that have between 2-6 response choices per item.
The short form of SF-36 can be interpreted using T-scores from the 8 domain scales and 2 summary scores defined below:
The physical component (PCS):

- Physical functioning (10 items: in question 3)
- Role limitations due to physical problems (4 items: question 4)
- Bodily pain (2 items: questions 7 and 8)
- General health perception (5 items: questions 1 and 11 a to 11d).
- Energy/vitality or Fatigue (4 items: questions 9 a, 9e, 9g, and 9i)

The mental component (MCS):

- Role limitations due to emotional problems (3 items: questions 5a, 5b, and 5c)
- General Mental health (5 items: questions 9b, 9c, 9d, 9f, and 9h),
- Social functioning (2 items: questions 6 and 10)

A scoring algorithm will be used to convert the raw scores into the eight dimensions listed above. The total domain scores of domain scales will be transformed into a range from zero where the respondent has the worst possible health to 100 where the respondent is in the best possible health. The scores (0-100) will then be standardized using means and standard deviation from 2009 U.S. general population and converted to norm-based scores using a T-score transformation (mean = 50, SD = 10) [12]. Two aggregate component scores will be derived as linear combination of the standardized (2009 U.S. norm) scores using weights from principal component analysis. Each aggregate component score will be transformed to the corresponding PCS T-score and MCS T-score (mean = 50 and SD = 10)[12]

The domain scale scores and component summary scores will be calculated using the Quality Metric Health Outcomes™ Scoring Software, version 4.5.1 or a later version. In case of missingness the Full Missing Score Estimation (MSE) method or Item Response Theory (IRT) will be used, if applicable, for imputation of missing values [12].
SF-36v2 questions 2, the health domain scale T-scores, PCS T-scores and MCS T-scores will be derived using OPTUM scoring software (Third party vendor).

8.4.2 Missing data

The score estimation techniques will use all missing data, OPTUM scoring software is able to input the missing scale scores and component scores and estimate the score even some items are missing.

8.5. PRO Analysis Methods

8.5.1 Baseline

The Day 1 ePRO data have been recorded few minutes after first administration dose, as these time differences between dose administration (Day1) and ePRO data collection on Day 1 are very small and in order to have baseline values for all subjects with ePRO data on Day 1, ePRO baseline is defined as values before or on the date of the first administration dose (Day1).

8.5.2 Analysis

A descriptive statistic of the actual values and change from baseline values at each timepoint (including baseline and available analysis time point) for ePRO derived scores will be displayed. In addition, mean changes from baseline values and summary measures will be explored per subgroup including (treatment group, subject population and stratification factors).
Frequency tabulation (number and percentage) of the response categories of question #2 of the SF-36v2 instrument will be displayed per time point for each treatment group.

For the EQ-5D descriptive system, tabulation of the number and percentage of subjects per problem level and per dimension will be displayed per time point for each treatment group.

For MOS-CFS Cog-R each of the 6 dimensions (having difficulty in reasoning and solving problems, having difficulty doing activities involving concentration and thinking, becoming confused and starting several actions at a time, forgetting things that happened recently, having trouble keeping attention and reacting slowly to things that are said or done) will be tabulated per time point for each treatment group.

For HBQOL questionnaires, tabulation of the number and percentage of subjects per dimension scale will be displayed per time point for each treatment group.

Tabulation of the number (and percentage) of subjects with clinically important improvement / worsening will be presented for SF-36v2, EQ-5D VAS and MOS-CFS Cog-R. There are no established thresholds for HBQOL. The clinically important thresholds are defined in the table below:

PRO Instrument	**Mean Change from baseline, threshold**	**Individual Subject's Change from baseline, threshold**
SF-36v2		
PCS	≥5 points	≥5 points
MCS	≥5 points	≥5 points
8 domain scores (T-scores)	≥5 points	≥5 points
EQ-5D VAS score		
	≥10 points	≥10 points
HBQOL	No threshold	No threshold
MOS-COG-R	≥5 point	≥5 point
This change refers to either an increase or a decrease >= threshold		

A cumulative distribution function will be drawn at different time points of the changes from baseline (Week 4 (for EQ-5D-5L and HBQoL), Week 8(for SF-36v2 and MOS-CFS Cog-R), EOT and the follow-up assessments).
In addition, effect sizes will be calculated to measure the magnitude of difference between means in all different treatment groups using a mixed effect model for repeated measurement, including treatment groups, different analysis time points (treated as discrete/categorical) and their interaction as fixed effects and subject as random effect in the model.
Lsmeans of the change from baseline at each analysis time points with estimates, SE, 95% CI, type 3 p-values will be presented.

A graphical representation will be presented for each of the questionnaire results including the questionnaire different time points on the x-axis and adjusted mean change from baseline and SE on the y-axis.

9. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS

Descriptive statistics (n, mean, SD, coefficient of variation, geometric mean, Q1, Q2, median, minimum, and maximum) will be calculated for the plasma concentrations of total JNJ-56136379 and/or NA (ETV or TDF), as applicable, and for the derived plasma and urine pharmacokinetic parameters. Actual and/or dose-normalized pharmacokinetic parameters will be graphically displayed for JNJ-56136379 and NA (ETV or TDF) when administered alone or in combination

A listing for plasma concentrations and pharmacokinetic parameters of those subjects who discontinued the study for an AE, or who experienced an AE ≥grade 3, or an SAE will be provided.

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APPENDIX 1: SAS PROGRAM FOR SAMPLE IMPLEMENTATION OF BAYESIAN MODEL

```
*-------------------------------------------------------------------------------------------------------------------------;
* SAMPLE IMPLEMENTATION OF BAYESIAN EFFICACY ANALYSIS USING PROC MCMC      ;
*   Subject Popn:    Currently Not Being Treated HBeAg+                    ;
*   MAP Prior:       0.7447 N(-0.3059, 0.01892) + 0.2553 N(-0.3122, 0.05255)  ;
*   Prior:           MAP Prior                                             ;
*   Data:            nS=4, nE=12 (simulated for illustration - to be replaced with actual trial data)  ;
*-------------------------------------------------------------------------------------------------------------------------;

** Analysis will be done by HBeAG status;
/**
Virologically suppressed population: HBeAG = Positive
2 number of components in the mixture
    Frist comp mean parameter (std)= 0.3809 N(-0.06528, 0.01440)
    Second comp mean parameter (std)= 0.6191 N(-0.05667, 0.004036)

With:
 0.3809 ,0.6191: weights of the two components (should add up to 1)
-0.3059, -0.3122: the two means of each component
 Sqrt(0.01892),sqrt(0.05255)): standard deviations of each of the two
components

Virologically suppressed population: HBeAg = Negative
    2:number of components in the mixture
    Frist comp mean parameter (std)= 0.3809 N(-0.06528, 0.01440)
    Second comp mean parameter (std)= 0.6191 N(-0.05667, 0.004036)

Currently not being treated population: HBeAG = Positive
    2: number of components in the mixture
    Frist comp mean parameter (std)= 0.7447 N(-0.3059, 0.01892)
    Secd comp mean parameter (std)= 0.2553 N(-0.3122, 0.05255)

Currently not being treated population: HBeAg = Negative
    3: number of components in the mixture
    Frist components mean parameter (std)= 0.0177 N(-0.01450, 0.1045)
    Secd components mean parameter (std)= 0.5728 N(-0.00925,0.005850)
    Third components mean parameter (std)= 0.4095 N(-0.01308,0.01988)

/* small difference*/
data current;
retain id trtcd trt y;
id =  n ;
input trt $ y;
if trt="EXP" then trtcd=1;
if trt="SOC" then trtcd=0;
cards;
EXP   -0.42049058
EXP    0.002817434
EXP    0.203074308
EXP   -2.80207664
EXP   -0.610704519
EXP   -0.679890698
EXP   -0.991367774
EXP   -0.525054268
EXP   -0.117132573
```

```
EXP    -0.817565631
EXP    -0.689900046
EXP    -0.431818543
SOC     0.585224988
SOC    -0.488106494
SOC    -0.307694965
SOC    -0.686285388
;
run;

/* strong difference*/
data current;
retain id trtcd trt y;
id =  n ;
input trt $ y;
if trt="EXP" then trtcd=1;
if trt="SOC" then trtcd=0;
cards;
EXP    -0.42049058
EXP     0.002817434
EXP     0.203074308
EXP    -2.80207664
EXP    -1.610704519
EXP    -1.679890698
EXP    -1.991367774
EXP    -1.525054268
EXP    -1.117132573
EXP    -1.817565631
EXP    -1.689900046
EXP    -1.431818543
SOC     0.585224988
SOC    -0.488106494
SOC    -0.307694965
SOC    -0.686285388
;
run;

ods listing close;
ods html path="%sysfunc(getoption(work))" gpath="%sysfunc(getoption(work))";
ods graphics on;

proc mcmc data=current outpost=out01 seed=123 nbi=100000 nmc=10000000 thin=100 plots=all
      diagnostics=all stats(alpha=0.1 percent=(5 10 20 50 80 90 95))
monitor=(mu_E mu_S s_E s_S delta pp1 pp2 pp3);
    parms mu_E -1 mu_S -0.5 s_E 2 s_S 1;
    prior mu_E ~ normal(0,var=100);
    prior s:   ~ igamma(0.01,s=0.01);
    pdfmix = logpdf("NORMALMIX", mu_S, 2, 0.3809, 0.6191, -0.06528,-
0.05667,
                                sqrt(0.01440),sqrt(0.004036));

    prior mu_S ~ general(pdfmix);
    delta = mu_E-mu_S;
    pp1 = (delta<0);
    pp2 = (delta<-0.5);
    pp3 = (delta<-1);
```

```
    if TRT01A="JNJ6379 75 mg + NA" then llike =
logpdf("normal",chg,mu_E,s_E);
    if TRT01A="Placebo 75 mg + NA" then llike =
logpdf("normal",chg,mu_S,s_S);
    model general(llike);
run;

ods graphics off;
ods html close;
ods listing;
```

APPENDIX 2: R CODE FOR DOSE RESPONSE

```
library(DoseFinding)
dose.range=c(0,dose.rat,1)
models=Mods(linear=NULL,emax=0.20,exponential=0.18,doses=c(dose.r
ange),maxEff=1,placEff=0)
optContr(models,w=c(2/8,3/8,3/8))

library(DoseFinding)
dose.range=c(0,dose.rat,1)
models=Mods(linear=NULL,emax=0.20,exponential=0.18,doses=c(dose.r
ange),maxEff=1,placEff=0)
optContr(models,w=c(2/8,3/8,3/8))
MCTtest(dose=dose.range,models=models,type="general",resp=c(mean.
placebo,mean.low,mean.high),S=matrix(nrow=3,ncol=3,c(se.mean.plac
ebo^2,0,0,0,se.mean.low^2,0,0,0,se.mean.high^2)
```

APPENDIX 3: SAS CODE FOR THE MMRM MODEL

```
proc mixed data=mod01 (where = (paramcd = 'LGHBSAG' ));
  by hbeagstat;
    class avisitn trtlon usubjid;
    model chg = avisitn trtlon trtlon*avisitn / ddfm=kr2;
    repeated / type=UN subject=usubjid ;
run;
```

hbeagstat = HBeAg status at baseline
avisitn = analysis visits
trtlon = Treatment groups
usubjid = subject ID
chg = change from baseline

In case the above leads to convergence issues, alternative within-subject covariance structures will be considered, in the following hierarchy:

```
proc mixed data= mod01 maxopt=1000;
by hbeagstat;
class avisitn trtlon usubjid;
model chg= avisitn trtlon trtlon*avisitn /dist=normal link=identity solution ddfm=kr2;
random intercept/subject=usubjid v vcorr;
random _residual_ /type=ante(1) subject=usubjid g gcorr;
covtest 'int' general 1    0 0 0 0 0 0 0 0     0 0 0 0 0 0 0 0;
covtest 'all var equal' general
          0        1 -1 0 0 0 0 0 0     0 0 0 0 0 0 0 0,
          0        0 1 -1 0 0 0 0 0     0 0 0 0 0 0 0 0,
          0        0 0 1 -1 0 0 0 0     0 0 0 0 0 0 0 0,
          0        0 0 0 1 -1 0 0 0     0 0 0 0 0 0 0 0,
          0        0 0 0 0 1 -1 0 0     0 0 0 0 0 0 0 0,
          0        0 0 0 0 0 1 -1 0     0 0 0 0 0 0 0 0,
          0        0 0 0 0 0 0 1 -1     0 0 0 0 0 0 0 0;
covtest 'all corr equal' general
          0        0 0 0 0 0 0 0 0          1 -1 0 0 0 0 0,
          0        0 0 0 0 0 0 0 0          0 1 -1 0 0 0 0,
          0        0 0 0 0 0 0 0 0          0 0 1 -1 0 0 0,
          0        0 0 0 0 0 0 0 0          0 0 0 1 -1 0 0,
          0        0 0 0 0 0 0 0 0          0 0 0 0 1 -1 0,
          0        0 0 0 0 0 0 0 0          0 0 0 0 0 1 -1;
covtest 'all var&corr equal' general
          0        1 -1 0 0 0 0 0 0     0 0 0 0 0 0 0 0,
          0        0 1 -1 0 0 0 0 0     0 0 0 0 0 0 0 0,
          0        0 0 1 -1 0 0 0 0     0 0 0 0 0 0 0 0,
          0        0 0 0 1 -1 0 0 0     0 0 0 0 0 0 0 0,
          0        0 0 0 0 1 -1 0 0     0 0 0 0 0 0 0 0,
          0        0 0 0 0 0 1 -1 0     0 0 0 0 0 0 0 0,
```

```
        0       0 0 0 0 0 0 1 -1     0 0 0 0 0 0 0,

        0       0 0 0 0 0 0 0 0          1 -1 0 0 0 0 0,
        0       0 0 0 0 0 0 0 0          0 1 -1 0 0 0 0,
        0       0 0 0 0 0 0 0 0          0 0 1 -1 0 0 0,
        0       0 0 0 0 0 0 0 0          0 0 0 1 -1 0 0,
        0       0 0 0 0 0 0 0 0          0 0 0 0 1 -1 0,
        0       0 0 0 0 0 0 0 0          0 0 0 0 0 1 -1;
run;

proc mixed data= mod01 maxopt=1000;
by hbeagstat;
class avisitn trtlon usubjid;
model chg= avisitn trtlon trtlon*avisitn /dist=normal link=identity solution ddfm=kr2;
random intercept/subject=usubjid v vcorr;
random _residual_ /type=arh(1) subject=usubjid g gcorr;
covtest 'int ' general 1  0 0 0 0 0 0 0 0    0 ;
covtest 'corr' general 0  0 0 0 0 0 0 0 0    1 ;
covtest 'all var equal' general
                0       1 -1 0 0 0 0 0 0     0 ,
                0       0 1 -1 0 0 0 0 0     0 ,
                0       0 0 1 -1 0 0 0 0     0 ,
                0       0 0 0 1 -1 0 0 0     0 ,
                0       0 0 0 0 1 -1 0 0     0 ,
                0       0 0 0 0 0 1 -1 0     0 ,
                0       0 0 0 0 0 0 1 -1     0 ;
run;


proc mixed data= mod01 maxopt=1000;
by hbeagstat;
class avisitn trtlon usubjid;
model chg= avisitn trtlon trtlon*avisitn /dist=normal link=identity solution ddfm=kr2;
random intercept/subject=usubjid v vcorr;
random _residual_ /type=ar(1) subject=usubjid g gcorr;
output out=overdisp2 pearson=pearson;
covtest 'int' general 1 0 0;
covtest 'ar1' general 0 1 0;
covtest 'int&ar1' general 1 0 0, 0 1 0;
run;
```

For the pool analysis include HBeAg status as fixed effect in the above models

APPENDIX 4: DIVISION OF AIDS (DAIDS) TOXICITY GRADING SCALE FOR DETERMINING THE SEVERITY OF ADVERSE EVENTS, MARCH 2017

See reference [7] above

APPENDIX 5: TIME AND EVENTS SCHEDULE – SCREENING AND TREATMENT PHASE

Phase	Screening	Treatment[ee,kk]									Treatment Extension[ee,kk]					
Day (D)/Week (W)	<Day -56	D1[a]	W1	W2	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48
Study Procedure																
Screening/Administrative																
Informed consent form (ICF)[b]	X															
ICF for optional pharmacogenomic samples	X															
Demographics	X															
Medical and surgical history	X															
Inclusion/exclusion criteria[c]	X															
Liver biopsy or Fibroscan[d]	X															
Ultrasound[e]	X															
Clinical status	X	X[f]														
Follicle-stimulating hormone test (postmenopausal women only)	X															
Serum pregnancy test (women of childbearing potential only)	X															
Testing for hepatitis A, B, C, D, and E virus and HIV-1 and -2	X															
HBV genotype[g]	X															
Visit with overnight stay[h]		X					X									
Check for eligibility for extension phase									X[ff]	X[ff,gg]						
Study Treatment Administration																
Randomization		X														

Phase	Screening	Treatment[ee,kk]									Treatment Extension[ee,kk]					
Day (D)/Week (W)	<Day -56	D1[a]	W1	W2	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48
Study Procedure																
Dispense study medication		X			X	X	X	X	X	X[hh]	X	X	X	X	X	X[ii]
Administer study medication[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Distribute diary[j]						X			X							
Collect diary[j]							X			X						
Safety Evaluations																
Complete physical examination[k]	X								X							
Symptom-directed physical examination[l]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Triplicate 12-lead ECG[n]	X	X			X		X			X			X			X
Clinical Laboratory Tests																
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry[o,p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood coagulation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Alpha-fetoprotein	X															
Urine pregnancy test (women of childbearing potential only)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Evaluations																
Fibroscan[r]		X								X						X
HBV Virology																
HBV DNA and HBV RNA[jj]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Viral genome sequencing[s]	X	X		X	X	X	X	X	X	X		X		X		X
HBV Serology																
Anti-HBs and anti-HBe	X	X								X						X
HBsAg and HBeAg[t] (qualitative)	X	X								X						X

Phase	Screening	Treatment[ee,kk]									Treatment Extension[ee,kk]					
Day (D)/Week (W)	<Day -56	D1[a]	W1	W2	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48
Study Procedure																
HBsAg and HBeAg[u] (quantitative)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBcrAg[jj]	X	X	X	X	X	X	X	X	X	X		X		X		X
Exploratory serology[v]		X		X	X	X	X	X	X	X		X		X		X
Pharmacokinetics																
Blood sampling for pharmacokinetics of JNJ-56136379 and/or NA (sparse)[w]		X	X	X	X	X	X		X	X	X	X	X		X	X
Blood sampling for pharmacokinetics of JNJ-56136379 and/or NA (semi-rich) (selected sites only)[x]		X					X									
Urine collection for pharmacokinetics of JNJ-56136379 and/or NA (selected sites only)[y]		X[z]					X									
Blood sampling for exploratory pharmacokinetics of hormonal contraceptives and their metabolites (women on hormonal contraceptives only[dd])		X					X		X	X						
Exploratory Biomarkers																
Host mRNA		X	X	X	X	X	X		X	X	X		X			X
Serum proteins		X	X	X		X	X	X	X	X	X		X		X	X
Immune cells (PBMCs) (selected sites only)[aa]		X			X		X			X						X
Pharmacogenomics (DNA)																
Exploratory host genotyping (optional)[bb]		X														
Patient-reported Outcome Evaluations[a]																
EQ-5D-5L		X			X					X						
HBQOL		X			X					X						

Phase	Screening	Treatment[ee,kk]									Treatment Extension[ee,kk]					
Day (D)/Week (W)	<Day -56	D1[a]	W1	W2	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48
Study Procedure																
MOS-CFS Cog-R		X				X				X						
SF-36v2		X				X				X						
Ongoing Participant Review																
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. Day 1 samples are to be collected before the first dose of study drugs.
b. The ICF must be signed before the first study-related activity.
c. Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Section **Error! Reference source not found.**. C heck clinical status again before first dose of study medication.
d. Liver disease staging assessments will be performed by means of a liver biopsy or Fibroscan during the screening period in case not performed within 1 year (in case of liver biopsy) or 6 months (in case of Fibroscan) prior to screening.
e. Subjects must have absence of signs of hepatocellular carcinoma (HCC) on an abdominal ultrasound performed within 2 months prior to screening or at the time of screening. In case of suspicious findings on conventional ultrasound the subject may still be eligible if HCC has been ruled out by a more specific imaging procedure (contrast enhanced ultrasound, computed tomography [CT] or magnetic resonance imaging [MRI]).
f. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drugs is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from (further) participation in the study.
g. HBV genotype will be determined at screening using standard genotyping assay if HBV DNA levels are sufficiently high. In virologically suppressed subjects, available historical data on previous HBV genotype assessment will be collected in the eCRF. Exploratory genotyping assays might be performed.
h. Only applicable to subjects undergoing semi-rich pharmacokinetic and 24-hour urine sampling (pharmacokinetic subgroup).
i. Study drugs should be taken in the morning at approximately the same time each day, together with breakfast, except for ETV which should be taken on an empty stomach. At each study visit, the study drugs should be taken on site under the supervision of the study staff. The time of study drug intake should be recorded.
j. A subject diary will be provided to the subjects in the pharmacokinetic subgroup, and female subjects using hormonal contraceptives. These subjects should report the times of study drug intake at home for 1 week prior to their Week 12 and Week 24 visits in this diary.
k. Complete physical examination, including height, body weight, temperature, skin examination, and other body systems.

l. Symptom-directed physical examination, including body weight and temperature.
m. Vital signs include supine systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate.
n. If blood sampling or vital signs measurement is scheduled for the same time point as ECG recording, the procedures should preferably be performed in the following order: ECG(s), vital signs, blood draw.
o. Biochemistry samples must be taken fasted for at least 10 hours for measurement of phosphorus, calcium, creatinine clearance, and lipids. Subjects should bring their study drug with them to each visit and have that day's intake at the site.
p. Creatinine clearance (estimated by the estimated Glomerular Filtration Rate [eGFR], which is calculated by the Modification of Diet in Renal Disease [MDRD] formula) will be assessed.
q. In case a of positive dipstick result, a urine sample will be set aside for additional examination of the positive parameter (eg, quantification as applicable).
r. Only applicable to subjects in the pharmacokinetic subgroup and subjects enrolled at a site with an on-site Fibroscan device.
s. Sequencing on Day 1 (predose) will be performed by default if HBV DNA levels are within the ranges required for the sequencing assay; other samples may be sequenced based on the sponsor virologist's request.
t. In virologically suppressed subjects, available historical data on HBeAg status before start of NA treatment will be collected in the eCRF.
u. Quantitative HBeAg assessment will only be performed in subjects who are defined HBeAg-positive at screening based on a qualitative HBeAg assay.
v. Exploratory serology samples may be analyzed at the sponsor's discretion. Samples may be used to assess virologic or serologic markers of HBV.
w. Sparse pharmacokinetic sampling will be performed for all subjects. One sample predose at all indicated time points (except on Day 1: one sample 2 hours postdose only). Study drug should be taken on site. The time of study drug intake will be recorded.
x. Approximately 35% of all subjects (at selected sites only) will undergo semi-rich pharmacokinetic sampling (pharmacokinetic subgroup) predose and 2, 4, 12, and 24 hours postdose. The study drug should be taken on site. The time of study drug intake will be recorded.
y. Approximately 35% of all subjects (at selected sites only) will have 24-hour urine sampling (pharmacokinetic subgroup) during the intervals 0-2, 2-12, and 12-24 hours postdose. This sampling schedule will require an overnight stay on site.
z. Applicable to Treatment Arms 4-5 and 9-10 only.
aa. Immune cell samples (peripheral blood mononuclear cells [PBMC]) may be collected (selected sites only).
bb. The pharmacogenomic (DNA) sample should preferably be collected at baseline. This sample is optional and will only be collected from subjects who consent separately to this component of the study.
cc. PRO assessments will be performed by subjects at sites where appropriate translations are available. Subjects will complete the 5-level EuroQol 5-Dimension (EQ-5D-5L), Hepatitis B Quality of Life Instrument (HBQOL), Medical Outcomes Study Cognitive Functioning Scale-Revised (MOS-CFS Cog-R), and Short Form 36 version 2 (SF-36v2) on an electronic device during the specified study visits. The PRO assessments are preferably to be completed immediately after dosing.
dd. For women on stable (≥3 months) hormonal contraceptive treatment at screening, as well as women starting hormonal contraceptive treatment during the study, in which case the first blood sampling should occur at the next scheduled visit.
ee. All study visits are to be scheduled relative to the baseline visit date and are to occur at the end of Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48. The visit window is ±2 days of the protocol-specified date at Weeks 2-4, ±5 days of the protocol-specified date through Week 48.
ff. Eligibility to enter the treatment extension phase will be determined at Week 20 and Week 24 of the initial 24-week treatment phase, ie, subjects must have completed the initial 24 weeks of treatment and must have achieved a virologic response by Week 20 (HBV DNA < LLOQ of the HBV DNA assay) without experiencing any safety concerns precluding continued study drug treatment as determined by the investigator.

gg. Subjects enrolled in the study before the Amendment 2 came into effect will need to consent separately for participation in the extension phase. Subjects choosing not to participate in the extension phase will complete their assigned 24-week treatment after which they will enter the 24-week follow-up period. Subjects who are enrolled after the Amendment 2 came into effect will consent to the possible treatment extension by signing the ICF at the start of the study.

hh. Dispensing of JNJ-56136379/placebo is only applicable for subjects who will enter the treatment extension phase. NA will be dispensed for subjects starting or continuing NA treatment in the treatment extension phase or the follow-up phase.

ii. Only applicable for subjects who do not meet the treatment completion criteria and start or continue NA treatment. No JNJ-56136379/placebo will be dispensed.

jj. HBcrAg and HBV RNA samples may be batched and only selected samples may be tested. Samples can be used for assessment of other serologic/virologic markers of HBV.

kk. Subjects who discontinue treatment early will have an early treatment withdrawal visit and will enter follow-up (see Schedule 1) unless they withdraw consent. Subjects who withdraw consent will be offered an optional safety follow-up visit

APPENDIX 6: TIME AND EVENTS SCHEDULE – POST-TREATMENT FOLLOW-UP PHASE (SCHEDULE 1)

This schedule is applicable for all subjects who complete study drug treatment at Week 24 and who do not continue treatment in the treatment extension phase, subjects who do not meet the treatment completion criteria and subjects who discontinue study treatment early (either 24 or 48 weeks, as applicable).

Phase	**Early Treatment Withdrawal Visit[p]**	**Post-treatment Follow-up[r]**			
Follow-up (FU) Week (W)		**FU W2**	**FU W4**	**FU W12**	**FU W24 end of study visit**
Study Procedure					
Study Treatment Dispensing					
Dispense NA[a]	X		X	X	
Safety Evaluations					
Complete physical examination[b]	X				
Symptom-directed physical examination[u]		X	X	X	X

Phase	Early Treatment Withdrawal Visit[p]	Post-treatment Follow-up[r]			
Follow-up (FU) Week (W)		FU W2	FU W4	FU W12	FU W24 end of study visit
Study Procedure					
Vital signs[v]	X	X	X	X	X
Triplicate 12-lead ECG[w]	X		X	X	X
Clinical Laboratory Tests					
Hematology	X	X	X	X	X
Blood chemistry[x,y]	X	X	X	X	X
Blood coagulation	X	X	X	X	X
Urinalysis	X	X	X	X	X
Urine pregnancy test (women of childbearing potential only)	X	X	X	X	X
Efficacy Evaluations					
Fibroscan[o]	X				X
HBV Virology					
HBV DNA and HBV RNA[q]	X	X	X	X	X
Viral genome sequencing[z]	X	X	X	X	X
HBV Serology					
Anti-HBs and anti-HBe	X	X	X	X	X
HBsAg and HBeAg (qualitative)	X	X	X	X	X
HBsAg and HBeAg[aa] (quantitative)	X	X	X	X	X
HBcrAg[q]	X	X	X	X	X
Exploratory serology[bb]	X	X	X	X	X
Pharmacokinetics					
Blood sampling for pharmacokinetics of JNJ-56136379 and/or NA (sparse)[cc]		X	X		
Blood sampling for exploratory pharmacokinetics of hormonal contraceptives and their metabolites (women on hormonal contraceptives only)			X		
Exploratory Biomarkers					
Host mRNA	X		X		X
Serum proteins	X		X		X
Immune cells (PBMCs) (selected sites only)[dd]	X		X		X

Phase	Early Treatment Withdrawal Visit[p]	Post-treatment Follow-up[r]			
Follow-up (FU) Week (W)		FU W2	FU W4	FU W12	FU W24 end of study visit
Study Procedure					
Patient-reported Outcome Evaluations[m]					
EQ-5D-5L	X[n]			X	
HBQOL	X[n]			X	
MOS-CFS Cog-R	X[n]				X
SF-36v2	X[n]				X
Ongoing Participant Review					
Concomitant therapy	X	X	X	X	X
Adverse events	X	X	X	X	X

a. Treatment with JNJ-56136379 and placebo will be stopped at Week 24 in all subjects who are not eligible to continue treatment in the extension phase, at Week 48 in subjects who continued treatment in the extension phase, and at time of discontinuation in all subjects who discontinue treatment early (24- or 48-week treatment). NA treatment (either ETV or TDF as per local practice) should be continued or, in case of JNJ-56136379 monotherapy during the 24-week treatment phase, started at Week 24 as per local treatment guidelines. An additional 24-week follow-up (as per local treatment guidelines), by their primary care physician outside of the study, is recommended after the 24-week follow-up phase in the study, for subjects who do not continue or start NA treatment at Week 24.
b. Complete physical examination, including body weight, temperature, and skin examination.
c. Symptom-directed physical examination, including body weight and temperature.
d. Vital signs include supine SBP, DBP, and pulse rate.
e. If blood sampling or vital signs measurement is scheduled for the same time point as ECG recording, the procedures should preferably be performed in the following order: ECG(s), vital signs, blood draw.
f. Biochemistry samples must be taken fasted for at least 10 hours for measurement of phosphorus, calcium, creatinine clearance, and lipids.
g. Creatinine clearance (estimated by the eGFR, which is calculated by the MDRD formula) will be assessed.
h. Samples may be sequenced based on the sponsor virologist's request.
i. Quantitative HBeAg assessment will only be performed in subjects who are defined HBeAg-positive at screening based on a qualitative HBeAg assay.
j. Exploratory serology samples may be analyzed at the sponsor's discretion. Samples may be used to assess virologic or serologic markers of HBV.
k. One sample at any time during the visit.
l. Immune cell samples (PBMC) may be collected (selected sites only).
m. PRO assessments will be performed by subjects at sites where appropriate translations are available. Subjects will complete the EQ-5D-5L, HBQOL, MOS-CFS Cog-R, and SF-36v2 questionnaires on an electronic device during the specified study visits. The PRO assessments are preferably to be completed **before** any tests, procedures or other consultations for that visit to prevent influencing the subject's perceptions.
n. PRO assessments are not needed at the early withdrawal visit if PRO was already assessed within 2 weeks prior to the early withdrawal visit.

o. Only applicable to subjects in the pharmacokinetic subgroup and subjects enrolled at a site with an on-site Fibroscan device.
p. If a subject discontinues study treatment before the end of the 24-week treatment phase or, if applicable, the 24-week treatment extension phase (ie, Week 48 visit), a treatment withdrawal visit should be performed after which the subject will enter the 24-week follow-up, unless the subject withdraws consent. NA treatment (either ETV or TDF as per local practice) should be continued or, in case of JNJ-56136379 monotherapy, started at the time of early discontinuation of study treatment as per local treatment guidelines. An additional 24-week follow-up (as per local treatment guidelines), by their primary care physician outside of the study, is recommended after the 24-week follow-up phase in the study, for subjects who do not continue or start NA treatment at Week 24 or 48. Subjects who withdraw consent will be offered an optional safety follow-up visit.
q. HBcrAg and HBV RNA samples may be batched and only selected samples may be tested. Samples can be used for assessment of other serologic/virologic markers of HBV.
r. Subjects withdrawing consent during the follow-up period will be offered an optional safety follow-up visit.

APPENDIX 7: TIME AND EVENTS SCHEDULE – POST-TREATMENT FOLLOW-UP PHASE (SCHEDULE 2)

This schedule is applicable for subjects who completed 48 weeks of treatment (treatment extension phase) and met the treatment completion criteria as described in Section **Error! Reference source not found.**.

Phase	**Post-treatment Follow-up[m,n]**										
Follow-up (FU) Week (W)	**FU W2**	**FU W4**	**FU W6**	**FU W8**	**FU W12**	**FU W16**	**FU W20**	**FU W24**	**FU W32**	**FU W40**	**FU W48 end of study visit**
Study Procedure											
Study Treatment Dispensing											
Dispense NA[a]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	
Safety Evaluations											
Complete physical examination[b]											
Symptom-directed physical examination[c]	X	X			X		X	X	X	X	X
Vital signs[d]	X	X			X		X	X	X	X	X
Triplicate 12-lead ECG[e]		X			X			X			X
Clinical Laboratory Tests											
Hematology	X	X			X		X	X	X	X	X
Blood chemistry[f,g]	X	X	X	X	X	X	X	X	X	X	X
Blood coagulation	X	X			X		X	X	X	X	X
Urinalysis	X	X			X		X	X	X	X	X
Urine pregnancy test (women of childbearing potential only)	X	X			X		X	X	X	X	X
Efficacy Evaluations											
Fibroscan[o]								X			X
HBV Virology											
HBV DNA and HBV RNA[p]	X	X	X	X	X	X	X	X	X	X	X
Viral genome sequencing[h]		X		X	X		X	X	X	X	X
HBV Serology											
Anti-HBs and anti-HBe		X			X			X			X
HBsAg and HBeAg (qualitative)		X			X			X			X
HBsAg and HBeAg[i] (quantitative)	X	X	X	X	X	X	X	X	X	X	X

Phase	Post-treatment Follow-up[m,n]										
Follow-up (FU) Week (W)	**FU W2**	**FU W4**	**FU W6**	**FU W8**	**FU W12**	**FU W16**	**FU W20**	**FU W24**	**FU W32**	**FU W40**	**FU W48 end of study visit**
Study Procedure											
HBcrAg[p]		X			X			X			X
Exploratory serology[j]	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics											
Blood sampling for pharmacokinetics of JNJ-56136379 and/or NA (sparse)[k]	X	X									
Blood sampling for exploratory pharmacokinetics of hormonal contraceptives and their metabolites (women on hormonal contraceptives only)		X									
Exploratory Biomarkers											
Host mRNA		X		X	X	X		X			X
Serum proteins		X		X	X	X		X		X	X
Immune cells (PBMCs) (selected sites only)[l]		X				X					X
Ongoing Participant Review											
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X

s. No JNJ-56136379 or placebo will be dispensed during the follow-up. Dispensing of NA is only applicable for subjects who meet the re-treatment criteria described in Section **Error! Reference source not found.** and, hence, should start NA (either ETV or TDF) treatment during the post-treatment follow-up.
t. Complete physical examination, including body weight, temperature, and skin examination.
u. Symptom-directed physical examination, including body weight and temperature.
v. Vital signs include supine SBP, DBP, and pulse rate.
w. If blood sampling or vital signs measurement is scheduled for the same time point as ECG recording, the procedures should preferably be performed in the following order: ECG(s), vital signs, blood draw.
x. Biochemistry samples must be taken fasted for at least 10 hours for measurement of phosphorus, calcium, creatinine clearance, and lipids.
y. Creatinine clearance (estimated by the eGFR, which is calculated by the MDRD formula) will be assessed.
z. Samples may be sequenced based on the sponsor virologist's request.
aa. Quantitative HBeAg assessment will only be performed in subjects who are defined HBeAg-positive at screening based on a qualitative HBeAg assay.
bb. Exploratory serology samples may be analyzed at the sponsor's discretion. Samples may be used to assess virologic or serologic markers of HBV.
cc. One sample at any time during the visit.

dd. Immune cell samples (PBMC) may be collected (selected sites only).
ee. All follow-up study visits are to be scheduled relative to the baseline visit date and are to occur at the end of Weeks 2, 4, 6, 8, 12, 16, 20, 24, 32, 40 and 48. The visit window is ±2 days of the protocol-specified date at Weeks 2-8, ±5 days of the protocol-specified date through Week 48. An unscheduled visit can be performed upon investigator's discretion, in case of ALT elevations during follow-up.
ff. Subjects who withdraw consent during follow-up will be offered an optional safety follow-up visit.
gg. Only applicable to subjects in the pharmacokinetic subgroup and subjects enrolled at a site with an on-site Fibroscan device.
hh. HBcrAg and HBV RNA samples may be batched and only selected samples may be tested. Samples can be used for assessment of other serologic/virologic markers of HBV.

APPENDIX 8: CARDIOVASCULAR SAFETY - ABNORMALITIES

ECG

All-important abnormalities from the ECG readings will be listed.

Abnormality Code	ECG parameter			
	HR	**PR**	**QRS**	**$QT_{corrected}$**
Abnormalities on actual values				
Abnormally low	< 45 bpm	NAP	-	-
Abnormally high	≥ 120 bpm	> 220 ms	≥ 120 ms	-
Borderline prolonged QT	-	-	-	450 ms < QTc ≤ 480 ms
Prolonged QT	-	-	-	480 ms < QTc ≤ 500 ms
Pathologically prolonged QT	-	-	-	QTc > 500 ms
Abnormalities on changes from baseline (ΔQTc)				
Normal QTc change	-	-	-	ΔQTc < 30 ms
Borderline QTc change	-	-	-	30 ms ≤ ΔQTc ≤ 60 ms
Abnormally high QTc change	-	-	-	ΔQTc > 60 ms

NAP = not applicable

For absolute QTc parameters the categories are defined based on the ICH E14 Guidance[a]

Vital Signs[b]

The following abnormalities will be defined for vital signs:

Abnormality Code	Vital Signs parameter		
	Pulse	**DBP**	**SBP**
Abnormalities on actual values			
Abnormally low	≤ 45 bpm	≤ 50 mmHg	≤ 90 mmHg
Grade 1 or mild	-	> 90 mmHg - < 100 mmHg	> 140 mmHg - < 160 mmHg
Grade 2 or moderate	-	≥ 100 mmHg - < 110 mmHg	≥ 160 mmHg - < 180 mmHg
Grade 3 or severe	-	≥ 110 mmHg	≥ 180 mmHg
Abnormally high	≥ 120 bpm	-	-

APPENDIX 9: RASH MANAGEMENT

For subjects reporting rash, the following should be done.

All rashes will be discussed between the investigator and the sponsor, and in case of a causal relationship between the rash and the study drug, then the following visits and assessments will be performed as indicated below and in the "Visit Schedule for Rash Management" (see Attachment4) Unscheduled follow-up visits for close follow-up of rash will be performed based on the grade (severity) of the rash. At the investigator's discretion, additional visits and assessments can be performed.

[a] The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs CHMP/ICH/2/04, May 2005.

[b] The classification of AEs related to hypotension and hypertension will be done according to the DAIDS grading scale.

The rash event should be captured in the AE Section of the eCRF, as well as in more detail in the specific rash assessment pages of the eCRF.

In case of rash, blood samples need to be taken for safety laboratory testing, and processed by the local laboratory. These samples need to be taken during the unscheduled visits as described below and in Attachment4. A copy of the local laboratory reports should be de-identified and will be collected by the monitor.

The following parameters need to be tested: AST, ALT, creatinine, erythrocyte sedimentation rate, and a complete blood cell count (including hemoglobin, hematocrit, RBC count, WBC count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count).

Digital pictures need to be taken as described below and in Attachment4. Digital pictures will be de-identified and stored on the sponsor's secure server. Only the study team will have access to the pictures.

The subject may be treated symptomatically until the rash resolves. If the rash is considered to be most likely due to concomitant illness or nonstudy medication, standard management, including discontinuation of the likely causative agent, should be undertaken, and the continuation of the subject in the study should be discussed with the sponsor.

Dermatologist fees for evaluating subjects who experience a rash will be reimbursed by the sponsor.

The following grades are based on the DAIDS Toxicity Grading Scale[7] with adaptations made by the sponsor.

Subjects should be informed that they should contact their doctor and visit the clinic immediately (unscheduled visit, Day 0 of the rash) when they notice any rash.

Grade 1 Rash

A grade 1 rash is defined as **erythema**.

a) Subjects may continue the intake of study drug(s) (at the investigator's discretion).

b) An unscheduled visit for initial rash evaluation (Day 0) is required.

c) Assessment of safety blood samples by the local laboratory is required. A copy of the local laboratory report should be made anonymous and will be collected by the monitor.

d) Digital pictures should be taken within 24 hours after the onset of the rash.

e) Referral to a dermatologist is only needed if the rash diagnosis is uncertain (preferably within 24 hours after the onset of the rash). A copy of the dermatologist's report should be made anonymous and will be collected by the monitor.

f) Cetirizine, levocetirizine, topical corticosteroids, or antipruritic agents may be prescribed.

g) The description of the rash should be reported per 'Unscheduled Visit in Case of Rash' in the eCRF (ie, the initial rash assessment pages).

For close follow-up of the rash, unscheduled visits will also be performed 1 and 7 days after the initial assessment of the rash. At these visits, safety blood samples and digital pictures should be taken. The follow-up rash assessment pages of the eCRF should be completed for all follow-up visits. For these and all subsequent local laboratory blood sample assessments: a copy of the local laboratory reports should be de-identified and will be collected by the monitor.

If the rash is unresolved after 7 days, additional unscheduled visits can be performed at the investigator's discretion. Upon resolution/stabilization of the rash, digital pictures should be taken and the final rash assessment pages of the eCRF should be completed.

The subject should be advised to contact the investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms appear, or if mucosal involvement develops.

In case the rash evolves from a grade 1 to a higher grade, additional unscheduled visits have to be conducted according to the guidelines for grade 2 or grade 3-4 rash, respectively.

Grade 2 Rash

A grade 2 rash is defined as **diffuse, maculopapular rash OR dry desquamation**.

h) Subjects will permanently discontinue the intake of study drugs and be withdrawn from the study. No rechallenge is allowed.

Note: Subjects experiencing grade 2 rash following the last intake of study drug may continue in the study as long as they are not re-exposed to suspect study drug.

i) An unscheduled visit for initial rash evaluation (Day 0) is required.

j) Assessment of safety blood samples by the local laboratory is required. A copy of the local laboratory report should be de-identified and will be collected by the monitor.

k) Digital pictures should be taken within 24 hours after the onset of the rash.

l) Referral to a dermatologist is required, preferably within 24 hours after the onset of the rash. A copy of the dermatologist's report should be de-identified and will be collected by the monitor.

m) A biopsy is performed (preferably within 24 hours after the onset of the rash) if advised by the dermatologist. A copy of the biopsy report should be de-identified and will be collected by the monitor.

n) Cetirizine, levocetirizine, topical corticosteroids, or antipruritic agents may be prescribed.

o) The description of the rash should be reported per 'Unscheduled Visit in Case of Rash' in the eCRF (ie, the initial rash assessment pages).

For close follow-up of the rash, unscheduled visits will also be performed 1 and 7 days after the initial assessment of the rash. At these visits, safety blood samples and digital pictures should be taken. The follow-up rash assessment pages of the eCRF should be completed for all follow-up

visits. For these and all subsequent local laboratory blood sample assessments: a copy of the local laboratory reports should be de-identified and will be collected by the monitor.

If the rash is unresolved after 7 days,

p) And there is an increase in AST/ALT of 1 or 2 times the baseline value OR an increase in AST/ALT of less than 5 times the ULN, subjects should be followed weekly with repeated local lab assessments and digital pictures until resolution of the AST/ALT abnormalities.

q) And there is no increase in AST/ALT, additional unscheduled visits (including local lab assessments and digital pictures) can be performed at the investigator's discretion.

Upon resolution/stabilization of the rash, digital pictures should be taken and the final rash assessment pages of the eCRF should be completed.

The subject should be advised to contact the investigator immediately if the rash fails to resolve (after more than 2 weeks), if there is any worsening of the rash, if any systemic signs or allergic symptoms develop, or if mucosal involvement develops.

In case the rash evolves from a grade 2 to a grade 3-4 rash, additional unscheduled visits have to be conducted according to the guidelines for grade 3-4 rash.

Grade 3 or Grade 4 Rash

A grade 3 rash is defined as:

1. **vesiculation, moist desquamation, or ulceration OR**
2. **cutaneous event with one of the following (revised by the sponsor):**

   elevations in AST/ALT more than 2 x baseline value and and ≥5 x ULN;

   fever > 38°C or 100°F;

   eosinophils > 1000/mm^3;

   serum sickness-like reaction.

A grade 4 rash is defined as:

3. **exfoliative dermatitis OR**
4. **a generalized rash with mucous membrane involvement, OR**
5. **erythema multiforme OR**
6. **Stevens-Johnson Syndrome, OR**
7. **rash associated with necrosis requiring surgery**

r) Subjects will **permanently discontinue** the intake of all study drug(s) and be withdrawn from the study. No rechallenge is allowed.

s) An unscheduled visit for initial rash evaluation (Day 0) is required.

t) Assessment of safety blood samples by the local laboratory is required on the day of initial rash evaluation and the day thereafter (Days 0 and 1), and as indicated below. A copy of the local laboratory report should be de-identified and will be collected by the monitor.

u) Digital pictures should be taken within 24 hours after the onset of the rash and on Day 1, and as indicated below.

v) Referral to a dermatologist is required, preferably within 24 hours after the onset of the rash. A copy of the dermatologist's report should be de-identified and will be collected by the monitor.

w) A biopsy should be performed within 24 hours after the onset of the rash. A copy of the biopsy report should be de-identified and will be collected by the monitor.

x) Appropriate management should be undertaken and subjects should be followed until resolution of the rash.

y) The description of the rash should be reported per 'Unscheduled Visit in Case of Rash' in the eCRF (ie, the initial rash assessment pages). The follow-up rash assessment pages of the eCRF should be completed for all follow-up visits.

For close follow-up of the rash, unscheduled visits will be performed as follows:

z) Follow-up visits on Days 2, 3 and 4 are required. Additional safety blood samples and digital pictures are to be taken on these days only if the subject's AST/ALT on Day 0 and/or Day 1 of rash >2 x baseline value, and/or ≥5 x ULN and/or in case of rash progression. For these and all subsequent local laboratory blood sample assessments: a copy of the local laboratory report should be de-identified and will be collected by the monitor.

aa) A follow-up visit on Day 5 is required and additional safety blood samples and digital pictures are to be taken regardless of the Day 0/1 AST/ALT levels or rash progression.

bb) Thereafter, weekly follow-up visits are required (or more frequently at the investigator's discretion) as long as grade 3-4 rash is present. Once grade 3-4 rash has resolved to ≤ grade 2 rash, follow-up should be done according to the instructions for follow-up visits for grade 1 or grade 2 rash, respectively.

cc) As long as the rash remains grade 3 or 4, additional safety blood samples and digital pictures are required at these weekly follow-up visits only if the subject's AST/ALT on Day 5 of rash is still >2 x baseline value and/or ≥5 x ULN and/or in case of rash progression, until resolution or stabilization of the AST/ALT elevations.

Upon resolution/stabilization of the rash, digital pictures should be taken and the final rash assessment pages of the eCRF should be completed.

Subjects should be advised to contact the investigator immediately if they notice any worsening of the rash.

A complete summary of the guidelines for rash management is given in Attachment4.

APPENDIX 10: Visit Schedule for Rash Management for Adult Subjects

This visit schedule summarizes the visits and assessments to be performed in case of rash. At the investigator's discretion, additional visits and assessments can be performed. For all rashes, please also complete the specific rash assessment pages of the eCRF for all visits. Local laboratory blood sample assessments will be documented/collected as described in the text above.

a) Table 2: Management of Rash Events by Severity Grade

	Definition	Study Drug Action	Activities by Day[a]	Referral to Dermatologist and Dermatology Activities
Grade 1 rash (with or without pruritus)[b]	Erythema	Study drug intake may be continued at the investigator's discretion	Day 0: optional on site visit for initial rash evaluation may be performed at the investigator's discretion. Safety laboratory assessments may be performed at the investigator's discretion (recommended if visit occurs). Determine if subject was adhering to the recommended sun-protective measures. If appropriate, provide sun protection counseling. Day 1 and thereafter: appropriate follow-up visits at the investigator's discretion until resolution of rash. Safety laboratory assessments may be performed at the investigator's discretion.	Not required

a) Table 2:	Management of Rash Events by Severity Grade			
	Definition	**Study Drug Action**	**Activities by Day[a]**	**Referral to Dermatologist and Dermatology Activities**
Grade 2 rash (with or without pruritus)[b]	Diffuse, maculopapular rash, or dry desquamation	Study drug intake may be continued at the investigator's discretion	Day 0: required on-site visit (if a visit is not possible, telephone contact with the subject should take place to collect information and give advice on the necessary measures to be taken). Safety laboratory assessments may be performed at the investigator's discretion (recommended). Determine if subject was adhering to the recommended sun-protective measures. If appropriate, provide sun protection counseling. Day 1 and thereafter: appropriate follow-up visits at the investigator's discretion until resolution of rash or until clinical stability is reached. Safety laboratory assessments are required on Day 1 and are required thereafter only if the previous values were abnormal (but may be performed at the investigator's discretion). If the rash progresses to a higher grade, safety laboratory assessments of the higher grade should be followed.	Referral to dermatologist at the discretion of the investigator[c] Biopsy not required, but may be performed at the dermatologist's discretion

a) Table 2:	Management of Rash Events by Severity Grade			
	Definition	**Study Drug Action**	**Activities by Day[a]**	**Referral to Dermatologist and Dermatology Activities**
Grade 3 rash[b]	Vesiculation, moist desquamation, or ulceration OR Any cutaneous event with 1 of the following: - Elevations in AST/ALT >2×baseline value - Fever >38°C or 100°F - Eosinophils >1.00×10^3/μL - Serum sickness-like reaction	Must permanently discontinue JNJ-56136379; no rechallenge allowed NA treatment may be discontinued based on investigator judgement in consultation with the sponsor	Day 0: required on-site visit. Safety laboratory assessments required to be performed. Determine if subject was adhering to the recommended sun-protective measures. If appropriate, provide sun protection counseling. Day 1: required on-site visit. Safety laboratory assessments required to be performed. Further visit(s): appropriate follow-up required until resolution of rash or until clinical stability is reached. Safety laboratory assessments are recommended to be performed until the rash severity resolves to Grade 2 or Grade 1.	Required[c] Biopsy not required, but may be performed at the dermatologist's discretion.

a) Table 2:	Management of Rash Events by Severity Grade			
	Definition	**Study Drug Action**	**Activities by Day[a]**	**Referral to Dermatologist and Dermatology Activities**
Grade 4 rash	Exfoliative dermatitis OR Mucous membrane involvement in at least 2 distinct sites OR Erythema multiforme major OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis OR Necrosis requiring surgery	Must permanently discontinue JNJ-56136379; no rechallenge allowed NA treatment may be discontinued based on investigator judgement in consultation with the sponsor	Day 0: required on-site visit. Safety laboratory assessments required to be performed. Determine if subject was adhering to the recommended sun-protective measures. If appropriate, provide sun protection counseling. Day 1: required on-site visit. Safety laboratory assessments required to be performed. Further visit(s): appropriate follow-up required until resolution of rash or until clinical stability is reached. Safety laboratory assessments are recommended to be performed until the rash severity resolves to Grade 2 or Grade 1.	Required[c] Biopsy required and to be performed as soon as possible after the onset of the rash.

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

[a] Day 0 of the rash is the first day of investigator assessment and not the first day of rash as reported by the subject. The initial visit should be conducted as soon as possible after the subject contacts the investigator to report the AE (ie, preferably on Day 0). The initial visit and subsequent visits to manage the rash may require unscheduled visit(s).

[b] The subject should be advised to contact the investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms appear, or if mucosal involvement develops. In case the rash evolves to a higher grade than that first observed, management of the rash should follow the guidelines indicated for the higher grade.

[c] If applicable, dermatologist visit should occur preferably within 24 hours after onset of rash.

Notes:

a) Local laboratory assessments are to be used for rash management. The values of the local laboratory assessments need to be transcribed in the eCRF by the study site personnel.

b) *A copy of the dermatologist's report, and biopsy if performed, should be made anonymous and will be collected by the monitor.*

When safety blood samples are drawn as per the rash management guidelines, these should be processed by the local laboratory. The following parameters will need to be tested: AST, ALT, sedimentation rate, complete blood cell count (including hemoglobin, hematocrit, RBC count, WBC count, differential count [neutrophils, lymphocytes, monocytes, eosinophils, and basophils], and platelet count), and creatinine. The values of the local laboratory assessments need to be transcribed in the eCRF by the study site personnel.

The subject may be treated symptomatically until the rash resolves. Oral antihistamines (eg, cetirizine, levocetirizine) and/or topical corticosteroids may provide symptomatic relief but effectiveness of these measures has not been established. If systemic corticosteroids for longer than 24 hours are required for treatment of rash, the study drug needs to be permanently discontinued. If the rash is considered to be most likely due to concomitant illness or non-study drugs, standard management, including discontinuation of the likely causative agent, should be undertaken.

Health Questionnaire

English version for the USA

APPENDIX 11: 5-LEVEL EUROQOL 5-DIMENSION QUESTIONNAIRE (EQ-5D-5L)

EQ-5D-5L	
EQ-5D-5L Tablet version	
English (USA)	Country (Language)
Health Questionnaire	Health Questionnaire
English version for the USA	Version (Target Language)
	Version (English)
Please tap the ONE box that best describes your health TODAY.	Instruction
MOBILITY	**Mobility**
I have no problems walking	MB1
I have slight problems walking	MB2
I have moderate problems walking	MB3
I have severe problems walking	MB4
I am unable to walk	MB5
SELF-CARE	**Self-care**
I have no problems washing or dressing myself	SC1
I have slight problems washing or dressing myself	SC2
I have moderate problems washing or dressing myself	SC3
I have severe problems washing or dressing myself	SC4
I am unable to wash or dress myself	SC5
USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*	**Usual Activities**
I have no problems doing my usual activities	UA1
I have slight problems doing my usual activities	UA2
I have moderate problems doing my usual activities	UA3
I have severe problems doing my usual activities	UA4
I am unable to do my usual activities	UA5
PAIN / DISCOMFORT	**Pain / Discomfort**
I have no pain or discomfort	PD1
I have slight pain or discomfort	PD2
I have moderate pain or discomfort	PD3
I have severe pain or discomfort	PD4
I have extreme pain or discomfort	PD5
ANXIETY / DEPRESSION	**Anxiety / Depression**
I am not anxious or depressed	AD1
I am slightly anxious or depressed	AD2
I am moderately anxious or depressed	AD3
I am severely anxious or depressed	AD4
I am extremely anxious or depressed	AD5
We would like to know how good or bad your health is TODAY.	Vas Line 1
This scale is numbered from 0 to 100.	Vas Line 2
100 means the best health you can imagine.	Vas Line 3
0 means the worst health you can imagine.	Vas Line 4
Please tap on the scale to indicate how your health is TODAY.	Vas Line 5
The best health you can imagine	Top Scale
The worst health you can imagine	Bottom Scale
YOUR HEALTH TODAY	Box Health
Next	button.next
Previous	button.previous
© EuroQol Research Foundation. EQ-5D™ is a trade mark of the EuroQol Research Foundation	
Disclaimer: *This is a preview of the EQ-5D instrument. It demonstrates the text, questions and response options included in this version. This preview does not represent the final product and should not be used as an official EQ-5D instrument.*	

HBQOL v1.0 QUESTIONNAIRE

Some people with hepatitis B say that having hepatitis B affects the way they feel socially and mentally.

Below is a list of statements about how hepatitis B might make you feel socially or mentally. Please read each one carefully and circle the number that best describes how frequently, if ever, you feel that way. Circle only one number for each statement and do not skip any items.

		Never	Rarely	Sometimes	A Lot of the Time	All of the Time
F1	I feel ashamed because of hepatitis B	1	2	3	4	5
F2	I feel stigmatized because of hepatitis B	1	2	3	4	5
F3	I feel sad because of hepatitis B	1	2	3	4	5
F4	I feel frustrated because of hepatitis B	1	2	3	4	5
F5	I feel worn out and tired because of hepatitis B	1	2	3	4	5
F6	I feel anxious because of hepatitis B	1	2	3	4	5
F7	I feel angry because of hepatitis B	1	2	3	4	5
F8	I feel isolated from others because of hepatitis B	1	2	3	4	5
F9	I feel like something bad might happen because of hepatitis B	1	2	3	4	5
F10	I feel my life is less enjoyable because of hepatitis B	1	2	3	4	5
F11	I feel like sexual activity is difficult for me because of hepatitis B	1	2	3	4	5
F12	I feel like I am less productive because of hepatitis B	1	2	3	4	5
F13	I feel scared because of hepatitis B	1	2	3	4	5

CONTINUE TO NEXT PAGE →

Some people have concerns about their hepatitis B.

Below there is a list of possible concerns that some people have expressed about hepatitis B. For each one, please think about whether you also have that concern and, if so, how much of a concern it is to you. Circle the number that best describes your level of concern for each statement. Circle only one number for each statement and do not skip any items.

	How concerned are you that…	Not at All Concerned	A Little Bit Concerned	Moderately Concerned	Quite a Bit Concerned	Extremely Concerned
C1	One day you could develop liver failure because of your hepatitis B	1	2	3	4	5
C2	You might develop liver cancer because of your hepatitis B	1	2	3	4	5
C3	Someone influential, like your boss, might find out about your hepatitis B	1	2	3	4	5
C4	You could transmit hepatitis B to a child	1	2	3	4	5
C5	Your hepatitis B may flare up at any time	1	2	3	4	5
C6	It is easier to get other illnesses because of having hepatitis B	1	2	3	4	5
C7	You could transmit hepatitis B to a partner through sex	1	2	3	4	5
C8	You have to watch what medicines you take because you have hepatitis B	1	2	3	4	5
C9	Hepatitis B might affect your life expectancy	1	2	3	4	5
C10	You are overly self-conscious because of hepatitis B	1	2	3	4	5

CONTINUE TO NEXT PAGE →

	How concerned are you that…	Not at All Concerned	A Little Bit Concerned	Moderately Concerned	Quite a Bit Concerned	Extremely Concerned
C11	You could be socially isolated because of hepatitis B	1	2	3	4	5
C12	Something serious might be wrong because of your hepatitis B	1	2	3	4	5
C13	You have to watch what you eat because you have hepatitis B	1	2	3	4	5
C14	You might be embarrassed because of your hepatitis B	1	2	3	4	5
C15	Your health might unexpectedly get worse because of hepatitis B	1	2	3	4	5

CONTINUE TO NEXT PAGE →

Some people with hepatitis B say that having hepatitis B affects the way they feel physically.

Below is a list of physical symptoms. Please read each one carefully and circle the number that best describes how frequently, if ever, you think that hepatitis B (as opposed to other conditions) causes that symptom.

	How frequently do you feel…	Never	Rarely	Sometimes	A Lot of the Time	All of the Time
P1	Tiredness	1	2	3	4	5
P2	Memory problems	1	2	3	4	5
P3	Muscle aches	1	2	3	4	5

**** END OF QUESTIONNAIRE ****

Thank you for your time and effort in answering these questions. Please check over your responses to make sure you did not skip any questions.

Scaling and Scoring Instructions

There are 31 scored items included in the HB-QOL, including 13 items regarding how HBV makes patients feel socially or mentally (F1-F13), 15 items regarding HBV-related concerns (C1-C15), and 3 items regarding HBV-related physical impacts.

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

Level 1 – 0 points
Level 2 – 25 points
Level 3 – 50 points
Level 4 – 75 points
Level 5 – 100 points

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

Psychological Well-Being (8 Items)

Anxious (F6)
Frustrated (F4)
Sad (F3)
Angry (F7)
Less Enjoyable (F10)
Scared (F13)
Bad (F19)
Isolated (F8)

Anticipation Anxiety (6 Items)

Concern Failure (C1)
Concern Cancer (C2)
Concern Worsen (C15)
Concern Serious (C12)
Concern Survival (C9)
Concern Flare (C5)

Vitality (5 Items)

Tiredness (P1)
Worn Out (F5)
Muscle Aches (P3)
Memory Problems (P2)
Unproductive (F13)

Stigma (6 Items)

Concern Embarrassed (C14)
Ashamed (F1)
Concern Self-Conscious (C10)
Concern Socially Isolated (C11)
Concern Boss (C3)
Stigmatized (F2)

Vulnerability (3 Items)

Concern Eat (C13)
Concern Sick Easily (C6)
Concern Medicines (C8)

Transmission (3 Items)

Concern Transmit Sex (C7)
Concern Transmit Child (C4)
Sex Difficult (F11)

Viral Response (4 Items)

Concern Transmit Sex (C7)
Concern Transmit Child (C4)
Concern Eat (C13)
Concern Medicines (C8)

In addition, there is a single **global score** that reflects the results on all 31 items.

Each subscale score is simply calculated as the average score among the items included in that subscale. The global score is simply the average score among all the items in the HBQOL.

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

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

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

APPENDIX 13: MEDICAL OUTCOMES STUDY COGNITIVE FUNCTIONING SCALE-REVISED (MOS-CFS COG-R)

(United Kingdom (English) MOS 6-Item Cognitive Functioning Scale
Single-Item Presentation Text–Revised)

MOS 6-Item Cognitive Functioning Scale

For each of the following questions, please select the one box that best describes your answer.

How much of the time, during the past 4 weeks:

Did you have difficulty reasoning and solving problems, for example, making plans, making decisions, learning new things?

All of the time
Most of the time
Some of the time
A little of the time
None of the time

How much of the time, during the past 4 weeks:

Did you have difficulty doing activities involving concentration and thinking?

All of the time
Most of the time
Some of the time
A little of the time
None of the time

How much of the time, during the past 4 weeks: Did you become confused and start several actions at a time? All of the time Most of the time Some of the time A little of the time None of the time
How much of the time, during the past 4 weeks: Did you forget things that happened recently, for example, where you put things and when you had appointments? All of the time Most of the time Some of the time A little of the time None of the time
How much of the time, during the past 4 weeks: Did you have trouble keeping your attention on any activity for long? All of the time Most of the time Some of the time A little of the time None of the time
How much of the time, during the past 4 weeks: Did you react slowly to things that were said or done? All of the time Most of the time Some of the time A little of the time None of the time

APPENDIX 14: SHORT FORM 36 VERSION 2 (SF-36V2) QUESTIONNAIRE

The SF-36v2 2000 version has been replaced by the 2010 version.

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

For each of the following questions, please select the one response that best describes your answer.

In general, would you say your health is:

Excellent
Very good
Good
Fair
Poor

Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago
Somewhat better now than one year ago
About the same as one year ago
Somewhat worse now than one year ago
Much worse now than one year ago

The following question is about activities you might do during a typical day. Does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
The following question is about activities you might do during a typical day. Does your health now limit you in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
The following question is about activities you might do during a typical day. Does your health now limit you in lifting or carrying groceries? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
The following question is about activities you might do during a typical day. Does your health now limit you in climbing several flights of stairs? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all

The following question is about activities you might do during a typical day. Does your health now limit you in climbing one flight of stairs? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
The following question is about activities you might do during a typical day. Does your health now limit you in bending, kneeling, or stooping? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
The following question is about activities you might do during a typical day. Does your health now limit you in walking more than a mile? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
The following question is about activities you might do during a typical day. Does your health now limit you in walking several hundred yards? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all

The following question is about activities you might do during a typical day. Does your health now limit you in walking one hundred yards? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
The following question is about activities you might do during a typical day. Does your health now limit you in bathing or dressing yourself? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities? Cut down on the amount of time you spent on work or other activities as a result of your physical health All of the time Most of the time Some of the time A little of the time None of the time
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities? Accomplished less than you would like as a result of your physical health All of the time Most of the time Some of the time A little of the time None of the time

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities? Were limited in the kind of work or other activities as a result of your physical health All of the time Most of the time Some of the time A little of the time None of the time
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities? Had difficulty performing the work or other activities as a result of your physical health (for example, it took extra effort) All of the time Most of the time Some of the time A little of the time None of the time
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities? Cut down on the amount of time you spent on work or other activities as a result of any emotional problems (such as feeling depressed or anxious) All of the time Most of the time Some of the time A little of the time None of the time

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? Not at all A little bit Moderately Quite a bit Extremely
This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks did you feel full of life? All of the time Most of the time Some of the time A little of the time None of the time
This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks have you been very nervous? All of the time Most of the time Some of the time A little of the time None of the time
This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks have you felt so down in the dumps that nothing could cheer you up? All of the time Most of the time Some of the time A little of the time None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks have you felt calm and peaceful?

All of the time
Most of the time
Some of the time
A little of the time
None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks did you have a lot of energy?

All of the time
Most of the time
Some of the time
A little of the time
None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks have you felt downhearted and depressed?

All of the time
Most of the time
Some of the time
A little of the time
None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks did you feel worn out? All of the time Most of the time Some of the time A little of the time None of the time
This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks have you been happy? All of the time Most of the time Some of the time A little of the time None of the time
This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks did you feel tired? All of the time Most of the time Some of the time A little of the time None of the time

How TRUE or FALSE is the following statement for you?

My health is excellent.

Definitely true
Mostly true
Don't know
Mostly false
Definitely false

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking more than a mile	☐ 1	☐ 2	☐ 3
h	Walking several hundred yards	☐ 1	☐ 2	☐ 3
i	Walking one hundred yards	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

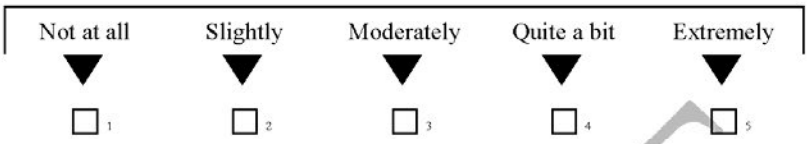
4. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

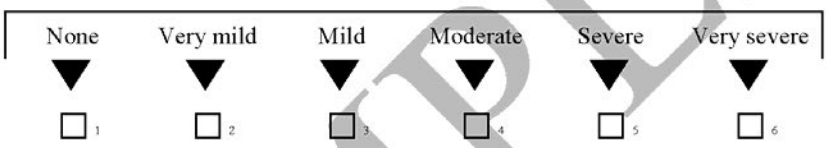
5. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

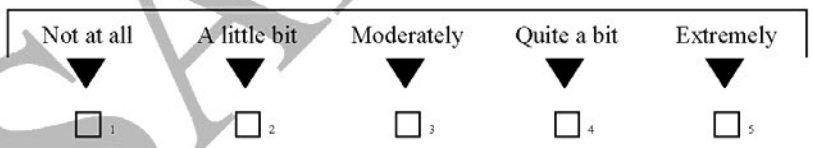
6. **During the <u>past week</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**



7. **How much <u>bodily</u> pain have you had during the <u>past week</u>?**



8. **During the <u>past week</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**



9. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!