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JNJ-56136379, an HBV Capsid Assembly Modulator, is Well-Tolerated and Has Antiviral Activity in a Phase 1 Study of Patients with Chronic Infection

Short title: JNJ-6379 Phase 1 in Chronic HBV infection

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All authors were involved in drafting and revising this manuscript.

FZ, JZY and OL were involved in the concept and design of the study, and acquisition/collection and analysis/interpretation of data. WT and JF were involved in the concept and design of the study, and analysis/interpretation of data. JJV participated in the concept and design of the study as well as analysis and interpretation of the pharmacokinetic data. AS-C and IM participated in the acquisition/collection of data. TVerbinnen, SB, MB, JC, JMP, CS, TVanwolleghe and US participated in the acquisition/collection and analysis/interpretation of data.

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FZ has participated in Advisory Committees or Review Panels for Janssen Pharmaceuticals, Gilead Sciences, Abbvie, Arbutus, Transgene, Contravir, Myrpharma, Spring Bank. He has received grant/research support from Roche and Sanofi and speaking and teaching support from Gilead Sciences. OL, JJV, WT, TV and US are all employees of Janssen Pharmaceuticals and may be Johnson & Johnson stockholders. IM declares no conflicts of interest. AS-C has received support for speaking and/or as a Principal Investigator for HBV clinical studies from: Arbutus, BMS, Janssen Pharmaceuticals and Gilead Sciences. SB has participated in Advisory Committees or Review Panels for: AbbVie, Gilead Sciences, MSD; Speaking and Teaching: Abbvie, BMS, Gilead Sciences. MB has participated in Advisory Committees or Review Panels for: Arbutus, Gilead Sciences, Janssen Pharmaceuticals, MSD, Roche, Spring Bank Board; Board Membership: Abbvie; She has also received grant/research support from Gilead Sciences, Janssen Pharmaceuticals; and speaking and teaching support from Gilead Sciences, Janssen Pharmaceuticals, and BMS. JC has participated in advisory committees or review panels for Gilead Sciences, Abbvie and MSD; has received grant/research support from Gilead Sciences, MSD/Merck. JMP has received speaking and teaching support from Gilead Sciences, Abbvie, MSD, and BMS. CS has participated in Advisory Committees or Review Panels for: Abbvie, Abbott, Gilead, Janssen, MSD/Merck; Grant/Research Support: Abbott, Gilead, Janssen, MSD/Merck, Siemens; Speaking and Teaching: Abbott, Abbvie, Gilead, Intercept, Janssen, MSD/Merck. TV is the recipient of a mandate of by the Belgian foundation against cancer, grant number 2014-087; has participated in Advisory Committees or Review Panels for: Janssen Pharmaceuticals, Gilead Sciences, Abbvie, BMS, WL Gore. He has also received grant/research support from: Gilead Sciences, Roche, BMS and speaking and teaching support from: Gilead Sciences, BMS. JF was an employee of Alios BioPharma Inc., part of Janssen Pharmaceuticals, at the time of

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All authors had access to the study data, and reviewed and approved the final manuscript.

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BACKGROUND & AIMS: JNJ-56136379 (JNJ-6379), a capsid assembly modulator that blocks hepatitis B virus (HBV) replication, was well tolerated and demonstrated dose-proportional pharmacokinetics in healthy participants in part 1 of its first clinical trial. In part 2, we have evaluated the safety, pharmacokinetics, and antiviral activity of multiple doses of JNJ-6379 in patients with chronic HBV infection.

METHODS: We performed a double-blind study of 57 treatment-naïve patients with HB e antigen-positive or -negative (74%) chronic HBV infection without cirrhosis. Patients were randomly assigned to groups given JNJ-6379 at 25 mg (100 mg loading dose), 75 mg, 150 mg or 250 mg or placebo daily for 4 weeks with an 8-week follow-up period.

RESULTS: Twenty-three of 41 patients (56%) given JNJ-6379 had at least 1 adverse event (AE) during treatment, compared with 10/16 patients (63%) given placebo. No serious AEs were reported during the treatment period. Three patients (7%) given JNJ-6379 vs none given placebo had grade 3 AEs; of these, 1 patient (150 mg) also had an isolated grade 4 increase in level of alanine aminotransferase that led to treatment discontinuation. JNJ-6379 exposure increased with dose, with time-linear pharmacokinetics. HBV-DNA and HBV-RNA decreased from baseline in patients receiving all doses of JNJ-6379, independently of viral genotype and HB e antigen status. On day 29, 13/41 patients (32%) had levels of HBV DNA below the lower limit of quantification. No clinically significant changes in levels of HB surface antigen were observed.

CONCLUSIONS: In a phase 1 study of treatment-naïve patients with chronic HBV infection, all doses tested of JNJ-6379 were well tolerated, showed dose-dependent pharmacokinetics, and had potent antiviral activity in patients with CHB. The findings support a phase 2a study to evaluate JNJ-6379±nucleos(t)ide analogs in patients with chronic HBV infection, which is underway.

ClinicalTrials.gov identifier: NCT02662712

Keywords: HBeAg, HBsAg, liver, drug

Introduction

Current treatments for chronic hepatitis B infection (CHB) often require long-term or life-long administration, and rarely lead to a functional cure.¹ Therefore, there is a need to develop novel targeted treatments for CHB with a finite treatment duration.²

The current optimal goal of therapy for the hepatitis B virus (HBV), referred to as 'functional cure', is defined as sustained undetectable hepatitis B surface antigen (HBsAg) and HBV-DNA in the serum, either with or without seroconversion to hepatitis B surface antibody (anti-HBs), accompanied by improvements of residual liver injury or fibrosis, which should result in a decreased risk of hepatocellular carcinoma over time.^{1,3} Treatment with pegylated interferon alfa is typically for one year, but is associated with frequent and difficult adverse events (AEs) and rarely leads to HBsAg seroclearance.⁴ Although nucleos(t)ide analogues (NA), including entecavir and tenofovir, are efficient in reducing liver inflammation and suppressing viral DNA in serum, low-level viral replication can persist, allowing replenishment of the covalently closed circular DNA (cccDNA) pool and resulting generally in relapse when NA treatment is stopped. Therefore, NA treatment is usually given life-long. Functional cure rates (i.e. HBsAg seroclearance) with NA treatment are low, at <1%/year in HBeAg-negative patients and 0–3%/year in HBeAg-positive patients.^{3,5}

The HBV core protein forms viral capsids containing HBV polymerase bound-pre-genomic RNA (pgRNA), which is reverse transcribed to viral DNA. Capsid assembly modulators (CAMs) interrupt this process by binding to HBV core proteins and interfering with encapsidation of pgRNA and formation of viral nucleocapsids. There are a number of CAMs in clinical development^{6,7} including, ABI-H0731,⁸ GLS4-JHS,⁹ RO7049389,¹⁰ JNJ-0440,¹¹ and JNJ-6379^{12–14} (more potent than NVR 3-778¹⁵), each with the potential to counter HBV by blocking encapsidation of pgRNA and/or degrading capsids. However, it is not possible to evaluate the relative antiviral activity of these CAMs, as head-to-head clinical trials have not been conducted. Interestingly, recently it was reported that the combination of ABI-H0731 with a NA resulted in additive effect on HBV DNA decline.⁸

Indeed, there are at least two classes of CAMs; recently proposed as CAM-A and CAM-N.¹⁶ CAM-A produce aberrant core structures, preventing encapsidation of pgRNA within capsids of the correct shape and size, and CAM-N induce formation of 'empty' capsids with the normal shape and size but devoid of RNA or DNA. CAMs have been proven to inhibit secretion of both HBV-DNA and HBV-RNA containing particles.^{17,18}

JNJ-56136379 (JNJ-6379) is a CAM-N that binds to the HBV core protein and interferes with the HBV viral life cycle at two steps.^{12,14,19} The 'primary' mode of action is to accelerate the kinetics of capsid assembly, forming intact 'empty' capsids and preventing encapsidation of pgRNA, which inhibits the release of HBV-RNA and HBV-DNA containing particles. In contrast, although NAs have been proven to inhibit viral replication and virion production, they do not prevent encapsidation of pgRNA and subsequent release of HBV-RNA containing particles.⁴ Additionally, in cultured hepatocytes, JNJ-6379 has been shown to inhibit *de novo* cccDNA formation dose-dependently during new infection and prevent cccDNA formation. Hence, JNJ-6379 may prevent replenishment of cccDNA during new rounds of infection *in vivo*. However, the 50% effective concentration (EC₅₀) of JNJ-6379 to interfere with capsid assembly (median EC₅₀ 93 nM, i.e. its 'primary' mechanism of action) is lower than the EC₅₀ for the prevention of *de novo* cccDNA formation (median EC₅₀ 876 nM, 'secondary' mechanism of action). Hence, higher JNJ-6379 concentrations in patients are likely to be required to achieve concentrations to engage the 'secondary' mechanism of action than those required for the 'primary' mechanism of action.¹²⁻¹⁴

This Phase 1, first-in-human study (NCT02662712) was conducted in two parts. In Part 1, 30 healthy volunteers received JNJ-6379 as single oral doses of up to 600 mg, or multiple ascending doses of 150 mg for two days followed by 100 mg once a day (QD) for 10 days.¹⁴ Pharmacokinetics of JNJ-6379 were dose proportional, clearance was low, and JNJ-6379 had a long half-life, supporting administration as QD doses.¹⁴ JNJ-6379 was well tolerated, with no dose-limiting toxicities or serious AEs.¹⁴ Most AEs were mild (grade 1) to moderate (grade 2) in severity, with only three study discontinuations.¹⁴ In the single-ascending dose phase, one volunteer discontinued after receiving 50 mg JNJ-6379 because of grade 3 pancreatic lipase and grade 2 amylase elevations not associated with clinical symptoms or signs, and considered mild in severity and very likely related to study drug.¹⁴ Another discontinuation after 150 mg JNJ-6379 was due to vertigo of moderate severity and considered possibly related to study drug. In the multiple-ascending dose phase, one volunteer discontinued because of lower abdominal pain and dizziness postural, both mild in severity and considered possibly related to study drug.¹⁴

Part 2 of the study, presented in this publication, was conducted in treatment-naïve, HBeAg-positive and HBeAg-negative patients with CHB infection, and was designed based on the safety, tolerability and pharmacokinetic results obtained from healthy volunteers. The primary objective of Part 2 was to assess safety and pharmacokinetics of JNJ-6379 in patients with untreated CHB, and the secondary objective was to assess antiviral activity.

Methods

Study Design

Patient Population

This double-blind, randomized, placebo-controlled study was conducted in treatment-naïve patients with HBeAg-positive or negative CHB. Patients were included (see supplementary materials) if they had plasma HBV-DNA ≥ 2000 IU/mL, were non-cirrhotic (Metavir stage $\leq F2$, as estimated by either liver biopsy or fibroscan assessment^{20,21}), and had alanine aminotransferase (ALT) levels less than 2.5 times the upper limit of normal (ULN). In order to facilitate recruitment, the original inclusion criteria for HBV-DNA was amended during the study from a cut-off of $\geq 20,000$ IU/mL to a cut-off of ≥ 2000 IU/mL, which was considered to be a sufficient level to evaluate the antiviral activity of JNJ-6379 and is in line with the recommended EASL indications for treatment.³ Exclusion criteria (see supplementary materials) included: co-infection with hepatitis A, C, D, or E, or human immunodeficiency virus type 1 (HIV-1) or HIV-2; a history of cardiac arrhythmias; one or more laboratory abnormalities at screening as defined by the World Health Organization Toxicity Grading Scale, excluding aspartate transaminase (AST) or ALT elevation; positive anti-HBs antibodies; evidence of hepatic decompensation, portal hypertension, or hepatocellular carcinoma; liver disease not related to HBV; a platelet count below normal range; or an elevated α -fetoprotein at screening. Originally, there was a requirement for a minimum number of hepatitis B e-antigen (HBeAg)-positive patients in each dose group, although this requirement was removed in order to improve the ease of recruitment (full details of inclusion criteria provided in the supplementary material). The study was approved by the relevant local independent ethics committees and regulatory authorities and conducted in compliance with Good Clinical Practice and applicable regulatory requirements. All patients provided written, informed consent to participate in the study. All authors had access to the study data, and reviewed and approved the final manuscript.

Study Dosing

Patients were randomized to receive JNJ-6379 or placebo in five dosing groups of 25 mg (2:1 ratio), 75 mg (two groups: Asian sites 2:1; European sites 3:1), 150 mg or 250 mg (both 3:1 ratio). Based on pharmacokinetic data from Part 1 that suggested a higher bioavailability under fed conditions,¹⁴ treatment was administered under fed conditions for a total of 28 days (4 weeks). For blinding/unblinding procedures see supplementary material.

The initial group received a starting dose of 100 mg JNJ-6379 on Day 1 (with the aim to reach a concentration 3 x the 90% effective concentration [EC₉₀] as obtained in primary human

hepatocytes¹² quickly) followed by 25 mg QD for 27 days, based on plasma concentrations observed in healthy volunteers in Part 1 of the study.¹⁴ The dose levels selected were expected to result in a steady state concentration approximately three times that required to inhibit viral replication *in vitro* (EC₉₀ of 226 nM in a stable replicating HepG2.117 cell line).^{12,14} Dosing was conducted sequentially; higher dose groups were initiated based on a review of available safety, tolerability, and pharmacokinetic data from the previous dose level.

In order for direct comparisons of potential pharmacokinetic, safety and antiviral activity differences due to HBV genotype between Asian and Caucasian participants, one 75 mg group was conducted at sites in Europe only with the other group conducted at sites in Asia only. The 25 mg group was conducted at European sites, and the remaining groups were evaluated at both European and Asian sites.

All patients were assessed regularly throughout the 4-week treatment period and for 8 weeks' post-treatment (see protocol; supplementary information).

End points

The co-primary end points were to evaluate safety and tolerability, and pharmacokinetic parameters, of multiple dose regimens of JNJ-6379 in patients with CHB infection. Secondary end points included: evaluation of antiviral activity, including changes in HBV-DNA, HBsAg and HBeAg levels from baseline to end of treatment and follow-up, and/or HBeAg seroconversion; the relationship between pharmacokinetics/pharmacodynamics and safety, and antiviral activity; impact of baseline HBV amino acid sequence variations and viral genotype on antiviral activity; and emergence of treatment-induced mutations in the HBV genome.

Exploratory endpoints included changes in serum HBV-RNA, which may be predictive of serological response,²² and hepatitis B core related antigen (HBcrAg), which correlates with cccDNA amount and activity.²³

Study Evaluations

Safety and tolerability

Safety and tolerability were assessed in all patients throughout the study and during follow-up. AEs were coded using Medical Dictionary for Regulatory Activities terms (version 21.0). Blood samples for biochemistry, blood coagulation and hematology, and urine samples for urinalysis were collected at pre-specified time points throughout the study duration. Electrocardiogram (ECG) and vital signs were also assessed at on-site visits.

Pharmacokinetics

Venous blood and urine samples were collected at pre-specified time points and analyzed to determine concentrations of total JNJ-6379. Plasma samples were analyzed using a validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) method, and urine samples were analyzed using a validated LC-MS/MS method, as used in Part 1.¹⁴ Pharmacokinetic parameters were estimated using non-compartmental analysis (Phoenix™ WinNonlin®, version 6.2.1, Tripos LP, USA) and included maximum observed plasma concentration (C_{max}), minimum plasma concentration (C_{min}), time to reach the maximum observed plasma concentration (t_{max}), and area under the curve from time of administration to 24 hours postdose (AUC_{24h}), on Days 1, 10, 15, and 28. Urine samples were assessed for excreted unchanged drug and renal clearance on Days 1 and 28. In order to allow an accurate comparison between Asian and Caucasian patients, pharmacokinetic results were corrected for body weight.

Antiviral Activity

HBV-DNA, HBV-RNA, and serology levels were determined from plasma samples collected before dosing on Day 1, and at pre-specified intervals throughout the study (see protocol; supplementary information). Plasma HBV-DNA levels were assessed at the central lab (Covance) using a Roche COBAS AmpliPrep/COBAS TaqMan HBV Test, v2.0, and mean changes from baseline (day prior to intake of study drug) were calculated. HBV-DNA lower limit of quantification (LLOQ) and limit of detection (LOD) was defined as 20 IU/mL. When HBV-DNA was detected by the assay but not quantifiable (i.e. was <20 IU/mL; target detected), results were imputed using an arbitrarily chosen value of 15 IU/mL for statistical analyses. When HBV-DNA was <20 IU/mL but not detected by the assay, a value of 5 IU/mL was imputed. Serum HBV-RNA was assessed at DDL Diagnostic Laboratory (Netherlands) using a validated qRT-PCR assay, which had an LOD of 2.49 log₁₀ cp/mL and an LLOQ of 4.04 log₁₀ cp/mL. For the exploratory analyses, all values detected were considered as quantitative values, and samples which were not detected by the assay were imputed with 5 cp/mL (0.7 log₁₀

cp/mL). HBcrAg was assessed using the Lumipulse platform (Fujirebio), which detects HBeAg, HBcAg and p22cr protein with a LLOQ of $3.0 \log_{10}$ U/mL and a LOD of $2.0 \log_{10}$ U/mL. For analysis purposes HBcrAg levels $<3.0 \log_{10}$ U/mL and $\geq 2.0 \log_{10}$ U/mL were arbitrarily imputed with $2.7 \log_{10}$ U/mL and HBcrAg $<2.0 \log_{10}$ U/mL with $1.7 \log_{10}$ U/mL. Qualitative and quantitative HBsAg and HBeAg levels were assessed using Abbott Architect™ assays. Anti-HBs and anti-HBe antibodies were determined using chemoluminescence immunoassays and/or enzyme-linked immunosorbent assay based assays. HBV virological breakthrough was defined as an on-treatment HBV-DNA increase by $>1 \log_{10}$ from the lowest recorded level or confirmed on-treatment HBV-DNA level >100 IU/mL in patients with HBV-DNA levels below the LLOQ.

HBV Genome Sequencing

The HBV genome was sequenced before and during treatment to monitor HBV variants present. Serum samples were collected at pre-specified time points during the study; HBV-DNA was extracted, and the full HBV genome was sequenced using next generation Illumina sequencing. Baseline amino acid polymorphisms were defined as changes versus the universal HBV reference sequence (NCBI ID X02763; considered if frequency of variant $>15\%$). The analysis focused on 28 HBV core protein amino acid positions within the CAM binding pocket.^{24–26} Selected mutations were defined as amino acid changes from patient-specific baseline sequences (frequency $<1\%$ at baseline and $\geq 15\%$ post-baseline). The impact of amino acid substitutions on JNJ-6379 in-vitro activity was assessed in a transient replication assay using a genotype D backbone.

Statistical Analyses

All patients who received JNJ-6379 were included in the safety, antiviral activity and pharmacokinetic analyses. Descriptive statistics (sample size [n], mean, standard deviation [SD], standard error [SE], median, and range) were calculated for continuous variables where appropriate.

Results

Patient Flow and Baseline Characteristics

Patients were enrolled into the study from 21 April 2016 to 09 April 2018 at 18 sites across nine countries in Europe and Asia. Overall, 205 potential participants consented and were assessed for eligibility; 130 participants failed to meet eligibility criteria (see supplementary materials) and 18 were excluded for other reasons, resulting in 57 patients being randomized (**Supplementary Figure 1**). The baseline demographics of all 57 patients are provided in **Table 1**. Patients were broadly comparable in terms of age, weight and body mass index across the five dosing groups and the pooled placebo group. Patients were predominantly male (75%) and White (67%). In the overall study population Metavir fibrosis scores, as predicted from elastography, were mainly F0/1, with 12% of patients having a fibrosis score of F2. Most of the sites participating were European, and as such the majority of patients enrolled had HBV genotype D (51%). Most patients (74%) were HBeAg-negative. Of note, patients in the groups evaluating higher JNJ-6379 doses had lower baseline HBV-DNA, which was consistent with fewer HBeAg positive patients; this trend was likely due to changes made to the inclusion criteria for HBV-DNA (see study design), along with removing the need for a minimum number of HBeAg-positive patients in each group. Mean baseline HBsAg levels were similar among all groups.

Safety and Tolerability

Overall, 56% (23/41) of patients receiving JNJ-6379 experienced at least one AE during the 28-day treatment period, compared with 63% (10/16) of patients on placebo (**Table 2**). The frequency and severity of AEs did not appear to have any relationship with the dose of JNJ-6379. 90% (20/23) of on-treatment AEs were mild or moderate (grade 1 or 2). The most commonly occurring AE was headache, which occurred in six patients on JNJ-6379, and seven patients on placebo (**Table 2**). Three of 41 (7%) patients who received JNJ-6379 had on-treatment grade 3 AEs (one in each of the 25 mg, 75 mg and 150 mg groups). One patient in the 25 mg group had an isolated grade 3 elevation in pancreatic amylase, which normalized on Day 8 with continued treatment. In the Caucasian 75 mg JNJ-6379 group, the grade 3 AE was an on-treatment grade 3 ALT elevation, which was grade 4 by follow-up Week 2–4, and NA therapy was introduced (**Supplementary Information**). This patient had 1–2 log₁₀ increases in HBeAg, HBV-DNA and HBV-RNA prior to treatment from screening to baseline. Reductions in HBV-DNA and HBV-RNA were observed on-treatment, which were not visibly affected by the grade 3 ALT elevation. The grade 4 elevation was accompanied by increased HBV-DNA during the follow up period, suggesting that this finding may be attributed to disease activity (**Supplementary Figure 2**). One patient in the 150 mg group had a grade 3 AST increase and a grade

4 ALT increase on Day 8 without any other laboratory or clinical symptoms, leading to treatment discontinuation as per protocol-defined criteria; the ALT/AST decreased and normalized over 16 days post-treatment discontinuation. The ALT/AST increase was accompanied with a decrease in HBV DNA. See Supplementary material for further information on the four patients who experienced a \geq grade 3 AE considered to be at least possibly related to study treatment. No clinically significant ECG changes or persistent/worsening vital sign abnormalities were observed. No serious AEs (SAEs) occurred during treatment. One patient experienced a SAE of right frontal lobe mass during follow-up, which was considered to be unrelated to the study drug. No deaths occurred during treatment or follow-up.

Treatment-emergent laboratory abnormalities were most commonly grade 1 or 2. Nineteen patients (46%) treated with JNJ-6379 experienced on-treatment \geq grade 2 laboratory abnormalities, compared with five patients (31%) in the placebo group (**Table 3**).

Pharmacokinetics

After repeat-dose administration, JNJ-6379 exposure increased in a dose-dependent manner, with time-linear pharmacokinetics. Mean C_{\max} (dose normalized to 25 mg) after 4-weeks of therapy was similar between all JNJ-6379 dose groups, ranging from 1329 ng/mL in the 75 mg Caucasian group, to 1832 ng/mL in the 75 mg Asian group. However, t_{\max} ranged from 2 hours in the 250 mg group to 12 hours in the 75 mg Asian group. Mean dose-normalized AUC_{24h} after 4-weeks of therapy was similar among all dose groups, ranging from 26,718 ng·h/mL in the 250 mg group to 36,202 ng·h/mL in the 75 mg Asian group. Renal clearance after 4 weeks was low, and similar across all doses, ranging from 0.127 L/h in the 25 mg group to 0.205 L/h in the 150 mg group. At the end of treatment, fluctuations in the pharmacokinetic profiles were moderate to low. JNJ-6379 is metabolized via the CYP3A4 pathway, and mean half-life ranged from 103–148 hours. In-line with this long terminal half-life, plasma concentrations of JNJ-6379 gradually became undetectable, with all patients reaching undetectable levels by Day 85 (**Figure 1**). The shapes of the plasma concentration-time concentration curves were similar for each dosing group (**Figure 1**). For most of the dosing period, JNJ-6379 concentrations remained above the EC_{90} of viral replication *in vitro*; C_{\min} on Day 28 ranged from 1009 ng/mL in the 25 mg group to 9373 ng/mL in the 250 mg group. Compared with healthy volunteers in Part 1, mean plasma clearance was lower and half-life was longer. For patients experiencing AEs grade 3 or higher, pharmacokinetic parameters were in line with other patients receiving the same dose regimens.

Antiviral Activity

A substantial reduction in HBV-DNA levels was observed in all groups during the treatment period from Day 2 of JNJ-6379 administration (**Figure 2**). At Day 29, mean (SD) HBV-DNA change from baseline was lowest in the 25 mg group ($-2.16 [0.49] \log_{10}$ IU/mL), with greater changes observed in the higher JNJ-6379 dose groups (range: $-2.70 [0.33]$ to $-2.92 [0.58] \log_{10}$ IU/mL), compared with a change of $-0.11 (0.34) \log_{10}$ IU/mL in patients receiving placebo (**Table 4**). HBV-DNA <LLOQ at the end of the treatment period was most frequent in the 250 mg group, occurring in 5/9 (57%) patients. Additionally, 3 patients in each of the 150 mg and 75 mg Caucasian groups, and 2 patients in the 75 mg Asian group achieved HBV-DNA <LLOQ at Day 29 (**Table 4; Supplementary Figure 3**). HBV-DNA decrease did not differ substantially between HBeAg-negative and HBeAg-positive patients, or between viral genotypes across all dosing groups (**Supplementary Figure 3**). No virological breakthrough was observed during the 4-week administration period.

The long plasma half-life and low clearance of JNJ-6379 meant that, in all patients, HBV-DNA levels gradually returned to, or towards, baseline after completion of study medication (**Supplementary Figure 4**). Consistent with the faster return to pre-treatment levels and levels <EC₉₀ during follow up in the lower dose groups, mean (SD) time to rebound (i.e. a $1 \log_{10}$ IU/mL increase from Day 29 value) was faster in the 25 mg group (20.2 [8.0] days) than in the 250 mg group (40.8 [12.0] days).

Consistent with HBV-DNA decline, potent HBV-RNA reductions were observed across all dose groups (**Table 4; Supplementary Figure 5**). However, given the baseline HBV-RNA levels, which were lowest in the higher dose groups and undetectable in some patients (**Table 4**), as well as the level of sensitivity of the HBV-RNA assay, maximal observable HBV-RNA declines were limited. Mean (SD) HBV-RNA reduction at Day 29 ranged from $1.43 \log_{10}$ cp/mL to $2.58 \log_{10}$ cp/mL, with 8/9 patients in the 250 mg group having undetectable HBV-RNA by the end of treatment (**Table 4**). HBV-RNA levels increased in all dosing groups following cessation of treatment (**Supplementary Figure 5**). In the one patient who started NAs during follow up, HBV-RNA continued to increase while HBV-DNA decreased, consistent with the mode of actions of NAs, which in contrast to CAMs do not directly inhibit the release of HBV-RNA-containing particles (**Supplementary Figure 2**).

Seventeen of 42 (40%) HBeAg-negative patients had HBcrAg levels $\geq 3.5 \log_{10}$ U/mL at baseline, sufficient to determine a $\geq 0.5 \log_{10}$ U/mL reduction in HBcrAg, of which 12 JNJ-6379-treated and 4 placebo-treated patients also had available Day 29 data. Treatment with JNJ-6379 for 28 days resulted in $\geq 0.5 \log_{10}$ U/mL (range 0.7 to 1.7) declines in HBcrAg from baseline in 6/12 (50%) HBeAg-

negative patients (75 mg Asian, n=1; 75 mg Caucasian, n=2; 150 mg, n=3) with baseline HBcrAg ≥ 3.5 log₁₀ U/mL, compared with 0/4 patients receiving placebo (**Supplementary Figure 6**). Five of 6 patients with ≥ 0.5 log₁₀ U/mL decline in HBcrAg had baseline ALT $>1\times$ ULN and $<2.5\times$ ULN. Among the 10 JNJ-6379-treated HBeAg-positive patients, one Caucasian patient treated with 75 mg JNJ-6379 experienced on-treatment decline of ≥ 0.5 log₁₀ U/mL in HBcrAg, compared with 0/5 placebo-treated patients (**Supplementary Figure 7**). This patient experienced grade 1 and 2 ALT elevation on-treatment, and grade 3/4 ALT elevation during follow-up. No changes in HBsAg or HBeAg were observed for any of the dose levels studied over a 4-week dosing period (mean changes in HBsAg from baseline at Day 29 ranged from -0.005 to +0.03 log₁₀ IU/mL, and mean changes in HBeAg ranged from -0.04 to +0.06 log₁₀ IU/mL across the JNJ-6379 dosing groups and placebo).

HBV Genome Sequencing

Baseline sequence data was available for 52/57 (91%) patients (data were unavailable in 5 patients, most likely because of sequence-specific differences between the respective sequences and primers used), and 28/52 (54%) patients had ≥ 1 polymorphism at any of the 28 HBV core protein amino acid positions of interest. Two patients had a baseline polymorphism known to reduce JNJ-6379 activity *in vitro* (Y118F, resulting in a 6.6 fold-change in the EC₅₀ value); one patient (75 mg Caucasian group) had a pronounced decline in HBV-DNA levels from baseline (2.77 log₁₀ IU/mL) at Day 29 and had reached HBV-DNA $< \text{LLOQ}$ by Day 21 (**Supplementary Figure 3**), while the other patient (150 mg group) had slower initial HBV-DNA decline than other 150 mg JNJ-6379-treated patients, but HBV-DNA decline continued until the end of treatment with a maximum decline of 2.19 log₁₀ IU/mL. Paired baseline and post-baseline sequences were available for 29 patients treated with JNJ-6379. Of these, one patient enrolled in the 150 mg group had selected T109S (JNJ-6379 FC value of 1.8) at follow-up Week 12 visit. This patient experienced a potent HBV DNA decline of 3.18 log₁₀ IU/mL at the end of treatment.

Comparison Between Caucasian and Asian 75 mg JNJ-6379 Dosing Groups

In the two 75 mg dosing groups, all patients were Caucasian at European sites, and Asian at Asian sites. Mean baseline HBV-DNA was similar between the Caucasian and Asian patients. Viral genotypes were A or D for the Caucasian patients, and B or C for the Asian patients treated with 75 mg. Mean weight was numerically lower in Asian patients than in Caucasian patients (**Table 1**).

No major differences were seen in the safety profiles. Among patients treated with the 75 mg dose, 57% in the Asian group and 50% in the Caucasian group reported an AE (**Table 2**). No SAEs or deaths occurred in any patients.

Following 29 days of dosing at 75 mg, mean (SD) change in HBV-DNA was -2.89 (0.48) log₁₀ IU/mL in the Asian group, and -2.92 (0.58) log₁₀ IU/mL in the Caucasian group; at the end of treatment, HBV-DNA was below LLOQ for two and three patients, respectively (**Table 4**).

Mean apparent clearance was lower in the 75 mg Asian group (0.754 L/h), compared with 0.928 L/h in the Caucasian group. Higher dose normalized C_{max} and AUC values were observed in the 75 mg Asian group than in the 75 mg Caucasian group. However, after correction for body weight, dose-normalized apparent clearance was broadly comparable between Caucasian and Asian patients, supporting use of JNJ-6379 in Asian patients without dose modification (**Supplementary Figure 8**).

Discussion

Through interfering with pgRNA encapsidation and assembly of viral nucleocapsids in infected hepatocytes, CAMs, including JNJ-6379, are able to target the viral life cycle in a different way from currently available treatments for CHB. Additionally, JNJ-6379 prevents *de novo* cccDNA formation during new rounds of infection in cultured hepatocytes, potentially by preventing disassembly of viral nucleocapsids.^{4,27} In contrast, it has been shown that low level viral replication persists in receiving long-term treatment with NAs.²⁸ As such, JNJ-6379 may offer a novel treatment concept for CHB that may reduce the pool of intrahepatic cccDNA by more efficiently inhibiting HBV replication than achieved with NAs alone.

In this study, JNJ-6379 administered orally for 28 days at doses up to 250 mg QD was well tolerated and demonstrated potent antiviral activity in treatment-naïve patients with CHB. These observations were consistent across genotypes, HBeAg-positive and -negative patients, and in one Asian cohort as well as Caucasian patients, supporting use in all of these subgroups without dose modifications. The ongoing Phase 2a study, which includes a larger number of study sites (including Asia), will evaluate this further. Two patients carried the HBV core protein baseline polymorphism Y118F (6.6-fold change in the *in vitro* EC₅₀ value), with no consistent impact on JNJ-6379 virological response during this 4-week study. No virological breakthrough was observed during JNJ-6379 treatment. Additional studies with longer administration periods will be required to further investigate the frequency of virological breakthrough.

In Part 1 of this study in 30 healthy volunteers, JNJ-6379 was well tolerated, with all AEs reported as mild (grade 1) to moderate (grade 2) in severity.¹⁴ There were no SAEs, dose-limiting toxicities, or apparent relationship to dose for any AE, and the most frequently occurring AE was headache.¹⁴ Consistent with data from Part 1, these same findings were observed in Part 2 of the study in CHB patients. In the single-ascending Part 1 of the study, three healthy volunteers experienced a treatment-emergent grade 1 increase in ALT, one receiving 150 mg, one receiving 50 mg then 300 mg after a ≥ 14 -day washout period, and one receiving 300 mg then placebo after the washout period. No other treatment emergent ALT increases were noted in the single- or multiple-dose ascending phases.¹⁴ In Part 2, in one CHB patient treated with JNJ-6379 150 mg, isolated grade 4 ALT/grade 3 AST increases occurred during the first 8 days of treatment and led to discontinuation. ALT/AST decreased and normalized over 16 days post-treatment discontinuation. ALT flares are a result of the altered cytolytic immune response against HBV infected hepatocytes, occur spontaneously during the course of chronic infection, and have been reported during treatment with pegylated interferon alfa and NAs.²⁹ Future clinical trials in CHB with JNJ-6379 should frequently monitor not only ALT/AST but also other liver function parameters, as well as signs and symptoms of hepatic dysfunction. Recent guidance³⁰ (based on FDA recommendations)³¹ on endpoints of clinical trials in CHB highlights the importance of closely monitoring all patients for ALT flares. In cases of excessive ALT elevation and/or signs and symptoms of hepatic dysfunction, the investigational agent should be discontinued and treatment with an NA (such as tenofovir or entecavir) initiated, based on investigator judgement.

JNJ-6379 pharmacokinetics were dose-proportional in treatment-naïve patients with CHB. Additionally, patients experiencing AEs \geq grade 3 had pharmacokinetic profiles of JNJ-6379 in line with the other patients in their respective dose groups, suggesting no relationship between JNJ-6379 exposure and safety.

CHB patients treated with JNJ-6379 experienced substantial decreases in HBV-DNA during 28 days of therapy, with some patients in the higher-dose groups achieving HBV-DNA $< \text{LLOQ}$ ($< 20 \text{ IU/mL}$) by Day 29. A smaller decrease in HBV-DNA was observed in the 25 mg JNJ-6379 group than in the patients receiving 75 mg or higher. Mean HBV-DNA reductions did not increase with increasing doses beyond 75 mg, although the highest proportion of patients achieving HBV DNA $< \text{LLOQ}$ was in the 250 mg JNJ-6379 group. This finding may have been due to the lower baseline HBV-DNA levels in the higher dose groups, coupled with a number of patients achieving HBV-DNA $< \text{LLOQ}$, meaning a maximal decline in HBV-DNA could not be established. The magnitude of observed HBV-DNA

changes in groups receiving JNJ-6379 doses of 75 mg and above (-2.70 to $-2.92 \log_{10}$ IU/mL) were similar to those observed previously with NAs. Following 28 days of treatment, patients receiving entecavir (0.05–1.0 mg) experienced a mean decrease in HBV-DNA of 2.21 to 2.81 \log_{10} IU/mL;³² and patients on tenofovir (alafenamide, 8–120 mg; disoproxil fumarate, 300 mg) had mean HBV decreases of 2.2 to 2.8 \log_{10} IU/mL.³³ In previous 28-day phase I studies, with two other CAMs NVR 3-778 and ABI-H0731, a mean (SE) HBV DNA reduction of 1.43 (0.25) \log_{10} IU/mL was reported with NVR 3-778 600 mg twice daily,¹⁵ and a mean (95% confidence interval) maximal reduction of 2.8 (2.0–3.6) \log_{10} IU/mL with a 300 mg dose of ABI-H0731.⁸ However, comparison of HBV DNA declines between studies need to be considered cautiously given potential differences in patient characteristics, as well as the fact that different proportions of patients with HBV DNA below the LLOQ can influence the mean changes reported.

Potent declines in HBV-RNA were observed across all dose groups, although a dose-proportional trend in HBV-RNA decrease could not be established since the theoretical maximal possible decline was limited by low baseline HBV-RNA levels, which were lowest in highest dose groups, and the quantification limits of the assay. These potent decreases in HBV-DNA and HBV-RNA are expected based on the ‘primary’ mode of action of JNJ-6379, i.e. accelerating the formation of ‘empty’ capsids that do not contain pgRNA, thus inhibiting the release of RNA- and DNA-containing viral particles. This is in contrast to the mechanism of action of NAs, which only reduce HBV-DNA levels and do not affect HBV-RNA levels directly. This is illustrated by the one patient who had pronounced reductions in HBV-DNA and HBV-RNA during treatment, and upon discontinuation of JNJ-6379 and starting NAs during follow-up, experienced a decrease in HBV-DNA, while HBV-RNA continued to increase. This effect has also been previously reported with a different CAM of the same class.⁸

Following 28 days of treatment with JNJ-6379, a $\geq 0.5 \log_{10}$ U/mL reduction in HBcrAg levels occurred in a subset of patients, mainly in those with ALT $>1 \times \text{ULN}$ and $<2.5 \times \text{ULN}$. No relevant changes in HBeAg (in HBeAg-positive patients) or HBsAg were noted following short-term JNJ-6379 treatment, suggesting that the HBcrAg reductions observed in some patients could possibly be due to direct inhibition of release of the HBV core protein, and not a decline in the pool of cccDNA that could have resulted in a decline of HBeAg and HBsAg. A decline of cccDNA was not expected in the short study duration. This finding will be examined further with longer term JNJ-6379 dosing in Phase 2a (NCT03361956).

The dual mechanism of action of this CAM-N, with the potential to prevent both new infections and *de novo* cccDNA formation, may offer an additional benefit compared with available HBV therapies.^{12,13,17–19} The exposures achieved with the higher doses of JNJ-6379 in this study are expected to engage the ‘secondary’ mechanism of action of JNJ-6379, i.e. the inhibition of *de novo* cccDNA formation, since C_{min} values achieved with 250 mg JNJ-6379 are multiples times above the EC_{90} value for this mechanism of action *in vitro*. It is widely recognized that combinations of antiviral therapy suppressing multiple steps in the HBV lifecycle will likely be needed to achieve a functional cure.^{1,3} Combining CAM-Ns with NAs or other drugs with novel mechanisms may have the potential to enhance antiviral response or increase the rate of functional cure. However, further studies with longer treatment duration of JNJ-6379 in combination with an NA and/or other agents are required to assess the potential value of JNJ-6379 in future HBV treatment regimens.

A limitation of the study is the change of inclusion criteria that occurred during the course of the study, which resulted in a low number of HBeAg positive patients and a low mean HBV-DNA level in the higher dose cohorts. While no impact on antiviral activity is expected, this limited the establishment of a dose response since a high proportion of patients in the lower dose groups reached HBV below the LLOQ during the study.

In the ongoing Phase 2a study, JNJ-6379 QD at doses of 75 mg and 250 mg for 24–48 weeks are being evaluated alone and in combination with NAs in currently untreated and virologically-suppressed patients with HBeAg-positive or -negative CHB. In addition, another clinical study is ongoing assessing JNJ-6379 in combination with the short-interfering RNA JNJ-3989 and an NA.

In conclusion, these results suggest that administration of JNJ-6379 was well tolerated for up to 28 days and demonstrates potent antiviral activity in patients with CHB, which justifies the evaluation of longer treatment durations in a larger cohort of patients in an ongoing Phase 2a study.

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Figure legends

Figure 1. Semi-Log mean plasma concentrations of JNJ-6379 after administration of multiple doses of JNJ-6379 for 28 days, and during follow up

Figure 2. Mean (SD) changes in HBV-DNA up to Day 29 during treatment with JNJ-6379 at doses of 25 mg, 75 mg, 150 mg, and 250 mg, and placebo

Plasma conc. of JNJ-6379 (ng/mL)

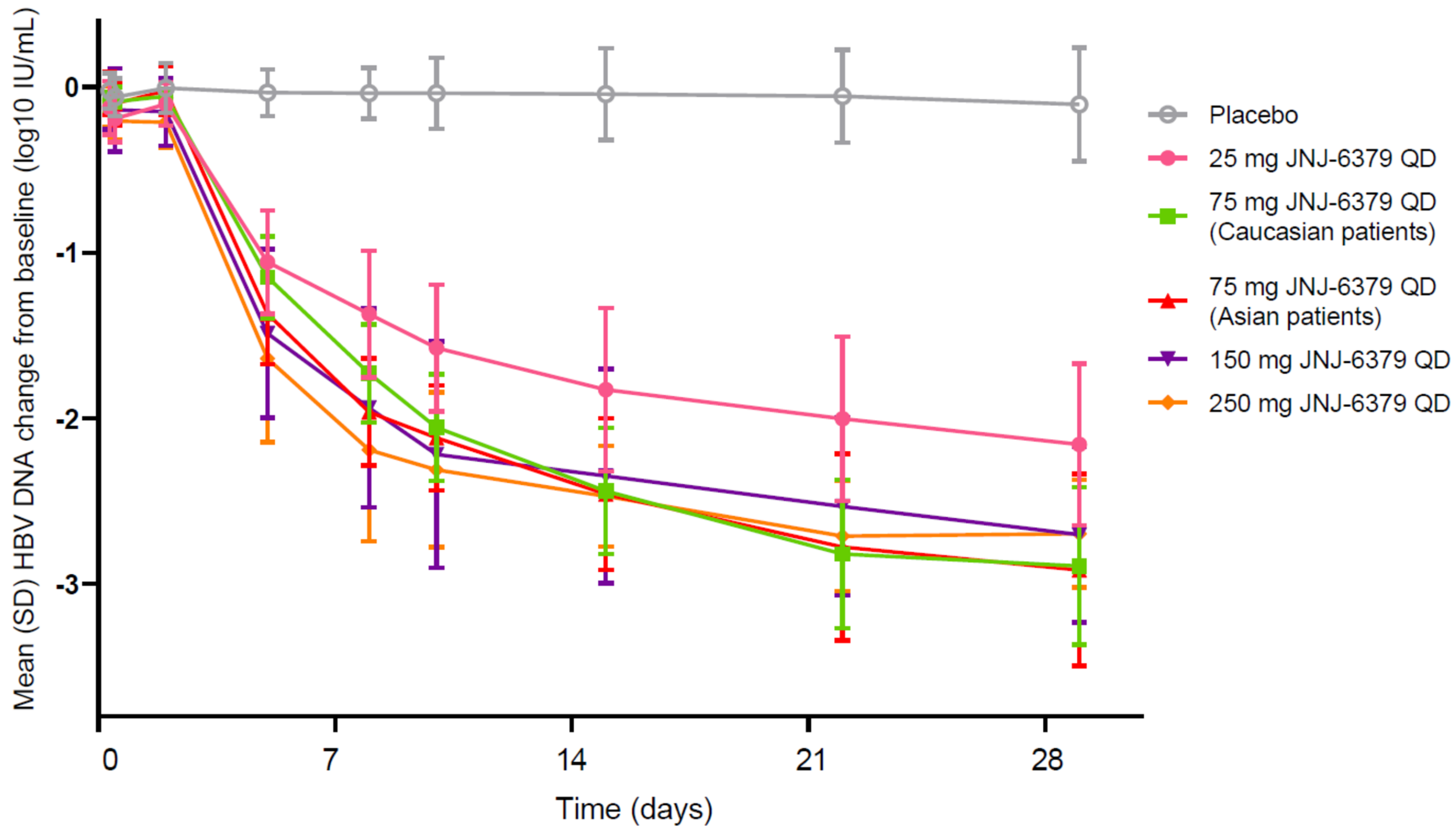
- 25 mg JNJ-6379 QD
- 75 mg JNJ-6379 QD (Caucasian patients)
- 75 mg JNJ-6379 QD (Asian patients)
- 150 mg JNJ-6379 QD
- 250 mg JNJ-6379 QD

Time (days)

100000
10000
1000
100
10

1 8 15 22 29 36 43 50 57 64 71 78 85

1 8 15 22 29 36 43 50 57 64 71 78 85



	JNJ-6379						
	25 mg (n = 8)	75 mg (Caucasian patients) (n = 8)	75 mg (Asian patients) (n = 7)	150 mg (n = 9)	250 mg (n = 9)	All JNJ-6379 (n = 41)	Pooled placebo (n = 16)
Age, years: mean (SD)	40.4 (11.5)	39.5 (11.1)	47.6 (12.9)	46.6 (9.3)	44.3 (9.6)	43.7 (10.8)	35.9 (11.1)
Male, n (%)	7 (88)	6 (75)	5 (71)	6 (67)	5 (56)	29 (71)	14 (88)
Weight, kg: mean (SD)	69.6 (10.6)	81.9 (18.7)	64.6 (12.5)	73.4 (16.7)	80.0 (15.3)	74.3 (15.7)	72.1 (10.5)
BMI, kg/m ² : mean (SD)	22.9 (2.6)	26.5 (3.9)	23.7 (3.1)	24.3 (4.0)	26.7 (3.9)	24.9 (3.7)	24.1 (3.3)
Race, n (%)							
Asian	3 (38)	0	7 (100)	1 (11)	1 (11)	12 (29)	2 (13)
Black or African American	0	0	0	1 (11)	0	1 (2)	2 (13)
White	4 (50)	8 (100)	0	7 (78)	8 (89)	27 (66)	11 (69)
Other	1 (13)	0	0	0	0	1 (2)	0
Not reported	0	0	0	0	0	0	1 (6)
METAVIR fibrosis stage ^b , n (%)							
F0	2 (25)	4 (50)	2 (29)	3 (33)	6 (67)	17 (42)	8 (50)
F1	5 (63)	3 (38)	5 (71)	6 (67)	2 (22)	21 (51)	4 (25)
F2	1 (13)	1 (13)	0	0	1 (11)	3 (7)	4 (25)
ALT (U/L), mean (SD)	38.1 (24.8)	41.4 (26.1)	22.1 (8.5)	41.3 (24.0)	31.9 (14.5)	35.4 (21.1)	35.3 (21.1)
HBeAg positive, n (%)	4 (50)	2 (25)	3 (43)	0	1 (11)	10 (24)	5 (31)
Mean HBV-DNA, log ₁₀ IU/mL (SD)	6.90 (1.9)	5.26 (1.5)	5.57 (2.1)	5.10 (1.6)	4.45 (1.5)	5.42 (1.8)	5.23 (1.7)
Mean HBsAg, log ₁₀ IU/mL (SD)	3.9 (1.2)	4.1 (0.5)	3.8 (1.0)	4.2 (0.5)	3.9 (0.7)	4.0 (0.8)	3.8 (0.7)
HBV genotype, n (%)							
A	1 (13)	2 (25)	0	1 (11)	1 (11)	5 (12)	1 (6)
B	0	0	3 (42)	0	0	3 (7)	2 (13)
C	3 (38)	0	4 (57)	1 (11) ^a	1 (11)	9 (22)	0
D	4 (50)	6 (75)	0	4 (44)	5 (56)	19 (46)	10 (63)
E	0	0	0	1 (11)	0	1 (2)	2 (13)
F	0	0	0	1 (11)	1 (11)	2 (5)	0
H	0	0	0	1 (11)	0	1 (2)	1 (6)

Table 1. Baseline Patient Demographics

^aPatient was recombinant genotype C/D based on sequence analyses; ^bPredicted from elastography

Table 2. On-Treatment Adverse Events (AEs) (28 Days)

	JNJ-6379						Placebo (n = 16)
	25 mg (n = 8)	75 mg (Caucasian patients) (n = 8)	75 mg (Asian patients) (n = 7)	150 mg (n = 9)	250 mg (n = 9)	All (n = 41)	
≥1 AE, n (%)	5 (63)	4 (50)	4 (57)	6 (67)	4 (44)	23 (56)	10 (63)
≥1 AE leading to discontinuation, n (%)	0	0	0	1 (11)	0	1 (2)	0
≥1 AE at least possibly related to JNJ-6379, n (%)	2 (25)	2 (25)	2 (29)	6 (67)	3 (33)	15 (37)	5 (31)
Common treatment-emergent AEs (≥2 patients in the all JNJ-6379 group)							
Any AE	6 (75)	4 (50)	4 (57)	7 (78)	4 (44)	25 (61)	11 (69)
Dyspepsia Grade 1	1 (17)	0	0	1 (14)	1 (25)	3 (12)	0
Nausea Grade 1	0	0	0	2 (29)	1 (25)	3 (12)	1 (10)
Headache Grade 1	2 (33)	0	1 (25)	3 (43)	0	6 (24)	7 (70)
Urinary tract infection Grade 1	0	1 (25)	0	1 (14)	1 (25)	3 (12)	0
Cough Grade 1	0	0	1 (25)	1 (14)	0	2 (8)	1 (10)
Hypophosphatemia Grade 1	0	1 (25)	0	1 (14)	0	2 (8)	0
Asthenia Grade 1	2 (33)	0	0	0	0	2 (8)	0
Treatment-emergent AEs with severity of at least grade 3							
Increased alanine amino transferase (ALT) Grade 4	0	1 (13) ^a	0	1 (11)	0	2 (5)	0
Increased aspartate amino transferase (AST) Grade 3	0	0	0	1 (14)	0	1 (2)	0
Increased pancreatic amylase Grade 3	1 (13)	0	0	0	0	1 (2)	0

^a One patient experienced Grade 4 ALT elevation at follow up

Table 3. Treatment-emergent Laboratory Abnormalities (≥Grade 2)

	JNJ-6379						Placebo (n = 16)
	25 mg (n = 8)	75 mg (Caucasian patients) (n = 8)	75 mg (Asian patients) (n = 7)	150 mg (n = 9)	250 mg (n = 9)	All (n = 41)	
Laboratory abnormalities, n (%)							
Increased alanine amino transferase (ALT)							
Grade 2	0	0	0	1 (11)	0	1 (2)	3 (19)
Grade 4	0	1 (13) ^a	0	1 (11)	0	2 (5)	0
Increased amylase							
Grade 2	1 (13)	0	0	0	0	1 (2)	0
Increased aspartate amino transferase (AST)							
Grade 2	0	0	0	0	0	0	1 (6)
Grade 3	0	1 (13) ^b	0	2 (22)	0	3 (7)	0
Elevated cholesterol							
Grade 2	1 (13)	0	0	2 (22)	4 (44)	7 (17)	2 (13)
Elevated triglycerides							
Grade 2	0	1 (13)	0	0	0	1 (2)	0
Grade 3	1 (13)	0	0	0	0	1 (2)	0
Hyperglycemia							
Grade 2	0	0	1 (14)	0	0	1 (2)	0
Hyperkalemia							
Grade 2	0	0	0	0	0	0	2 (13)
Grade 3	0	0	0	1 (11)	0	1 (2)	0
Hypoglycemia							
Grade 2	0	0	0	1 (11)	0	1 (2)	0
Hypophosphatemia							
Grade 2	0	0	0	1 (11)	0	1 (2)	0
Prothrombin time							
Grade 2	0	1 (13)	0	0	0	1 (2)	0
Elevated LDL cholesterol							
Grade 2	0	0	1 (14)	1 (11)	4 (44)	6 (15)	2 (13)
Increased lipase							
Grade 2	0	0	0	1 (11)	0	1 (2)	0
Grade 3	0	0	1 (14)	0	0	1 (2)	0
Increased pancreatic amylase ^c	n = 5	n = 2	n = 2	n = 5	n = 1	n = 15	n = 4
Grade 2	0	0	2 (100)	0	0	2 (18)	0
Grade 3	1 (33)	0	0	0	0	1 (9)	0

^a One patient experienced Grade 4 ALT elevation at follow up; ^bOne patient experienced Grade 3 AST elevation at follow-up;

^cPancreatic amylase values only available for some patients in each group.

Table 4. Antiviral Activity

	JNJ-6379					Placebo (n = 16)
	25 mg (n = 8)	75 mg (Caucasian patients) (n = 8)	75 mg (Asian patients) (n = 7)	150 mg (n = 9)	250 mg (n = 9)	
HBV-DNA						
Mean (SD) baseline (log ₁₀ IU/mL)	6.90 (1.91)	5.26 (1.50)	5.57 (2.10)	5.10 (1.56)	4.45 (1.48)	5.23 (1.72)
Mean change (SD) from baseline at Day 15 (log ₁₀ IU/mL)	-1.83 (0.49)	-2.44 (0.38)	-2.46 (0.46)	-2.35 (0.65)	-2.47 (0.30)	-0.04 (0.28)
Patients with HBV- DNA <LLOQ at Day 15, n (%)	0	1 (13)	1 (14)	3/8 (38)	4 (44)	0
Mean change (SD) from baseline at Day 29 (log ₁₀ IU/mL)	-2.16 (0.49)	-2.89 (0.48)	-2.92 (0.58)	-2.70 (0.53) ^a	-2.70 (0.33)	-0.11 (0.34)
Patients with HBV- DNA <LLOQ at Day 29, n (%)	0	3 (38)	2 (29)	3/8 (38)	5 (56)	0
HBV-RNA						
Patients with HBV- RNA not detected at baseline	0	0	2	1	3	5
Mean (SD) baseline (log ₁₀ cp/mL)	5.59 (2.37)	3.39 (2.21)	4.03 (2.05)	3.37 (1.67)	2.58 (1.94)	3.39 (2.61)
Mean change (SD) from baseline at Day 15 (log ₁₀ cp/mL)	-2.07 (0.61)	-1.49 (1.12)	-2.34 (0.28) ^b	-2.23 (1.23)	-1.44 (1.04)	-0.02 (0.83)
Patients with HBV- RNA not detected at Day 15, n (%)	3 (38)	5 (63)	2 (50)	8 (100)	6 (86)	6 (38)
Mean change (SD) from baseline at Day 29 (log ₁₀ cp/mL)	-2.30 (0.59)	-1.85 (1.42)	-2.58 (0.36) ^b	-1.83 (0.93) ^c	-1.43 (1.13)	-0.02 (1.03)
Patients with HBV- RNA not detected at Day 29, n (%)	3 (38)	6 (75)	2 (50)	7 (88)	8 (89)	5 (31)

HBV-DNA <LLOQ (20 IU/mL) target detectable was imputed by 15 IU/mL; HBV DNA <LLOQ target not detected was imputed with 5 IU/mL. Imputed values were used to calculate change from baseline when applicable. All RNA quantitative changes were used to calculate changes from baseline. HBV-RNA not detected results were imputed with 5 cp/mL.

^aHBV-DNA at Day 29 is available for eight patients; ^bData was available for four patients at Days 15 and 29; ^cHBV-RNA at Day 29 was available for eight patients.