Janssen Research & Development *

Clinical Protocol

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
AMENDMENT 5

JNJ-56136379

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This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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Prepared by:	Janssen Research & Development, a division of Janssen Pharmaceutica NV
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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	20 October 2017
Amendment 1	18 December 2017
Amendment 2	6 March 2018
Amendment 3	18 June 2018
Amendment 4	20 February 2019
Amendment 5	This document

Amendments below are listed beginning with the most recent amendment.

Amendment 5 (This document)

The overall reason for the amendment:
To specify that subjects with pre-existing conditions of glycosuria (ie, when linked to TDF treatment or a concomitant disease and its medication) should not be discontinued from the study treatment.

In addition, the genito-urinary examination was updated in line with standard practice.

The table below gives an overview of the rationale for each change and all applicable sections.

Rationale: The Sponsor considers that subjects with pre-existing conditions of urinalysis abnormalities, who have not developed a new or worse condition, should have the possibility to continue study treatment. Therefore, the protocol has been amended so that study treatment will be discontinued only in case of confirmed treatment-emergent urinalysis abnormalities ≥grade 3 which cannot be attributed to a pre-existing condition or concomitant treatment.

During interim analysis, 2 subjects with pre-existing conditions of glycosuria, by concomitant treatment or condition, met discontinuation criterion #9 as listed in Section 10.2 of the protocol. These subjects were not discontinued, considering their pre-existing condition or relationship to NA treatment. One subject was diabetic and experienced grade 3 urinalysis abnormalities at screening and baseline that continued during treatment. The other subject was receiving TDF (initiated 5 years prior to screening) and experienced grade 2 urinalysis abnormalities at screening and baseline. This subject had grade 3 urinalysis abnormalities at 2 consecutive visits (Week 24 and 28) which returned to normal at the Week 32 and 36 visits.

9.9 Safety Evaluations
10.2 Discontinuation of Study Treatment/Withdrawal from the Study

Rationale: In line with standard practice, the Sponsor has made the genito-urinary examination optional and at the investigator's discretion, which will avoid undue protocol deviations.

9.9 Safety Evaluations

Rationale: Sponsor's responsible medical officer was updated to reflect current organizational structure.

INVESTIGATOR AGREEMENT

Amendment 4 (20 February 2019)

The overall reason for the amendment:
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. As an additional precautionary measure, the Sponsor has implemented a stringent futility rule in the JNJ-56136379 250 mg monotherapy arm.

The table below gives an overview of the rationale for each change and all applicable sections.

Rationale: In light of cases of virological breakthroughs in the JNJ-56136379 open-label 75 mg monotherapy arm (Treatment Arm 1), the DRC recommended to discontinue treatment with JNJ-56136379 in all subjects in this monotherapy arm. The procedure of 'urgent safety measure' has been initiated for immediate notification and implementation of this decision.

At the decision time point (6 February 2019), virological breakthrough, as defined by the protocol (ie, confirmed on-treatment HBV DNA increase >1 $\log_{10}$ from nadir level or 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), was observed in 5 out of the 28 subjects on JNJ-56136379 75 mg monotherapy. Per protocol, treatment with JNJ-56136379 75 mg was discontinued in these subjects and NA treatment started. In addition, there were 2 subjects who met the virological breakthrough threshold but, due to the change of treatment, the virological breakthrough could not confirmed. Although not a safety concern, all remaining subjects on JNJ-56136379 75 mg monotherapy should stop the treatment as soon as possible to avoid unnecessary exposure to a regimen which has a potential risk of virological breakthrough which may impact future capsid assembly modulator (CAM) treatment options. A study visit should be planned within the next 7 days of receiving the instruction (letter) in order to start treatment with NA. Subjects will enter the post-treatment follow-up phase as outlined in the Time and Events schedule (Schedule 1).

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1.3.5 Overall Benefit/Risk Assessment
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Rationale: Based on clinical data available to date, JNJ-56136379 250 mg monotherapy (Treatment Arm 6) is expected to provide greater antiviral activity compared to JNJ-56136379 75 mg monotherapy. In addition, no virological breakthroughs have been observed in this treatment arm to date. Therefore, the 250 mg monotherapy arm will continue but with the following changes:

- Subjects 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, limiting the duration of JNJ-56136379 monotherapy.
- A futility rule for this 250 mg monotherapy arm has been included in the protocol as a precautionary measure to safeguard the subjects in this treatment arm: if ≥1 subject in the 250 mg monotherapy arm experiences virological breakthrough during the first 24 weeks of treatment, NA treatment will be added to JNJ-56136379 treatment as soon as possible for all remaining subjects. These subjects will continue the visit schedule as planned. Subjects with virological breakthrough will discontinue JNJ-56136379 treatment and should start NA treatment as per the protocol.

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1.3.5 Overall Benefit/Risk Assessment
3.1 Overview of Study Design
6 DOSAGE AND ADMINISTRATION
6.1 Treatment Duration
6.2 Futility Rule (new section)

Rationale: To be able to assess compliance of subjects to the assigned treatment regimen over the entire study treatment phase, a pharmacokinetic (PK) sample for JNJ-56136379 and/or NA has been added at Week 16.

TIME AND EVENTS SCHEDULE – SCREENING AND TREATMENT PHASE

Rationale: A treatment duration of 48 weeks was introduced, for subjects who met pre-specified criteria (see Section 6.1 of the protocol), to evaluate the effect of extended study drug treatment on efficacy and safety.

To increase the chance for subjects (1) with high baseline HBV DNA and a pronounced decline in HBV DNA but who have not achieved HBV DNA <LLOQ at Week 20 and (2) those with HBV RNA fluctuating near the LLOQ ("blips") at Week 20, to be able to enter the extension phase, the requirement for HBV DNA to be <LLOQ at Week 20 was revised to <200 IU/mL at Week 20. Changing the threshold for HBV DNA from <LLOQ to <200 IU/mL is expected to allow substantially more subjects to continue JNJ-56136379 beyond Week 24. This will allow exploration of the efficacy and safety of 48 weeks of JNJ-56136379 treatment in a greater proportion of subjects with pronounced early HBV declines and will increase the learnings from this study.

Note that subjects in the JNJ-56136379 250 mg monotherapy arm (Treatment Arm 6) who meet the treatment extension criteria will receive JNJ-56136379 in combination with NA treatment from Week 24 to Week 48.

SYNOPSIS
TIME AND EVENTS SCHEDULE – SCREENING AND TREATMENT PHASE
3.1 Overview of Study Design
6.1 Treatment Duration

Rationale: Based on aggregate safety review of all available clinical safety data, and in line with the updated Investigator's Brochure Edition 4 (February 2019)[a], amylase and lipase elevations are no longer considered laboratory abnormalities of interest. The protocol has been adjusted accordingly.

1.1 Background
1.3.4 Potential Risks
1.3.5 Overall Benefit/Risk Assessment
11.10 Safety Analyses

Rationale: Minor grammatical, formatting, or spelling changes were made throughout the protocol.

Amendment 3 (18 June 2018)

The overall reason for the amendment: 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.

The table below gives an overview of the rationale for each change and all applicable sections.

Rationale: The dose to be administered in Part B will be 250 mg given once daily and has been selected by the sponsor, in agreement with the Data Review Committee (DRC), based on all safety, pharmacokinetic (PK), and antiviral activity data available following completion of the highest JNJ-56136379 dose group (who received 250 mg once daily) in the Phase 1 study 56136379HPB1001 in treatment-naïve chronic hepatitis B (CHB)-infected subjects treated for 28 days. The dose of 250 mg once daily was selected to maximize antiviral activity in broad patient populations, and is supported by the good safety profile observed to date. The observed exposure on Day 28 in CHB-infected subjects at 250 mg JNJ-56136379 administered once daily was well in line with population PK predictions and was lower than the predetermined ceiling of exposure (based on toxicity studies in animals).

[a] Investigator's Brochure: JNJ-56136379 Edition 4. Janssen Research & Development, 7 February 2019.

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11.12 Data Review Committee

Rationale: As complete data on the 9-month dog study have become available, the non-clinical data section of the introduction was updated accordingly, In addition, further clarifications and explanations were added to this section.

1.1 Background

Rationale: The introduction has been updated with new available antiviral activity and safety data following completion of the higher dose groups (150 mg and 250 mg JNJ-56136379 once daily) in the Phase 1 study 56136379HPB1001 in treatment-naïve CHB-infected subjects treated for 28 days. These data have also led to the selection of the 250 mg dose to be administered in Part B of the study. In addition, the introduction has been updated with a pooled analysis of available safety data from Phase 1 studies in healthy volunteers.

1.1 Background

Rationale: Additional information on the liver biopsy substudy (at selected sites only) was included in the protocol. It was specified that the protocol for the substudy will be provided separately, that the ICF will be collected separately, and the results of the liver biopsy substudy will be reported separately.

SYNOPSIS
3.1 Overview of Study Design

Rationale: According to inclusion criterion 3, CHB infection is to be documented based on a positive serum hepatitis B surface antigen (HBsAg) test at screening and at least 6 months prior to screening. However, in clinical practice in certain countries, once the treatment for CHB with nucleos(t)ide analogs (NAs) is initiated, routine monitoring is performed by hepatitis B virus (HBV) DNA rather than by HBsAg. Therefore, documented historical HBsAg results (ie, HBsAg results from at least 6 months prior to screening) may not be available in such patients when they are recruited for a clinical trial. It has been clarified in this amendment that, in such cases, HBV DNA results at least 6 months prior to screening may substitute for HBsAg results.

SYNOPSIS
4.1 Inclusion Criteria

Rationale: A clarification was added to inclusion criterion 5 to indicate that virologically suppressed subjects can either be on a branded entecavir (ETV) or tenofovir disoproxil fumarate (TDF) treatment or on a locally approved generic alternative (including different salt forms [eg, tenofovir maleate or succinate]) at the time of screening. It was also clarified that, during the study, subjects will receive branded ETV (Baraclude®) or TDF (Viread®) treatment, as applicable.

SYNOPSIS
4.1 Inclusion Criteria

Rationale: It was clarified that not only subjects with a current hepatitis C infection will be excluded from the study, but also subjects with a history of hepatitis C infection. Exclusion criterion 2 has been updated accordingly.

SYNOPSIS
4.2 Exclusion Criteria

Rationale: An exclusion criterion (exclusion criterion 21) was added to clearly specify that subjects with an organ transplant cannot be included in the study. These subjects were already implicitly excluded based on the exclusion of subjects taking disallowed immunosuppressive therapies. Now it has been explicitly stated that these subjects cannot be included.

SYNOPSIS
4.2 Exclusion Criteria

Rationale: To reduce the risk of relapse, the cut-off for the treatment completion criterion with respect to HBsAg levels after 48 weeks of treatment was lowered from <1,000 IU/mL to ≤500 IU/mL.

6.2 Individual Subject Treatment Completion Criteria

Rationale: It has been clarified that the recommended period of evaluation and confirmation of re-treatment criteria is at least 4 weeks. However, confirmation of these criteria and initiation of re-treatment can be done in less than 4 weeks, at the discretion of the investigator. In case re-treatment will be initiated, the investigator should contact the sponsor.

6.3 Re-treatment Criteria During Follow-up

Rationale: The protocol has been updated to clarify that diltiazem is not to be used (ie, disallowed therapy). In the previous versions (original and Amendments 1 and 2) of the protocol, there was a discrepancy on the usage of diltiazem, which was listed both as a disallowed therapy as well as a therapy to be taken with caution.

8 CONCOMITANT THERAPY

Rationale: Biotin intake will be restricted to 30 µg daily (either alone or as a part of multivitamins) from the time of screening until the end of the study, because of the possible interference in serologic assays from high levels of biotin intake as a supplement.[31]

8 CONCOMITANT THERAPY

Rationale: At the planned time points for semi-rich JNJ-56136379 PK sampling on Day 1 and Week 12, blood samples for exploratory hormonal contraceptive PK assessments will also be collected from all female subjects who are on a hormonal contraceptive treatment and who are included in the PK subgroup. From study 56136379HPB1004, it is anticipated that coadministration with ethinylestradiol-containing contraceptives will result in an increased exposure to ethinylestradiol. Therefore, this more intensive sampling scheme will allow for a better characterization of the hormonal contraceptive PK profile when co-administered with JNJ-56136379. In the context of these contraceptive PK assessments, information will be collected on the start of the last initiated hormonal contraceptive cycle (if applicable for the type of contraception).

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9.1.2 Screening Phase
9.4.1 Evaluations

Rationale: It was clarified that the PRO assessments will be part of the follow-up procedures for subjects who entered the treatment extension phase and received a 48-week treatment (in line with the follow-up procedures for subjects who received a 24-week treatment and did not meet the criteria for the extension phase),

TIME AND EVENTS SCHEDULE

Rationale: For consistency with the other visits, and in order to provide flexibility to the patient/investigator, it has been clarified that a time window of ±2 days is also allowed for the Week 1 visit in the treatment phase.

TIME AND EVENTS SCHEDULE

Rationale: Time windows for the visits were inadvertently omitted in the previous version of the protocol for the Time and Event Schedule 1 (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 at Week 48, and subjects who discontinue study treatment early). Now these have been included and are in line with Schedule 2 (for the post-treatment follow-up phase for subjects who complete 48 weeks of treatment).

TIME AND EVENTS SCHEDULE

Rationale: For subjects who meet the treatment completion criteria (Time and Events Schedule 2), it has been clarified that unscheduled visits in the follow-up phase can occur at the discretion of the investigator at any sign of worsening of liver disease (including HBV DNA or ALT elevations), or for any other reason.

TIME AND EVENTS SCHEDULE

Rationale: Clarifications on photography assessments in case of rash were added to the rash management instructions. For events of rash >grade 2, or events of rash grade 2 when consultation with a dermatologist is required (see column "Referral to Dermatologist and Dermatology Activities" in Table 8), photographs are recommended. The digital pictures are to be provided to the sponsor as a record for rash assessment by the sponsor or by external experts (if needed), or for review by the regulatory authorities (if requested). Photographs are optional for events of rash of grade 1 and 2 (when no consultation with a dermatologist is required).
Attachment 3
Rationale: Minor updates and clarifications were made and inconsistencies corrected.
Throughout the document.

Amendment 2 (6 March 2018)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

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.

The table below gives an overview of the rationale for each change and all applicable sections

Rationale: A treatment extension phase of 24 weeks is added to the study design to allow for the evaluation of the effect of 48 weeks of study treatment on HBsAg decline. Available 9-month dog toxicity data supporting the safe use of JNJ-56136379 in humans for treatment durations longer than 24 weeks are added to the protocol. Subjects eligible for the extension must have completed the initial 24 weeks of treatment and must have achieved a virologic response by Week 20 (hepatitis B virus [HBV] DNA <lower limit of quantification [LLOQ] of the HBV DNA assay) without experiencing any safety concerns precluding continued study drug treatment as determined by the investigator. 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.

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Rationale: For subjects who continue study drugs until Week 48, treatment completion criteria are introduced to explore the possibility of finite treatment. The treatment completion criteria have been selected to ensure that only subjects with a chance of sustained off-treatment response are allowed to complete all treatment. Subjects who completed all treatment at Week 48 will be followed-up for 48 weeks for signs of viral relapse. Re-treatment criteria are introduced to manage subjects who experience increases in HBV DNA and/or ALT in the off-treatment follow-up period. Subjects who meet these criteria will need to re-start nucleos(t)ide analog NA treatment according to local standard of care. Subjects who do not meet the treatment completion criteria should continue (when NA treatment was part of the study treatment) or start NA treatment (in case of JNJ-56136379 monotherapy) as per local treatment guidelines. These subjects will be followed-up for 24 weeks after the end of JNJ-56136379/placebo treatment.

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9.2 Efficacy Evaluations
10.1 Completion
11.3.3 Other Analyses
11.11 Interim Analyses

Rationale: Based on results from the Phase 1 healthy volunteer study 56136379HPB1002, which are added to the protocol, lipase and amylase elevations are identified as laboratory abnormalities of interest. In addition, based on preclinical findings in rats and dogs, increased cholesterol is also identified as a laboratory abnormality of interest.

1.1 Background
1.3.4 Potential Risks
1.3.5 Overall Benefit/Risk Assessment
11.10 Safety Analyses

Rationale: It is clarified in the protocol that all subjects who received at least 1 dose of study drugs and are randomized will be included in the efficacy analysis. All subjects who received at least 1 dose of study drugs, whether randomized or not, will be included in the safety analysis.

SYNOPSIS
11.3 Efficacy Analyses

Rationale: The possibility of a liver biopsy substudy, which might be conducted at selected sites, is introduced in the protocol. If the substudy is conducted, details, including objectives and study design, will be described in a separate protocol.

SYNOPSIS
3.1 Overview of Study Design

Rationale: It is clarified in the protocol that at the unblinded Week 24 interim analysis (and subsequent analyses), the sponsor study team members involved in safety monitoring of the treatment extension phase as well as the investigator, site personnel and subjects will remain blinded to the treatment/randomization codes. The sponsor study team members involved in safety monitoring of the treatment extension phase will remain blinded until the end of the treatment extension phase while the investigator, site personnel and subjects will remain blinded until the end of the study.

SYNOPSIS
11.11 Interim Analyses

Rationale: Following Health Authority feedback, a clarification is added explaining that the dosing interval for ETV or TDF may be adjusted as per the package insert. In addition, reference to the package insert is added in case a dose of NA is missed and it is clarified that ETV should be taken on an empty stomach.

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6 DOSAGE AND ADMINISTRATION
7 TREATMENT COMPLIANCE
9.1.3 Treatment Phase (Partially-Blind)
9.9 Safety Evaluations

Rationale: Following Health Authority feedback, it is clarified that subjects with eGFR <60mL/min/1.73m² (MDRD equation) will be excluded from the study. The exclusion criteria are adjusted accordingly. In addition, the treatment discontinuation criteria are adjusted, subjects with a ≥grade 3 serum creatinine or urinalysis abnormality must not only discontinue JNJ-56136379 but also NA treatment.

4.2 Exclusion Criteria
9.9 Safety Evaluations
10.2 Discontinuation of Study Treatment/Withdrawal from the Study

Rationale: Since several clinical laboratory parameters often fluctuate between normal range and grade 1 in subjects with CHB, it is felt appropriate not to exclude subjects with Grade 1 laboratory abnormalities. The exclusion criteria are adjusted accordingly.

4.2 Exclusion Criteria

Rationale: Rash management guidelines were revised and inconsistencies were corrected.

9.9 Safety Evaluations
10.2 Discontinuation of Study Treatment/Withdrawal from the Study
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Rationale: The protocol Amendment 1, dated 18 December 2017, indicates that JNJ-56136379 treatment must be discontinued if the subject is reported with a specific AE/SAE as listed per Section 9.9 Safety Evaluations and/or meets one of the treatment discontinuation criteria as per Section 10.2 Discontinuation of Study Treatment/Withdrawal from the Study. However, study drugs include JNJ-56136379 and placebo, as well as NA (either ETV or TDF) and in the event a subject has an AE/SAE it will be difficult to assign causality to a specific component of the study drug. Therefore, it is clarified that a subject's JNJ-56136379 must be discontinued and NA treatment may be discontinued based on investigator judgement in consultation with the sponsor if he/she meets one of the study treatment discontinuation criteria outlined in Section 9.9 and 10.2.

9.9 Safety Evaluations
10.2 Discontinuation of Study Treatment/Withdrawal from the Study

Rationale: Per the protocol Amendment 1, dated 18 December 2017, Fibroscan assessments as part of the efficacy evaluations are performed in subjects from the pharmacokinetic subgroup. The protocol is amended to also have Fibroscan assessments performed in subjects enrolled at sites with an on-site Fibroscan device.

SYNOPSIS
TIME AND EVENTS SCHEDULE

Rationale: Based on Health Authority feedback, the evaluation of the potential effect of JNJ-56136379 on the pharmacokinetics (PK) of ethinyl estradiol (EE) when coadministered, already planned per Protocol Amendment 1 (dated 18 December 2017), is added as an exploratory objective in the current Amendment 2. Furthermore, it is clarified that population PK assessments for EE may be applied. Various generalized linear (mixed effects) models will be explored to evaluate the effect of JNJ-56136379 on the exposure of EE.

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ABBREVIATIONS
2.1 Objectives and Endpoints
11.6 Exploratory Pharmacokinetic Analysis of Hormonal Contraceptives

Rationale: The possibility of the emergence of viral variants with reduced susceptibility or resistance to JNJ-56136379, following JNJ-56136379 treatment is added as a potential risk.

1.3.4 Potential Risks

Rationale: Minor updates and clarifications were made and inconsistencies corrected.

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17.9.2 Study Termination
ATTACHMENTS

Amendment 1 (18 December 2017)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

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).

The table below gives an overview of the rationale for each change and all applicable sections

Rationale: Clarification that, after the 24-week JNJ-56136379 treatment period, NA treatment (ETV or TDF) will be continued or started based on local treatment guidelines, ensuring subjects qualifying for HBV treatment are treated adequately.

SYNOPSIS
TIME AND EVENTS SCHEDULE
1.3.5 Overall Benefit/Risk Assessment
3.1 Overview of Study Design
10.2 Discontinuation of Study Treatment/Withdrawal from the Study

Rationale: 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.

SYNOPSIS
TIME AND EVENTS SCHEDULE
3.1 Overview of Study Design

Rationale: 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.

TIME AND EVENTS SCHEDULE
4.1 Inclusion Criteria
8 CONCOMITANT THERAPY

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

12.1.3 Severity Criteria

Rationale: 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.

SYNOPSIS
TIME AND EVENTS SCHEDULE
3.1 Overview of Study Design

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

SYNOPSIS
6 DOSAGE AND ADMINISTRATION
10.2 Discontinuation of Study Treatment/Withdrawal from the Study

Rationale: 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.

4.1 Inclusion Criteria

Rationale: Clarification on instructions in case of missed dose.

7 TREATMENT COMPLIANCE

Rationale: 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.

8 CONCOMITANT THERAPY

Rationale: 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.

TIME AND EVENTS SCHEDULE

Rationale: 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.

9.9 Safety Evaluations

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

9.9 Safety Evaluations
Attachment 3

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

14.5 Drug Accountability

Rationale: Replacement of incorrect version of:
- EQ-5D-5L (tablet version rather than paper version)
- SF-36v2 (2010 version rather than 2000 version)

Attachment 5
Attachment 8

Rationale: Minor updates
- Abbreviation for entecavir corrected (ETV rather than ETF)
- IB addendum reference updated with final date

10.2 Discontinuation of Study Treatment/Withdrawal from the Study
REFERENCES

SYNOPSIS

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.

JNJ-56136379 is an orally administered capsid assembly modulator (CAM) that is being developed for the treatment of chronic hepatitis B virus (HBV) infection (CHB).

JNJ-56136379 binds to the HBV core protein and interferes with the viral capsid assembly process, thereby preventing the polymerase-bound pregenomic ribonucleic acid encapsidation. This results in the formation of HBV capsids, devoid of HBV deoxyribonucleic acid (DNA) (non-functional capsids), and ultimately in the inhibition of HBV replication in vitro. In addition, JNJ-56136379 also acts at an early stage of the viral life cycle by inhibiting the de-novo formation of covalently closed circular DNA potentially by interfering with the capsid disassembly process.

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

The following objectives and endpoints will be evaluated by study regimen (ie, JNJ-56136379 [at two dose levels] and NA [entecavir {ETV} or tenofovir disoproxil fumarate {TDF}] as monotherapy or coadministered), by subject population (ie, subjects currently not being treated or virologically suppressed by current NA treatment), and by hepatitis B e antigen (HBeAg) status:

Objectives	Endpoints
Primary	
• To evaluate efficacy of 24 weeks of study treatment, in terms of changes in hepatitis B surface antigen (HBsAg) levels.	• Change from baseline in HBsAg levels at Week 24.
Secondary	
• To evaluate the safety and tolerability of study treatment.	• Safety and tolerability data including but not limited to (S)AEs, physical examinations, vital signs, 12-lead electrocardiograms (ECGs), and clinical laboratory tests (including hematology, blood biochemistry, blood coagulation, and urinalysis) throughout the study.
• To evaluate efficacy in terms of changes in HBsAg levels.	• Change from baseline in HBsAg levels during study treatment and follow-up. • Proportion of subjects with HBsAg levels by response subcategory, such as HBsAg <1,000 or <100 IU/mL, or with >0.5 or >1 $\log_{10}$ IU/mL reduction in HBsAg from baseline as detailed in the Statistical Analysis Plan (SAP) during study treatment and follow-up.
• To evaluate efficacy in terms of changes in HBV DNA levels.	• Change from baseline in HBV DNA levels during study treatment and follow-up. • Proportion of subjects with HBV DNA levels by response subcategory as detailed in the SAP during study treatment and follow-up.
• To evaluate efficacy in terms of changes in HBeAg levels (in HBeAg-positive subjects only).	• Change from baseline in HBeAg levels during study treatment and follow-up. • Proportion of subjects with HBeAg levels by response subcategory as detailed in the SAP during study treatment and follow-up.

Objectives	Endpoints
• To evaluate efficacy in terms of HBsAg (in all subjects) or HBeAg (in HBeAg-positive subjects only) seroclearance and/or seroconversion.	• Proportion of subjects with HBsAg or HBeAg seroclearance (defined as HBsAg or HBeAg negativity, respectively, based on the assay used) during study treatment and follow-up. • Proportion of subjects with HBsAg or HBeAg seroconversion (defined as HBsAg or HBeAg negativity and anti-HBs or anti-HBe antibody positivity, respectively) during study treatment and follow-up.
• To evaluate the frequency of subjects with biochemical response.	• Proportion of subjects with alanine aminotransferase (ALT) improvement and normalization during study treatment and follow-up.
• To evaluate the frequency of HBV virological breakthrough.	• Proportion of subjects with virological breakthrough during study treatment defined as confirmed on-treatment HBV DNA increase by >1 $\log_{10}$ from nadir level or 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.
• To evaluate the potential effect of JNJ-56136379 on the pharmacokinetics of NA when coadministered.	• Pharmacokinetics of NA when administered as monotherapy or when coadministered with JNJ-56136379.
• To evaluate the pharmacokinetics of JNJ-56136379 when administered as monotherapy. • To evaluate the potential effect of NA on the pharmacokinetics of JNJ-56136379 when coadministered.	• Pharmacokinetics of JNJ-56136379 when administered as monotherapy or when coadministered with an NA.
• To assess changes in the HBV genome sequence.	• Emergence of treatment-associated mutations during study treatment and follow-up.
Exploratory	
• To explore changes in 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.
• To explore the relationship of pharmacokinetics with selected pharmacodynamic (PD) parameters of efficacy and safety.	• Relationship of various pharmacokinetic parameters with selected efficacy and safety endpoints.
• To explore efficacy in terms of changes in HBV ribonucleic acid (RNA) and hepatitis B core-related antigen (HBcrAg) levels.	• Changes from baseline in HBV RNA and HBcrAg levels during study treatment and follow-up.
• To explore the effect of viral and host baseline factors on efficacy and safety.	• Impact of viral and host baseline factors on different efficacy and safety parameters.
• To explore the effect of baseline amino acid substitutions in the HBV genome on efficacy.	• Impact of baseline HBV sequence variations on efficacy parameters.

Objectives	Endpoints
• To explore the impact of HBV treatment on symptoms, functioning, and health-related quality of life (HRQoL) using patient-reported outcomes (PROs).	• Impact of HBV treatment on symptoms, functioning, and HRQoL using PROs, ie: – 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.
• To explore the potential effect of JNJ-56136379 on the pharmacokinetics of ethinyl estradiol (EE) when coadministered.	• Pharmacokinetics of EE when coadministered with JNJ-56136379.

The following objectives and endpoints are applicable to the treatment extension phase only.

Objectives	Endpoints
• To evaluate the proportion of subjects able to complete all treatment at Week 48.	• Proportion of subjects meeting the treatment completion criteria as outlined in Section 6.3.
• To evaluate the frequency of sustained off-treatment response.	• Proportion of subjects with sustained reduction/suppression and/or sero-clearance considering single and multiple markers such as HBsAg, HBeAg, HBV DNA and ALT levels at FU Week 12, 24 and 48.
• To evaluate the frequency of virologic and clinical relapse after EOT.	• Proportion of subjects with virologic relapse defined as confirmed post-treatment increases in HBV DNA >2,000 IU/mL after having met the treatment completion criteria. • Proportion of subjects with clinical relapse defined as confirmed post-treatment increases in HBV DNA >2,000 IU/mL after having met the treatment completion criteria, in association with confirmed ALT value >2 x ULN.
• To evaluate the proportion of subjects requiring NA re-treatment during follow-up.	• Proportion of subjects who meet the re-treatment criteria as outlined in Section 6.4.
• To evaluate the efficacy of NA re-treatment during follow-up.	• Proportion of subjects with decline in HBV DNA, ALT and/or HBsAg levels after re-start of NA treatment during follow-up.

Hypothesis

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

OVERVIEW OF STUDY DESIGN

This is a multicenter, interventional, randomized, partially-blind, placebo-controlled, two-part study to assess the efficacy, safety, and pharmacokinetics of treatment with two doses of JNJ-56136379 administered as monotherapy and in combination with NA (either ETV or TDF as per local practice) in HBeAg-positive and -negative CHB-infected subjects. Subjects who completed the initial 24 weeks of treatment with a virologic response by Week 20 (HBV DNA <200 IU/mL of the HBV DNA assay) and without experiencing any safety concerns precluding continued study drug treatment as determined by the investigator, will continue study drugs up to 48 weeks in a treatment extension phase.

The study will initially consist of 2 parts, Part A and Part B. For each part, a sample size of 110 subjects is targeted who will receive JNJ-56136379 at two dose levels as monotherapy or in combination with an NA. Additional parts may be added through a protocol amendment based on emerging data.

Each part will consist of 2 types of CHB-infected subject populations: (1) subjects who are currently not being treated for their CHB infection (including CHB treatment-naïve subjects) and (2) subjects virologically suppressed by current NA treatment (either ETV or TDF as per local practice).

Part A:

Approximately 70 subjects who are currently not being treated for their CHB infection will be randomized in a 3:1:3 ratio to receive one of the following treatments:

- Treatment Arm 1: JNJ-56136379 (N=30) (open-label)

  After full recruitment, this treatment arm was discontinued early per Protocol Amendment 4. All subjects were to stop further dosing with JNJ-5613379 75 mg, start treatment with NA, and enter the post-treatment follow-up phase (Schedule 1).
- Treatment Arm 2: Placebo + NA (ETV or TDF) (N=10)
- Treatment Arm 3: JNJ-56136379 + NA (ETV or TDF) (N=30)

At the same time, approximately 40 subjects who are virologically suppressed by current NA treatment will be randomized in a 1:3 ratio to receive one of the following treatments:

- Treatment Arm 4: Placebo + NA (ETV or TDF) (N=10)
- Treatment Arm 5: JNJ-56136379 + NA (ETV or TDF) (N=30)

Part B:

Part B (ie, Treatment Arms 6 to 10) will follow the same format as Part A, with a different dose of JNJ-56136379.

Randomization in each part will be stratified by:

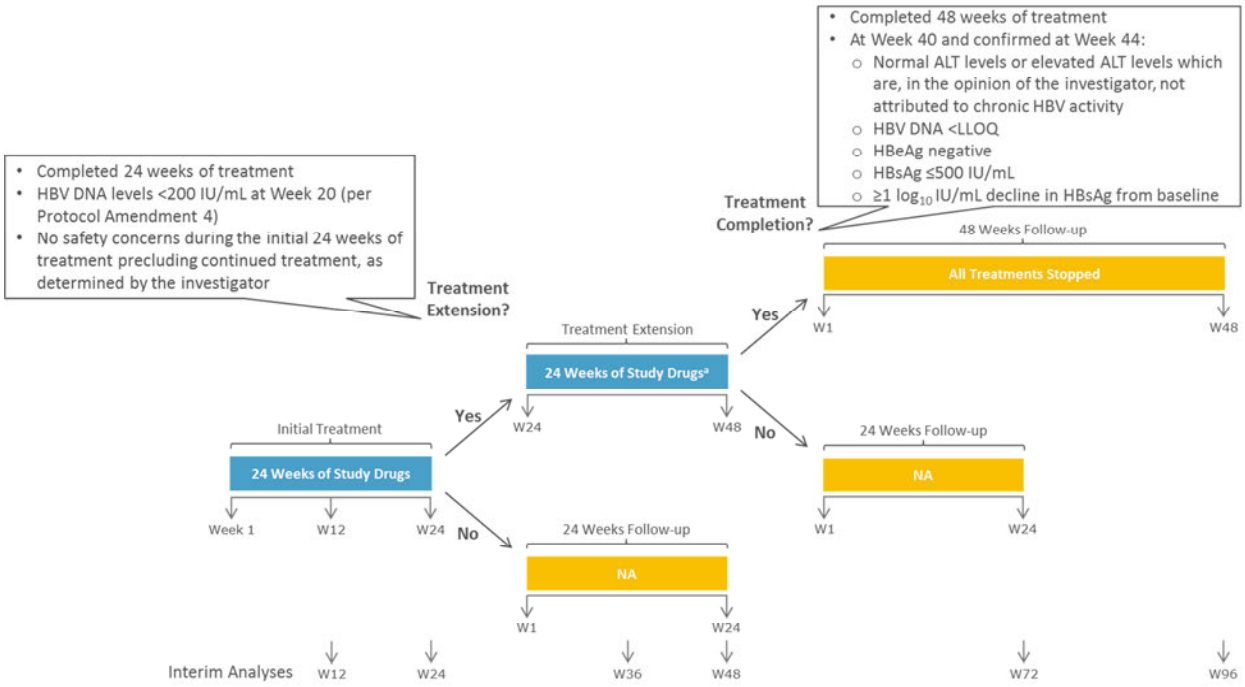
- HBeAg status at screening (positive versus negative);
- HBsAg level at screening (≥10,000 versus <10,000 IU/mL for HBeAg-positive subjects currently not being treated and ≥1,000 versus <1,000 IU/mL for all other subjects).

The aim is to have approximately 40% HBeAg-positive subjects who are currently not being treated and 30% HBeAg-positive virologically suppressed subjects. To this end, enrollment of HBeAg-negative subjects may be capped at 60% in subjects who are currently not being treated and at 70% in virologically suppressed subjects.

A Data Review Committee (DRC) will be established for this study and will monitor safety and efficacy data in an unblinded manner on a regular basis throughout the study.

Part A will start first and will evaluate a 75-mg once-daily (qd) dose of JNJ-56136379. The JNJ-56136379 dose to be administered in Part B of the study will be 250 mg given once daily. This dose has been selected by the sponsor, in agreement with the DRC, based on all safety, PK, and antiviral activity data available following completion of the highest JNJ-56136379 dose group (who received 250 mg once daily) in the Phase 1 study 56136379HPB1001 in treatment-naïve CHB-infected subjects treated for 28 days.

Each part of the study will consist of a screening phase (up to 8 weeks), a treatment phase (24 weeks or 48 weeks, depending on treatment response), and a post-treatment follow-up phase (24 weeks or 48 weeks, depending on treatment response). A high-level overview of the study design is provided below.



[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.

All subjects are planned to be treated for at least 24 weeks. Following this initial treatment period, subjects who completed the 24-week treatment period with virologic response by Week 20 (HBV DNA <200 IU/mL of the HBV DNA assay) and without experiencing any safety concerns precluding continued study drug treatment as determined by the investigator, will continue study drugs up to 48 weeks in a treatment extension phase. 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.

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.

In addition, a futility rule for this 250 mg monotherapy arm has been installed: if ≥1 subject in the 250 mg monotherapy arm experiences virological breakthrough during the first 24 weeks of treatment, NA treatment will be added to JNJ-56136379 treatment as soon as possible for all remaining subjects. These subjects will continue the visit schedule as planned. Subjects with virological breakthrough will discontinue JNJ-56136379 treatment and should start NA treatment per protocol.

For subjects who are not eligible to participate in the treatment extension phase:

- Subjects will be considered to have completed the study treatment if they have completed 24 weeks of study drug administration, after which they will discontinue JNJ-56136379 or placebo treatment. NA treatment (either ETV or TDF as per local practice) should be started (in case of JNJ-56136379 monotherapy, ie, Treatment Arms 1 and 6) or continued (in case NA treatment was part of the assigned study treatment, ie, Treatment Arms 2 to 5 and 7 to 10) as per local treatment guidelines.
- Subjects will be considered to have completed the study if they have completed the assessments of the end of study visit (Follow-up [FU] Week 24 [Schedule 1]).
- For subjects who do not continue or start NA treatment at Week 24, an additional 24-week follow-up (as per local treatment guidelines) by their primary care physician, outside of the study, is recommended after study completion.

For subjects who continue treatment in the extension phase:

- Subjects will be considered to have completed the study treatment if they have completed 48 weeks of study drug administration, after which they will discontinue JNJ-56136379 or placebo treatment. At Week 48:
    - Subjects who meet all of the Individual Subject Treatment Completion Criteria (see Section 6.2 of the protocol) will complete all treatment. These subjects will be followed-up until 48 weeks after EOT (Schedule 2). If, during the 48-week follow-up, a subject meets one of the re-treatment criteria described in Section 6.3 of the protocol, NA treatment (ETV or TDF) should be re-started.
    - Subjects who do not meet the Individual Subject Treatment Completion Criteria should start (in case of JNJ-56136379 monotherapy, ie, Treatment Arms 1 and 6) or continue (in case NA treatment was part of the assigned study treatment, ie, Treatment Arms 2 to 5 and 7 to 10) NA treatment as per local treatment guidelines. These subjects will be followed-up until 24 weeks after the end of study treatment (Schedule 1).
- Subjects will be considered to have completed the study if they have completed the assessments of the end of study visit (FU Week 24 [Schedule 1] or FU Week 48 [Schedule 2]).
- For subjects who do not meet the Individual Subject Treatment Completion Criteria and do not start or continue 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 study completion.

The duration of individual participation will be approximately up to 56 weeks (subjects not eligible to continue treatment in the extension phase), up to 80 weeks (subjects continuing treatment in the extension phase but not meeting the treatment completion criteria), or up to 104 weeks (subjects meeting treatment completion criteria).

The study is considered completed with the last visit of the last subject participating in the study.

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), follow-up assessments should be obtained until 24 weeks after EOT (Schedule 1) 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 (Schedule 1), for subjects who do not continue or start NA treatment after early study treatment discontinuation.

If a subject withdraws before completing the study, the reason for withdrawal is to be documented in the electronic Case Report Form (eCRF) and in the source document. Subjects who withdraw consent will be offered an optional safety follow-up visit.

Safety and tolerability will be assessed throughout the study from the time that the informed consent form (ICF) is signed until the completion of the last study-related activity.

A liver biopsy substudy may be performed at selected study sites. Patients need to provide consent for the substudy by signing a separate ICF. Refusal to participate in or withdrawal of consent for the substudy does not affect participation in the main study. A liver biopsy will be performed at different time points. The substudy assessments will be described in a separate substudy protocol, which will only be submitted for approval by regulatory authorities (Health Authority/Institutional Review Board [IRB]/Independent Ethics Committee [IEC]) for the selected sites. Results of the liver biopsy substudy will be reported in a separate report.

SUBJECT POPULATION

Key Inclusion Criteria

- Subjects must be 18 to 70 years of age, inclusive.
- Subjects must have CHB infection documented by:
  - Serum HBsAg-positive at screening and serum HBsAg- or HBV DNA-positive at least 6 months prior to screening;
  - Serum immunoglobulin M (IgM) anti-HBc antibody negative at screening.
- In subjects currently not being treated (Treatment Arms 1-2-3 and 6-7-8):
  - Subjects must not be receiving any CHB treatment at screening, ie,
    - Have never received treatment with HBV antiviral medicines, including NAs or interferon (IFN) products, OR
    - Have not been on treatment with HBV antiviral medicines, including NAs or IFN products, within 6 months prior to baseline (first intake of study drugs), AND
  - Subjects must be HBeAg-positive and have HBV DNA ≥20,000 IU/mL, OR be HBeAg-negative and have HBV DNA ≥2,000 IU /mL at screening, AND
  - Subjects must have HBsAg >250 IU/mL at screening, AND
  - Subjects must have ALT > upper limit of normal (ULN) and ≤5 x ULN at screening, determined in the central laboratory.

    Note: If subjects were treated with investigational anti-HBV agents more than 6 months before screening, the sponsor should be contacted to discuss the case. Subjects who have received treatment with a CAM for more than 4 weeks any time prior to screening are excluded.

- In virologically suppressed subjects (Treatment Arms 4-5 and 9-10):
  - Subjects must be virologically suppressed by current NA treatment (ETV or TDF) as defined by HBV DNA <60 IU/mL at screening and at least 6 months prior to screening, AND
  - Subjects must be on the same NA treatment (ETV or TDF) and the same dose for ≥12 months prior to screening, AND
  - Subjects must have HBsAg >250 IU/mL at screening, AND
  - Subjects must have ALT ≤2x ULN at screening.

    Note: If subjects were treated with investigational anti-HBV agents more than 6 months before screening, the sponsor should be contacted to discuss the case. Subjects who have received treatment with a CAM for more than 4 weeks any time prior to screening are excluded.

    Note: The current NA treatment can either be a branded product or a locally approved generic alternative (including different salt forms [eg, tenofovir maleate or succinate]). During the study, subjects will receive branded ETV (Baraclude®) or TDF (Viread®) treatment, as applicable.
- Subjects must have:
  - A liver biopsy result classified as Metavir F0-F2 within 1 year prior to screening or at the time of screening, OR
  - FibroScan™ liver stiffness measurement <8.0 kPa within 6 months prior to screening or at the time of screening.

Key Exclusion Criteria

- Subjects who test positive for anti-HBs antibodies.
- Subjects with current hepatitis A virus infection (confirmed by hepatitis A antibody IgM), hepatitis D virus (HDV) infection (confirmed by HDV antibody), hepatitis E virus infection (confirmed by hepatitis E antibody IgM), or human immunodeficiency virus type 1 (HIV-1) or HIV-2 infection (confirmed by antibodies) at screening; subjects with a history of or current HCV infection (confirmed by HCV antibody). Evidence of other active infection (bacterial, viral, fungal, including acute tuberculosis) deemed clinically relevant by the investigator that would interfere with study conduct or its interpretation will also lead to exclusion.
- Subjects with any evidence of hepatic decompensation at any time point prior to or at the time of screening:
  - Direct bilirubin >1.2x ULN, or
  - International normalized ratio >1.5x ULN, or
  - Serum albumin < lower limit of normal (LLN), or
  - Documented history or current evidence of variceal bleeding, ascites, or hepatic encephalopathy.
- Subjects with any evidence of liver disease of non-HBV etiology. This includes but is not limited to hepatitis virus infections mentioned above, drug- or alcohol-related liver disease, autoimmune hepatitis, hemochromatosis, Wilson's disease, Gilbert's syndrome, α-1 antitrypsin deficiency, primary biliary cirrhosis, primary sclerosing cholangitis, or any other non-HBV liver disease considered clinically significant by the investigator.
- Subjects who have 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]).

- Subjects who have received an organ transplant.

DOSAGE AND ADMINISTRATION

Study drugs (JNJ-56136379/NA/placebo) will be administered orally. JNJ-56136379 will be provided as 25-mg and/or 100-mg tablets and placebo as matching tablets. Subjects should be instructed to take JNJ-56136379/placebo in the morning at approximately the same time each day, together with breakfast. The tablets should be swallowed as a whole. At each study visit, the study drug should be taken on site under the supervision of the study staff. The time of study drug intake should be recorded in the eCRF.

A subject diary will be provided to the subjects undergoing semi-rich pharmacokinetic sampling and 24-hour urine sampling (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.

Subjects will receive commercially available Baraclude® (ETV) or Viread® (TDF) during the study (will be provided through this study), as applicable. Subjects who are already being treated with Baraclude® or Viread® at screening, will continue this NA treatment. Subjects will be switched to these branded NA treatments for the course of the study in case they are on another originator branded or a generic ETV or TDF treatment, respectively, at screening.

For subjects who are not receiving any CHB treatment at screening, the choice of NA (ETV or TDF) will be at the investigator's discretion, as per local practice. However, subjects with any NA treatment experience prior to screening, should be treated with TDF. In case the investigator's preference is to start ETV treatment in subjects with prior ETV experience without evidence of resistance, the sponsor should be contacted to agree on the NA to be used in the study.

NA (ETV or TDF) will be taken as per the package insert (Baraclude® and Viread®, respectively). In the event of decline in renal function, dosing interval for ETV or TDF may be adjusted as per the package insert.

Description of Interventions

Treatment Overview

Part A		
Treatment	Dosing Regimen	Formulation
Subjects currently not being treated:		
Arm 1[e]	75 mg JNJ-56136379 once daily (open-label)	3 x 25-mg tablets of JNJ-56136379[a]
Arm 2	Matching placebo + NA (0.5 mg ETV or 300 mg TDF) once daily	3 tablets of matching placebo + 1 tablet of ETV[b] or TDF[c]
Arm 3	75 mg JNJ-56136379 + NA (0.5 mg ETV or 300 mg TDF) once daily	3 x 25-mg tablets of JNJ-56136379 + 1 tablet of ETV or TDF
Virologically suppressed subjects:		
Arm 4	Matching placebo + NA (0.5 mg ETV or 300 mg TDF) once daily	3 tablets of matching placebo + 1 tablet of ETV or TDF
Arm 5	75 mg JNJ-56136379 + NA (0.5 mg ETV or 300 mg TDF) once daily	3 x 25-mg tablets of JNJ-56136379 + 1 tablet of ETV or TDF

Part B		
Treatment	Dosing Regimen	Formulation
Subjects currently not being treated:		
Arm 6	250 mg JNJ-56136379 [d] once daily (open-label) from Day 1 to Week 24[f]	2 x 100-mg and 2 x 25-mg tablet(s) of JNJ-56136379 from Day 1 to Week 24
	250 mg JNJ-56136379 [d] + NA once daily (open-label) from Week 24 to Week 48	2 x 100-mg and 2 x 25-mg tablet(s) of JNJ-56136379 + 1 tablet of ETV or TDF from Week 24 to Week 48
Arm 7	Matching placebo + NA (0.5 mg ETV or 300 mg TDF) once daily	Tablet(s) of matching placebo + 1 tablet of ETV or TDF
Arm 8	250 mg JNJ-56136379 [d] + NA (0.5 mg ETV or 300 mg TDF) once daily	2 x 100-mg and 2 x 25-mg tablet(s) of JNJ-56136379 + 1 tablet of ETV or TDF
Virologically suppressed subjects:		
Arm 9	Matching placebo + NA (0.5 mg ETV or 300 mg TDF) once daily	Tablet(s) of matching placebo + 1 tablet of ETV or TDF
Arm 10	250 mg JNJ-56136379 [d] + NA (0.5 mg ETV or 300 mg TDF) once daily	2 x 100-mg and 2 x 25-mg tablet(s) of JNJ-56136379 + 1 tablet of ETV or TDF

[a] JNJ-56136379 is formulated as 25-mg (G008) and 100-mg (G009) tablets (matching placebo: G010 and G011, respectively).
[b] ETV (Baraclude®) is formulated as 0.5-mg film-coated tablets (commercially available), and is to be taken on an empty stomach. Lamivudine-refractory subjects should be treated with TDF instead.
[c] TDF (Viread®) is formulated as 300-mg film-coated tablets (commercially available), and is to be taken with food.
[d] The dose for Part B has been selected based on all safety, PK, and antiviral activity data available upon completion of the highest JNJ-56136379 dose group (who received 250 mg once daily) in the Phase 1 study 56136379HPB1001 in treatment-naïve CHB-infected subjects treated for 28 days.
[e] Treatment Arm 1 was discontinued early per Protocol Amendment 4. All subjects were to stop further dosing with JNJ-5613379 75 mg, start treatment with NA, and enter the post-treatment follow-up phase (Schedule 1).
[f] Per protocol Amendment 4, a futility rule has been installed: if ≥1 subject in the 250 mg monotherapy arm experiences virological breakthrough during the first 24 weeks of treatment, NA treatment will be added to JNJ-56136379 treatment as soon as possible for all remaining subjects.

EFFICACY EVALUATIONS

Qualitative and quantitative HBsAg and HBeAg, and quantitative HBcrAg as well as anti-HBs and anti-HBe antibodies will be determined using standard serologic assays in a central laboratory. Samples for the determination of HBsAg and HBeAg will be processed in real-time using an assay such as the ARCHITECT platform (Abbott Laboratories). Samples for the determination of HBcrAg can be analyzed in batch and at the sponsor's discretion.

HBV DNA and HBV RNA will be quantified at a central laboratory using in vitro nucleic acid amplification tests for the quantification of HBV DNA and HBV RNA. Samples for the determination of HBV DNA will be processed in real-time using a test such as the COBAS® TaqMan® HBV Test, v2.0 (Roche Molecular Systems). Samples for the determination of HBV RNA can be analyzed in batch and at the sponsor's discretion.

Post-baseline results from HBsAg, HBeAg, anti-HBs, and anti-HBe antibody testing will be provided to the investigator and the sponsor from Week 20 onwards. HBV DNA results will be provided to the investigator and the sponsor from screening until FU Week 24 or 48, as applicable. It is the responsibility of the investigator:

- To monitor HBV DNA results and ensure that JNJ-56136379 treatment is discontinued in subjects with viral breakthrough and in treatment-naïve subjects with <1 $\log_{10}$ IU/mL decline from baseline at Week 4 and Week 8 (Section 10.2 of the protocol)
- To monitor HBV DNA to assess if treatment extension criteria (Section 6.1 of the protocol) are met
- To assess if treatment completion criteria (Section 6.2 of the protocol) are met
- To assess whether re-start of NA treatment during follow up is needed (Section 6.3 of the protocol).

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.

In subjects from the pharmacokinetic subgroup and subjects enrolled at a site with an on-site Fibroscan device, Fibroscan assessments will be performed to determine changes in fibrosis.

Samples may be used by the sponsor for additional exploratory assessments analyzing the serologic and virologic characteristics of HBV infection and efficacy or safety of the study treatment, including viral genotypic and phenotypic assessments.

PHARMACOKINETIC EVALUATIONS

Venous blood samples will be collected for the determination of plasma concentrations of total JNJ-56136379 and/or NA (ETV or TDF), as applicable.

24-hour urine sampling will be performed in approximately 35% of all subjects (pharmacokinetic subgroup, at selected sites only) for the determination of JNJ-56136379 or NA (ETV or TDF) concentrations, as applicable, on Day 1 and Day 84 (Week 12) (0-2, 2-12, and 12-24 hours postdose). This 24-hour sampling schedule will require an overnight stay on site.

Plasma samples will also be collected from female subjects using hormonal contraceptives that can be analyzed further for determination of plasma concentrations of hormonal contraceptives and their metabolites. These samples will be analyzed at the sponsor's discretion. The start of contraceptive administration at the last initiated cycle (if applicable for the type of contraception) will be documented in the eCRF.

At the sponsor's discretion, plasma and urine samples may be analyzed for metabolite profiling using a qualified method. In addition, plasma and urine pharmacokinetic samples may be stored for future exploratory analysis of protein binding or the metabolite profile.

PHARMACOKINETIC/PHARMACODYNAMIC EVALUATIONS

Relationships of pharmacokinetic parameters for JNJ-56136379 and NA (ETV or TDF), as applicable, with selected efficacy and with selected safety endpoints will be evaluated.

BIOMARKER EVALUATIONS

The study includes collection of blood samples for exploratory analysis of host blood biomarkers at the host mRNA, protein, and cell level.

Phenotypic and functional characterization of the immune response may be performed using immune cell-based assays. Samples for these analyses will be obtained at selected sites only.

Samples can only be used for research related to JNJ-56136379, NA (ETV or TDF), CHB infection, or HBV-related disease or may be used to develop tests/assays related to JNJ-56136379, NA (ETV or TDF), or HBV.

PHARMACOGENOMIC (DNA) EVALUATIONS

A blood sample for pharmacogenomics (DNA) research will be taken, preferentially at baseline. This sample is optional and will only be collected from subjects who consent separately to this component of the study. This sample can be used to investigate the potential association of genetic factors with efficacy, safety, or pharmacokinetics of JNJ-56136379, NA (ETV or TDF), CHB infection, or HBV-related disease or may be used to develop tests/assays related to JNJ-56136379, NA (ETV or TDF), or HBV.

PATIENT-REPORTED OUTCOMES

The impact of HBV treatment on subjects, including symptoms, functioning and HRQoL will be assessed using PROs at predefined time points. The following PRO instruments will be used: EQ-5D-5L, HBQOL, MOS-CFS Cog-R, and SF-36v2.

SAFETY EVALUATIONS

Safety and tolerability will be assessed throughout the study from the time that the ICF is signed until the completion of the last study-related activity. The evaluations of safety and tolerability will include monitoring of (S)AEs, physical examinations, vital signs measurements, 12-lead ECGs, and clinical laboratory tests (including hematology, blood biochemistry, blood coagulation, and urinalysis) at predefined time points. Any clinically relevant changes occurring during the study must be recorded in the AE section of the eCRF. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

Specific toxicity management plans in line with the known pharmacological profile of the study drugs (and the drug classes) evaluated in this study will be implemented.

STATISTICAL METHODS

Sample Size

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

The adequacy of the sample size for the different parts of the study has been assessed by evaluating the performance of the planned analyses on the primary endpoint (mean HBsAg change from baseline at Week 24) comparing JNJ-56136379+NA with placebo+NA. Baseline is defined as the last assessment prior to the first intake of study drug (JNJ-56136379/NA/placebo) on Day 1.

Power was assessed using simulations (10,000 replicates per scenario) with means and standard deviations (SDs) for the placebo+NA and JNJ-56136379+NA arms as listed in the table below. Mean and SD may depend on HBeAg status at baseline and prior treatment (currently not being treated or virologically suppressed). Treatment with JNJ-56136379 was set to result in one additional mean $\log_{10}$ IU/mL decline in HBsAg from baseline at Week 24. Data were simulated from mixture distributions which reflect the skewed distributions which are typical HBsAg decline data. It is assumed that HBeAg-positive subjects will enroll slower than HBeAg-negative subjects, particularly in virologically suppressed subjects. Therefore, the aim is to have at least 40% HBeAg-positive subjects currently not being treated and 30% HBeAg-positive virologically suppressed subjects.

For the dose-response modeling (multiple contrast test) the placebo+NA arms of Parts A and B will be pooled and the HBeAg subgroups will be pooled per dose. Assuming the treatment effect does not depend on HBeAg status, the power to detect a dose-response signal (α=0.10, one-sided) depends on the assumed effect of the low dose: ranging from 91% when the low dose has no effect to 99% when the low dose has the same effect as the high dose. Sensitivity analyses will be done investigating differences across Parts A and B and differences between the two HBeAg subgroups.

A Bayesian analysis will be conducted for Part A and Part B separately to compare the mean HBsAg change from baseline at Week 24 of JNJ-56136379 as monotherapy and in combination with NA versus placebo+NA by HBeAg subgroup. This Bayesian analysis will incorporate historical data for the placebo+NA arm(s) in an informative meta-analytic predictive (MAP) prior with robustness modifier. For the current sample size simulations, historical data comes from an ongoing systematic literature review on HBsAg declines during NA treatment, resulting in 20 studies including around 2,835 subjects. More details on the eventual historical data, including all references to all studies, will be provided in the Modeling and Simulation Report/SAP. The Bayesian equivalent of power, ie, the likelihood that the posterior probability that the mean change from baseline of HBsAg at Week 24 is larger in the JNJ-56136379+NA arm than in the placebo+NA arm is at least 90%, was determined. The results are summarized in the table below.

It is concluded that, under the assumptions made, the posterior distribution of the estimate of treatment difference between the placebo+NA and JNJ-56136379+NA arm will be precise enough to allow meaningful conclusions. The probability to detect a treatment effect with at least 90% confidence is 0.80 or higher for the HBeAg-negative subgroup in both subjects currently not being treated and virologically suppressed subjects. For the HBeAg-positive subgroup, power is substantially lower which increases the risk of inconclusive results. However, if the interim analysis at Week 12 or Week 24 indicates no safety concerns and a potential benefit, a moderate sample size increase for HBeAg-positive subjects to a maximum of 6 subjects on placebo+NA and 18 subjects on JNJ-56136379 monotherapy and JNJ-56136379+NA per study part may be considered. This will increase the probability to detect a treatment effect in these subgroups from 64% or 57% to around 84%.

Bayesian Power Analysis for the Different Prior Treatment and HBeAg Status Subgroups: HBsAg Change From Baseline

	HBeAg Status	HBsAg (log_{10} IU/mL) Change From Baseline		Sample Size (Placebo+NA/ JNJ-56136379+NA)	Power[a]
		Mean ±SD Placebo+NA	Mean ±SD JNJ-56136379 +NA		
Currently not being treated	Positive	-0.35±0.6	-1.35±2.16	4/12[b]	0.64
	Negative	-0.05±0.4	-1.05±2.16	6/18[b]	0.84
Virologically suppressed	Positive	-0.05±0.4	-1.05±2.16	3/9[c]	0.57
	Negative	-0.05±0.4	-1.05±2.16	7/21[c]	0.89

[a] The probability to conclude that the difference in Week 24 HBsAg change from baseline between JNJ-56136379+NA and placebo+NA is larger than 0 with 90% confidence
[b] Expected sample size when 40% of the subjects are HBeAg-positive
[c] Expected sample size when 30% of the subjects are HBeAg-positive

Efficacy Analyses

All subjects who received at least 1 dose of study drug and were randomized will be included in the efficacy analysis.

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.

These comparisons will be done overall, by subject population (ie, subjects currently not being treated or virologically suppressed by current NA treatment) and by HBeAg status. Additionally, the JNJ-56136379 dose-response relation will be evaluated.

The primary endpoint for these efficacy comparisons is the change from baseline in HBsAg levels, while additional virological and serologic markers will also be assessed in these comparisons as secondary and exploratory efficacy objectives.

Analysis of Primary Endpoint (Change From Baseline in HBsAg Levels at Week 24)

Within Part A and Part B, the magnitude of the effect of JNJ-56136379+NA as compared to placebo+NA will be evaluated using the posterior distribution of the treatment effect (difference between JNJ-56136379+NA and placebo+NA) obtained in a Bayesian analysis. This Bayesian analysis will incorporate historical data for the placebo+NA arm(s) in an informative MAP prior with robustness modifier. For the current sample size simulations, historical data comes from an ongoing systematic literature review on HBsAg declines during NA treatment, resulting in 20 studies including around 2,835 subjects. More details on the eventual historical data, including all references to all studies, will be provided in the Modeling and Simulation Report/SAP. For each study part and HBeAg status subgroup the appropriate historical prior will be used. Within Part A and Part B, JNJ-56136379+NA will also be compared with JNJ-56136379 as monotherapy but without including historical data as both arms include experimental treatments and appropriate historical data are consequently missing. In addition a similar analysis but without historical data in a frequentist approach will also be conducted as a sensitivity analysis.

The dose-response of JNJ-56136379 in an NA background regimen will be studied by a multiple contrast test (MCP) using 3 model-based contrasts covering the 3 possible shapes (linear, convex, and concave) with a control group (placebo+NA) and 2 doses. This analysis uses the data of these 3 treatment groups together to evaluate a dose-response signal, assuming a similar dose effect for each HBeAg subgroup and no difference in placebo+NA across Parts A and B. Sensitivity analyses will be done investigating differences across Parts A and B and differences between the two HBeAg subgroups.

Resistance Analyses

The results of HBV viral sequencing will be evaluated by the sponsor virologist. Pretreatment amino acid and/or nucleic acid substitutions in the HBV pre-core and core regions and RT domain in all subjects and relevant changes in the HBV pre-core and core region and RT domain in subjects not responding to treatment tabulated and described. The effect of pretreatment HBV pre-core and core protein substitutions on efficacy will be evaluated.

Additional exploratory characterization of the HBV viral sequence and phenotype may be performed and reported separately.

Other Analyses

Mean changes and maximum mean decrease from baseline in HBsAg, HBeAg, and HBV DNA levels over time will be tabulated by study treatment together with respective SDs. The proportion of subjects with seroclearance and seroconversion of HBsAg and HBeAg will also be tabulated by study treatment. The proportion of subjects with virologic response and the proportion of subjects with virologic and clinical relapse, defined as HBeAg, HBsAg, and/or HBV DNA levels below or above certain thresholds at different time points, respectively, will be categorized as detailed in the SAP, as applicable. Data will also be presented graphically by study phase, study treatment and by individual subject. All individual values will be presented in subject listings.

The least squares (LS) mean change from baseline in serologic parameters and HBV DNA for each study treatment and time point will be estimated with a repeated measurement model (mixed-effects model for repeated measures) including study treatment and time point as fixed effect. The model will allow for unequal variances between study treatments. A 95% confidence interval (CI) will be constructed around the difference between the LS mean of each study treatment. Other methods to evaluate the changes in serologic parameters and HBV DNA may include slope estimation, time-to-event or proportions of subjects who reach a certain level or who exceed a certain reduction.

The proportion of subjects with sustained reduction/suppression and/or sero-clearance, including but not limited to functional and partial cure, will be determined during follow-up. Single and multiple markers such as HBsAg, HBeAg, HBV DNA and ALT levels will be taken into consideration in this analysis.

Other efficacy endpoints, eg, HBV RNA and HBcrAg, will be analyzed descriptively. For continuous variables, descriptive statistics (n, mean, SD, median, minimum, maximum) will be calculated; mean difference and CIs may be calculated where appropriate and, if appropriate, 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 CIs may be calculated where appropriate.

Analyses, tabulations and visualizations will be done for both on-treatment and follow-up phases.

Pharmacokinetic Analyses

Descriptive statistics (n, mean, SD, coefficient of variation, geometric mean, 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.

For each subject, plasma concentration-time data of JNJ-56136379 and NA (ETV or TDF) will be graphically presented. Similarly, graphs of the mean plasma concentration-time profiles and overlay graphs with combined individual plasma concentration-time profiles will be produced. Pharmacokinetic parameters will be subjected to an exploratory graphical analysis, including various transformations, to get a general overview.

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 and as function of the dose to explore dose-linearity and dose-proportionality.

Predose plasma concentrations (C_{trough}) at Weeks 1, 2, 4, 8, 12, 20, and 24 will be compared graphically to assess the achievement of steady-state concentrations and population PK predictions of JNJ-56136379 and NA (ETV or TDF), as applicable. C_{trough} at Weeks 28, 32, 36, 44 and 48 in the treatment extension phase will be compared with population PK predictions of JNJ-379 and NA, as applicable. Plasma concentrations of JNJ-56136379 and NA (ETV or TDF) at FU Weeks 2 and 4 will be determined to assess the elimination of JNJ-56136379 and NA after EOT.

The pharmacokinetic parameters of JNJ-56136379 and NA (ETV or TDF) at steady-state and on Day 1 (treatment with JNJ-56136379 after one dose) will be graphically displayed and descriptive statistics will be performed to determine the multiple dose pharmacokinetic (accumulation ratio) of JNJ-56136379 and NA (ETV or TDF). The pharmacokinetic parameters will be C_{max}, C_{τ}, and AUC_{τ}.

Special attention will be paid to the 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.

Population PK (popPK) analysis of plasma concentration-time data of JNJ-56136379 will be performed using nonlinear mixed-effects modeling. Data may be combined with those of a selection of Phase 1 studies to support a relevant structural model. Available subject characteristics (eg, demographics, laboratory variables, genotypes) will be tested as potential covariates affecting pharmacokinetic parameters. Details will be given in a population pharmacokinetic analysis plan and results of the popPK analysis will be presented in a separate report.

Pharmacokinetic/Pharmacodynamic Analyses

Relationships of pharmacokinetic parameters for JNJ-56136379 and NA (ETV or TDF) with selected efficacy and with selected safety endpoints will be evaluated and graphically displayed.

Modeling of key pharmacodynamic parameters (eg, HBsAg, HBV DNA) may be performed using population pharmacokinetics/pharmacodynamics (PK/PD). If PK/PD modeling of key efficacy endpoints is performed, possible covariates such as disease progression and/or treatment effect will be investigated. Other biomarkers may be explored at the sponsor's discretion. Details of the PK/PD analyses will be described in a population PK/PD analysis plan and results will be presented in a separate report.

Exploratory Pharmacokinetic Analysis of Hormonal Contraceptives

Plasma concentrations of hormonal contraceptives and their metabolites will be summarized by study treatment and displayed graphically. The relationship between JNJ-56136379 exposure and hormonal contraceptive (parent and metabolite) exposure will be evaluated. Further exploration of pharmacokinetic interaction with hormonal contraceptive may be conducted in a physiological-based pharmacokinetics (PBPK) model. Population pharmacokinetics assessments for EE will be applied. Various generalized linear (mixed effects) models will be explored to evaluate the effect of JNJ-56136379 on the exposure of EE. If applied, the details of the PBPK and population PK modeling approach and its results will be presented in a separate report.

Exploratory Biomarker Analysis

Statistical approaches to explore correlations between clinical outcome and blood biomarkers vary and depend on the different data types of the applied technology platforms, as well as on the extent of observed differences between subjects. Analyses will be conducted at the sponsor's discretion, will always be under the sponsor's supervision, and results will be presented the clinical study report or in a separate report.

Pharmacogenomic (DNA) Analyses

The statistical approach for analyzing the exploratory host DNA research may depend on the objective of the analyses (efficacy, safety, and pharmacokinetics) and possibly relevant genes at the time of analysis. Analyses will be conducted at the sponsor's discretion, will always be under the sponsor's supervision, and will be presented in the clinical study report or a separate report.

Patient-Reported Outcome Analyses

PRO scores will be analyzed descriptively by study treatment as mean scores over time, and evaluated based on the proportion of subjects experiencing a clinically important improvement or worsening (if applicable) in PRO scores from baseline during treatment phase and at the follow-up Week 12 visit (EQ-5D-5L and HBQOL) and follow-up Week 24 visit (MOS-CFS Cog-R and SF-36v2). In addition, effect sizes will be calculated to measure the magnitude of difference between means.

Safety Analyses

The population for the safety analysis will consist of all subjects who received at least one dose of study drug. Baseline is defined as the last assessment prior to the first study drug administration.

The incidence of AEs will be summarized by body system and preferred term for each study treatment. Actual values and changes from baseline in clinical laboratory values, vital signs, and ECG parameters will be presented descriptively (n, mean, SD, median, minimum, maximum). The percentage of subjects with abnormal clinical laboratory findings, vital signs, and ECG parameters will be presented by study treatment and study phase. Physical examination findings and changes from baseline will be summarized.

Interim Analyses

At the Week 12 interim analyses, the sponsor study team will remain blinded to the randomization codes (unless the DRC recommends unblinded analyses, see below) and data will be analyzed using dummy identification and aggregated efficacy summary statistics. At the unblinded Week 24 interim analyses (and subsequent analyses) the sponsor study team members involved in safety monitoring of the treatment extension phase as well as the investigator, site personnel and subjects will remain blinded to the treatment/randomization codes. The sponsor study team members involved in safety monitoring of the treatment extension phase will remain blinded to the treatment/randomization codes until the end of the treatment extension phase while investigator, site personnel, and subjects will remain blinded until the end of the study. Note that blinding does not apply to the JNJ-56136379 monotherapy arms.

Interim analyses, encompassing efficacy, safety, and pharmacokinetics, may be conducted for Part A and Part B at study Week 12, 24, 36, 48 and 72 separately when at least 80% of subjects have completed the respective visit (ie, Week 12, Week 24 for all subjects, FU Week 12/Week 36 and FU Week 24/Week 48 for subjects receiving 24/48 weeks of study treatment, and, FU Week 24 for subjects receiving 48 weeks of study treatment, respectively) or have discontinued earlier.

At the sponsor's discretion, 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 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 last study-related follow-up visit or have discontinued earlier.

Data Review Committee

A DRC, comprised of sponsor personnel outside of the sponsor study team responsible for managing the study, supplemented with an external certified hepatologist, will be established. The DRC will monitor efficacy and safety data in an unblinded manner during study conduct on a regular basis and/or ad hoc in case of emergent safety signals identified through medical monitoring. The DRC will also review interim data and formulate recommended decisions/actions in accordance with the objectives of the interim analysis.

The DRC can also recommend to conduct an additional unblinded interim analysis. The DRC will provide instructions to the sponsor study team with respect to any changes to study conduct that it deems necessary in light of the emerging safety and efficacy data. This may include the addition, modification, or closure of treatment arms. The sponsor, in agreement with the DRC, selected the JNJ-56136379 dose for Part B based on all safety, PK, and antiviral activity data available following completion of the highest JNJ-56136379 dose group (who received 250 mg once daily) in the Phase 1 study 56136379HPB1001 in treatment-naïve CHB-infected subjects treated for 28 days.

The DRC may also endorse any sponsor recommendations for the addition of further parts to the study.

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															
Serum immunoglobulin M (IgM) anti-HBc antibody test	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														
Dispense study medication		X			X	X	X	X	X	X[hh,pp]	X	X	X	X	X	X[ii]
Administer study medication[i]		X	X	X	X	X	X	X	X	X[pp]	X	X	X	X	X	X
Distribute diary[j]						X			X							
Collect diary[j]							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																
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
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

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																
Pharmacokinetics																
Blood sampling for pharmacokinetics of JNJ-56136379 and/or NA (sparse)[w]		X[nn]	X	X	X	X	X[nn]	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[nn]					X[nn]									
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 (sparse, all women on hormonal contraceptives)[dd,ll]		X[nn]					X[nn]		X	X						
Blood sampling for exploratory pharmacokinetics of hormonal contraceptives and their metabolites (semi-rich, all women on hormonal contraceptives included in the PK subgroup)[dd,mm]		X[nn]					X[nn]									
Information on hormonal contraceptive cycle[oo]	X	X					X		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[cc]																
EQ-5D-5L		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																
HBQOL		X			X					X						
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 17.4. Check 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 (regardless of type and route of administration). 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 of a 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 (note: all hormonal contraceptives, regardless of type and route of administration).
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 1-4, ±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 <200 IU/mL 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.
ll. Sparse pharmacokinetic sampling will be performed for all female subjects on hormonal contraceptive treatment (regardless of type and route of administration). One sample predose on Day 1 and one sample at 1 hour postdose at all other indicated time points (also refer to footnote nn). On sampling days, female subjects on oral hormonal contraceptive treatment should take their contraceptive treatment as usual, and time of intake will be recorded.
mm. All female subjects that are on a hormonal contraceptive treatment (regardless of type and route of administration) and that are included in the PK subgroup will undergo semi-rich pharmacokinetic sampling predose and at 2, 4, 12, and 24 hours postdose. The oral contraceptive treatment should be taken as usual, and time of intake will be recorded.
nn. For subjects who are included in the PK subgroup (ie, those who undergo semi-rich sampling), only the sample for the semi-rich sampling set needs to be taken on Day 1 and Week 12 (no sparse sampling on these days and time points).
oo. For female subjects on a hormonal contraceptive regimen (regardless of type and route of administration), the start of contraceptive administration at the last initiated cycle (if applicable for the type of contraception) will be documented in the eCRF.
pp. Subjects in the JNJ-56136379 250 mg monotherapy arm (Treatment Arm 6) who meet the treatment extension criteria (see Section 6.1), will receive JNJ-56136379 in combination with NA treatment from Week 24 to Week 48.

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 at Week 48 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,t]**			
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[c]		X	X	X	X
Vital signs[d]	X	X	X	X	X
Triplicate 12-lead ECG[e]	X		X	X	X
Clinical Laboratory Tests					
Hematology	X	X	X	X	X
Blood chemistry[f,g]	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[h]	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[i] (quantitative)	X	X	X	X	X
HBcrAg[q]	X	X	X	X	X
Exploratory serology[j]	X	X	X	X	X
Pharmacokinetics					
Blood sampling for pharmacokinetics of JNJ-56136379		X	X		

Phase	Early Treatment Withdrawal Visit[p]	Post-treatment Follow-up[r,t]			
Follow-up (FU) Week (W)		**FU W2**	**FU W4**	**FU W12**	**FU W24 end of study visit**
Study Procedure					
and/or NA (sparse)[k]					
Blood sampling for exploratory pharmacokinetics of hormonal contraceptives and their metabolites (sparse, all women on hormonal contraceptives)[k]			X		
Information on hormonal contraceptive cycle[s]			X		
Exploratory Biomarkers					
Host mRNA	X		X		X
Serum proteins	X		X		X
Immune cells (PBMCs) (selected sites only)[l]	X		X		X
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.
s. For female subjects on a hormonal contraceptive regimen (regardless of type and route of administration), the start of contraceptive administration at the last initiated cycle (if applicable for the type of contraception) will be documented in the eCRF.
t. All follow-up study visits are to be scheduled relative to the last dose of JNJ-56136379 and are to occur at the end of Weeks 2, 4, 12, and 24. The visit window is ±2 days of the protocol-specified date at Weeks 2-4, ±5 days of the protocol-specified date through Week 24.

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 6.3.

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
HBcrAg[p]		X			X			X			X
Exploratory serology[j]	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											
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 (sparse, all women on hormonal contraceptives)[k]		X									
Information on hormonal contraceptive cycle[q]		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
Patient-reported Outcome Evaluations[r]											
EQ-5D-5L					X						
HBQOL					X						
MOS-CFS Cog-R								X			
SF-36v2								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

a. 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 6.4 and, hence, should start NA (either ETV or TDF) treatment during the post-treatment follow-up.
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. All follow-up study visits are to be scheduled relative to the last dose of JNJ-56136379 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 HBV DNA elevations, ALT elevations, other signs of worsening of liver disease, or for any other reason during follow-up.
n. Subjects who withdraw consent during follow-up will be offered an optional safety follow-up visit.
o. Only applicable to subjects in the pharmacokinetic subgroup and subjects enrolled at a site with an on-site Fibroscan device.
p. 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.
q. For female subjects on a hormonal contraceptive regimen (regardless of type and route of administration), the start of contraceptive administration at the last initiated cycle (if applicable for the type of contraception) will be documented in the eCRF.
r. 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.

ABBREVIATIONS

AE	adverse event
Ae	amount of unchanged drug excreted into urine
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{0\text{-}xh}$	area under the plasma concentration-time curve from time 0 to *x* hours after dosing
AUC_{∞}	area under the plasma concentration-time curve from time 0 to infinity
AUC_{last}	area under the plasma concentration-time curve from time 0 to the time of the last measurable (non-below quantification limit [BQL]) concentration
AUC_{τ}	area under the plasma concentration-time curve from time 0 to τ hours postdose
$AUC_{\tau,ss}$	steady-state area under the plasma concentration-time curve from time 0 to τ hours postdose
bpm	beats per minute
BQL	below quantification limit
CAM	capsid assembly modulator
C_{avg}	average plasma concentration
cccDNA	covalently closed circular DNA
CHB	chronic hepatitis B
CI	confidence interval
CL/F	total apparent oral clearance
CL_R	renal clearance
C_{max}	maximum observed plasma concentration
$C_{max,ss}$	maximum steady-state plasma concentration
C_{min}	minimum observed plasma concentration
CT	computed tomography
C_{trough}	predose plasma concentration
CYP	cytochrome P450
DAIDS	Division of AIDS
DBP	diastolic blood pressure
DNA	deoxyribonucleic acid
DRC	Data Review Committee
EC_{50}	50% effective concentration
EC_{90}	90% effective concentration
ECG	electrocardiogram
(e)CRF	(electronic) case report form
eDC	electronic data capture
eGFR	estimated Glomerular Filtration rate
EE	ethinyl estradiol
EOT	end-of-treatment
EQ-5D-5L	5-level EuroQol 5-Dimension
ESI	event of special interest
ETV	entecavir
FI	percentage fluctuation
FSH	follicle-stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
HBcrAg	hepatitis B core-related antigen
HBeAg	hepatitis B e antigen
HBQOL	Hepatitis B Quality of Life Instrument
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
HIV	human immunodeficiency virus
HRQoL	health-related quality of life

HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IFN	interferon
IgM	immunoglobulin M
INR	international normalized ratio
IRB	Institutional Review Board
IWRS	interactive web response system
LC-MS/MS	liquid chromatography-mass spectrometry/mass spectrometry
LLN	lower limit of normal
LLOQ	lower limit of quantification
LS	least squares
λ_z	apparent terminal elimination rate constant
MAP	meta-analytic predictive
MCH	mean corpuscular hemoglobin
MCS	Mental Component Summary
MDRD	Modification of Diet in Renal Disease
MoA	mode of action
MOS-CFS Cog-R	Medical Outcomes Study Cognitive Functioning Scale-Revised
MRI	magnetic resonance imaging
NA	nucleos(t)ide analog
NOAEL	no-observed-adverse-effect-level
PBMC	peripheral blood mononuclear cell
PBPK	physiological-based pharmacokinetics
PCS	Physical Component Summary
PegIFN(α)	pegylated interferon (alpha)
PK	pharmacokinetic(s)
PK/PD	pharmacokinetic(s)/pharmacodynamic(s)
popPK	population pharmacokinetics
PQC	Product Quality Complaint
PRO	patient-reported outcome(s)
QTcF	QT interval corrected for heart rate according to Fridericia
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SF-36v2	Short Form 36 version 2
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2term}$	apparent terminal elimination half-life
TDF	tenofovir disoproxil fumarate
t_{max}	time to reach maximum plasma concentration
ULN	upper limit of normal
VAS	Visual Analog Scale
Vd/F	apparent volume of distribution
WBC	white blood cell

1. INTRODUCTION

JNJ-56136379 is an orally administered capsid assembly modulator (CAM) that is being developed for the treatment of chronic hepatitis B (CHB) virus (HBV) infection.

JNJ-56136379 binds to the HBV core protein and interferes with the viral capsid assembly process, thereby preventing the polymerase-bound pregenomic ribonucleic acid encapsidation. This results in the formation of HBV capsids, devoid of HBV deoxyribonucleic acid (DNA) (non-functional capsids), and ultimately in the inhibition of HBV replication in vitro. In addition, JNJ-56136379 also acts at an early stage of the viral life cycle by inhibiting the de-novo formation of covalently closed circular DNA (cccDNA) potentially by interfering with the capsid disassembly process.

Despite the availability of an efficacious prophylactic vaccine, more than 240 million people worldwide are affected by CHB infection, a potentially fatal liver disease.[27] Approximately 680,000 people worldwide die yearly from cirrhosis and liver cancer due to CHB infection.

The natural history of CHB is the consequence of a complex interaction between the virus and the host which evolves over the duration of the infection. This results in different phases determined by the balance between the host immune system and HBV (Table 1). Note that differences in the definition and naming of these phases exist in different countries/regions.

Table 1: Various Stages of HBV – Terminology and Characteristics (EASL 2017)

	HBeAg positive		HBeAg negative	
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis
HBsAg	High	High/intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	$>10^7$ IU/ml	10^4-10^7 IU/ml	<2,000 IU/ml**	>2,000 IU/ml
ALT	Normal	Elevated	Normal	Elevated*
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis

*Persistently or intermittently. °°HBV DNA levels can be between 2,000 and 20,000 IU/ml in some patients without signs of chronic hepatitis.

The primary treatment goals for patients with HBV infection are to prevent progression of the disease, particularly to cirrhosis, liver failure, and hepatocellular carcinoma (HCC). There are multiple risk factors that influence progression of CHB, such as persistently elevated levels of HBV DNA and alanine aminotransferase (ALT), male sex, older age, and coinfection with hepatitis D virus (HDV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV).

Therapy is generally recommended for patients with hepatitis B e antigen (HBeAg)-positive or -negative chronic hepatitis B (Table 1).[4,9,24,30] Approved therapies for CHB infection comprise pegylated (Peg) interferon alpha (IFNα) (PegIFNα) products and nucleoside/nucleotide inhibitors of the HBV polymerase/reverse transcriptase. While nucleos(t)ide analogs (NAs) are effective at suppressing viral DNA in the blood, it is now understood that viral suppression does not confer the same benefit as hepatitis B surface antigen (HBsAg) seroclearance or host immune control of the infection, and that in the context of viral DNA suppression alone the risk of developing HCC remains. To maintain suppression of HBV replication and reduce liver injury, life-long treatment with HBV NAs is recommended, but this treatment approach is associated with side effects and

patient noncompliance.[5,8,16,17,25,29,34] PegIFN is associated with a slightly higher rate of HBsAg seroclearance and total treatment duration is 48 weeks, but is administered subcutaneously and is associated with substantial toxicity.

With the continued worldwide prevalence of HBV-associated mortality and the low rate of post-treatment durable HBsAg seroclearance with current treatments, there is a medical need for effective finite treatment with long-term clinical benefits (ie, reduced mortality and morbidity from cirrhosis and HCC) comparable to those achieved by patients with self-limited HBV infections.

For the most comprehensive nonclinical and clinical information regarding JNJ-56136379, refer to the latest version of the Investigator's Brochure (IB) for JNJ-56136379.[15]

1.1. Background

JNJ-56136379 displayed potent and selective antiviral activity with a median 50% effective concentration (EC_{50}) and 90% effective concentration (EC_{90}) values of 54 nM (22.6 ng/mL) and 226 nM (94.6 ng/mL), respectively in a stable HBV-replicating HepG2.117 cell line and in HBV-infected primary human hepatocytes with an EC_{50} and EC_{90} value of 118 nM (49.4 ng/mL) and 347 nM (145 ng/mL), respectively. In addition, these studies showed that JNJ-56136379 when added together with the viral inoculum, in contrast to NA polymerase inhibitors, also inhibits early steps of the HBV viral life cycle (ie, steps before formation of cccDNA) potentially by interfering with the capsid disassembly process.

JNJ-56136379 remained active against a diverse panel of genotype A to H clinical isolates. In vitro combination studies of JNJ-56136379 with entecavir (ETV) and tenofovir disoproxil fumarate (TDF) resulted in additive to synergistic anti-HBV activity.

Nonclinical Data

Following 6 months of treatment, the kidney and female reproductive tract (irregular estrus cycle) were identified as target organs in rats. The no-observed-adverse-effect-levels (NOAELs) in the rat study were considered to be 30 mg eq./kg/day for male rats and 100 mg eq./kg/day for female rats. However, after further assessment of the kidney findings and their clinical relevance, it is deemed unlikely that the retrograde nephropathy seen in 1 out of 20 male rats following 6 months of dosing with JNJ-56136379 at 100 mg eq./kg/day are relevant for the clinical studies, including the current Phase 2a study. The retrograde nephropathy was partially recovered after a 9-week recovery period. The corresponding exposures noted in male rats at 100 mg eq./kg/day (maximum observed plasma concentration [C_{max}]=13,600 ng/mL and area under the plasma concentration-time curve [AUC] from 0 to 24 hours after dosing [AUC_{0-24h}]=180,000 ng.h/mL) are above those at the NOAEL. In the 6-month rat study, female rats (at 200 mg eq./kg/day) showed an irregular estrus cycle, from which they recovered at the end of the 9-week treatment-free period. These irregular estrus cycles were also apparent in the female fertility studies (main and mechanistic). These changes were related to lowered hormone levels (luteinizing hormone, progesterone, estradiol). JNJ-56136379, however, did not affect female fertility. The fetal loss seen during the early stages of pregnancy was considered to result from

low hormone levels. Progesterone is considered essential for the establishment and maintenance of mammalian pregnancy and low progesterone levels are associated with fetal loss during the early stages of pregnancy. In the dog study, no changes were observed in the reproductive tract at higher exposures in dogs.

In the 9-month dog study, the target organs identified were the adrenal glands and bone marrow. The adrenal glands did not show degenerative changes or loss of function and were therefore considered as non-adverse target organs. One female dog dosed at 25 mg eq./kg/day was sacrificed on Day 61, after showing poor health condition. A JNJ-56136379 plasma level of 42,000 ng/mL was observed for this animal on Day 61, at approximately 24 hours after last dosing. Pronounced clinical pathologic changes were noted. Marked increase in plasma cell-like cells was seen in the bone marrow during histopathologic examination, resulting in a marked reduction of hematopoietic tissue and extramedullary hematopoiesis in liver and spleen. The cause of the deteriorating condition was likely related to changes in the bone marrow.

Compared to the 6-month dog study, no new toxicity was seen in surviving animals in the 9-month dog study. Therefore, the NOAEL was considered to be 25 mg/kg/day for male dogs (C_{max}=30,000 ng/mL and AUC_{0-24h}=606,000 ng.h/mL) and 12.5 mg/kg/day for female dogs (C_{max}=22,500 ng/mL and AUC_{0-24h}=383,000 ng.h/mL).

Animal/human ratios at the NOAEL in rat and dog for human exposure at 75 mg and 250 mg JNJ-56136379 once daily for 28 days are displayed in Table 2 and Table 3, respectively.

Table 2: Animal/Human (A/H) Ratios at the NOAEL in Rat and Dog (Human Exposure at 75 mg JNJ-56136379 Once Daily for 28 Days [Study 56136379HPB1001])

	Sex	NOAEL (mg eq./kg/day)	C_{max} (ng/mL)	AUC_{0-24h} (ng.h/mL)	Ratio Total Concentration		Ratio Concentration Corrected for Plasma Protein Binding[b]	
					C_{max} A/H Ratio	AUC_{0-24h} A/H Ratio	C_{max} A/H Ratio	AUC_{0-24h} A/H Ratio
Human exposure[a]			3,465	83,161	-	-		
6M rat	M	30	7,540	93,100	2.2	1.1	3.6	1.9
	M	100[c]	13,600[d]	180,000[d]	3.9	2.2	6.6	3.6
	F	100	19,900	233,000	5.7	2.8	9.6	4.7
9M dog	M	25	30,000	606,000	8.7	7.3	15	11
	F	12.5	22,500	383,000	6.5	4.6	10	7.0

[a] 75 mg JNJ-56136379 once daily for 28 days (Study 56136379HPB1001).
[b] Ratio of the total C_{max} or AUC corrected for species difference in plasma unbound fraction. Calculation: [animal C_{max} or AUC_{0-24h} x animal free fraction] / [human C_{max} or AUC_{0-24h} x human free fraction].
[c] A dose of 100 mg eq./kg/day in male rats is considered to be above the NOAEL due to kidney findings in male rats, which are likely not relevant for human.
[d] The plasma C_{max} of 13,600 ng/mL and AUC_{0-24h} of 180,000 ng.h/mL in male rats at 100 mg eq./kg/day corresponds to an unbound C_{max} of 1,754 ng/mL and AUC_{0-24h} of 23,220 ng h/mL (fraction unbound rat plasma=12.9%). This unbound plasma exposure will be achieved in humans at a total plasma C_{max} of 22,784 ng/ml and AUC_{0-24h} of 301,558 ng.h/mL (fraction unbound in human plasma=7.7%).

Table 3: Animal/Human (A/H) Ratios at the NOAEL in Rat and Dog (Human Exposure at 250 mg JNJ-56136379 Once Daily for 28 Days [Study 56136379HPB1001])

	Sex	NOAEL (mg eq./kg/day)	C_{max} (ng/mL)	AUC_{0-24h} (ng h/mL)	Ratio Total Concentration		Ratio Concentration Corrected for Plasma Protein Binding[b]	
					C_{max} A/H Ratio	AUC_{0-24h} A/H Ratio	C_{max} A/H Ratio	AUC_{0-24h} A/H Ratio
Human exposure[a]			13,798	265,384	-	-		
6M rat	M	30	7,540	93,100	0.6	0.4	0.9	0.6
	M	100[c]	13,600[d]	180,000[d]	1.0	0.7	1.7	1.1
	F	100	19,900	233,000	1.4	0.9	2.4	1.5
9M dog	M	25	30,000	606,000	2.2	2.3	3.3	3.5
	F	12.5	22,500	383,000	1.6	1.4	2.5	2.2

250 mg JNJ-56136379 once daily for 28 days (Study 56136379HPB1001).

[b] Ratio of the total C_{max} or AUC corrected for species difference in plasma unbound fraction. Calculation: [animal C_{max} or AUC_{0-24h} x animal free fraction] / [human C_{max} or AUC_{0-24h} x human free fraction].

[c] A dose of 100 mg eq./kg/day in male rats is considered to be above the NOAEL due to kidney findings in male rats, which are likely not relevant for human.

[d] The plasma C_{max} of 13,600 ng/mL and AUC_{0-24h} of 180,000 ng.h/mL in male rats at 100 mg eq./kg/day corresponds to an unbound C_{max} of 1,754 ng/mL and AUC_{0-24h} of 23,220 ng h/mL (fraction unbound rat plasma=12.9%). This unbound plasma exposure will be achieved in humans at a total plasma C_{max} of 22,784 ng/ml and AUC_{0-24h} of 301,558 ng.h/mL (fraction unbound in human plasma=7.7%).

Clinical Studies

In total, 98 healthy and 34 CHB-infected subjects have been dosed with JNJ-56136379 in 3 completed and 1 ongoing Phase 1 studies:

Study 56136379HPB1003 is a completed Phase 1, randomized, double-blind, placebo-controlled study in healthy Japanese adult subjects to investigate the pharmacokinetics, tolerability, and safety of oral administration of JNJ-56136379 single doses from 25 mg up to 500 mg, in fasted conditions (n=32).

Study 56136379HPB1001 is an ongoing Phase 1, randomized, double-blind, placebo-controlled, first-in-human study. Part 1 in healthy adult subjects is completed and evaluated the safety, tolerability, and pharmacokinetics of single ascending doses of oral JNJ-56136379 (25 to 600 mg [n=18]) and one multiple-dose regimen (150 mg twice daily [bid] for 2 days, followed by 100 mg once daily [qd] for 10 days [n=12]) (Part 1, completed). The effect of food on the pharmacokinetics of a single-dose level of JNJ-56136379 was also evaluated. In the ongoing Part 2, adult CHB-infected subjects are administered different oral multiple-dose regimens for 28 days, including 25 mg qd following a 100-mg loading dose (Session 8, completed [n=12]), 75 mg qd (Session 9, completed [n=12]), 150 mg qd (Session 10, completed [n=12]) and 250 mg qd (Optional Session A, completed [n=12]). Session 11 is currently ongoing and includes dosing with JNJ-56136379 for 28 days at 75 mg qd.

Study 56136379HPB1004 is a completed Phase 1 open-label study in healthy adult female subjects to investigate the effect of JNJ-56136379 at steady-state on the single-dose pharmacokinetics of ethinylestradiol and drospirenone (oral contraceptive) and on the

single-dose pharmacokinetics of midazolam (probe substrate for cytochrome P450 [CYP] 3A4) (n=18).

Study 56136379HPB1002 is a completed Phase 1 open-label study in healthy adult subjects to assess the bioavailability of single doses of JNJ-56136379 administered as new oral tablets under fasted and fed conditions, and as an oral solution and a micro suspension under fed conditions (n=30).

Human Pharmacokinetics and Product Metabolism

The current population pharmacokinetic (popPK) model based on data in healthy subjects allows to make predictions on exposures at different doses in CHB-infected subjects.

In healthy subjects, JNJ-56136379 is rapidly absorbed from the oral tablets, with a median t_{max} ranging between 1.26 and 3 hours in fasting conditions, and around 4 hours in fed conditions. C_{max} increased proportionally between 25 and 500 mg, but was later (median t_{max} 4 hours) and less than dose proportionally at the dose of 600 mg. The AUC from time 0 to infinity (AUC_{∞}) increased proportionally between 25 to 600 mg single doses, and was approximately 16% higher in Asians. A single dose of 150 mg in 5 non-Asian subjects in fed conditions increased AUC_{∞} by approximately 27%. The mean apparent volume of distribution (Vd/F) after single dose was ranging between 151 and 194 L in study 56136379HPB1001 and between 119 and 137 L in 56136379HPB1003 (Japanese subjects). JNJ-56136379 has a low systemic clearance, with total apparent oral clearance (CL/F) values ranging from 1.28 L/h and 1.41 L/h in study 56136379HPB1001 and from 0.852 to 1.03 L/h in study 56136379HPB1003. Mean terminal half-life ($t_{1/2term}$) was comparable between studies 56136379HPB1001 and 56136379HPB1003, ranging between 93.3 and 116 hours across the dose levels in both studies, suggesting no significant difference in clearance between Asian and non-Asian subjects. In study 56136379HPB1003, approximately 18% of the administered dose was excreted via the kidney, resulting in a mean renal clearance of 0.161 L/h. This was comparable to what was observed in study 56136379HPB1001 Part 1.

After a 100-mg once-daily multiple-dose administration in healthy subjects (study 6136379HPB1001 Part 1), an average plasma concentration (C_{avg}) of 3,670 ng/mL was obtained with a mean steady-state C_{max} ($C_{max,ss}$) of 4,653 ng/mL. Fluctuations in plasma concentrations during one dosing interval were moderate to low and averaged 43.0%. In study 56136379HPB1004, in healthy female subjects, a once-daily dose of 170 mg resulted in a C_{avg} of 6,759 ng/mL with a mean $C_{max,ss}$ of 8,032 ng/mL and a fluctuation index of 34%, indicating dose proportional pharmacokinetics when comparing with repeated 100 mg qd dose (study 56136379HPB1001 Part 1). The mean observed CL/F was 1.15 L/h in study 56136379HPB1001 Part 1 and 1.11 L/h in study 56136379HPB1004, which was in line with the observations after single dose. The steady-state AUC from time 0 to τ hours postdose ($AUC_{\tau,ss}$) was 88,101 ng.h/mL for 100 mg once daily and 162,224 ng.h/mL for 170 mg once daily.

In CHB-infected subjects, the C_{avg} at Day 28 was 1,155 ng/mL for 25 mg once daily and 3,465 ng/mL for the 75-mg once-daily dose, with a mean C_{max} of 1,415 and 3,986 ng/mL respectively. AUC_{0-24h} at Day 28 was 27,720 ng.h/mL for the 25-mg and 83,161 ng.h/mL for the 75-mg dose level. CL/F in CHB-infected subjects was 0.989 and 0.928 and L/h for the 25-mg and 75-mg dose level respectively, indicating no significant change in clearance of JNJ-56136379 in CHB-infected subjects compared to healthy subjects.

Antiviral Activity

Antiviral activity is examined in the ongoing Part 2 of study 56136379HPB1001 (Sessions 8 to 11), in CHB-infected subjects.

Interim data from the 25- to 250-mg dose show that JNJ-56136379 administration leads to reduction in HBV DNA. A mean (±SD) reduction in plasma HBV DNA levels of 2.16 (0.49) log_{10} IU/mL (25 mg), 2.89 (0.48) log_{10} IU/mL (75 mg), 2.70 (0.53) log_{10} IU/mL (150 mg), and 2.70 (0.33) log_{10} IU/mL (250 mg) from baseline was observed at Day 29. In the 250-mg dosing group, 5 out of 12 subjects achieved HBV DNA levels below the LLOQ of the HBV DNA assay, while 3 out of 12 subjects in both the 75-mg and 150-mg dosing groups and none (out of 12) of the subjects in the 25-mg dosing group achieved this.

A more pronounced and consistent decline in HBV DNA levels was observed across subjects in the 75-mg, 150-mg, and 250-mg group compared with the 25-mg group.

HBV RNA was assessed as an exploratory endpoint using a validated research assay. In line with HBV DNA levels, reductions in HBV RNA levels were observed with JNJ‑56136379 treatment. Baseline levels of HBV RNA were generally low and in some instances undetectable, especially in the higher dose groups, limiting the HBV RNA decline observable in this study.

No notable changes in HBsAg or HBeAg were observed.

Safety

Healthy Subjects

Of the 123 adult healthy subjects included in the pooling, 98 subjects received at least one dose of JNJ-56136379. Eleven subjects did not complete their treatment: due to withdrawal by subject (such as withdrawal of consent or withdrawal due to personal reasons) (4 [3.3%] subjects), lost to follow-up (1 [0.8%] subject), other reasons (2 [1.6%] subjects) or due to adverse events (AEs) (4 [3.3%] subjects, see below).

There were no deaths and 2 subjects experienced a serious adverse event (SAE), both considered not related to JNJ-56136379: one during the screening phase (spontaneous abortion; moderate) in study 5636379HPB1004, and the other (wrist fracture right; severe) in study 563679HPB1002, 24 days after the last single dose of JNJ-56136379. Apart from the severe wrist fracture, no severe AEs were reported. In most cases AEs were mild and not considered related to JNJ-56136379.

Two subjects in study 56136379HPB1001 Part 1, single dose escalation phase, discontinued from further dosing with JNJ-56136379 in subsequent sessions due to an AE. One subject in study 56136379HPB1001 Part 2, multiple dose phase, discontinued JNJ-56136379 treatment after administration of JNJ-56136379 150 mg bid for 2 days, followed by JNJ-56136379 100 mg for 9 days due to the AEs abdominal pain lower and dizziness postural. These AEs were considered by the investigator of mild severity and possibly related to JNJ-56136379, and resolved after discontinuation.

Overall, the most common treatment-emergent AEs, experienced by >10% of all subjects treated with JNJ-56136379 was headache (27 [27.6%] subjects on JNJ-56136379 versus 3 [12.0%] subjects on placebo).

Most graded laboratory abnormalities were grade 1 or 2, except for a grade 3 amylase and grade 4 lipase elevation in 1 subject in study 56136379HPB1002 (both observed during follow-up), a grade 3 lipase elevation in another subject in study 56136379HPB1002 (observed when subject on treatment) (see below), and 2 grade 3 LDL cholesterol elevations in one subject each from study 56136379HPB1002 and study 56136379HPB1003 (both observed when subjects on treatment). For the subject with grade 4 lipase elevation, a grade 3 lipase elevation was already observed when the subject was on treatment. Hypotension was reported in one subject in study 56136379HPB1004 and palpitations in 3 subjects in study 56136379HPB1004.

In studies 56136379HPB1001 Part 1 and 56136379HPB1004, no subjects tested positive for proteinuria. There were no plasma urea abnormalities and creatinine abnormalities. The urinary and plasma findings indicated that there was no deterioration in the kidney function.

In the Phase 1 study 56136379HPB1002, there were 3 subjects who experienced lipase and/or amylase elevations >grade 2 (or above normal limits for pancreatic amylase) (laboratory abnormalities) which were reported as AE, detailed below. (For 2 of these subjects there were no clinical signs of pancreatitis, for the third subject there was a suspicion of underlying pancreatic disorder, as baseline lipase was elevated [grade 2], see below.) Based on these cases, lipase and amylase have been identified as laboratory abnormalities of interest. The pooled data show that 5 (5.1%) and 6 (6.1%) subjects on JNJ-56136379 had lipase and amylase elevations, respectively versus none on placebo. Except for the grade 3 and 4 elevations discussed below, all other abnormalities were grade 1 or 2.

The first subject experienced two isolated laboratory abnormalities of grade 3 lipase elevation and pancreatic amylase elevation above normal limits, following single dose treatment, which were recorded by the investigator as moderate and mild AE respectively, both possibly related to study drug. The second subject experienced grade 3 abnormalities of lipase elevation and pancreatic amylase above normal limits following single dose treatment and grade 4 and grade 3 laboratory abnormalities of lipase and amylase elevation during follow-up (35 days after second dose of JNJ-56136379). These lipase elevations were recorded by the investigator as moderate AEs, possibly related to JNJ-56136379, and (pancreatic) amylase elevations were recorded as mild or moderate AEs, possibly related to JNJ-56136379. The last lipase and amylase values recorded during follow-up (ie, 25 days after worst grade elevations) were within normal limits.

The investigator had suspected an underlying pancreatic disorder as the subject had a grade 2 elevated lipase prior to dosing. The subject was advised to be followed up by the physician after the study. The third subject experienced an isolated laboratory abnormality of pancreatic amylase elevation above normal limits, which was recorded as moderate AE probably related to study drug by the investigator. All AEs resolved before study end.

In summary, these data suggest that JNJ-56136379 single dose administration (up to 600 mg, in healthy subjects, including Japanese subjects) and multiple dose administration (150 mg bid for 2 days, followed by 100 mg qd for 10 days, in healthy subjects) is generally safe and well tolerated. There were no deaths, and there was only 1 treatment-emergent SAE (wrist fracture, no related to JNJ-56136379). Other than this SAE, there were no severe treatment-emergent AEs and there were few discontinuations due to AEs (only 1 of which during multiple dosing). Most AEs were mild and not considered treatment-related. No safety signal was identified.

CHB Infected Subjects

In the unblinded 25-250 mg sessions of Part 2 of study 56136379HPB1001 in CHB-infected subjects, no deaths were reported. No other SAEs, AEs leading to discontinuation or grade 4 AEs were observed in the 25, 75 and 250 mg treatment groups.

One subject in the JNJ-56136379 150 mg treatment group experienced several grade 3 SAEs (idiopathic intracranial hypertension, headache, epilepsy, gliosis, brain edema, brain neoplasm, brain compression) 2 days after completing treatment with JNJ-56136379. The subject was withdrawn from the study. All SAEs were considered not related to study drug with outcome unknown. Despite several attempts to reach the patient, the patient was lost to follow-up.

One subject experienced the grade 3 AE AST increased and grade 4 AE ALT increased during JNJ-56136379 150 mg treatment. Both AEs were considered probably related to study drug, which was withdrawn, due to the protocol defined stopping criteria. The AEs were considered resolved after end of treatment. The subject also had the AEs liver tenderness (grade 1, possibly related, resolved before end of treatment) and abdominal distension (grade 1, not related, resolved after end of treatment) for which study drug was withdrawn.

Other grade 3 AEs were reported for 1 subject during JNJ-56136379 25 mg treatment (amylase increased, possibly related, resolved before end of treatment), for 1 subject during JNJ-56136379 75 mg treatment (ALT increased, possibly related, resolved after end of treatment) and 1 subject after JNJ-56136379 150 mg treatment (AST increased, probably related, resolved).

The most frequently reported treatment-emergent AEs across all doses (>1 subject) on JNJ-56136379 were headache (4 [11.8%] subjects on JNJ-56136379 versus 6 [42.9%] subjects on placebo), nausea (2 [5.9%] subjects versus 0 subjects, respectively), dyspepsia (2 [5.9%] subjects versus 0 subjects, respectively), ALT increased (2 [5.9%] subjects versus 1 [7.1%] subject, respectively), amylase increased (2 [5.9%] subjects versus 0 subjects, respectively), and hypophosphatemia (2 [5.9%] subjects versus 0 subjects, respectively). All

other AEs were reported in 1 subject at most. No dose-related trend in AEs was observed. The majority of AEs were grade 1.

The majority of laboratory abnormalities were grade 1 or 2. No grade 3 or 4 laboratory abnormalities were observed in the 250 mg treatment group. Grade 4 ALT elevations were observed in 1 subject each in the 75 and 150 mg treatment groups and were related to the AEs discussed above (for the subject in the 75 mg treatment group, this was observed during follow-up). Grade 3 pancreatic amylase (discussed above as AE) and grade 3 triglycerides (observed during follow-up) were observed in 1 subject each in the 25 mg treatment group. Grade 3 AST elevation was observed in 1 subject in the 75 mg treatment group (observed during follow-up) and in 2 subjects in the 150 mg group (for 1 subject observed during follow-up) (discussed as AE above). Grade 3 hyperkalemia was observed in 1 subject in the 150 mg treatment group.

No ECG-related or vital sign-related AEs were reported. No clinically relevant changes from baseline in ECG or vital signs values were observed.

1.2. Combination Therapy

Entecavir is an HBV NA reverse transcriptase inhibitor indicated for the treatment of CHB infection in adults and children at least 2 years of age with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or aspartate aminotransferase [AST]) or histologically active disease. The most common adverse reactions (≥3% of subjects) are headache, fatigue, dizziness, and nausea.

Tenofovir disoproxil fumarate is a first-generation oral prodrug of tenofovir that is indicated for the treatment of HBV infection in adult and pediatric patients at least 12 years of age. In addition, TDF in combination with other antiretrovirals is indicated for the treatment of HIV-1 infection in adult and pediatric patients at least 2 years of age. The most common adverse reactions (≥10% of subjects) are abdominal pain, nausea, insomnia, pruritus, vomiting, dizziness, and pyrexia.

The kidney is identified as target organ for both JNJ-56136379 and TDF. In rats, as previously indicated, a probably rat-specific retrograde nephropathy was observed in male rats dosed with JNJ-56136379. This is not due to a direct effect of the compound on the kidney, but secondary to calculi formation in the lower urinary tract and subsequent retrograde changes. With TDF, only slight elevations in serum creatinine were observed without any histopathology correlation in rats. In the 6-month dog study with JNJ-56136379, no kidney findings were observed when reaching high exposures. Chronic administration of TDF (10 mg/kg/day for 42 weeks) in dogs (ie, the species most sensitive to effects in the kidney) included individual cell necrosis, tubular dilatation, degeneration/regeneration, pigment accumulation, and interstitial nephritis. Therefore, no additive or synergistic toxicities are expected.

In addition, no clinically relevant drug-drug interactions are expected between JNJ-56136379 and ETV or TDF. Therefore, combination toxicity and drug-drug interaction studies are not deemed warranted to support the current Phase 2a study, and no drug-drug interaction studies are

planned before the start of Phase 2a. However, in order to verify the potential for impact of JNJ-56136379 on the pharmacokinetics of concomitantly administered NA, the sponsor plans to perform a popPK assessment including a characterization of renal clearance of concomitantly administered NAs in a subset of subjects (pharmacokinetic subgroup).

For further information regarding ETV and TDF, refer to the respective prescribing information.[1,2,32,33]

1.3. Benefit-risk Evaluations

For the benefit-risk evaluation of ETV and TDF, refer to the respective prescribing information.[1,2,32,33]

1.3.1. Known Benefits

The clinical benefit of JNJ-56136379 remains to be established.

1.3.2. Potential Benefits

Results from JNJ-56136379 clinical studies may be useful for the development of CAMs as a novel therapeutic approach for CHB infection.

Based on data from study 56136379HPB1001 (n=54) it is anticipated that JNJ-56136379 will have a similar effect on HBV DNA as the standard of care (NAs) when given as monotherapy. In addition, some studies have shown that there is ongoing low-level HBV replication in NA-suppressed subjects, which may contribute to the persistence of the HBV cccDNA pool.[20] The combination of JNJ-56136379 with NAs may result in a more profound and/or stable/sustained reduction in HBV DNA levels, which ultimately might lead to reduction in HBsAg levels and may allow completion of treatment in a subset of subjects.

1.3.3. Known Risks

As a formal adverse drug reaction analysis has not yet been conducted for JNJ-56136379, known risks associated with JNJ-56136379 have not been identified from clinical observations in the Phase 1 studies.

1.3.4. Potential Risks

All therapies have the potential to cause adverse experiences.

In total, 98 healthy and 34 CHB-infected subjects have been dosed with JNJ-56136379 in 3 completed and 1 ongoing Phase 1 studies.

Please refer to Section 1.1 for details on the reported AEs and laboratory/ECG abnormalities in the studies conducted to date.

Based upon the limited clinical data and considering the early stage of development of JNJ-56136379, no AEs or clinically significant laboratory abnormalities, abnormalities in vital signs parameters, ECG abnormalities, or physical examination findings indicative of a safety

concern have been identified. Based on data from Study 56136379HPB1002 (see Section 1.1), lipase and amylase elevations were identified as laboratory abnormalities of interest but based on aggregate safety review of all available clinical safety data, these are no longer considered of interest. Based on preclinical findings in rats and dogs, increased cholesterol was identified as laboratory abnormality of interest.

Based on preclinical data, JNJ-56136379 is considered to be devoid of genotoxic activity. Fertility was not affected up to C_{max} of 16,300 ng/mL and AUC_{0-24h} of 170,000 ng.h/mL in male rats (which translates to a human C_{max} of 27,308 ng/mL and human AUC_{0-24h} of 284,805 ng/ml.h after correction for species differences in plasma protein binding) and C_{max} of 5,530 ng/mL and AUC_{0-24h} of 79,900 ng/mL in female rats (which translates to a human C_{max} of 9,266 ng/mL and human AUC_{0-24h} of 133,859 ng/mL.h after correction for species differences in plasma protein binding). Embryofetal development was not affected up to C_{max} of 5,190 ng/mL and AUC_{0-24h} of 84,000 ng.h/mL in rats (which translates to a human C_{max} of 8,695 ng/mL and human AUC_{0-24h} of 140,727 ng/mL.h after correction for species differences in plasma protein binding) and C_{max} of 6,880 ng/mL and AUC_{0-24h} of 99,200 ng.h/mL in rabbits (which translates to a human C_{max} of 10,901 ng/mL and human AUC_{0-24h} of 157,174 ng/mL.h after correction for species differences in plasma protein binding). Carcinogenicity studies have not been conducted.

Treatment with JNJ-56136379 may lead to emergence of viral variants with reduced susceptibility or resistance to JNJ-56136379. Based on pre-clinical data, these variants remain susceptible to TDF and ETV but might affect treatment options with CAMs in the future.

As of 6 February 2019, virological breakthrough, as defined by the protocol (ie, confirmed on-treatment HBV DNA increase >1 $\log_{10}$ from nadir level or confirmed on-treatment HBV DNA level >200 IU/mL in subjects who had HBV DNA level below the LLOQ of the HBV DNA assay), was observed in 5 out of the 28 subjects on JNJ-56136379 75 mg monotherapy. In addition, there were 2 subjects who met the virological breakthrough threshold but, due to the change of treatment, the virological breakthrough could not confirmed. The virological breakthrough in these subjects is expected to be associated with viral resistance to JNJ-56136379. An HBV DNA decline was observed in these subjects upon initiation of NA treatment confirming pre-clinical data showing that viral variants resistant to JNJ-56136379 remain susceptible to NA treatment.

Given the virological breakthroughs observed in the JNJ-56136379 75 mg monotherapy arm (Treatment Arm 1), this treatment arm was discontinued early per Protocol Amendment 4. All subjects were to stop further dosing with JNJ-5613379 75 mg, start treatment with NA, and enter the post-treatment follow-up phase (Schedule 1).

In addition, per Protocol Amendment 4, the duration of treatment with JNJ-56316379 250 mg monotherapy has been limited to a maximum of 24 weeks (see Section 6.1). As an additional precautionary measure to safeguard the subjects, a stringent futility rule has been implemented in the JNJ-56136379 250 mg monotherapy arm (see Section 6.2).

1.3.5. Overall Benefit/Risk Assessment

Based on the available data and proposed safety measures, the overall risk/benefit assessment for JNJ-56136379 clinical studies is deemed acceptable for the following reasons:

- Continued careful assessment of the safety, efficacy, and pharmacokinetics during treatment is included in this study.
- Safety and efficacy monitoring is continued after the end of study treatment during a 24-week follow-up period for all subjects who complete 24 or who complete 48 weeks of treatment and do not meet the Individual Treatment completion criteria or who discontinue treatment early. During the follow-up subjects should be treated with NA (either TDV or ETV), which will be offered to the subjects as per local treatment guidelines. After the end of the study, the continuation of NA treatment and subsequent monitoring will be under the responsibility of the treating physician and based on local treatment guidelines.
- Subjects who meet the Individual Subject Treatment Completion Criteria (Section 6.3) after 48 weeks of treatment will be monitored for an additional 48 weeks with frequent follow-up visits (Schedule 2) and pre-defined retreatment criteria in case of relapse (Section 6.4).
- Preclinical studies up to 6-month treatment duration in rats and up to 9-month treatment duration in dogs were completed, (see Section 1.1), supporting a treatment duration of 48 weeks in humans.
- No clinically significant safety concerns have previously been raised based on the safety information from studies in healthy adult subjects and CHB-infected subjects and most observed AEs and laboratory abnormalities were mild to moderate in severity and considered not related to JNJ-56136379 by the investigator (see Section 1.1).
- Based on preclinical findings in rats and dogs, increased cholesterol is identified as a laboratory abnormality of interest. These abnormalities of interest will be monitored continuously in this study.
- In rat toxicology studies (6-month treatment), retrograde nephropathy was seen in 1 out of 20 male rats following 6 months of dosing with JNJ-56136379 at 100 mg eq./kg/day (Section 1.1). Therefore, the protocol of the current study includes monitoring for renal safety parameters (refer to Section 9.9 [Specific Toxicities – Renal Complications]).
- To minimize potential risk and stress to subjects:
  - A Data Review Committee (DRC) will be established to monitor safety data in an unblinded manner on a regular basis to ensure the continuing safety of the subjects enrolled in the current study (see Section 11.12).
  - Part A of the current study will start with the low dose of 75 mg of JNJ-56136379 once daily. The JNJ-56136379 dose to be administered in Part B of the study will be 250 mg given once daily. This dose has been selected by the sponsor, in agreement with the DRC, based on all safety, PK, and antiviral activity data available following completion of the highest JNJ-56136379 dose group (who received 250 mg once daily) in the Phase 1 study 56136379HPB1001 in treatment-naïve CHB-infected subjects treated for 28 days. The dose of 250 mg once daily is supported by the safety profile observed to date.
  - In light of the virological breakthroughs observed in the JNJ-56136379 75 mg monotherapy arm (Treatment Arm 1), the duration of JNJ-56136379 monotherapy has

been limited to a maximum of 24 weeks of treatment (see Section 6.1). As an additional precautionary measure, a stringent futility rule has been implemented in the JNJ-56136379 250 mg monotherapy arm (see Section 6.2).

- Only subjects who meet all of the inclusion criteria and none of the exclusion criteria will be allowed to participate in this study (see Sections 4.1 and 4.2). These criteria include adequate provisions to minimize the risk and protect the well-being of subjects in the study.
- Only subjects with a liver biopsy result Metavir F0-F2 (or a FibroScan™ liver stiffness measurement <8.0 kPa) within 1 year prior to screening or at the time of screening are allowed in this study. Subjects with any evidence of liver disease of non-HBV etiology (eg, primary biliary cirrhosis) are excluded.
- Subjects will be closely monitored throughout the study (see Section 17.8).
- Discontinuation and withdrawal criteria are in place (see Section 10.2).

1.4. Overall Rationale for the Study

The main goal of the study is to evaluate the change from baseline in HBsAg levels with two doses of JNJ-56136379 as monotherapy or in combination with an NA. On-treatment changes in HBsAg have been suggested as a useful marker to assess proof of concept for novel HBV regimens in early exploratory studies.[9,18,30] On-treatment HBsAg reduction can result in subsequent HBsAg seroclearance (HBsAg loss).[10,19,28]

In order to assess the potential of finite treatment duration, all treatment will be completed in subjects who meet the Individual Treatment Completion Criteria (Section 6.3) following 48 weeks of study treatment.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

The following objectives and endpoints will be evaluated by study regimen (ie, JNJ-56136379 [at two dose levels] and NA [ETV or TDF] as monotherapy or coadministered), by subject population (ie, subjects currently not being treated or virologically suppressed by current NA treatment), and by HBeAg status:

Objectives	Endpoints
Primary	
• To evaluate efficacy of 24 weeks of study treatment, in terms of changes in HBsAg levels.	• Change from baseline in HBsAg levels at Week 24.
Secondary	
• To evaluate the safety and tolerability of study treatment.	• Safety and tolerability data including but not limited to (S)AEs, physical examinations, vital signs, 12-lead electrocardiograms (ECGs), and clinical laboratory tests (including hematology, blood biochemistry, blood coagulation, and urinalysis) throughout the study.

Objectives	Endpoints
• To evaluate efficacy in terms of changes in HBsAg levels.	• Change from baseline in HBsAg levels during study treatment and follow-up. • Proportion of subjects with HBsAg levels by response subcategory, such as HBsAg <1,000 or <100 IU/mL, or with >0.5 or >1 $\log_{10}$ IU/mL reduction in HBsAg from baseline as detailed in the Statistical Analysis Plan (SAP) during study treatment and follow-up.
• To evaluate efficacy in terms of changes in HBV DNA levels.	• Change from baseline in HBV DNA levels during study treatment and follow-up. • Proportion of subjects with HBV DNA levels by response subcategory as detailed in the SAP during study treatment and follow-up.
• To evaluate efficacy in terms of changes in HBeAg levels (in HBeAg-positive subjects only).	• Change from baseline in HBeAg levels during study treatment and follow-up. • Proportion of subjects with HBeAg levels by response subcategory as detailed in the SAP during study treatment and follow-up.
• To evaluate efficacy in terms of HBsAg (in all subjects) or HBeAg (in HBeAg-positive subjects only) seroclearance and/or seroconversion.	• Proportion of subjects with HBsAg or HBeAg seroclearance (defined as HBsAg or HBeAg negativity, respectively, based on the assay used) during study treatment and follow-up. • Proportion of subjects with HBsAg or HBeAg seroconversion (defined as HBsAg or HBeAg negativity and anti-HBs or anti-HBe antibody positivity, respectively) during study treatment and follow-up.
• To evaluate the frequency of subjects with biochemical response.	• Proportion of subjects with ALT improvement and normalization during study treatment and follow-up.
• To evaluate the frequency of HBV virological breakthrough.	• Proportion of subjects with virological breakthrough during study treatment defined as confirmed on-treatment HBV DNA increase by >1 $\log_{10}$ from nadir level or 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.
• To evaluate the potential effect of JNJ-56136379 on the pharmacokinetics of NA when coadministered.	• Pharmacokinetics of NA when administered as monotherapy or when coadministered with JNJ-56136379.

Objectives	Endpoints
• To evaluate the pharmacokinetics of JNJ-56136379 when administered as monotherapy. • To evaluate the potential effect of NA on the pharmacokinetics of JNJ-56136379 when coadministered.	• Pharmacokinetics of JNJ-56136379 when administered as monotherapy or when coadministered with an NA.
• To assess changes in the HBV genome sequence.	• Emergence of treatment-associated mutations during study treatment and follow-up.
Exploratory	
• To explore changes in 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.
• To explore the relationship of pharmacokinetics with selected pharmacodynamic (PD) parameters of efficacy and safety.	• Relationship of various pharmacokinetic parameters with selected efficacy and safety endpoints.
• To explore efficacy in terms of changes in HBV RNA and hepatitis B core-related antigen (HBcrAg) levels.	• Changes from baseline in HBV RNA and HBcrAg levels during study treatment and follow-up.
• To explore the effect of viral and host baseline factors on efficacy and safety.	• Impact of viral and host baseline factors on different efficacy and safety parameters.
• To explore the effect of baseline amino acid substitutions in the HBV genome on efficacy.	• Impact of baseline HBV sequence variations on efficacy parameters.
• To explore the impact of HBV treatment on symptoms, functioning, and health-related quality of life (HRQoL) using patient-reported outcomes (PROs).	• Impact of HBV treatment on symptoms, functioning, and HRQoL using PROs, ie: – 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.
• To explore the potential effect of JNJ-56136379 on the pharmacokinetics of ethinyl estradiol (EE) when coadministered.	• Pharmacokinetics of EE when coadministered with JNJ-56136379.

The following objectives and endpoints are applicable to the treatment extension phase only.

Objectives	Endpoints
• To evaluate the proportion of subjects able to complete all treatment at Week 48.	• Proportion of subjects meeting the treatment completion criteria as outlined in Section 6.3.
• To evaluate the frequency of sustained off-treatment response.	• Proportion of subjects with sustained reduction/suppression and/or sero-clearance considering single and multiple markers such as HBsAg, HBeAg, HBV DNA and ALT levels at FU Week 12, 24 and 48.
• To evaluate the frequency of virologic and clinical relapse after EOT.	• Proportion of subjects with virologic relapse defined as confirmed post-treatment increases in HBV DNA >2,000 IU/mL after having met the treatment completion criteria. • Proportion of subjects with clinical relapse defined as confirmed post-treatment increases in HBV DNA >2,000 IU/mL after having met the treatment completion criteria, in association with confirmed ALT value >2 x ULN.
• To evaluate the proportion of subjects requiring NA re-treatment during follow-up.	• Proportion of subjects who meet the re-treatment criteria as outlined in Section 6.4.
• To evaluate the efficacy of NA re-treatment during follow-up.	• Proportion of subjects with decline in HBV DNA, ALT and/or HBsAg levels after re-start of NA treatment during follow-up.

2.2. Hypothesis

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

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a multicenter, interventional, randomized, partially-blind, placebo-controlled, two-part study to assess the efficacy, safety, and pharmacokinetics of treatment with two doses of JNJ-56136379 administered as monotherapy and in combination with NA (either ETV or TDF as per local practice) in HBeAg-positive and -negative CHB-infected subjects. Subjects who completed the initial 24 weeks of treatment with a virologic response by Week 20 (HBV DNA <200 IU/mL of the HBV DNA assay) and without experiencing any safety concerns precluding continued study drug treatment as determined by the investigator, will continue study drugs up to 48 weeks in a treatment extension phase.

The study will initially consist of 2 parts, Part A and Part B. For each part, a sample size of 110 subjects is targeted who will receive JNJ-56136379 at two dose levels as monotherapy or in combination with an NA. Additional parts may be added through a protocol amendment based on emerging data.

Each part will consist of 2 types of CHB-infected subject populations: (1) subjects who are currently not being treated for their CHB infection (including CHB treatment-naïve subjects) and (2) subjects virologically suppressed by current NA treatment (either ETV or TDF as per local practice).

Part A:

Approximately 70 subjects who are currently not being treated for their CHB infection will be randomized in a 3:1:3 ratio to receive one of the following treatments:

- Treatment Arm 1: JNJ-56136379 (N=30) (open-label)

  After full recruitment, this treatment arm was discontinued early per Protocol Amendment 4. All subjects were to stop further dosing with JNJ-5613379 75 mg, start treatment with NA, and enter the post-treatment follow-up phase (Schedule 1).
- Treatment Arm 2: Placebo + NA (ETV or TDF) (N=10)
- Treatment Arm 3: JNJ-56136379 + NA (ETV or TDF) (N=30)

At the same time, approximately 40 subjects who are virologically suppressed by current NA treatment will be randomized in a 1:3 ratio to receive one of the following treatments:

- Treatment Arm 4: Placebo + NA (ETV or TDF) (N=10)
- Treatment Arm 5: JNJ-56136379 + NA (ETV or TDF) (N=30)

Part B:

Part B (ie, Treatment Arms 6 to 10) will follow the same format as Part A, with a different dose of JNJ-56136379 (see Figure 1).

Randomization in each part will be stratified by:

- HBeAg status at screening (positive versus negative);
- HBsAg level at screening (≥10,000 versus <10,000 IU/mL for HBeAg-positive subjects currently not being treated and ≥1,000 versus <1,000 IU/mL for all other subjects).

The aim is to have approximately 40% HBeAg-positive subjects who are currently not being treated and 30% HBeAg-positive virologically suppressed subjects. To this end, enrollment of HBeAg-negative subjects may be capped at 60% in subjects who are currently not being treated and at 70% in virologically suppressed subjects.

A DRC will be established for this study (see Section 11.12) and will monitor safety and efficacy data in an unblinded manner on a regular basis throughout the study.

Part A will start first and will evaluate a 75-mg once-daily dose of JNJ-56136379. The dose to be administered in Part B will be 250 mg given once daily. This dose has been selected by the sponsor, in agreement with the DRC, based on all safety, PK, and antiviral activity data available following completion of the highest JNJ-56136379 dose group (who received 250 mg once

daily) in the Phase 1 study 56136379HPB1001 in treatment-naïve CHB-infected subjects treated for 28 days. (For a rationale on dose selection refer to the Study Design Rationale below.)

Each part of the study will consist of a screening phase (up to 8 weeks), a treatment phase (24 weeks or 48 weeks, depending on treatment response), and a post-treatment follow-up phase (24 weeks or 48 weeks, depending on treatment response). For an overview of the study design, see Figure 1.

All subjects are planned to be treated for at least 24 weeks. Following this initial treatment period, subjects who completed the 24-week treatment period with virologic response by Week 20 (HBV DNA <200 IU/mL of the HBV DNA assay) and without experiencing any safety concerns precluding continued study drug treatment as determined by the investigator, will continue study drugs up to 48 weeks in a treatment extension phase. 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.

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 (see Section 6.1), will receive JNJ-56136379 in combination with NA treatment from Week 24 to Week 48. In addition, if ≥1 subject in the JNJ-56136379 250 mg monotherapy (Treatment Arm 6) experiences virological breakthrough during the first 24 weeks of treatment, NA treatment will be added to JNJ-56136379 treatment as soon as possible for all remaining subjects (futility rule, see Section 6.2).

For subjects who are not eligible to participate in the treatment extension phase:

- Subjects will be considered to have completed the study treatment if they have completed 24 weeks of study drug administration, after which they will discontinue JNJ-56136379 or placebo treatment. NA treatment (either ETV or TDF as per local practice) should be started (in case of JNJ-56136379 monotherapy, ie, Treatment Arms 1 and 6) or continued (in case NA treatment was part of the assigned study treatment, ie, Treatment Arms 2 to 5 and 7 to 10) as per local treatment guidelines.
- Subjects will be considered to have completed the study if they have completed the assessments of the end of study visit (Follow-up [FU] Week 24 [Schedule 1]).
- For subjects who do not continue or start NA treatment at Week 24, an additional 24-week follow-up (as per local treatment guidelines) by their primary care physician, outside of the study, is recommended after study completion.

For subjects who continue treatment in the extension phase:

- Subjects will be considered to have completed the study treatment if they have completed 48 weeks of study drug administration, after which they will discontinue JNJ-56136379 or placebo treatment. At Week 48:

  - Subjects who meet all of the Individual Subject Treatment Completion Criteria (see Section 6.3) will complete all treatment. These subjects will be followed-up until 48 weeks after EOT (Schedule 2). If, during the 48-week follow-up, a subject meets one of the re-treatment criteria described in Section 6.4, NA treatment (ETV or TDF) should be re-started.
  - Subjects who do not meet the Individual Subject Treatment Completion Criteria should start (in case of JNJ-56136379 monotherapy, ie, Treatment Arms 1 and 6) or continue (in case NA treatment was part of the assigned study treatment, ie, Treatment Arms 2 to 5 and 7 to 10) NA treatment as per local treatment guidelines. These subjects will be followed-up until 24 weeks after the end of study treatment (Schedule 1).

- Subjects will be considered to have completed the study if they have completed the assessments of the end of study visit (FU Week 24 [Schedule 1] or FU Week 48 [Schedule 2]).
- For subjects who do not meet the Individual Subject Treatment Completion Criteria and do not start or continue 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 study completion.

The duration of individual participation will be up to approximately 56 weeks (subjects not eligible to continue treatment in the extension phase), up to 80 weeks (subjects continuing treatment in the extension phase but not meeting the treatment completion criteria), or up to 104 weeks (subjects meeting treatment completion criteria).

Efficacy will be evaluated through different measures (see Section 9.2).

Samples for HBV genome sequence will be taken at the time points indicated in the TIME AND EVENTS SCHEDULE (see Section 9.3). Sequencing of baseline samples will be performed by default if HBV DNA levels are within the ranges required for the sequencing assay. The sequencing of samples obtained 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.

Pharmacokinetic assessments during the study will be performed using a popPK model (see Section 9.4).

Pharmacokinetic/pharmacodynamics relations will be evaluated (see Section 9.5).

The study includes collection of blood samples for exploratory analysis of host blood biomarkers at the host mRNA, protein, and cell level (see Section 9.6).

An optional blood sample for pharmacogenomics (DNA) research can be taken and will only be collected from subjects who consent separately to this component of the study (see Section 9.7).

Patient-reported outcome instruments (EQ-5D-5L, HBQOL, MOS-CFS Cog-R, and SF-36v2) will be used to assess the impact of HBV treatment on subjects (see Section 9.8).

Safety and tolerability, including AEs, laboratory assessments, ECGs, physical examination, and vital signs will be assessed throughout the study from the time that the informed consent form (ICF) is signed until the completion of the last study-related activity (see Section 9.9).

Interim analyses may be performed as indicated in Section 11.11.

The TIME AND EVENTS SCHEDULE summarizes the frequency and timing of efficacy, safety, and pharmacokinetic assessments.

The study is considered completed with the last visit of the last subject participating in the study.

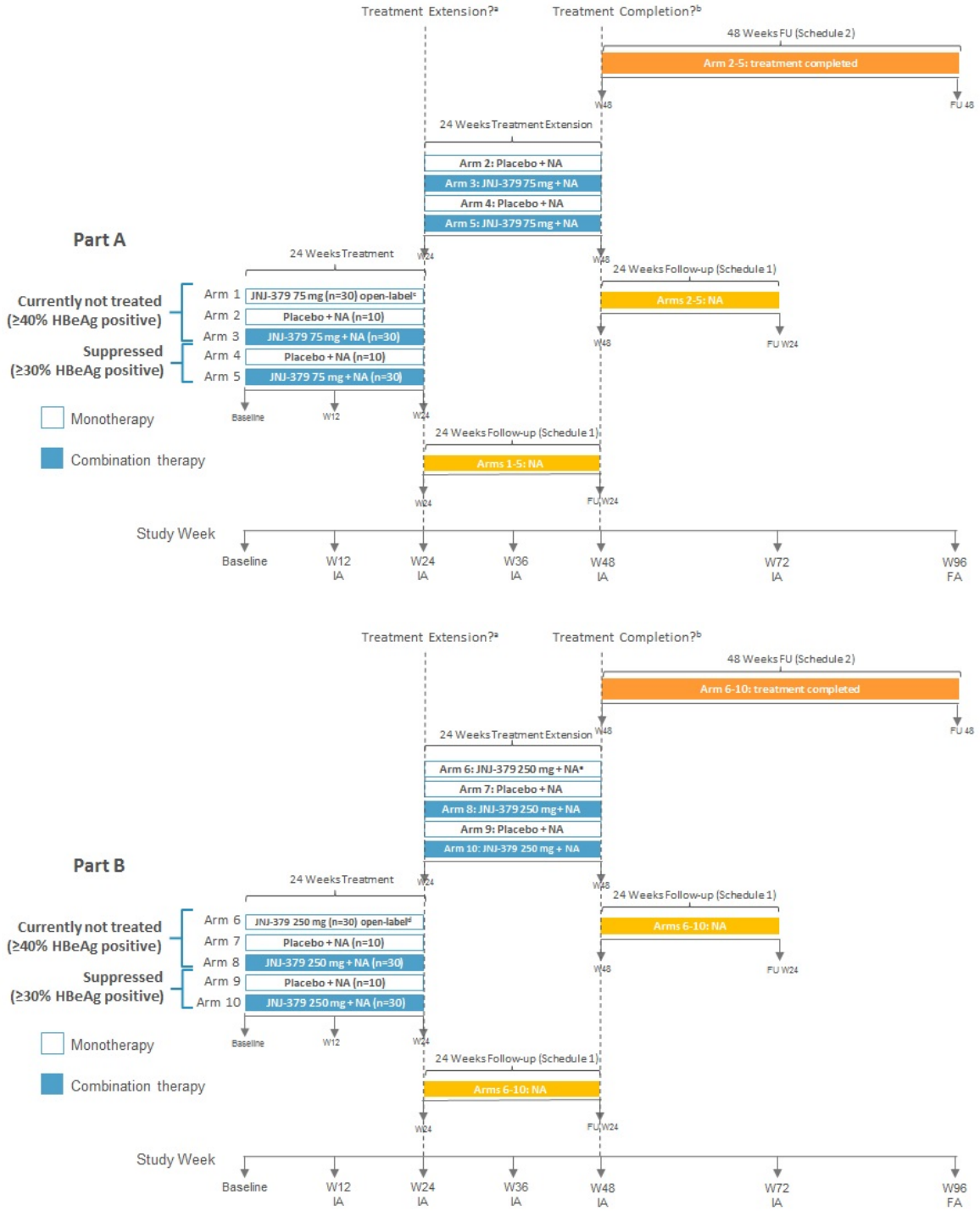
If a subject discontinues study treatment before the end of the 24-week treatment phase or, if applicable, the 24-week treatment extension phase (ie, Week 48 visit), follow-up assessments should be obtained until 24 weeks after EOT (Schedule 1) unless the subject withdraws consent. NA treatment (either 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 (Schedule 1), for subjects who do not continue or start NA treatment after early study treatment discontinuation.

If a subject withdraws before completing the study, the reason for withdrawal is to be documented in the electronic Case Report Form (eCRF) and in the source document. Subjects who withdraw consent will be offered an optional safety follow-up visit.

A liver biopsy substudy may be performed at selected study sites. Patients need to provide consent for the substudy by signing a separate ICF. Refusal to participate in or withdrawal of consent for the substudy does not affect participation in the main study. A liver biopsy will be performed at different time points. The substudy assessments will be described in a separate substudy protocol, which will only be submitted for approval by regulatory authorities (Health Authority/Institutional Review Board (IRB)/Independent Ethics Committee [IEC]) for the selected sites. Results of the liver biopsy substudy will be reported in a separate report.

A diagram of the study design is provided in Figure 1.

Figure 1: 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 <200 IU/mL by Week 20 and 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 (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 6.3) are met. For these subjects, follow-up assessments will be obtained until 48 weeks after EOT (Schedule 2). A subject should re-start NA treatment (ETV or TDF) during the 48 weeks of post-treatment follow-up (Schedule 2) if he/she meets one of the criteria described in Section 6.4. 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 (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 study completion.

[c] After full recruitment, the JNJ-56136379 treatment arm (Treatment Arm 1) was discontinued early per Protocol Amendment 4. All subjects were to stop further dosing with JNJ-5613379 75 mg, start treatment with NA, and enter the post-treatment follow-up phase (Schedule 1).

[d] Per Protocol Amendment 4, if ≥1 subject in the JNJ-56136379 250 mg monotherapy arm (Treatment Arm 6) experiences virological breakthrough during the first 24 weeks of treatment, NA treatment will be added to JNJ-56136379 treatment for all remaining subjects (futility rule, see Section 6.2).

[e] 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.

Study Design Rationale

Combination of JNJ-56136379 with an NA, compared to NA or JNJ-56136379 monotherapy, is postulated to intensify the virologic suppression by further blocking HBV replication at multiple steps leading to a reduction of the transcriptional active cccDNA pool and a concomitant reduction and/or seroclearance of viral antigens, potentially through hepatocyte turnover. In addition, the profound suppression of HBV replication may restore the anti-HBV immune response in a larger proportion of subjects which might also lead to increased HBsAg reduction and/or seroclearance. JNJ-56136379 will also be administered as monotherapy in the current study to better understand the safety and efficacy of JNJ-56136379 treatment with a duration of >4 weeks and to compare efficacy, safety, and pharmacokinetics between JNJ-56136379 monotherapy and JNJ-56136379 in combination with ETV or TDF.

Two different study populations will be included, allowing the exploration of potential differences in response: (1) subjects who are currently not being treated for their CHB infection, including CHB treatment-naïve subjects and (2) subjects who are virologically suppressed by their current NA treatment (ETV or TDF as per local practice; branded product or a locally approved generic alternative).

The treatment duration that will be explored in this study will allow to more extensively characterize the antiviral activity in terms of HBV DNA reduction/suppression and to assess changes in HBeAg and HBsAg levels. Based on the mode of action of JNJ-56136379, it is expected that continued complete suppression of virus production and new cell infection over many months is required to achieve reduction of the transcriptional active cccDNA pool, which is considered a prerequisite for HBsAg reduction and/or seroclearance. Therefore, subjects who have completed 24 weeks of treatment, who have HBV DNA levels <200 IU/mL by Week 20 and who have no safety concerns that preclude continued treatment as determined by the

investigator will continue their assigned study treatment for another 24 weeks (until Week 48) in a treatment extension phase. Furthermore, a 48-week treatment duration will also allow to evaluate the safety of JNJ-56136379 when administered as monotherapy or in combination with an NA (either ETV or TDF as per local practice) over this time period.

For subjects who continue study drugs until Week 48, treatment completion criteria (Section 6.3) are included to explore the possibility of finite treatment. The treatment completion criteria which take ALT, HBV DNA, HBeAg and HBsAg levels into consideration, have been selected to ensure that only subjects with a chance of sustained off-treatment response are allowed to complete all HBV treatment. Multiple studies have shown that patients with low HBsAg levels and/or with on-treatment reduction in HBsAg have an improved likelihood of off-treatment response. Thus, inclusion of the HBsAg parameters in the treatment completion criteria should ensure that patients have experienced a treatment response in terms of HBsAg reduction and reached a favorable HBsAg level. From a safety perspective, data from the 9 months toxicity data in dogs support a treatment duration of 48 weeks in humans. (Section 1.1).

Two doses of JNJ-56136379 will be evaluated in this Phase 2a study. Based on all available data from the Phase 1 study 56136379HPB1001 in treatment-naïve CHB-infected subjects treated for 28 days, 75 mg was selected as the JNJ-56136379 low dose. The mean HBV DNA reductions observed with 4 weeks of 75 mg monotherapy (2.89 $\log_{10}$ IU/mL) were similar to the HBV DNA declines observed with ETV and TDF suggesting similar potency to NAs at therapeutic doses with the low 75 mg dose.

The JNJ-56136379 dose to be administered in Part B will be 250 mg given once daily. This dose has been selected by the sponsor, in agreement with the DRC, based on all safety, PK, and antiviral activity data available following completion of the highest JNJ-56136379 dose group (who received 250 mg once daily) in the Phase 1 study 56136379HPB1001 in treatment-naïve CHB-infected subjects treated for 28 days. No SAEs or AEs leading to treatment discontinuation were reported for CHB-infected subjects who received 250 mg JNJ-56136379 once daily for 28 days, and all AEs were grade 1. In addition, no treatment-emergent laboratory abnormalities of >grade 2, ECG or vital signs abnormalities of ≥grade 2 were reported for these subjects, and no abnormalities were reported as AEs. The dose of 250 mg once daily has been selected to efficiently inhibit HBV DNA replication across a broad spectrum of patients and viral variants (see Section 1.1 [Clinical Studies; Antiviral Activity]). In addition, 250 mg is expected to increase the potential to trigger the secondary mode of action (MoA) (ie, inhibition of de novo cccDNA formation) which requires about 10-fold higher concentrations of JNJ-56136379 than the primary MoA of inhibition, ie, interfering with capsid assembly (EC_{90} primary MoA=376 nM and EC_{90} secondary MoA=4019 nM).

The observed exposure on Day 28 in CHB-infected subjects at 250 mg JNJ-56136379 administered once daily was 265,384 ng.h/mL (AUC_{τ}) with a C_{max} of 13,798 ng/mL. This exposure was proportional to the exposure at 25, 75 and 150 mg once daily, and well in line with popPK predictions (mean popPK predicted AUC_{τ} was 245,098 ng/h/mL in a non-Asian population and 294,118 ng.h/mL in an Asian population). The exposure at 250 mg is lower than the ceiling of exposure defined by the preclinical findings (AUC_{τ} of 301,558 ng.h/mL and a C_{max}

of 22,748 ng/mL, see footnote d to Table 2 and Table 3). Therefore, the sponsor considers a dose of up to 250 mg once daily in study 56136379HPB2001 justified.

A liver biopsy substudy may be performed at selected study sites. A liver biopsy will be performed at different time points. The substudy assessments will be described in a separate substudy protocol, which will only be submitted for approval by regulatory authorities (Health Authority/IRB/IEC) for the selected sites and results of the liver biopsy substudy will be reported in a separate report.

Blinding, Control, Study Phase/Periods, Treatment Groups

For the combination with an NA, a placebo control for JNJ-56136379 will be used to establish the frequency and magnitude of changes in virologic and clinical endpoints that may occur in the absence of active treatment. The use of a placebo control will allow for any AEs or laboratory abnormalities observed during the course of the study to be evaluated properly, ie, to differentiate between events potentially related to the use of JNJ-56136379 versus those related to the underlying disease.

Randomization within each study part will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across intervention treatment groups, and to enhance the validity of statistical comparisons across intervention groups. If Part B is opened while Part A is still enrolling, randomization will occur across Parts A and B during that specific period of overlap. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints. In Treatment Arms 1 and 6, JNJ-56136379 is administered as monotherapy in an unblinded (open-label) fashion. For ethical reasons there is no placebo control for the JNJ-56136379 monotherapy as enrolled subjects are treatment eligible and should not be deprived of treatment for 24 or 48 weeks.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 56 days before administration of the study intervention.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. Subjects must be 18 (or older legal age of consent as per local requirements) to 70 years

of age, inclusive.

2. Subjects must have a body mass index (weight in kg divided by the square of height in meters) of 18.0 to 35.0 kg/m^2, extremes included.

3. Criterion modified per Amendment 3

   3.1. Subjects must have CHB infection documented by:

   - Serum HBsAg-positive at screening and serum HBsAg- or HBV DNA-positive at least 6 months prior to screening;
   - Serum immunoglobulin M (IgM) anti-HBc antibody negative at screening.

4. In subjects currently not being treated (Treatment Arms 1-2-3 and 6-7-8):

   a. Subjects must not be receiving any CHB treatment at screening, ie,
      - Have never received treatment with HBV antiviral medicines, including NAs or IFN products, OR
      - Have not been on treatment with HBV antiviral medicines, including NAs or IFN products within 6 months prior to baseline (first intake of study drugs), AND
   b. Subjects must be HBeAg-positive and have HBV DNA ≥20,000 IU/mL, OR be HBeAg-negative and have HBV DNA ≥2,000 IU /mL at screening, AND
   c. Subjects must have HBsAg >250 IU/mL at screening, AND
   d. Subjects must have ALT > upper limit of normal (ULN) and ≤5 x ULN at screening, determined in the central laboratory.

   Note: If subjects were treated with investigational anti-HBV agents more than 6 months before screening, the sponsor should be contacted to discuss the case. Subjects who have received treatment with a CAM for more than 4 weeks any time prior to screening are excluded.

5. Criterion modified per Amendment 3

   5.1. In virologically suppressed subjects (Treatment Arms 4-5 and 9-10):

   a. Subjects must be virologically suppressed by current NA treatment (ETV or TDF) as defined by HBV DNA <60 IU/mL at screening and at least 6 months prior to screening, AND
   b. Subjects must be on the same NA treatment (ETV or TDF) and the same dose for ≥12 months prior to screening, AND
   c. Subjects must have HBsAg >250 IU/mL at screening, AND
   d. Subjects must have ALT ≤2x ULN at screening.

   Note: If subjects were treated with investigational anti-HBV agents more than

6 months before screening, the sponsor should be contacted to discuss the case. Subjects who have received treatment with a CAM for more than 4 weeks any time prior to screening are excluded.

Note: The current NA treatment can either be a branded product or a locally approved generic alternative (including different salt forms [eg, tenofovir maleate or succinate]). During the study, subjects will receive branded ETV (Baraclude®) or TDF (Viread®) treatment, as applicable.

6. Subjects must have:

   a. A liver biopsy result classified as Metavir F0-F2 within 1 year prior to screening or at the time of screening, OR

   b. FibroScan™ liver stiffness measurement <8.0 kPa within 6 months prior to screening or at the time of screening.

Note: Conventional imaging procedures (eg, conventional liver ultrasound, computed tomography [CT] or magnetic resonance imaging [MRI]) and serum marker panels are not allowed to rule out severe fibrosis or cirrhosis.

7. Female subjects of childbearing potential must have a negative highly sensitive serum pregnancy test (β-human chorionic gonadotropin) at screening.

8. Female subjects must be (as defined in Attachment 1)

   a. Not of childbearing potential

   b. Of childbearing potential and

      - Practicing a highly effective, preferably user-independent method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study treatment and until 90 days after last dose of JNJ-56136379. Examples of highly effective methods of contraception are provided in Attachment 1.

        Note: Female subjects of childbearing potential who are on a stable treatment regimen with hormonal contraceptives (ie, same dose and not starting or stopping hormonal contraceptive use) for ≥3 months prior to screening should continue the same dose regimen until 12 weeks after EOT. Ethinylestradiol-containing contraceptives are only allowed if the ethinylestradiol content is ≤20 µg. For female subjects of childbearing potential who will start a hormonal contraceptive treatment during the study, ethinylestradiol-containing contraceptives are not allowed. Please refer to Section 8.

9. A female subject must agree not to donate eggs (ova, oocytes) during the study until at least 90 days after the last dose of JNJ-56136379.

10. A male subject must agree to wear a condom when engaging in any activity that allows for passage of ejaculate to another person during the study until at least 90 days after the

last dose of JNJ-56136379.

11. A male subject must agree not to donate sperm during the study and for at least 90 days after receiving the last dose of JNJ-56136379.

12. Subject must sign an ICF indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

13. Subject must sign a separate ICF if he or she agrees to provide an optional DNA sample for research. Refusal to give consent for the optional DNA research sample does not exclude a subject from participation in the study.

14. In the investigator's opinion, the subject must be able to understand and comply with protocol requirements, instructions, and lifestyle restrictions (Section 4.3) and be likely to complete the study as planned.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1. Subjects who test positive for anti-HBs antibodies.

2. Criterion modified per Amendment 3

   2.1. Subjects with current hepatitis A virus infection (confirmed by hepatitis A antibody IgM), HDV infection (confirmed by HDV antibody), hepatitis E virus infection (confirmed by hepatitis E antibody IgM), or HIV-1 or HIV-2 infection (confirmed by antibodies) at screening; subjects with a history of or current HCV infection (confirmed by HCV antibody). Evidence of other active infection (bacterial, viral, fungal, including acute tuberculosis) deemed clinically relevant by the investigator that would interfere with study conduct or its interpretation will also lead to exclusion.

3. Subjects with any evidence of hepatic decompensation at any time point prior to or at the time of screening:

   a. Direct bilirubin >1.2x ULN, or

   b. International normalized ratio (INR) >1.5x ULN, or

   c. Serum albumin < lower limit of normal (LLN), or

   d. Documented history or current evidence of variceal bleeding, ascites, or hepatic encephalopathy.

4. Subjects with any evidence of liver disease of non-HBV etiology. This includes but is not limited to hepatitis virus infections mentioned in exclusion criterion 2, drug- or alcohol-related liver disease, autoimmune hepatitis, hemochromatosis, Wilson's

disease, Gilbert's syndrome, α-1 antitrypsin deficiency, primary biliary cirrhosis, primary sclerosing cholangitis, or any other non-HBV liver disease considered clinically significant by the investigator.

5. Subjects who have signs of 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, CT or MRI).

6 Criterion modified per Amendment 2

6.1. Subjects with one or more of the following laboratory abnormalities at screening:

a. Any laboratory abnormality > grade 1 (as defined by the Division of AIDS [DAIDS] Toxicity Grading Scale), with the exception of ALT/AST, considered to be clinically significant by the investigator at screening.

b. Alpha-fetoprotein outside the normal range.

7. Subjects with abnormal sinus rhythm (heart rate <50 or >100 beats per minute [bpm]); QT interval corrected for heart rate according to Fridericia (QTcF) >450 ms; QRS interval ≥120 ms; PR interval >200 ms; abnormal clinically significant conduction including bundle branch block; or any other clinically significant abnormalities on a 12-lead ECG at screening.

Note: Retesting of an abnormal ECG that may lead to exclusion will be allowed once without prior asking approval from the sponsor. Retesting will take place during an unscheduled visit in the screening phase. Subjects with an ECG without clinically significant abnormalities at retest may be included.

8. Subjects with a history of cardiac arrhythmia (eg, extrasystoli, tachycardia at rest), history of risk factors for Torsades de Pointes syndrome (eg, hypokalemia, family history of long QT syndrome) or history or other clinical evidence of significant or unstable cardiac disease (eg, angina, congestive heart failure, myocardial infarction, diastolic dysfunction, significant arrhythmia, coronary heart disease, and/or clinically significant ECG abnormalities [see exclusion criterion 7]), moderate to severe valvular disease, or uncontrolled hypertension at screening.

9. Subjects with a history of portal hypertension, especially any endoscopic signs of portal hypertension such as esophageal varices.

10 Criterion modified per Amendment 2

10.1 Subjects with any current or previous illness for which, in the opinion of the investigator and/or sponsor, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments. This may include but is not limited to renal dysfunction (eGFR <60 mL/min/1.73m^2 by MDRD equation), significant cardiac, vascular, pulmonary (eg, chronic obstructive pulmonary disease), gastrointestinal (eg, significant diarrhea, gastric stasis, or constipation that in the

investigator's opinion could influence drug absorption or bioavailability), endocrine (eg, diabetes mellitus, thyroid disease), neurologic, hematologic, rheumatologic, psychiatric, neoplastic, or metabolic disturbances. Any condition possibly affecting drug absorption (eg, gastrectomy or other significant gastrointestinal tract surgery, such as gastroenterostomy, small bowel resection, or active enterostomy) will also lead to exclusion.

11 Criterion modified per Amendment 2

11.1 Subjects with a current or history of confirmed skin disease requiring intermittent or chronic treatment such as, but not limited to, dermatitis, eczema, drug rash, psoriasis, food allergy, and urticaria.

12. Subjects with known allergies, hypersensitivity, or intolerance to JNJ-56136379 or its excipients (refer to the IB[15]).

13. Subjects with contraindications to the use of ETV or TDF per local prescribing information.[1,2,31,33]

14. Subjects who have taken any disallowed therapies as noted in Section 8 before the planned first dose of study drug.

15. Subjects having received an investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 6 months, or having received a biological product within 6 months or 5 half-lives (whichever is longer) before the planned first dose of study drugs, or currently enrolled in a non-observational clinical study with an investigational product.

16. Female subjects who are pregnant, breastfeeding, or planning to become pregnant while on JNJ-56136379 treatment or within 90 days after the last dose of JNJ-56136379 (or longer, if dictated by local regulation).

17. Male subjects who plan to father a child while on JNJ-56136379 treatment or within 90 days after the last dose of JNJ-56136379.

18. Subjects who had major surgery (requiring general anesthesia) within 12 weeks prior to screening, or will not have fully recovered from surgery, or have surgery planned during study treatment, or within 12 weeks after the last dose of study drug.

Note: Subjects with planned surgical procedures to be conducted under local anesthesia may participate.

19. Vulnerable subjects (eg, incarcerated individuals).

20. Subjects who are employees of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

21. Subjects who have received an organ transplant.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. Retesting to assess eligibility will be allowed once, using an unscheduled visit during the screening period. 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 intervention is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Refer to Section 8 for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Subjects will be randomly assigned to one of the treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by HBeAg status at screening (positive versus negative) and HBsAg level at screening (≥10,000 versus <10,000 IU/mL for HBeAg-positive subjects currently not being treated and ≥1,000 versus <1,000 IU/mL for all other subjects). The aim is to have approximately 40% HBeAg-positive subjects who are currently not being treated and 30% HBeAg-positive virologically suppressed subjects. To this end, enrollment of HBeAg-negative subjects may be capped at 60% in subjects who are currently not being treated and at 70% in virologically suppressed subjects. The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

Blinding

Since the JNJ-56136379 monotherapy arms (Treatment Arms 1 and 6) are not blinded, this is a partially blinded study.

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, if an interim analysis is specified, the randomization codes and, if required, the translation of randomization codes into intervention and control groups will be disclosed to those authorized (ie, the DRC) and only for those subjects included in the interim analysis. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment by contacting the IWRS. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented in the appropriate section of the eCRF. The documentation received from the IWRS indicating the code break is filed in the Trial Master File.

6. DOSAGE AND ADMINISTRATION

The subjects will receive the treatments as described in Table 4. Study drugs (JNJ-56136379/NA/placebo) will be administered orally.

JNJ-56136379 will be provided as 25-mg and/or 100-mg tablets and placebo as matching tablets. Subjects should be instructed to take JNJ-56136379/placebo in the morning at approximately the same time each day, together with breakfast. The tablets should be swallowed as a whole. At each study visit, the study drug should be taken on site under the supervision of the study staff. The time of study drug intake should be recorded in the eCRF.

A subject diary will be provided to the subjects undergoing semi-rich pharmacokinetic sampling and 24-hour urine sampling (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. To ensure compliance, the investigator or study-site personnel will review the recorded data in the subject's diary.

Subjects who are already being treated with ETV or TDF at screening, will continue NA treatment which will be provided through this study. Subjects will receive Baraclude® (ETV) or Viread® (TDF) during the study, as applicable. Subjects will be switched to these branded NA treatments for the course of the study in case they are on another originator branded or a generic ETV or TDF treatment, respectively, at screening.

For subjects who are not receiving any CHB treatment at screening, the choice of NA (ETV or TDF) will be at the investigator's discretion, as per local practice. However, subjects with any NA treatment experience prior to screening, should be treated with TDF. In case the investigator's preference is to start ETV treatment in subjects with prior ETV experience without evidence of resistance, the sponsor should be contacted to agree on the NA to be used in the study.

NA (ETV or TDF) will be taken as per the package insert (Baraclude® and Viread®, respectively). In the event of decline in renal function, dosing interval for ETV or TDF may be adjusted as per the package insert.

Table 4: Treatment Overview

Treatment	Dosing Regimen	Formulation
Part A		
Subjects currently not being treated:		
Arm 1[e]	75 mg JNJ-56136379 once daily (open-label)	3 x 25-mg tablets of JNJ-56136379[a]
Arm 2	Matching placebo + NA (0.5 mg ETV or 300 mg TDF) once daily	3 tablets of matching placebo + 1 tablet of ETV[b] or TDF[c]
Arm 3	75 mg JNJ-56136379 + NA (0.5 mg ETV or 300 mg TDF) once daily	3 x 25-mg tablets of JNJ-56136379 + 1 tablet of ETV or TDF
Virologically suppressed subjects:		
Arm 4	Matching placebo + NA (0.5 mg ETV or 300 mg TDF) once daily	3 tablets of matching placebo + 1 tablet of ETV or TDF
Arm 5	75 mg JNJ-56136379 + NA (0.5 mg ETV or 300 mg TDF) once daily	3 x 25-mg tablets of JNJ-56136379 + 1 tablet of ETV or TDF
Part B		
Subjects currently not being treated:		
Arm 6	250 mg JNJ-56136379 [d] once daily (open-label) from Day 1 to Week 24	2 x 100-mg and 2 x 25-mg tablet(s) of JNJ-56136379from Day 1 to Week 24
	250 mg JNJ-56136379 [d] + NA once daily (open-label) from Week 24 to Week 48	2 x 100-mg and 2 x 25-mg tablet(s) of JNJ-56136379 + 1 tablet of ETV or TDF from Week 24 to Week 48
Arm 7	Matching placebo + NA (0.5 mg ETV or 300 mg TDF) once daily	Tablet(s) of matching placebo + 1 tablet of ETV or TDF
Arm 8	250 mg JNJ-56136379 [d] + NA (0.5 mg ETV or 300 mg TDF) once daily	2 x 100-mg and 2 x 25-mg tablet(s) of JNJ-56136379 + 1 tablet of ETV or TDF
Virologically suppressed subjects:		
Arm 9	Matching placebo + NA (0.5 mg ETV or 300 mg TDF) once daily	Tablet(s) of matching placebo + 1 tablet of ETV or TDF
Arm 10	250 mg JNJ-56136379 [d] + NA (0.5 mg ETV or 300 mg TDF) once daily	2 x 100-mg and 2 x 25-mg tablet(s) of JNJ-56136379 + 1 tablet of ETV or TDF

[a] JNJ-56136379 is formulated as 25-mg (G008) and 100-mg (G009) tablets (matching placebo: G010 and G011, respectively).
[b] ETV (Baraclude®)[1,2] is formulated as 0.5-mg film-coated tablets (commercially available), and is to be taken on an empty stomach. Lamivudine-refractory subjects should be treated with TDF instead.
[c] TDF (Viread®)[32,33] is formulated as 300-mg film-coated tablets (commercially available), and is to be taken with food.
[d] The dose for Part B has been selected based on all safety, PK, and antiviral activity data available upon completion of the highest JNJ-56136379 dose group (who received 250 mg once daily) in the Phase 1 study 56136379HPB1001 in treatment-naïve CHB-infected subjects treated for 28 days.
[e] Treatment Arm 1 was discontinued early per Protocol Amendment 4. All subjects were to stop further dosing with JNJ-5613379 75 mg, start treatment with NA, and enter post-treatment follow-up phase (Schedule 1).

6.1. Treatment Duration

All subjects will be treated for at least 24 weeks, unless they discontinue treatment early. Treatment will be extended for another 24 weeks in a treatment extension phase for subjects who meet the following criteria:

- Subject completed 24 weeks of treatment
- Subject had HBV DNA levels <200 IU/mL by Week 20 of the initial 24-week treatment period
- During the initial 24 weeks of treatment the subject did not have any safety concerns that would preclude continued treatment, as determined by the investigator
- For subjects who were enrolled in the study before the Amendment 2 came into effect: subject needs to consent for participation in the extension phase.

Subjects in the JNJ-56136379 250 mg monotherapy arm (Treatment Arm 6) who meet the treatment extension criteria, will receive JNJ-56136379 in combination with NA treatment from Week 24 to Week 48.

Subjects not meeting the above criteria will be followed-up until 24 weeks after EOT. These subjects should continue or, in case of JNJ-56136379 monotherapy, start NA treatment at the end of the 24-week study treatment as per local treatment guidelines.

6.2. Futility Rule

Per Protocol Amendment 4, as a precautionary measure to safeguard the subjects, a futility rule for the JNJ-56136379 250 mg monotherapy arm (Treatment Arm 6) has been installed: if ≥1 subject in the 250 mg monotherapy arm experiences virological breakthrough during the first 24 weeks of treatment, NA treatment will be added to JNJ-56136379 treatment as soon as possible for all remaining subjects. These subjects will continue the visit schedule as planned. Subjects with virological breakthrough will discontinue JNJ-56136379 treatment (see Section 10.2) and should start NA treatment.

6.3. Individual Subject Treatment Completion Criteria

After completion of 48 weeks of treatment with JNJ-56136379/placebo (with or without NA) within this study, a subject will complete all treatment if all of the following criteria are met at Week 40 and are confirmed at Week 44:

- The subject has:
  - normal ALT levels, OR
  - elevated ALT levels which are in the opinion of the investigator not attributed to chronic HBV activity.
- The subject has HBV DNA <LLOQ.
- The subject is HBeAg negative.
- The subject has HBsAg ≤500 IU/mL.
- The subject has ≥1 $\log_{10}$ IU/mL decline in HBsAg from baseline.

For these subjects, follow-up assessments will be obtained until 48 weeks after EOT (Schedule 2).

Subjects who do not meet above criteria after 44 weeks of study drug treatment, should continue or, in case of JNJ-56136379 monotherapy, start NA treatment at the end of the 48-week study treatment as per local treatment guidelines. For these subjects, follow-up assessments will be obtained until 24 weeks after EOT (Schedule 1).

6.4. Re-treatment Criteria During Follow-up

Subjects who met the Subject Treatment Completion Criteria in Section 6.3 should start either ETV or TDF treatment during the post-treatment follow-up, according to local standard of care, in the following cases:

- Confirmed post-treatment increases in HBV DNA >2,000 IU/mL and ALT >2 x ULN, OR
- Confirmed post-treatment increases in HBV DNA >20,000 IU/mL, OR
- In the event of worsening signs of liver function during follow-up assessments.

  Note: It is recommended that the original HBV DNA and/or ALT test and the corresponding confirmation test used to decide on re-treatment are at least 4 weeks apart. Confirmation tests and initiation of re-treatment within 4 weeks are at the discretion of the investigator.

  Note: The investigator should contact the sponsor in case re-treatment will be initiated.

7. TREATMENT COMPLIANCE

All study drug intakes at the study site must be witnessed by the investigator or by study-site personnel dedicated to the study.

For intake of study drugs at home, the subjects in the pharmacokinetic subgroup should report the times of intake of study drug for 1 week prior to their Week 12 and Week 24 visits in a subject diary which will be provided for this purpose.

The subjects will be requested to bring unused study drugs and empty packaging to the study site at each visit.

Every effort should be made to have the subject take the study drugs as indicated in the TIME AND EVENTS SCHEDULE, especially in subjects who have previously been treated. In case a dose of JNJ-56136379 was missed, the dose should be given as soon as possible but within 12 hours after the scheduled time. Otherwise, the dose should be skipped and the next dose should be given at the next scheduled time point per the initial dosing schedule. If more than 3 subsequent doses are missed, the investigator should be contacted and the case should be discussed with the sponsor. If a dose of NA is missed, the subject should follow the guidelines in the package insert.

If a subject's drug intake is not according to the protocol, the investigator will take the necessary measures to ensure future adherence to the protocol.

8. CONCOMITANT THERAPY

Prestudy therapies (prescription or over-the-counter medications, including vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) administered within 30 days before the start of screening and different from the study treatment must be recorded in the eCRF at screening. The subject's last anti-HBV treatment prior to screening must also be recorded if applicable. Recorded information will include a description of the type of drug, treatment period, dosing regimen, route of administration, and its indication.

An overview of disallowed concomitant medication is presented in Table 5. An overview of concomitant medication that should be used with caution is described in Table 6.

Potential subjects should not stop any chronic, prescribed medication being taken at the direction of a physician, without obtaining agreement from that physician. Subjects on disallowed medication (see Table 5) are excluded from the study.

Stable hormone replacement therapy (HRT) in postmenopausal women (ie, same dose and not starting or stopping HRT for 2 weeks prior to baseline until 12 weeks after EOT) is allowed. The use of HRT should be recorded in the Concomitant Therapy Section of the eCRF. Applicable procedures and treatment guidance based on package inserts should be respected.

Based on results from drug-drug interaction study 56136379HPB1004 investigating the potential effect of coadministration of JNJ-56136379 with oral contraceptives, it is not anticipated that the efficacy of oral contraceptives will be impacted during coadministration with JNJ-56136379 since the exposure of a progestin sensitive to CYP3A4 induction was not significantly affected by coadministration of JNJ-56136379. In contrast, it is anticipated that coadministration with ethinylestradiol-containing contraceptives will result in an increased exposure to ethinylestradiol. In the current study, female subjects of childbearing potential who are on a stable treatment regimen with hormonal contraceptives (ie, same dose and not starting or stopping hormonal contraceptive use) for ≥3 months prior to screening, should continue the same dose regimen until 12 weeks after EOT. Ethinylestradiol-containing contraceptives are only allowed if the ethinylestradiol content is ≤20 µg. For female subjects of childbearing potential who will start a hormonal contraceptive treatment during the study, ethinylestradiol-containing contraceptives are not allowed, given the observed increase in ethinylestradiol in study 56136379HPB1004.

Coadministration of JNJ-56136379 170 mg qd with oral midazolam as a CYP3A4 probe showed a reduction of 41.7% in C_{max} and 53.9% in AUC (study 56136379HPB1004), implying that JNJ-56136379 may induce the metabolism of CYP3A4 sensitive substrates. Therefore, the therapeutic efficacy of coadministered CYP3A4 sensitive substrates will be monitored throughout the study and a dose adjustment will be established when deemed necessary (Table 6).

Table 5: Disallowed Medication

Disallowed from screening until the end of follow-up:

- For virologically suppressed subjects:
  - Any anti-HBV drug (including vaccines) (other than the NA [ETV or TDF] taken as part of the study treatment)
    Note: Subjects must not have received treatment with a CAM for more than 4 weeks any time prior to screening.
    Note: Prior hepatic treatment with herbal or nutritional products is allowed but should be stopped at screening.
- For all subjects:
  - Biotin at a daily dose of >30 µg, either taken alone or as part of a multivitamin formulation.[31]

Disallowed from 3 months prior to screening until 12 weeks after end of JNJ-56136379 treatment:

- Ethinylestradiol-containing contraceptives with an ethinylestradiol content >20 µg

Disallowed from 6 months prior to screening until the end of follow-up:

- For subjects currently not being treated:
  - Any anti-HBV drug (including vaccines) (other than the NA [ETV or TDF] taken as part of the study treatment)
    Note: Subjects must not have received treatment with a CAM for more than 4 weeks any time prior to screening.
    Note: Prior hepatic treatment with herbal or nutritional products is allowed but should be stopped at screening.
- Any systemically (eg, intravenously, intramuscularly, orally, subcutaneously) administered medication that directly or indirectly interferes with immune responses (eg, cyclosporine, interleukins, IFN, corticosteroids in immunosuppressive dose).
- Any investigational agent (small molecules), investigational vaccine, invasive investigational medical device, or investigational biological product.

Disallowed from 30 days prior to screening until 12 weeks after end of JNJ-56136379 treatment:

- Over-the-counter products, herbal medications, dietary supplements including products containing *Hypericum perforatum* (St. John's wort) other than those for the treatment of hepatitis B
- Moderate and potent inhibitors of CYP3A4 (eg, azole antifungals, macrolide antibiotics, diltiazem, verapamil)
- Moderate and potent inducers of CYP3A4 (anti-epileptics: eg, carbamazepine, oxcarbazapine, [fos]phenytoin, and phenobarbital; anti-tuberculosis drugs: rifabutin, rifampin, and rifapentine)

Disallowed from 30 days prior to screening until the end of follow-up:

- Any medication that reduces renal function or competes for active tubular secretion from screening onwards (eg, cimetidine, probenecid, quinidine)
- Inhibitors of P-glycoprotein transporter (eg, amiodarone, azithromycin clarithromycin, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, quinidine, ritonavir, verapamil)

Note: The list of disallowed concomitant medication is not exhaustive; for products falling in one of the categories and not mentioned by name, the sponsor should be contacted to determine whether the product can be allowed.
Note: The use of vitamins is allowed (on the condition that the restrictions on biotin intake are taken into account; see above) and will be documented in the eCRF.

Table 6: Concomitant Medication to be Used With Caution

The following concomitant medication is allowed, but should be used with caution with monitoring of AEs and desired efficacy. When started during JNJ-56136379 treatment, the lowest possible dose should be used. • Analgesics: ergaloid mesylates, ergotamine tartrate, dihydroergotamine and methylergonovine. • Calcium channel blockers: eg, amlodipine, bepridil, nicardipine, nifedipine, and nisoldipine. • Lipid-lowering drugs: eg, atorvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin. • Phosphodiesterase 5 inhibitors: sildenafil, vardenafil, tadalafil. • Sedatives/anxiolytics: midazolam, triazolam. • Acid-reducing agents: antacids (eg, aluminium and magnesium hydroxide) (recommended to separate antacid and study drug administration by 4 hours). • Ethinylestradiol-containing contraceptives (only allowed if on a stable treatment regimen for ≥3 months prior to screening and the ethinylestradiol content is ≤20 µg. Starting treatment with ethinylestradiol-containing contraceptives during the study is not allowed) or HRT.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Concomitant Medication and Special Conditions

- In case of cutaneous reaction/rash and/or an allergic reaction, the use of cetirizine, levocetirizine, topical corticosteroids, or antipruritic agents in the recommended dosing scheme is permitted.
- In case of nausea, the use of antiemetics is permitted.
- In case of diarrhea, the use of antidiarrheals is permitted.

In case any of these medications are used as concomitant therapy, the dose and dose regimen must be recorded in the Concomitant Therapy Section of the eCRF.

For any concomitant therapy given as treatment for a new condition or a worsening of an existing condition, the condition must be documented in the AE Section of the eCRF. Applicable procedures and treatment guidance based on package inserts should be respected.

The prescribing information for ETV and TDF should be consulted for any additional prohibited medication.[1,2,32,33]

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The TIME AND EVENTS SCHEDULE summarizes the frequency and timing of efficacy, pharmacokinetic, pharmacogenomic, viral genome sequencing, biomarker and safety measurements applicable to this study.

If multiple assessments are scheduled for the same time point, it is recommended that procedures be performed in the following sequence: ECG, vital signs, clinical parameters, blood sampling,

and physical examination. Actual dates and times of assessments will be recorded in the source documentation and eCRF.

Blood collections for pharmacokinetic assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified time points if needed.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

The maximum amount of blood drawn from each subject in this study will not exceed 500 mL of blood each 90-day interval throughout the study, which is within the limits of standard blood donation.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1.2. Screening Phase

The procedures specified in the TIME AND EVENTS SCHEDULE will only be performed after written informed consent has been obtained.

At the screening visit, after signing of the ICF(s), concomitant disease and concomitant medication will be recorded. The subject's characteristics, demographic data, and medical and surgical history will be recorded. The overall eligibility of the subject to participate in the study will be assessed and documented in the eCRF.

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.

At the screening visit, a hepatitis A, B, C, D, and E virus test, and HIV-1 and -2 test will be performed. A serum pregnancy test will be performed for women of childbearing potential, and a follicle-stimulating hormone (FSH) test will be performed for postmenopausal women.

For female subjects on a hormonal contraceptive regimen (regardless of type and route of administration), the start of contraceptive administration at the last initiated cycle (if applicable for the type of contraception) will be documented in the eCRF.

A blood sample for hematology, blood chemistry and coagulation, and a urine sample for urinalysis will be taken. Creatinine clearance will be assessed (estimated by the estimated Glomerular Filtration rate [eGFR], which is calculated by the Modification of Diet in Renal Disease [MDRD] formula[22]). Vital signs (supine systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate) and triplicate ECG will be recorded.

An ultrasound, CT or MRI (if applicable) will be performed. Alpha-fetoprotein will be measured, and HBV virology (HBV genotyping, HBV DNA, and HBV RNA) and HBV serology (HBsAg

[qualitative and quantitative], anti-HBs, HBeAg [qualitative; quantitative for subjects with HBeAg-positive status only], anti-HBe, HBcrAg) will be performed at screening.

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. In virologically suppressed subjects, available historical data on HBeAg status before start of NA treatment will be collected in the eCRF.

9.1.3. Treatment Phase (Partially-Blind)

Assessments to be performed during the treatment phase are specified in the TIME AND EVENTS SCHEDULE.

Eligible subjects will be randomized on Day 1. Study drug 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.

9.1.4. Treatment Extension Phase (Partially-Blind)

For subjects who participate in the treatment extension phase, treatment will be continued without interruptions. Study drugs should be taken in the morning at approximately the same time each day with breakfast, except for ETV which should be taken on an empty stomach.

Assessments to be performed during the treatment extension phase are specified in the TIME AND EVENTS SCHEDULE.

At the Week 20 visit and the Week 24 visit, eligibility to participate in the treatment extension phase will be checked. The procedures are specified in the TIME AND EVENTS SCHEDULE.

9.1.5. Post-Treatment Phase (Follow-Up)

For details on the follow-up after the last study drug intake of the study treatment phase (Week 24 or Week 48) or in case of dropout, please refer to the TIME AND EVENTS SCHEDULE for the post-treatment (follow-up) phase. All subjects who received 24 weeks of treatment, who received 48 weeks of treatment and did not meet the treatment completion criteria as described in Section 6.3, or who discontinued study treatment early (either 24 or 48 weeks of study treatment) will be followed-up for 24 weeks (Schedule 1). Subjects who meet the study completion criteria (see Section 6.3) will be followed-up for 48 weeks (Schedule 2).

If a subject withdraws from the study (ie, withdrawal of consent), the subject will be offered an optional safety follow-up visit.

9.2. Efficacy Evaluations

Efficacy assessments will be performed at the time points indicated in the TIME AND EVENTS SCHEDULE.

Qualitative and quantitative HBsAg and HBeAg, and quantitative HBcrAg as well as anti-HBs and anti-HBe antibodies will be determined using standard serologic assays in a central laboratory. Samples for the determination of HBsAg and HBeAg will be processed in real-time using an assay such as the ARCHITECT platform (Abbott Laboratories). Samples for the determination of HBcrAg can be analyzed in batch and at the sponsor's discretion.

HBV DNA and HBV RNA will be quantified at a central laboratory using in vitro nucleic acid amplification tests for the quantification of HBV DNA and HBV RNA. Samples for the determination of HBV DNA will be processed in real-time using a test such as the COBAS® TaqMan® HBV Test, v2.0 (Roche Molecular Systems). Samples for the determination of HBV RNA can be analyzed in batch and at the sponsor's discretion.

Post-baseline results from HBsAg, HBeAg, anti-HBs, and anti-HBe antibody testing will be provided to the investigator and the sponsor from Week 20 onwards. HBV DNA results will be provided to the investigator and the sponsor from screening until FU Week 24 or 48, as applicable. It is the responsibility of the investigator:

- To monitor HBV DNA results and ensure that JNJ-56136379 treatment is discontinued in subjects with viral breakthrough and in treatment-naïve subjects with <1 $\log_{10}$ IU/mL decline in HBV DNA from baseline at Week 4 and Week 8 (see Section 10.2)
- To monitor HBV DNA to assess if treatment extension criteria (see Section 6.1) are met
- To assess if treatment completion criteria (see Section 6.3) are met
- To assess whether re-start of NA treatment during follow-up is needed (see Section 6.4).

In subjects from the pharmacokinetic subgroup and subjects enrolled at a site with an on-site Fibroscan device, Fibroscan assessments will be performed to determine changes in fibrosis.

The blinded data collected from baseline onwards will be provided to the investigator at the end of the study to complete the subject's medical records.

Samples may be used by the sponsor for additional exploratory assessments analyzing the serologic and virologic characteristics of HBV infection and efficacy or safety of the study treatment.

9.3. Sequencing

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 the TIME AND EVENTS SCHEDULE. Samples at baseline will be sequenced by default if HBV DNA levels are within the ranges required for the sequencing assay. 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.

Samples may be used by the sponsor for additional assessments analyzing the serologic and virologic characteristics of the HBV infection and efficacy of the study treatment, including viral genotypic and phenotypic assessments.

9.4. Pharmacokinetics

9.4.1. Evaluations

Venous blood samples will be collected for the determination of plasma concentrations of total JNJ-56136379 and/or NA (ETV or TDF), as applicable, at time points specified in the TIME AND EVENTS SCHEDULE.

24-hour urine sampling will be performed in approximately 35% of all subjects (pharmacokinetic subgroup, at selected sites only) for the determination of JNJ-56136379 or NA (ETV or TDF) concentrations, as applicable, on Day 1 and Day 84 (Week 12) (0-2, 2-12, and 12-24 hours postdose). This 24-hour sampling schedule will require an overnight stay on site.

Based on the individual plasma concentration-time data, using the actual dose taken and the actual sampling times, pharmacokinetic parameters and exposure information of JNJ-56136379 will be derived using popPK modeling. Data may be combined with those of a selection of Phase 1 studies to support a relevant structural model. Available subject characteristics (eg, demographics, laboratory variables, genotypes) will be tested as potential covariates affecting pharmacokinetic parameters.

Plasma samples will also be collected from female subjects using hormonal contraceptives that can be analyzed further for determination of plasma concentrations of hormonal contraceptives and their metabolites. These samples will be analyzed at the sponsor's discretion. The start of contraceptive administration at the last initiated cycle (if applicable for the type of contraception) will be documented in the eCRF.

9.4.2. Analytical Procedures

A selection of plasma samples will be analyzed to determine concentrations of total JNJ-56136379 and NA (ETV or TDF) using a validated liquid chromatography-mass spectrometry (LC-MS/MS) method by or under the supervision of the sponsor. A selection of urine samples will be analyzed to determine JNJ-56136379 and NA (ETV or TDF) concentrations using a qualified LC-MS/MS method. In addition, plasma samples may be analyzed for hormonal contraceptives and important metabolites, at the sponsor's discretion.

At the sponsor's discretion, plasma and urine samples may be analyzed for metabolite profiling using a qualified method. In addition, plasma and urine pharmacokinetic samples may be stored for future exploratory analysis of protein binding or the metabolite profile.

To allow selection of samples, the bioanalytical laboratory will receive randomization lists per planned interim analysis and/or upon request of the bioanalytical scientist. Unblinding of the treatment code will be performed at the bioanalytical laboratory only, and will be subjected to a procedure that will ensure that codes will not be revealed to anyone involved in the execution of the study. Note that blinding does not apply to the JNJ-56136379 monotherapy arms.

9.4.3. Pharmacokinetic Parameters

9.4.3.1. Pharmacokinetic Analysis on Plasma Samples

Based on the individual plasma concentration-time data, using the actual sampling times (see TIME AND EVENTS SCHEDULE), the following pharmacokinetic parameters will be derived for JNJ-56136379 and/or NA (ETV or TDF) as applicable:

- On Day 1: t_{max}, C_{max}, C_{τ}, AUC_{τ}, CL/F
- At Weeks 1, 2, 4, 8, 20, 24, 28, 32, 36, 44 and 48 and FU Weeks 2 and 4: C_{trough}
- On Day 84 (Week 12): C_{trough}, t_{max}, C_{max}, C_{min}, C_{τ}, AUC_{τ}, C_{avg}, FI, Ratio CL/F$^{\$}$, λ_z, $t_{1/2term}$, Ratio $C_{\tau,test/ref}$*, Ratio $C_{max,test/ref}$*$^{\$}$, and Ratio $AUC_{\tau,test/ref}$*$^{\$}$

  * test = steady-state, and ref = Day 1 (to evaluate the accumulation index)
  $ test = NA coadministered with JNJ-56136379, and ref = NA[a]
  Other pharmacokinetic parameters may be estimated as appropriate for exploration of the data.

For the plasma pharmacokinetic parameters, definitions and methods of calculation are:

- C_{max} maximum observed plasma concentration
- C_{min} minimum observed plasma concentration
- C_{trough} predose plasma concentration
- C_{τ} observed plasma concentration from time 0 to τ hours postdose (τ = treatment interval)
- t_{max} time to reach C_{max}
- AUC_{τ} AUC from time 0 to τ hours postdose, calculated by linear-linear trapezoidal summation
- $AUC_{0\text{-}24h}$ AUC from time 0 to 24 hours postdose, calculated by linear-linear trapezoidal summation
- AUC_{last} AUC from time 0 to the time of the last measurable (non-below quantification limit [BQL]) concentration, calculated by linear-linear trapezoidal summation

[a] This is not applicable to the monotherapy arms.

- AUC_{∞} AUC from time 0 to infinity, calculated as $AUC_{last} + C_{last}/\lambda_z$, where C_{last} is the last observed measurable (non-BQL) concentration; extrapolations of more than 20.00% of the total AUC are reported as approximations
- C_{avg} average plasma concentration at steady-state over the treatment interval (τ) calculated by AUC_{τ}/τ at steady-state
- FI percentage fluctuation (variation between maximum and minimum concentration at steady-state), calculated as: 100 x ($[C_{max} - C_{min}] / C_{avg}$)
- CL/F total apparent oral clearance, calculated as dose/AUC_{∞} after single dose, or as dose/AUC_{τ} at steady-state
- V_d/F apparent volume of distribution, calculated as dose/ (λ_z *AUC_{∞})
- λ_z apparent terminal elimination rate constant, estimated by linear regression using the terminal log-linear phase of the log transformed concentration versus time curve
- $t_{1/2term}$ apparent terminal elimination half-life, calculated as $0.693/\lambda_z$
- Ratio $C_{max,test/ref}$ ratio of individual C_{max} values between test and reference
- Ratio $AUC_{last,test/ref}$ ratio of individual AUC_{last} values between test and reference
- Ratio $AUC_{\infty,test/ref}$ ratio of individual AUC_{∞} values between test and reference
- Ratio $C_{\tau,test/ref}$ ratio of individual C_{τ} values between test and reference
- Ratio $AUC_{\tau,test/ref}$ ratio of individual AUC_{τ} values between test and reference

Dose-normalization will be done by dividing the relevant pharmacokinetic parameter by the dose (D).

Actual sampling times will be checked for major aberrations. Deviation of scheduled time points is allowed, however in case a major aberration occurs for an actual sampling time of >20.00% deviation from the scheduled time, or a sample is not taken on the scheduled day, this plasma concentration will be excluded from descriptive statistics in the plasma concentration table.

9.4.3.2. Pharmacokinetic Analysis on Urine Samples

For urine samples, the following pharmacokinetic parameters will be derived for JNJ-56136379 and/or NA (ETV or TDF), as applicable:

- On Day 1 (**for NA in Treatment Arms 4-5 and 9-10 only**): CL_R
- On Day 84 (Week 12): CL_R

For urine-derived parameters, definitions and methods of calculation are:

- Ae_{x-y} amount of unchanged drug excreted into urine over a given time interval, calculated from the urinary drug concentration of the collection interval x to y hours postdose multiplied with the associated

urine volume of the interval

- Ae_{total} total amount of unchanged drug excreted into urine, calculated by adding the amounts of the individual intervals together
- Ae,%Dose total percentage of the dose excreted into urine as unchanged drug, calculated as $100*(Ae_{total}/Dose)$
- CL_R renal clearance, calculated as Ae_{total}/AUC_{∞} or Ae_{τ}/AUC_{τ} at steady-state

9.5. Pharmacokinetic/Pharmacodynamic Evaluations

Relationships of pharmacokinetic parameters for JNJ-56136379 and NA (ETV or TDF), as applicable, with selected efficacy and with selected safety endpoints will be evaluated.

9.6. Biomarkers

The study includes collection of blood samples for exploratory analysis of host blood biomarkers at the host mRNA, protein, and cell level. Sampling will be performed in all subjects at the time points indicated in the TIME AND EVENTS SCHEDULE.

Phenotypic and functional characterization of the immune response may be performed using immune cell-based assays. Samples for these analyses will be obtained at selected sites only.

Samples can only be used for research related to JNJ-56136379, NA (ETV or TDF), CHB infection, or HBV-related disease or may be used to develop tests/assays related to JNJ-56136379, NA (ETV or TDF), or HBV.

These analyses will be performed at the sponsor's discretion, will always be under the sponsor's supervision, and may be reported separately from the main study report.

9.7. Pharmacogenomic (DNA) Evaluations

A blood sample for pharmacogenomics (DNA) research will be taken, preferentially at baseline. This sample is optional and will only be collected from subjects who consent separately to this component of the study. This sample can be used to investigate the potential association of genetic factors with efficacy, safety, or pharmacokinetics of JNJ-56136379, NA (ETV or TDF), CHB infection, or HBV-related disease or may be used to develop tests/assays related to JNJ-56136379, NA (ETV or TDF), or HBV.

These analyses will be performed at the sponsor's discretion, will always be under the sponsor's supervision, and may be reported separately.

9.8. Patient-Reported Outcomes

The impact of HBV treatment on subjects, including symptoms, functioning and HRQoL will be assessed using PROs at predefined time points. The following PRO instruments will be used: EQ-5D-5L, HBQOL, MOS-CFS Cog-R, and SF-36v2 (see Attachment 4, Attachment 5, Attachment 6, and Attachment 7, respectively).

PRO assessments will be performed by all subjects at sites where appropriate translations are available. Subjects should complete these assessments in their native language or if there is no version available in their native language, a version in a language in which the subject is fluent and literate. It is preferable that subjects are able to read and write to complete the assessments by themselves. If a subject is unable to read or has visual or other physical limitations that make it difficult to read or complete the assessments, trained study-site personnel may read the questions and responses aloud exactly as they appear on the assessment and record the subject's responses.

Study-site personnel will record in the eCRF whether the PRO assessments were performed during the study visit.

Subjects will complete the PRO assessments electronically during study site visits on a touch-screen tablet provided for this study. The subject should be provided a quiet place to complete the PRO assessments, and instructed how to complete the PRO assessment on the tablet. When deciding which answer to report, subjects should not receive any help from anyone accompanying them (such as family members and friends) or study-site personnel; the responses should reflect the subject's interpretation and response.

Subjects' responses to the PRO questionnaires will not be reported as AEs or SAEs.

5-level EuroQol 5-Dimension

The EQ-5D-5L questionnaire is a brief, 2-page, generic HRQoL assessment that evaluates a subject's self-rated health state on 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Additionally, a Visual Analog Scale (VAS) records the subject's self-rated health on a vertical VAS where the endpoints are labelled 'best imaginable health state' (100) and 'worst imaginable health state' (0). This information can be used as a quantitative measure of health outcome as judged by the subject. EQ-5D scores include the following:

- EQ-5D Valuation Index score (a weighted scoring of the 5 dimension scores with a possible range from 0 to 1);
- EQ-5D VAS score (with a possible range from 0 [worst imaginable health] to 100 [best imaginable health]);
- EQ-5D descriptive system scores (5 scores reflecting each of the 5 dimensions ranging from 0 [no limitation] to 4 [incapacity]).

It takes about 2 minutes to complete the EQ-5D-5L questionnaire. See Attachment 4 for a representative example of the EQ-5D-5L.

Hepatitis B Quality of Life

The HBQOL version 1 is a 31-item disease-specific instrument designed to measure HRQoL for subjects with CHB. The instrument includes 7 subscales/domains, including psychological well-being, anticipation anxiety, vitality, stigma, vulnerability, transmission, and viral response. Each of the 31 items is scored on a 5-level response scale. Each subscale score is simply calculated as the average score among the items included in that subscale. In addition to the 7 subscales, there is a single global score that reflects the results on all 31 items. The global score is simply the average score among all the items in the HBQOL. Responses are transformed along a 0 to 100-point scale, where lower scores denote less HRQoL impact, and higher scores denote more HRQoL impact (ie, 0=best score; 100=worst score).

It takes about 10 minutes to complete the HBQOL version 1. See Attachment 5 for a representative example of the HBQOL version 1.

Medical Outcomes Study Cognitive Functioning Scale-Revised

The MOS-CFS Cog-R is a patient-reported instrument that measures a range of cognitive functions using the following 6 items: having difficulty in reasoning and solving problems (eg, making decisions), 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 on any activity for a longer time, and reacting slowly to things that are said or done. The response options for each of the items are on a 5-point scale (all, most, some, a little, or none of the time). Responses for all items yield a single overall score.

It takes about 2 minutes to complete the MOS-CFS Cog-R questionnaire. See Attachment 6 for a representative example of the MOS-CFS Cog-R.

Short Form 36 version 2

SF-36v2 is a generic 36-item instrument designed to measure health status that can be interpreted using 2 summary scores – Physical Component Summary (PCS) and Mental Component Summary (MCS) – as well as domain subscales. The SF-36v2 consists of 8 subscales. Although SF-36v2 PCS and MCS scores include information from all 8 SF-36 domain subscales, the PCS score gives more weight to physical aspects of HRQoL as represented in the Physical functioning, Physical role limitations, Pain, and General health perception domain scores. The MCS score gives more weight to the emotional and social aspects of HRQoL as assessed by the Vitality, Social function, Social role limitations, and Mental health domain scores. Participants self-report on items that have between 2-6 response options per item using Likert-type responses (eg, none of the time, some of the time, etc.). Summations of item scores of the same subscale give the subscale scores, which are transformed into a range from 0 to 100; 0=worst HRQoL, 100=best HRQoL. PCS and MCS scores are constructed as a T-score with a mean of 50 and SD of 10; higher scores indicate better health status. The 4-week recall version will be used.

It takes about 10 minutes to complete the SF-36v2 questionnaire. See Attachment 7 for a representative example of the SF-36v2.

9.9. Safety Evaluations

Safety and tolerability will be assessed throughout the study from the time that the ICF is signed until the completion of the last study-related activity. The evaluations of safety and tolerability will include monitoring of (S)AEs, physical examinations, vital signs measurements, 12-lead ECGs, and clinical laboratory tests (including hematology, blood biochemistry, blood coagulation, and urinalysis) at predefined time points as specified in the TIME AND EVENTS SCHEDULE.

Specific toxicity management plans in line with the known pharmacological profile of the study drugs (and the drug classes) evaluated in this study will be implemented.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

Details regarding the DRC are provided in Section 11.12.

Any clinically relevant changes occurring during the study must be recorded in the AE section of the eCRF.

The study will include the following evaluations of safety and tolerability according to the time points provided in the TIME AND EVENTS SCHEDULE:

Adverse Events

Adverse events will be reported by the subject for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12.

Special attention will be paid to those subjects who discontinue the study for an AE, or who experience an AE of at least grade 3, or an SAE.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology and a urine sample for urinalysis will be collected. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

Subjects need to have fasted for at least 10 hours before biochemistry samples are taken 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.

In case a grade 3 or grade 4 laboratory abnormality occurs, a confirmatory test must be performed preferably within 48 hours but no later than 72 hours after the results have become available.

The following tests will be performed by the selected laboratory:

- Hematology Panel

  -hemoglobin
  -hematocrit
  -red blood cell (RBC) count
  -RBC parameters
  *mean corpuscular hemoglobin (MCH)
  *MCH concentration
  *mean corpuscular volume
  -white blood cell (WBC) count with differential
  -WBC differential (including %)
  *neutrophils
  *lymphocytes
  *monocytes
  *eosinophils
  *basophils
  -platelet count

  A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. A RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.

- Serum Chemistry Panel

  -sodium
  -potassium
  -chloride
  -bicarbonate
  -blood urea nitrogen
  -creatinine
  -glucose
  -AST
  -ALT
  -gamma-glutamyltransferase
  -total, conjugated and unconjugated bilirubin
  -alkaline phosphatase
  -creatine phosphokinase
  -lactic acid dehydrogenase
  -uric acid
  -calcium
  -phosphate
  -albumin
  -total protein
  -total cholesterol
  -high-density lipoprotein cholesterol
  -low-density lipoprotein cholesterol
  -triglycerides
  -magnesium
  -α_1-acid glycoprotein
  -calculated creatinine clearance (by MDRD formula)
  -lipase
  -amylase (reflex testing of pancreatic amylase should be done in case of post-screening amylase or lipase increase)
  -fibrinogen (on blood)
  -C-reactive protein

- Urinalysis

  A urine sample must be provided for urinalysis. Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, and leukocyte esterase will be determined using dipstick. In case of positive dipstick results, the sediment will be examined microscopically for RBCs, WBCs, and epithelial cells and an additional examination will be performed on the positive urinary parameter (eg, quantification as applicable). Crystals, casts and bacteria will only be reported if they are present.

- At screening, a serum pregnancy test will be performed for women of childbearing potential.
- At screening, an FSH test will be performed for postmenopausal women.

- At time points as indicated in the TIME AND EVENTS SCHEDULE, a urine pregnancy test will be performed (women of childbearing potential only).
- At screening, a HIV-1 and -2 test, and hepatitis A, B, C, D, and E tests will be performed.
- At screening and time points as indicated in the TIME AND EVENTS SCHEDULE, tests will be performed for HBsAg, HBeAg, HBcrAg, and anti-HBs and anti-HBe antibodies.
- At screening and time points as indicated in the TIME AND EVENTS SCHEDULE, determination of coagulation parameters will be performed. INR will be calculated by the central laboratory.
- At screening, alpha-fetoprotein will be measured.

In case of **rash**, blood samples (mandatory blood sample for safety in case of Grade 3 or Grade 4 rash and at the discretion of the investigator in case of Grade 1 or Grade 2 rash) need to be taken for safety laboratory testing, and are to be processed by the local laboratory. These samples need to be taken at unscheduled visits as described in Attachment 3. The following parameters need to be tested: AST, ALT, erythrocyte sedimentation rate, creatinine, and a complete blood cell count (including hemoglobin, hematocrit, RBC count, WBC count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count).

Electrocardiogram

Twelve-lead triplicate ECGs will be collected at the time points specified in the TIME AND EVENTS SCHEDULE and when clinically indicated.

During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. 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.

At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 10 minutes.

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

Preferably, all ECGs (read centrally) will be read and interpreted under supervision of one and the same qualified person. Day 1, pre-dose ECG assessment will also be done locally on-site to determine eligibility.

Clinically relevant abnormalities occurring during the study should be recorded in the AE Section of the eCRF.

Vital Signs

Blood pressure and pulse/heart rate measurements will be assessed with a completely automated device, if possible. All values will preferably be registered on a built-in recorder so that measurements are observer independent. Manual techniques will be used only if an automated device is not available.

Systolic and diastolic blood pressure and pulse rate (supine after at least 5 minutes rest) measured in a quiet setting without distractions (eg, television, cell phones) will be recorded.

Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

Clinically relevant abnormalities (as defined in Attachment 2) occurring during the study should be recorded in the AE section of the eCRF.

Physical Examination

A complete physical examination (including height, body weight, and body systems) will be performed at screening and early withdrawal. A symptom-directed physical examination (including body weight) will be performed at the time points indicated in the TIME AND EVENTS SCHEDULE.

A complete physical examination includes the following: general appearance, eyes, ears, nose, throat, cardiovascular system, respiratory system, gastro-intestinal system, and skin and mucous membranes. A neurological and musculoskeletal examination will be performed, as well as an examination of the lymph nodes. Body weight and temperature will be measured. Height will be measured at the screening visit only. The skin examination includes an examination of the mucous membranes, but does not include a vaginal or rectal examination. However, if the subject develops a cutaneous reaction/rash, vaginal and rectal examinations may be done if clinically relevant. Additionally, a genito-urinary system examination may be done if deemed clinically relevant by the investigator.

At the other visits, a symptom-directed physical examination will be performed as indicated in the TIME AND EVENTS SCHEDULE.

Any clinically relevant changes occurring during the study must be recorded in the AE Section of the eCRF.

Specific Toxicities

For subjects reporting rash, acute systemic allergic reactions, AST/ALT elevations, renal complications, nausea and diarrhea, or other gastro-intestinal complaints, the following should be done.

Rash

For subjects reporting rash, please see Attachment 3.

Acute Systemic Allergic Reactions

Grade 1 (Localized Urticaria [Wheals] With no Medical Intervention Indicated)

Subjects may continue the intake of study drugs.

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

Subjects should be advised to contact the investigator immediately if there is any worsening of the acute systemic allergic reaction.

Grade 2 (Localized Urticaria With Medical Intervention Indicated, or Mild Angioedema With no Medical Intervention Indicated)

Subjects may continue the intake of study drugs.

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

Subjects should be advised to contact the investigator immediately if there is any worsening of the acute systemic allergic reaction, in which case the subject will permanently discontinue the intake of JNJ-56136379. Rechallenge is not allowed. The subject's NA treatment may be discontinued based on investigator judgement in consultation with the sponsor.

Grade 3 (Generalized Urticaria, Angioedema With Medical Intervention Indicated, or Symptomatic Mild Bronchospasm) and Grade 4 (Acute Anaphylaxis, Life-Threatening Bronchospasm, or Laryngeal Edema)

Subjects will permanently discontinue the intake of JNJ-56136379. Rechallenge is not allowed. The subject's NA treatment may be discontinued based on investigator judgement in consultation with the sponsor.

Subjects will be treated as clinically appropriate. Subjects should be followed until resolution of the AE and standard management should be undertaken.

AST and ALT Elevation

Grade 1 (≥1.25 to <2.50 x ULN), or Grade 2 (≥2.50 to <5.00 x ULN)

Subjects may continue the intake of study drugs.

Subjects should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation (to be agreed upon with the sponsor).

Grade 3 (≥5.00 to <10.00 x ULN), or Grade 4 (≥10.00 x ULN)

The investigator should contact the sponsor to discuss the case when:

- the ALT and/or AST elevations during treatment are ≥2 times the value at baseline, OR
- the ALT and/or AST values increase by ≥2 grades compared to the grade at baseline.
- the ALT and/or AST values increase to grade 4, regardless of the baseline value or grade.

Subjects should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.

Renal Complications

If renal complications develop, subjects should be closely monitored for disturbances in serum creatinine and for abnormalities in urine analysis (eg, proteinuria). Additional investigations can be performed at the investigator´s discretion. Subjects must be treated as clinically appropriate.

Subjects who develop **grade 1** or **2** abnormalities in **serum creatinine** or **urinalysis** may continue the intake of study drugs (unless they develop abnormalities in serum creatinine or urinalysis considered at least possibly related to the study drugs by the investigator) or be withdrawn from further study treatment based on the investigator's clinical judgment.

Subjects who develop confirmed **grade 3** or **4** abnormalities in **serum creatinine** will permanently discontinue the intake of JNJ-56136379 regardless of the relationship to the study drugs. The subject may continue ETV or switch from TDF to ETV at the investigator's discretion.

Subjects who are receiving TDF and develop confirmed treatment-emergent **grade 3** or **4** abnormalities in **urinalysis,** considered at least possibly related to TDF, may switch to ETV and continue JNJ-56136379 for 4-8 weeks. If the urinalysis abnormality persists at the end of the 4-8 weeks NA switching phase, JNJ-56136379 must be discontinued. Subjects may continue NA treatment at the investigator's discretion and enter follow-up. Subjects on TDF or ETV treatment will be able to continue study treatment (JNJ-56136379 + TDF or ETV), without the need for treatment modification, if the **urinalysis** abnormality can be attributed to any other concomitant disease and its medication (eg, diabetes mellitus).

If the confirmed **grade 3** or **4 urinalysis** abnormality is not considered at least possibly related to TDF or ETV, or any other concomitant disease and its medication, JNJ-56136379 must be discontinued. Subjects may continue NA treatment at the investigator's discretion and enter follow-up. For further details on study treatment discontinuation, refer to Section 10.2.

All subjects who develop confirmed **grade 3** or **4** abnormalities in **serum creatinine or urinalysis** should be followed appropriately until resolution of AE or toxicity. Rechallenge of JNJ-56136379 is not allowed in subjects who need to discontinue treatment with JNJ-56136379.

The grades are based on the DAIDS Toxicity Grading Scale.[7]

Nausea (With or Without Vomiting)

Grade 1 (Transient [<24 Hours] or Intermittent Nausea With no or Minimal Interference With Oral Intake)

Subjects may continue the intake of study drugs and may be treated as needed with anti-emetics given orally or rectally.

Grade 2 (Persistent Nausea Resulting in Decreased Oral Intake for 24 to 48 Hours)

Subjects may be treated as needed with anti-emetics given orally or rectally. If the nausea persists despite anti-emetics or increases in severity, subjects will permanently discontinue the intake of JNJ-56136379. The subject's NA treatment may be discontinued based on investigator judgement in consultation with the sponsor.

Grade 3 (Persistent Nausea Resulting in Minimal Oral Intake for >48 Hours, or Rehydration Indicated) and Grade 4 (Life-Threatening Consequences)

Subjects will permanently discontinue the intake of JNJ-56136379. Rechallenge is not allowed. The subject's NA treatment may be discontinued based on investigator judgement in consultation with the sponsor.

Diarrhea

Grade 1 (Transient or Intermittent Episodes of Unformed Stools, or Increase of ≤3 Stools Over Baseline per 24-Hour Period)

Subjects may continue the intake of study drugs. Loperamide can be administered.

Grade 2 (Persistent Episodes of Unformed to Watery Stools, or Increase of 4 to 6 Stools Over Baseline per 24-Hour Period)

Subjects may continue the intake of study drugs. Loperamide can be administered.

Grade 3 (Increase of ≥7 Stools per 24-Hour Period, or Intravenous Fluid Replacement Indicated) or Grade 4 (Life-Threatening Consequences)

Subjects will permanently discontinue the intake of JNJ-56136379. Subjects should be followed until resolution of the AE. Rechallenge is not allowed. The subject's NA treatment may be discontinued based on investigator judgement in consultation with the sponsor.

9.10. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form.

Refer to the TIME AND EVENTS SCHEDULE for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. Completion

For subjects who are not eligible to participate in the treatment extension phase:

- Subjects will be considered to have completed the study treatment if they have completed 24 weeks of study drug administration, after which they will discontinue JNJ-56136379 or placebo treatment. NA treatment (either ETV or TDF as per local practice) should be started (in case of JNJ-56136379 monotherapy, ie, Treatment Arms 1 and 6) or continued (in case NA treatment was part of the assigned study treatment, ie, Treatment Arms 2 to 5 and 7 to 10) as per local treatment guidelines.
- Subjects will be considered to have completed the study if they have completed the assessments of the end of study visit (Follow-up [FU] Week 24 [Schedule 1]).
- For subjects who do not continue or start NA treatment at Week 24, an additional 24-week follow-up (as per local treatment guidelines) by their primary care physician, outside of the study, is recommended after study completion.

For subjects who continue treatment in the extension phase:

- Subjects will be considered to have completed the study treatment if they have completed 48 weeks of study drug administration, after which they will discontinue JNJ-56136379 or placebo treatment. At Week 48:
    - Subjects who meet all of the Individual Subject Treatment Completion Criteria (see Section 6.3) will complete all treatment. These subjects will be followed-up until 48 weeks after EOT (Schedule 2). If, during the 48-week follow-up, a subject meets one of the re-treatment criteria described in Section 6.4, NA treatment (ETV or TDF) should be re-started.
    - Subjects who do not meet the Individual Subject Treatment Completion Criteria should start (in case of JNJ-56136379 monotherapy, ie, Treatment Arms 1 and 6) or continue (in case NA treatment was part of the assigned study treatment, ie, Treatment Arms 2 to 5 and 7 to 10) NA treatment as per local treatment guidelines. These subjects will be followed-up until 24 weeks after the end of study treatment (Schedule 1).
- Subjects will be considered to have completed the study if they have completed the assessments of the end of study visit (FU Week 24 [Schedule 1] or FU Week 48 [Schedule 2]).

- For subjects who do not meet the Individual Subject Treatment Completion Criteria and do not start or continue 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 study completion.

The study is considered completed with the last visit of the last subject participating in the study.

10.2. Discontinuation of Study Treatment/Withdrawal from the Study

Discontinuation of Study Treatment

A subject will not be automatically withdrawn from the study if he or she has to discontinue study treatment before the end of the 24- or 48 week treatment phase, as applicable.

A subject's JNJ-56136379 treatment must be discontinued and NA may be discontinued based on investigator judgement in consultation with the sponsor if:

1. The subject withdraws consent.
2. The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the subject to discontinue study treatment.
3. The subject becomes pregnant.
4. The subject has a ≥ grade[a] 3 rash (see Attachment 3).
5. The subject has a ≥ grade 3 allergic reaction, nausea, or diarrhea.
6. The subject has a grade 4 AE or confirmed laboratory abnormality (with the exception of ALT/AST elevations) considered at least possibly related to study drugs by the investigator.
7. The subject experiences a treatment-emergent elevation of ALT >2x baseline value, in combination with either direct bilirubin >1.2x ULN or INR >1.5x ULN or serum albumin < LLN, confirmed by retesting.
8. The subject has signs of hepatic decompensation (ie, clinical evidence of ascites, bleeding varices, or hepatic encephalopathy).
9. The subject has a confirmed ≥ grade 3 serum creatinine abnormality, regardless of the relationship to the study drugs. In this case, JNJ-56136379 must be discontinued. The subject may continue ETV or switch from TDF to ETV at the investigator's discretion and enter follow-up.

   Subjects who are receiving TDF and develop confirmed treatment-emergent ≥ grade 3 abnormalities in urinalysis**,** considered at least possibly related to TDF, may switch to ETV and continue JNJ-56136379 for 4-8 weeks. If the urinalysis abnormality persists at the end of the 4-8 weeks NA switching phase, JNJ-56136379 must be discontinued. Subjects may continue NA treatment at the investigator's discretion and enter follow-up.

[a] Grades in this list are per the DAIDS Toxicity Grading Scale.

If the confirmed ≥ grade 3 urinalysis abnormality is not considered at least possibly related to TDF or ETV, or any other concomitant disease and its medication, JNJ-56136379 must be discontinued. Subjects may continue NA treatment at the investigator's discretion and enter follow-up.

10. The subject has a QTcF prolongation (defined as a QTcF value of >500 ms, or an increase from baseline of >60 ms) at any given time point (confirmed by repeat ECG).
11. The subject has at Week 4 <1 $\log_{10}$ IU/mL decline in HBV DNA from baseline, confirmed by retesting at the Week 8 visit (treatment-naïve only).
12. The subject has confirmed HBV virological breakthrough (ie, confirmed on-treatment HBV DNA increase by >1 $\log_{10}$ IU/mL from nadir level or confirmed on-treatment HBV DNA level >200 IU/mL in subjects who had HBV DNA level <LLOQ of the HBV DNA assay).
13. The subject requires treatment with any of the disallowed medications listed in Section 8.

Retesting for confirmation of the above-mentioned abnormal safety parameters (ie, not applicable to criteria 11 and 12 listed above) should take place within 72 hours after the initial results become available and may require an unscheduled visit.

Withdrawal From the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up.
- Withdrawal of consent.
- Death.

If a subject discontinues study treatment before the end of the 24-week treatment phase or the 24-week treatment extension phase, follow-up assessments should be obtained until 24 weeks after EOT (Schedule 1) unless the subject withdraws consent.

If a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Subjects who withdraw consent will be offered an optional safety follow-up visit. Study treatment assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

If a subject is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

10.3. Withdrawal From the Use of Research Samples

A subject who withdraws from the study will have the following options regarding the pharmacogenomics (host DNA) research samples:

- The collected samples will be retained and used in accordance with the subject's original separate informed consent for pharmacogenomics (host DNA) research.

- The subject may withdraw consent for pharmacogenomics (host DNA) research, in which case the samples will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study-site contact of withdrawal of consent for the pharmacogenomics (host DNA) research and to request sample destruction. The sponsor study-site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

Withdrawal From the Optional Research Samples While Remaining in the Main Study

The subject may withdraw consent for pharmacogenomics (host DNA) research while remaining in the study. In such a case, the pharmacogenomics (host DNA) research samples will be destroyed. The sample destruction process will proceed as described above.

Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF and in the separate ICF for pharmacogenomics (host DNA) research.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the SAP.

11.1. Subject Information

For all subjects who receive at least 1 dose of study drug descriptive statistics will be provided.

All demographic (eg, age, length, weight, race, gender) and other initial subject characteristics (eg, physical examination, medical and surgical history, family history, concomitant diseases) will be tabulated and analyzed descriptively by study treatment.

11.2. Sample Size Determination

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

The adequacy of the sample size for the different parts of the study has been assessed by evaluating the performance of the planned analyses on the primary endpoint (mean HBsAg change from baseline at Week 24) comparing JNJ-56136379+NA with placebo+NA as outlined in Section 11.3. Baseline is defined as the last assessment prior to the first intake of study drugs (JNJ-56136379/NA/placebo) on Day 1.

Power was assessed using simulations (10,000 replicates per scenario) with means and SDs for the placebo+NA and JNJ-56136379+NA arms as listed in Table 7. Mean and SD may depend on HBeAg status at baseline and prior treatment (currently not being treated or virologically

suppressed). Treatment with JNJ-56136379 was set to result in one additional mean $\log_{10}$ IU/mL decline in HBsAg from baseline at Week 24. Data were simulated from mixture distributions which reflect the skewed distributions which are typical HBsAg decline data. It is assumed that HBeAg-positive subjects will enroll slower than HBeAg-negative subjects, particularly in virologically suppressed subjects. Therefore, the aim is to have at least 40% HBeAg-positive subjects currently not being treated and 30% HBeAg-positive virologically suppressed subjects.

For the dose-response modeling (multiple contrast test) the placebo+NA arms of Parts A and B will be pooled and the HBeAg subgroups will be pooled per dose. Assuming the treatment effect does not depend on HBeAg status, the power to detect a dose-response signal (α=0.10, one-sided) depends on the assumed effect of the low dose: ranging from 91% when the low dose has no effect to 99% when the low dose has the same effect as the high dose. Sensitivity analyses will be done investigating differences across Parts A and B and differences between the two HBeAg subgroups.

A Bayesian analysis will be conducted for Part A and Part B separately to compare the mean HBsAg change from baseline at Week 24 of JNJ-56136379 as monotherapy and in combination with NA versus placebo+NA by HBeAg subgroup. This Bayesian analysis will incorporate historical data for the placebo+NA arm(s) in an informative meta-analytic predictive (MAP)[21] prior with robustness modifier.[26] For the current sample size simulations, historical data comes from an ongoing systematic literature review on HBsAg declines during NA treatment, resulting in 20 studies including around 2,835 subjects. More details on the eventual historical data, including all references to all studies, will be provided in the Modeling and Simulation Report/SAP. The Bayesian equivalent of power, ie, the likelihood that the posterior probability that the mean change from baseline of HBsAg at Week 24 is larger in the JNJ-56136379+NA arm than in the placebo+NA arm is at least 90%, was determined. The results are summarized in Table 7.

It is concluded that, under the assumptions made, the posterior distribution of the estimate of treatment difference between the placebo+NA and JNJ-56136379+NA arm will be precise enough to allow meaningful conclusions. The probability to detect a treatment effect with at least 90% confidence is 0.80 or higher for the HBeAg-negative subgroup in both subjects currently not being treated and virologically suppressed subjects. For the HBeAg-positive subgroup, power is substantially lower which increases the risk of inconclusive results. However, if the interim analysis at Week 12, Week 24 or Week 48 indicates no safety concerns and a potential benefit, a moderate sample size increase for HBeAg-positive subjects to a maximum of 6 subjects on placebo+NA and 18 subjects on JNJ-56136379 monotherapy and JNJ-56136379+NA per study part may be considered. This will increase the probability to detect a treatment effect in these subgroups from 64% or 57% to around 84%.

Table 7: Bayesian Power Analysis for the Different Prior Treatment and HBeAg Status Subgroups: HBsAg Change From Baseline

	HBeAg Status	HBsAg (log_{10} IU/mL) Change From Baseline		Sample Size (Placebo+NA/ JNJ-56136379+NA)	Power[a]
		Mean ±SD Placebo+NA	Mean ±SD JNJ-56136379 +NA		
Currently not being treated	Positive	-0.35±0.6	-1.35±2.16	4/12[b]	0.64
	Negative	-0.05±0.4	-1.05±2.16	6/18[b]	0.84
Virologically suppressed	Positive	-0.05±0.4	-1.05±2.16	3/9[c]	0.57
	Negative	-0.05±0.4	-1.05±2.16	7/21[c]	0.89

[a] The probability to conclude that the difference in Week 24 HBsAg change from baseline between JNJ-56136379+NA and placebo+NA is larger than 0 with 90% confidence
[b] Expected sample size when 40% of the subjects are HBeAg-positive
[c] Expected sample size when 30% of the subjects are HBeAg-positive

11.3. Efficacy Analyses

All subjects who received at least 1 dose of study drug and were randomized will be included in the efficacy analysis.

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.

These comparisons will be done overall, by subject population (ie, subjects currently not being treated or virologically suppressed by current NA treatment), and by HBeAg status. Additionally, the JNJ-56136379 dose-response relation will be evaluated.

The primary endpoint for these efficacy comparisons is the change from baseline in HBsAg levels, while additional virological and serologic markers will also be assessed in these comparisons as secondary and exploratory efficacy objectives.

11.3.1. Analysis of Primary Endpoint (Change From Baseline in HBsAg Levels at Week 24)

Within Part A and Part B, the magnitude of the effect of JNJ-56136379+NA as compared to placebo+NA will be evaluated using the posterior distribution of the treatment effect (difference between JNJ-56136379+NA and placebo+NA) obtained in a Bayesian analysis. This Bayesian analysis will incorporate historical data for the placebo+NA arm(s) in an informative MAP[21] prior with robustness modifier.[26] For the current sample size simulations, historical data comes from an ongoing systematic literature review on HBsAg declines during NA treatment, resulting in 20 studies including around 2,835 subjects. More details on the eventual historical data, including all references to all studies, will be provided in the Modeling and Simulation

Report/SAP. For each study part and HBeAg status subgroup the appropriate historical prior will be used. Within Part A and Part B, JNJ-56136379+NA will also be compared with JNJ-56136379 as monotherapy but without including historical data as both arms include experimental treatments and appropriate historical data are consequently missing. In addition a similar analysis but without historical data in a frequentist approach will also be conducted as a sensitivity analysis.

The dose-response of JNJ-56136379 in an NA background regimen will be studied by a multiple contrast test (MCP) using 3 model-based contrasts covering the 3 possible shapes (linear, convex, and concave) with a control group (placebo+NA) and 2 doses. This analysis uses the data of these 3 treatment groups together to evaluate a dose-response signal, assuming a similar dose effect for each HBeAg subgroup and no difference in placebo+NA across Parts A and B. Sensitivity analyses will be done investigating differences across Parts A and B and differences between the two HBeAg subgroups.

11.3.2. Resistance Analyses

The results of HBV viral sequencing will be evaluated by the sponsor virologist. Pretreatment amino acid and/or nucleic acid substitutions in the HBV pre-core and core regions and RT domain in all subjects and relevant changes in the HBV pre-core and core region and RT domain in subjects not responding to treatment tabulated and described. The effect of pretreatment HBV pre-core and core protein substitutions on efficacy will be evaluated.

Additional exploratory characterization of the HBV viral sequence and phenotype may be performed and reported separately.

11.3.3. Other Analyses

Mean changes and maximum mean decrease from baseline in HBsAg, HBeAg, and HBV DNA levels over time will be tabulated by study treatment together with respective SDs. The proportion of subjects with seroclearance and seroconversion of HBsAg and HBeAg will also be tabulated by study treatment. The proportion of subjects with virologic response and the proportion of subjects with virologic or clinical relapse, defined as HBeAg, HBsAg, and/or HBV DNA levels below and above certain thresholds at different time points, respectively, will be categorized as detailed in the SAP, as applicable. Data will also be presented graphically by study phase, study treatment and by individual subject. All individual values will be presented in subject listings.

The least squares (LS) mean change from baseline in serologic parameters and HBV DNA for each study treatment and time point will be estimated with a repeated measurement model (mixed-effects model for repeated measures) including study treatment and time point as fixed effect. The model will allow for unequal variances between study treatments. A 95% confidence interval (CI) will be constructed around the difference between the LS mean of each study treatment. Other methods to evaluate the changes in serologic parameters and HBV DNA may include slope estimation, time-to-event or proportions of subjects who reach a certain level or who exceed a certain reduction.

The proportion of subjects with sustained reduction/suppression and/or sero-clearance, including but not limited to functional and partial cure, will be determined during follow-up. Single and multiple markers such as HBsAg, HBeAg, HBV DNA and ALT levels will be taken into consideration in this analysis.

Other efficacy endpoints, eg, HBV RNA and HBcrAg, will be analyzed descriptively. For continuous variables, descriptive statistics (n, mean, SD, median, minimum, maximum) will be calculated; mean difference and CIs may be calculated where appropriate and, if appropriate, 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 CIs may be calculated where appropriate.

Analyses, tabulations and visualizations will be done for both treatment and follow-up phases.

11.4. Pharmacokinetic Analyses

Descriptive statistics (n, mean, SD, coefficient of variation, geometric mean, 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.

For each subject, plasma concentration-time data of JNJ-56136379 and NA (ETV or TDF) will be graphically presented. Similarly, graphs of the mean plasma concentration-time profiles and overlay graphs with combined individual plasma concentration-time profiles will be produced. Pharmacokinetic parameters will be subjected to an exploratory graphical analysis, including various transformations, to get a general overview.

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 and as function of the dose to explore dose-linearity and dose-proportionality.

Predose plasma concentrations (C_{trough}) at Weeks 1, 2, 4, 8, 12, 20, and 24 will be compared graphically to assess the achievement of steady-state concentrations and population PK predictions of JNJ-56136379 and NA (ETV or TDF), as applicable. C_{trough} at Weeks 28, 32, 36, 44 and 48 in the treatment extension phase will be compared with population PK predictions of JNJ-56136379 and NA, as applicable. Plasma concentrations of JNJ-56136379 and NA (ETV or TDF) at FU Weeks 2 and 4 will be determined to assess the elimination of JNJ-56136379 and NA after EOT.

The pharmacokinetic parameters of JNJ-56136379 and NA (ETV or TDF) at steady-state and on Day 1 (treatment with JNJ-56136379 after one dose) will be graphically displayed and descriptive statistics will be performed to determine the multiple dose pharmacokinetic (accumulation ratio) of JNJ-56136379 and NA (ETV or TDF). The pharmacokinetic parameters will be C_{max}, C_{τ}, and AUC_{τ}.

Special attention will be paid to the 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.

PopPK analysis of plasma concentration-time data of JNJ-56136379 will be performed using nonlinear mixed-effects modeling. Data may be combined with those of a selection of Phase 1 studies to support a relevant structural model. Available subject characteristics (eg, demographics, laboratory variables, genotypes) will be tested as potential covariates affecting pharmacokinetic parameters. Details will be given in a popPK analysis plan and results of the popPK analysis will be presented in a separate report.

11.5. Pharmacokinetic/Pharmacodynamic Analyses

Relationships of pharmacokinetic parameters for JNJ-56136379 and NA (ETV or TDF) with selected efficacy and with selected safety endpoints will be evaluated and graphically displayed.

Modeling of key pharmacodynamic parameters (eg, HBsAg, HBV DNA) may be performed using population pharmacokinetics/pharmacodynamics (PK/PD). If PK/PD modeling of key efficacy endpoints is performed, possible covariates such as disease progression and/or treatment effect will be investigated. Other biomarkers may be explored at the sponsor's discretion. Details of the PK/PD analyses will be described in a population PK/PD analysis plan and results will be presented in a separate report.

11.6. Exploratory Pharmacokinetic Analysis of Hormonal Contraceptives

Plasma concentrations of hormonal contraceptives and their metabolites will be summarized by study treatment and displayed graphically. The relationship between JNJ-56136379 exposure and hormonal contraceptive (parent and metabolite) exposure will be evaluated. Further exploration of pharmacokinetic interaction with hormonal contraceptive may be conducted in a physiological-based pharmacokinetics (PBPK) model. Population pharmacokinetics assessments for EE will be applied. Various generalized linear (mixed effects) models will be explored to evaluate the effect of JNJ-56136379 on the exposure of EE. If applied, the details of the PBPK and the population PK modeling approach and its results will be presented in a separate report.

11.7. Exploratory Biomarker Analysis

Statistical approaches to explore correlations between clinical outcome and blood biomarkers vary and depend on the different data types of the applied technology platforms, as well as on the extent of observed differences between subjects. Analyses will be conducted at the sponsor's discretion, will always be under the sponsor's supervision, and results will be presented in the clinical study report or a separate report.

11.8. Pharmacogenomic (DNA) Analyses

The statistical approach for analyzing the exploratory host DNA research may depend on the objective of the analyses (efficacy, safety, and pharmacokinetics) and possibly relevant genes at the time of analysis. Analyses will be conducted at the sponsor's discretion, will always be under

the sponsor's supervision, and results will be presented in the clinical study report or a separate report.

11.9. Patient-Reported Outcome Analyses

PRO scores will be analyzed descriptively by study treatment as mean scores over time, and evaluated based on the proportion of subjects experiencing a clinically important improvement or worsening (if applicable) in PRO scores from baseline during the treatment phase and at the follow-up Week 12 visit (EQ-5D-5L and HBQOL) and follow-up Week 24 visit (MOS-CFS Cog-R and SF-36v2). In addition, effect sizes will be calculated to measure the magnitude of difference between means.[6,11,12]

11.10. Safety Analyses

All subjects who received at least 1 dose of study drug will be included in the safety analysis. Baseline is defined as the last assessment prior to the first study drug administration.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities. Treatment-emergent AEs are AEs with onset during the treatment phase or that have worsened since baseline. For each AE (treatment-emergent and other), the percentage of subjects who experience at least 1 occurrence of the given event will be tabulated by study treatment. In addition, comparisons between treatment groups will be provided if appropriate.

Frequency tabulations, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, or who experience an AE of at least grade 2, at least possibly related, or an SAE.

For this study events of special interest (ESIs) are liver enzyme increases (eg, AST/ALT elevation). All ESIs will be listed in conjunction with other symptoms and laboratory abnormalities: eg, information on time of onset, duration of events, time to resolution, concomitant therapies, and relationship to study treatment.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Descriptive statistics (n, mean, standard error [SE], SD, 95% CI, minimum, median, and maximum) of the actual values and changes from baseline per time point will be tabulated per treatment.

The laboratory abnormalities will be determined according to the criteria specified in the DAIDS Toxicity Grading Scale[7] and in accordance with the normal ranges of the clinical laboratory if no gradings are available.

Based on current data review, for this study cholesterol increased is considered a laboratory abnormality of interest.

The percentage of the subjects who experience (worst) laboratory abnormalities will be tabulated by study treatment.

Electrocardiogram

Descriptive statistics (n, mean, SE, SD, 95% CI, minimum, median, and maximum) for actual values and changes from baseline will be tabulated for the parameters listed below at each scheduled time point, by study treatment.

The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and corrected QT (QTc) interval using the following correction methods: QT corrected according to Bazett's formula, QTcF.[3,13,14,23]

All clinically relevant abnormalities in ECG waveform that are changes from the baseline readings will be reported (eg, changes in T-wave morphology or the occurrence of U-waves).

The abnormalities in ECG parameters will be determined according to the criteria specified in the Cardiovascular Safety – Abnormalities Table (Attachment 2).

The percentage of subjects who experience (worst) abnormalities in ECG parameters will be tabulated by study treatment.

Vital Signs

Descriptive statistics (n, mean, SE, SD, 95% CI, median, minimum, and maximum) for the actual values and changes from baseline per time point will be tabulated for analysis for the following variables, by study treatment: supine SBP, DBP, and pulse rate, and body temperature.

The abnormalities in vital signs will be determined according to the criteria specified in the Cardiovascular Safety – Abnormalities Table (Attachment 2).

The percentage of the subjects who experience (worst) abnormalities in vital signs will be tabulated by study treatment.

Physical Examination

Physical examination results and abnormalities will be listed.

11.11. Interim Analyses

At the Week 12 interim analyses, the sponsor study team will remain blinded to the randomization codes (unless the DRC recommends unblinded analyses, see below) and data will be analyzed using dummy identification and aggregated efficacy summary statistics. At the unblinded Week 24 interim analyses (and subsequent analyses), the sponsor study team members involved in safety monitoring of the treatment extension phase as well as the investigator, site personnel and subjects will remain blinded. The sponsor study team members involved in safety monitoring of the treatment extension phase will remain blinded to the treatment/randomization codes until the end of the treatment extension phase while the investigator, site personnel and

subjects will remain blinded until the end of the study. Note that blinding does not apply to the JNJ-56136379 monotherapy arms.

Interim analyses, encompassing efficacy, safety, and pharmacokinetics, may be conducted for **Part A** and **Part B** at study Week 12, 24, 36, 48 and 72 separately when at least 80% of subjects have completed the respective visit (ie, Week 12, Week 24 for all subjects, FU Week 12/Week 36 and FU Week 24/Week 48 for subjects receiving 24/48 weeks of study treatment, and, FU Week 24 for subjects receiving 48 weeks of study treatment, respectively) or have discontinued earlier (see also Figure 1).

At the sponsor's discretion, 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 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 last study-related follow-up visit or have discontinued earlier.

11.12. Data Review Committee

A DRC, comprised of sponsor personnel outside of the sponsor study team responsible for managing the study, supplemented with an external certified hepatologist, will be established. The DRC will monitor efficacy and safety data in an unblinded manner during study conduct on a regular basis and/or ad hoc in case of emergent safety signals identified through medical monitoring. The DRC will also review interim data and formulate recommended decisions/actions in accordance with the objectives of the interim analysis.

The DRC can also recommend to conduct an additional unblinded interim analysis. The DRC will provide instructions to the sponsor study team with respect to any changes to study conduct that it deems necessary in light of the emerging safety and efficacy data. This may include the addition, modification, or closure of treatment arms. The sponsor, in agreement with the DRC, selected the JNJ-56136379 dose for Part B based on all safety, PK, and antiviral activity data available following completion of the highest JNJ-56136379 dose group (who received 250 mg once daily) in the Phase 1 study 56136379HPB1001 in treatment-naïve CHB-infected subjects treated for 28 days.

The DRC may also endorse any sponsor recommendations for the addition of further parts to the study.

A detailed description of the roles and responsibilities of the DRC will be documented in the DRC charter.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Method of Detecting Adverse Events and Serious Adverse Event

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrence.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Council for Harmonization [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to Section 12.3.1).

Serious Adverse Event

An SAE based on ICH and European Union Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For JNJ-56136379, the expectedness of an AE will be determined by whether or not it is listed in the IB.

Adverse Event Associated With the Use of the Drug

An AE is considered associated with the use of the intervention if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Not Related

An AE that is not related to the use of the intervention.

Doubtful

An AE for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An AE that might be due to the use of the intervention. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An AE that might be due to the use of the intervention. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

An assessment of severity grade will be made by the investigator using the general categorical descriptors outlined in the DAIDS Toxicity Grading Scale[7].

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on a sponsor study intervention that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug.
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject exposure to the sponsor study drug, eg, name confusion)
- Exposure to a sponsor study drug from breastfeeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the eCRF.

12.3. Procedures

12.3.1. All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure, which may include contact for follow-up of safety. Serious AEs, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the SAE Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

All AEs, regardless of seriousness, severity, or presumed relationship to study drugs, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of

the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the SAE Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax).

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drugs or to factors unrelated to study conduct

- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF).
  Note: Hospitalizations that were planned before the signing of the ICFs, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

The cause of death of a subject in a study whether or not the event is expected or associated with the study intervention, is considered an SAE.

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the SAE Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further JNJ-56136379 treatment.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure

appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.3.2). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

JNJ-56136379 supplied for this study is formulated as oral tablets containing 25 mg and 100 mg JNJ-56136379-AAA. It will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.[15]

The matching placebo consists of the oral tablet without active drug substance. The placebo tablets will be manufactured and provided under the responsibility of the sponsor.

The NAs ETV (Baraclude®) and TDF (Viread®) (both commercially available) are formulated as oral film-coated tablets of 0.5-mg and 300-mg strength, respectively. The US-marketed Viread® tablet contains 300 mg TDF which is equivalent to tenofovir disoproxil 245 mg or tenofovir 136 mg.

14.2. Packaging

JNJ-56136379 and placebo will be packaged either as blister cards or in bottles with each unit labeled with a unique medication ID number.

All study drugs will be dispensed in child-resistant packaging.

No study drugs can be repacked without prior approval from the sponsor.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

Commercial supplies will be sourced for NA and a clinical study label will be applied.

14.4. Handling and Storage

JNJ-56136379 must be stored on site in the original package at controlled temperatures ranging from 15°C to 30°C.

The NAs ETV (Baraclude®) and TDF (Viread®) must be stored on site in the original package at controlled temperatures ranging from 15°C to 25°C.

Refer to the pharmacy manual/study site investigational product and procedures manual for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drugs received at the site is inventoried and accounted for throughout the study. The study drugs administered to the subject must be documented on the drug accountability form. All study drugs will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drugs must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drugs must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drugs will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for intervention accountability purposes.

Study drugs should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drugs will be supplied only to subjects participating in the study. Returned study drugs must not be dispensed again, even to the same subject, with the exception of NA (ETV or TDF as per local practice) which can be re-dispensed to the same subject. Study drugs may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- JNJ-56136379 IB and any addenda
- Pharmacy manual/study site investigational product and procedures manual
- Laboratory manual

- Electronic device for assessments of patient-reported symptoms and functioning
- Specimen collection kits for pharmacokinetic, safety blood, and urine samples
- Contact information page(s)
- IWRS manual
- eCRF completion guidelines
- Sample ICF
- Subject diaries

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The total blood volume to be collected is considered to be acceptable.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF(s) (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda

- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF(s) and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study drugs
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICFs that are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

Subjects will be asked for consent to provide optional samples for host DNA (pharmacogenomic) research where local regulations permit. After informed consent for the study is appropriately obtained, the subject will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the

optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the subject.

If the subject is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject is obtained.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory biomarker research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples can only be used for research related to JNJ-56136379, NA (ETV or TDF), CHB infection, or HBV-related disease or may be used to develop tests/assays related to JNJ-56136379, NA (ETV or TDF), or HBV. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.3).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 16.1.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drugs to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator

- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth (as allowed by local regulations). In cases where the subject is not randomized into the study, the date seen and date of birth (as allowed by local regulations) will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; study drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drugs or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the eCRF and will be considered source data:

- Race
- History of smoking (including e-cigarettes or the equivalent of e-cigarettes)
- Blood pressure and heart rate
- Height and weight
- Details of physical examination

The PRO assessments will be completed by subjects on touch-screen computers provided at the study site. The results will be recorded directly into the ePRO database and will be considered source data.

The minimum source documentation requirements for Section 4.1 and Section 4.2 that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the eCRF in the protocol include the electronic source system but information collected through

the electronic source system may not be limited to that found in the eCRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All data relating to the study must be recorded in the eCRF. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documents. Data must be entered into eCRF in English. The eCRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the electronic data capture (eDC) tool. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will use a combination of monitoring techniques as specified in the monitoring guidelines to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will

be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed with the last visit for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject visit at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further development of JNJ-56136379

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a

regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding JNJ-56136379 or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of JNJ-56136379, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of pharmacogenomic or exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication

data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

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ATTACHMENTS

Attachment 1: Contraceptive and Barrier Guidance

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a,b] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of ≤1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*

USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal – injectables
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of >1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[d]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[d]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)
a) Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies. b) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. c) Hormonal contraception may be susceptible to interaction with JNJ-56136379, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with JNJ-56136379. d) Male condom and female condom should not be used together (due to risk of failure with friction).

Attachment 2: 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	-	-

[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.

Attachment 3: Rash Management

For subjects reporting rash, the following should be done.

Subjects should be informed that they should contact their doctor immediately when they notice any skin reaction. The skin reaction should be evaluated in the clinic the same day (if possible) or the next day.

All rash events should be captured in the AE section of the eCRF. A separate Rash page will be completed in case of a rash event.

Grading of rash events will be based on the DAIDS Toxicity Grading Scale.

Monitoring of the evolution of rash events will be performed as described in Table 8.

Table 8: 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). Digital pictures* of skin lesions may be taken at the investigator's discretion. 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 and photography (digital pictures* of skin lesions) may be performed at the investigator's discretion. * Digital pictures to be taken at the clinical site.	Not required
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	Referral to dermatologist at the discretion of the investigator[c] Biopsy not required, but may be performed at the dermatologist's

Table 8: Management of Rash Events by Severity Grade

	Definition	Study Drug Action	Activities by Day[a]	Referral to Dermatologist and Dermatology Activities
			discretion (recommended). Digital pictures* of skin lesions may be taken at the investigator's discretion. Digital pictures* of skin lesions are recommended in case consultation of a dermatologist is required.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. Digital pictures* of skin lesions may be taken at the investigator's discretion. * Digital pictures to be taken at the clinical site.	discretion

Table 8: 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 >$1.00\times10^3/\mu L$ - 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. Digital pictures* of skin lesions may be taken 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: required on-site visit. Safety laboratory assessments required to be performed. Digital pictures* of skin lesions may be taken at the investigator's discretion (recommended). Further visit(s): appropriate follow-up required until resolution of rash or until clinical stability is reached. Safety laboratory assessments and photography (digital pictures* of skin lesions) are recommended to be performed until the rash severity resolves to Grade 2 or Grade 1. * Digital pictures to be taken at the clinical site.	Required[c] Biopsy not required, but may be performed at the dermatologist's discretion.

Table 8: 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. Digital pictures* of skin lesions may be taken 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: required on-site visit. Safety laboratory assessments required to be performed. Digital pictures* of skin lesions may be taken at the investigator's discretion (recommended). Further visit(s): appropriate follow-up required until resolution of rash or until clinical stability is reached. Safety laboratory assessments and photography (digital pictures* of skin lesions) are recommended to be performed until the rash severity resolves to Grade 2 or Grade 1. * Digital pictures to be taken at the clinical site.	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

Table 8: Management of Rash Events by Severity Grade

	Definition	Study Drug Action	Activities by Day[a]	Referral to Dermatologist and Dermatology Activities

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:

- *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.*
- *A copy of the dermatologist's report, and biopsy if performed, should be made anonymous and will be collected by the monitor.*
- *Digital pictures will be de-identified and stored on the sponsor's secure server.*

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.

Attachment 4: 5-level EuroQol 5-Dimension Questionnaire (EQ-5D-5L)

The EQ-5D-5L paper version has been replaced by the tablet version.

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.*	

Attachment 5: Hepatitis B Quality of Life Instrument (HBQOL)

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.

Attachment 6: 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

Attachment 7: 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 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 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 of the time have you had any of the following problems with your work or other regular daily activities? Did work or other activities less carefully than usual 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, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups? Not at all Slightly Moderately Quite a bit Extremely
How much bodily pain have you had during the past 4 weeks? None Very mild Mild Moderate Severe Very Severe

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

During the past 4 weeks, 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
How TRUE or FALSE is the following statement for you? I seem to get sick a little easier than other people. Definitely true Mostly true Don't know Mostly false Definitely false
How TRUE or FALSE is the following statement for you? I am as healthy as anybody I know. Definitely true Mostly true Don't know Mostly false Definitely false
How TRUE or FALSE is the following statement for you? I expect my health to get worse. Definitely true Mostly true Don't know Mostly false Definitely false

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

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

SIGNATURES

Signed by	Date	Justification
PPD	02Aug2019, 15:02:57 PM, UTC	Document Approval