Original research

Randomised phase 2 study (JADE) of the HBV capsid assembly modulator JNJ-56136379 with or without a nucleos(t)ide analogue in patients with chronic hepatitis B infection

Harry L A Janssen,[1,2] Jinlin Hou ,[3] Tarik Asselah ,[4] Henry L Y Chan,[5] Fabien Zoulim ,[6] Yasuhito Tanaka,[7] Ewa Janczewska,[8] Ronald G Nahass,[9] Stefan Bourgeois,[10] Maria Buti,[11] Pietro Lampertico ,[12,13] Oliver Lenz,[14] Thierry Verbinnen,[14] Joris Vandenbossche,[14] Willem Talloen,[14] Ronald Kalmeijer,[15] Maria Beumont,[15] Michael Biermer ,[14] Umesh Shukla[15]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2022-328041).

For numbered affiliations see end of article.

Correspondence to
Dr Michael Biermer, Janssen Pharmaceutica NV, Beerse B-2340, Antwerpen, Belgium; mbiermer@its.jnj.com

Received 10 June 2022
Accepted 22 December 2022

To cite: Janssen HLA, Hou J, Asselah T, *et al*. *Gut* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/gutjnl-2022-328041

ABSTRACT

Objective We present the final analysis results of the phase 2 JADE study (ClinicalTrials.gov Identifier: NCT03361956).

Design 232 patients with chronic hepatitis B (CHB) not currently treated at study start (NCT) at study start or virologically suppressed were randomised to receive 75 mg (part 1) or 250 mg (part 2) JNJ-56136379, a hepatitis B virus (HBV)–capsid assembly modulator, one time per day or placebo with nucleos(t)ide analogue (NA) (tenofovir disoproxil fumarate/entecavir) or JNJ-56136379 alone (NCT-only) for ≥24 and ≤48 weeks.

Results In patients who are NCT hepatitis B e-antigen (HBeAg) positive, JNJ-56136379 75 mg+NA and 250 mg+NA showed limited mean (SE) hepatitis B surface antigen (HBsAg) declines (0.14 (0.10) and 0.41 (0.15), respectively) from baseline at Week 24 (primary endpoint; placebo+NA: 0.25 (0.11) log_{10} international unit (IU)/mL).

In patients who are NCT HBeAg positive, mean (SE) HBV DNA declines at Week 24 were 5.53 (0.23) and 5.88 (0.34) for JNJ-56136379 75 mg+NA and 250 mg+NA, respectively, versus 5.21 (0.42) log_{10} IU/mL for placebo+NA. In NCT patients, mean (SE) HBV RNA declines were 2.96 (0.23) and 3.15 (0.33) versus 1.33 (0.32) log_{10} copies/mL, respectively. Patients with HBsAg declines had HBeAg and hepatitis B core-related antigen (HBcrAg) declines and some early on-treatment isolated alanine aminotransferase flares. Viral breakthrough occurred with JNJ-56136379 monotherapy with the emerging resistant-variant T33N, but not with JNJ-56136379+NA. JNJ-56136379 treatment beyond Week 24 had a generally small additional effect on viral markers.

No study treatment-related serious adverse events or clinically significant changes in laboratory parameters occurred.

Conclusions In patients with non-cirrhotic CHB, JNJ-56136379+NA showed pronounced reductions in HBV DNA and HBV RNA, limited HBsAg or HBeAg declines in patients who are NCT HBeAg positive, and was well tolerated, but no clear benefit with regards to efficacy of JNJ-56136379 over NA was observed.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ First-line antiviral therapies for chronic hepatitis B (CHB) are nucleos(t)ide analogues (NA) and pegylated interferon alpha.
⇒ However, these treatments only provide low rates of functional cure, which highlights the need for novel therapeutic strategies.

WHAT THIS STUDY ADDS

⇒ JNJ-56136379, a class-N capsid assembly modulator (CAM), plus an NA resulted in pronounced reductions in hepatitis B virus (HBV) DNA and HBV RNA over 24–48 weeks in patients with CHB and was well tolerated.
⇒ A limited reduction in hepatitis B surface antigen and hepatitis B e-antigen (HBeAg) in HBeAg-positive patients who were currently not treated for their infection was observed.
⇒ Viral breakthrough occurred with JNJ-56136379 monotherapy with emerging resistant-variant T33N.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings provide Week 48 data for a CAM in combination with/without NA and showed pronounced HBV DNA and HBV RNA reduction but limited to no effect on HBsAg and HBeAg with a risk of viral resistance when given as long-term monotherapy.

INTRODUCTION

Approximately 296 million people worldwide are infected with chronic hepatitis B (CHB), which left untreated is associated with a high risk of death from cirrhosis and hepatocellular carcinoma (HCC).[1] The ultimate clinical goal for patients with CHB is to achieve a ‘functional cure’, defined as undetectable serum hepatitis B surface antigen (HBsAg) and hepatitis B virus (HBV) DNA that is sustained when off treatment for ≥24 weeks, with or without HBsAg seroconversion.[2] Therapies include nucleos(t)ide analogues (NA), entecavir (ETV), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide or pegylated interferon alpha (peg-IFNα).[3 4] These treatments lead to low rates of functional cure: ≈3% with NA and ≈10% with peg-IFNα.[2] Treatment with peg-IFNα is associated with adverse effects, while NA therapy, which significantly reduces the risk of liver cirrhosis, decompensation and death, usually requires life-long treatment.[3 4] There is a need for novel treatments for CHB that are of finite duration and increase functional cure rates to improve clinical outcomes, further reduce the risk of HCC, and address a significant stigma burden for patients.[5 6]

One strategy is to combine HBV antiviral agents with different mechanisms of action (MoA) to intensify viral suppression and reduce levels of immune suppressive HBsAg.[7 8] Capsid assembly modulators (CAMs) inhibit viral replication by interfering with HBV capsid assembly—a key step in virus production.[6 9] CAM-N compounds, such as JNJ-56136379,[10–12] JNJ-64530440[13] and vebicorvir (ABI-H0731)[14 15] induce formation of morphologically intact but empty, non-functional capsids (N: normal structure). CAM-A agents, including RO7049389 (RG7907)[16 17] and morphothiadin (GLS4)/ritonavir,[18 19] result in the formation of pleiomorphic non-capsid structures (A: aberrant particle).

JNJ-56136379 binds to the HBV core protein and interferes with HBV viral replication at late and early stages via a dual MoA. The ‘primary’ MoA is interference with capsid assembly kinetics, preventing polymerase-pregenomic RNA (pgRNA) encapsidation and blocking HBV replication (median 50% effective concentration (EC_{50})/EC_{90}=102 nM/376 nM). The ‘secondary’ MoA is inhibition of de novo covalently closed circular DNA (cccDNA) formation by interfering with disassembly of the capsid (median EC_{50}/EC_{90}=876 nM/4019 nM).[9 11 12] NAs inhibit viral replication and virion production, but do not prevent encapsidation of pgRNA and release of HBV RNA-containing particles.[20]

In a recently completed phase 1 study, JNJ-56136379 was well tolerated, with dose-proportional pharmacokinetics (PK) in healthy adults,[10] and demonstrated antiviral activity with oral doses of JNJ-56136379 of 25–250 mg one time per day (qd) for 28 days in patients with treatment-naïve CHB.[12]

The final analysis results from the JADE study, evaluating efficacy, safety and PK of JNJ-56136379 administered alone or with an NA in patients with CHB are reported here.

METHODS

Additional methodology is included in the online supplemental methods.

Study design and population

JADE (56136379HPB2001; ClinicalTrials.gov Identifier: NCT03361956) was a phase 2, randomised, partially-blinded, multicentre, interventional, placebo-controlled, two-part study in patients with CHB evaluating oral JNJ-56136379 administered as monotherapy or in combination with ETV or TDF (figure 1). Two, otherwise identical parts, explored 75 mg (part 1) and 250 mg (part 2) of JNJ-56136379 administered qd. The study included patients with non-cirrhosis aged 18–70 years with documented hepatitis B e-antigen (HBeAg) positive or negative CHB infection who were not currently treated at study start (NCT) or virologically suppressed (VS) with TDF or ETV at study start (inclusion and exclusion criteria provided in online supplemental table S1).

Each part comprised a screening (≤8 weeks), treatment (24 weeks plus a 24-week extension, depending on response) and follow-up phase (24 weeks or 48 weeks, depending on response). NCT patients were randomised 3:1:3 to receive open-label JNJ-56136379 monotherapy, placebo+NA or JNJ-56136379+NA. Patients who were VS were randomised 1:3 to receive placebo+NA or JNJ-56136379+NA. Randomisation was balanced and stratified according to HBeAg status (positive versus negative) and HBsAg level at screening (≥10 000 versus <10 000 international unit (IU)/mL for NCT patients who are HBeAg positive and ≥1000 versus <1000 IU/mL for all other patients).

Patients who completed the 24-week treatment phase and demonstrated a virological response by Week 20 (initially, HBV DNA <20 IU/mL; revised, HBV DNA <200 IU/mL), without any safety concerns, continued treatment for 24 weeks in a treatment extension phase. Patients meeting treatment completion criteria after 48 weeks were planned to stop all treatment and entered a 48-week follow-up phase. Patients undergoing 24 weeks of treatment not qualifying for treatment extension and patients who continued in the treatment extension phase and did not satisfy treatment completion criteria after 48 weeks, received NA monotherapy during a 24-week follow-up phase.

This study was conducted at 75 sites across 19 countries (Belgium, Canada, China, France, Germany, Hong Kong, Italy, Japan, South Korea, Malaysia, Poland, Russia, Spain, Taiwan, Thailand, Turkey, Ukraine, UK and USA). The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, International Conference on Harmonisation guidelines on Good Clinical Practices and applicable regulatory requirements, and approved by the relevant Independent Ethics Committee/Institutional Review Board. All patients provided written informed consent to participate in the study.

Patient and public involvement

Patients were invited by the investigator to participate in the study after ethics committee protocol approval. Patients were not involved in the study design or plans to disseminate study results. They were informed about the burden of intervention and could withdraw from the study at any time.

Endpoints

The primary endpoint was 1 log_{10} IU/mL mean decline in HBsAg levels from baseline to Week 24 for JNJ-56136379±NA versus placebo+NA. Secondary endpoints included antiviral activity on HBsAg, HBV DNA and HBeAg (in patients who are HBeAg positive only) measured during treatment (up to Week 48) and follow-up: (1) changes from baseline in levels, (2) proportion of patients with levels by predefined response category, and (3) proportion of patients with seroclearance and/or seroconversion.

Study evaluations

Study visits were scheduled at baseline and Weeks 1, 2, 4, 8, 12, 16, 20 and 24 during treatment and at Weeks 28, 32, 36, 44 and 48 during the treatment extension period. Patients who discontinued treatment prior to Week 48 or did not meet the treatment completion criteria at 48 weeks, had visits scheduled at follow-up Weeks 2, 4, 12 and 24 (end of study visit).

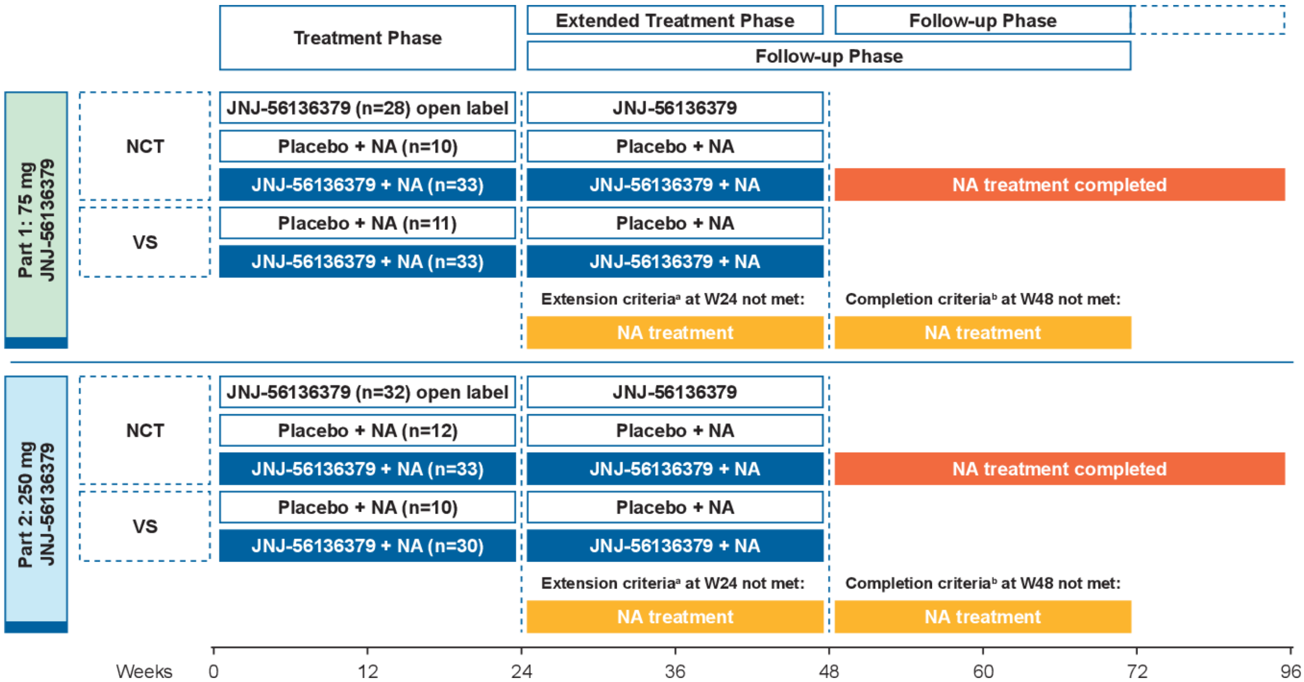


Figure 1 Study design. [a]JNJ-56136379 treatment was extended to 48 weeks if response criteria were met, which were patients who completed the 24-week treatment phase and demonstrated a virological response by Week 20 (HBV DNA <200 IU/mL), without any safety concerns precluding continued treatment. The exceptions to this were the open label JNJ-56136379 monotherapy arms: the 75 mg arm was terminated early, and all patients switched to NA monotherapy and entered follow-up, while the 250 mg arm had NA added during treatment extension. Patients undergoing 24 weeks of treatment and choosing not to participate in the treatment extension phase, or not satisfying treatment extension criteria, switched to NA monotherapy and entered a 24-week follow-up phase. [b]Patients who satisfied treatment completion criteria (normal ALT levels or elevated ALT levels that in the opinion of the investigator are not attributed to chronic HBV activity; and HBV DNA<LLOQ; and HBeAg negative; and HBsAg ≤500 IU/mL; and ≥1 $\log_{10}$ IU/mL decline in HBsAg from baseline) after 48 weeks stopped all treatment and entered a 48-week follow-up phase. NA treatment (either ETV or TDF), according to local standard of care, was restarted during this period if a patient satisfied any one of the retreatment criteria (confirmed post-treatment increases in HBV DNA >2000 IU/mL and ALT >2 x ULN; or confirmed post-treatment increases in HBV DNA >20 000 IU/mL; or worsening signs of liver function during follow-up assessments). Patients who did not satisfy treatment completion criteria after 48 weeks switched to NA monotherapy and entered a 24-week follow-up phase. For patients who did not continue or start NA treatment at Week 24 or did not meet the treatment completion criteria and did 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, was recommended after study completion. ALT, alanine aminotransferase; ETV, entecavir; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IU, international unit; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogue; NCT, not currently treated at study start; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal; VS, virologically suppressed; W, week.

Efficacy

Levels of HBsAg, HBeAg, HBV DNA and HBV RNA were measured in plasma samples collected prior to dosing on Day 1 and at predefined time points throughout the study. Additional details for assessments are described in the online supplemental methods.

Safety

Safety and tolerability were assessed in all patients during study participation. Adverse events (AEs) and serious AEs (SAEs) were monitored. Physical examinations, vital signs measurements, 12-lead triplicate electrocardiograms and clinical laboratory tests were conducted at predefined time points.

Pharmacokinetics

Venous blood samples were collected to determine plasma concentrations of total JNJ-56136379 and NA using a validated liquid chromatography–mass spectrometry/mass spectrometry method. Urine samples were obtained at 24 hours in ≈35% of the participants (PK subgroup at selected sites) to determine concentrations of JNJ-56136379 and NA.

HBV genome sequencing

HBV DNA was extracted from plasma samples, and next-generation sequencing (Illumina) with a 1% cut-off was performed for the full HBV genome.

Statistical analyses

No formal statistical hypotheses were evaluated. The target sample size was 220 patients, with 110 patients in each part (NCT: n=70; VS: n=40). Enrolment was planned to include ≈40% of the NCT patients and ≈30% of VS patients who were HBeAg positive. The probability to detect a treatment effect of 1 mean $\log_{10}$ IU/mL decline in HBsAg from baseline to Week 24 for JNJ-56136379+NA versus placebo+NA, with ≥90% confidence, was 0.84 and 0.89 for patients who are HBeAg negative in the NCT and VS groups, respectively, and 0.64 and 0.57, respectively, for patients who are HBeAg positive.

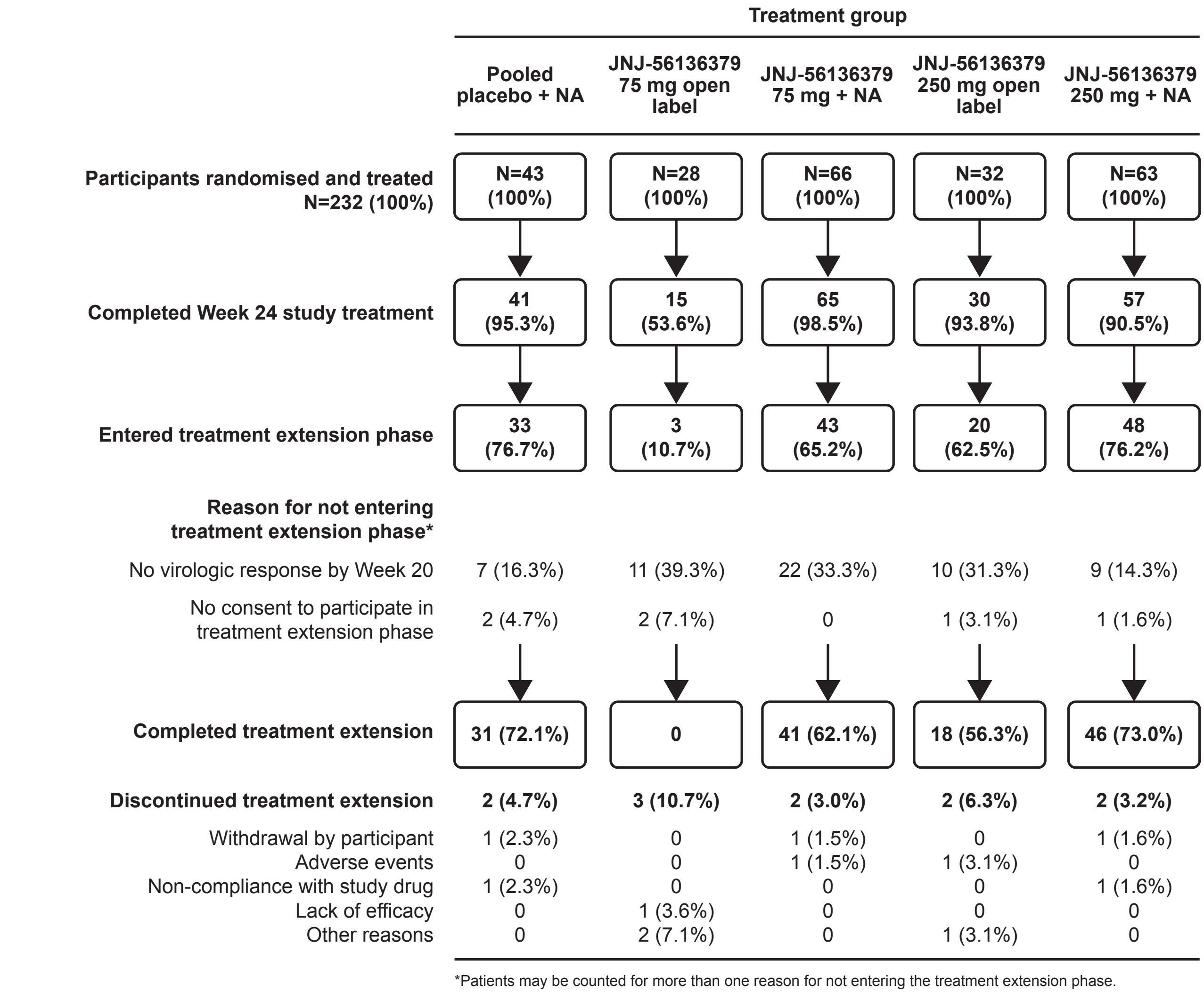


Figure 2 Patient disposition. The majority of patients were assessed with the initial extension criteria (<20 IU/mL). IU, international unit; NA, nucleos(t)ide analogue.

Efficacy and safety analyses were conducted for all randomised patients who received ≥1 dose of study drug. Comparisons among the pooled placebo+NA, JNJ-56136379 75 mg+NA and JNJ-56136379 250 mg+NA treatment arms were described. Non-compartmental PK analyses of plasma and urine concentration-time data were performed. Descriptive statistics were used to compare plasma PK parameters for different treatments.

RESULTS

Patient disposition and characteristics

The first patient was enrolled in February 2018; last observation for the last patient was in August 2020. Overall, 488 patients were screened and 232 (NCT: n=148; VS: n=84) were enrolled and randomised (figure 2). Patients were ineligible for the study due to failure to meet eligibility criteria (250 (51%)), patient withdrawal (4 (0.8%)), HBeAg enrolment target met (1 (0.2%)) and lost to follow-up (1 (0.2%)). Screen failure rate was mainly high in NCT patients (patients not meeting the NCT criteria). It was particularly high at the beginning of the study (≈88%) and decreased over time during study conduct. The placebo/JNJ-56136379+NA treatment arms included 172 patients (NCT: n=88; VS: n=84), where 43, 66 and 63 patients were included in the pooled placebo+NA arms, JNJ-56136379 75 mg+NA and JNJ-56136379 250 mg+NA arms, respectively.

Sixty patients received JNJ-56136379 open-label monotherapy via staggered randomisation, where patients received 75 mg in part 1 and 250 mg in part 2 (75 mg: n=28; 250 mg: n=32). Following a viral breakthrough in five patients receiving the 75 mg dose between Weeks 16–20, JNJ-56136379 was discontinued in all 28 patients, and patients received NA. In the 250 mg monotherapy arm, viral breakthrough in one patient at Week 8 was followed by initiation of NA treatment plus ongoing JNJ-56136379 therapy in all patients.

Demographics and disease characteristics for patients in the NCT group of each treatment arm were broadly comparable, as were those for the VS patients in each arm (table 1 and online supplemental table S2). Across the treatment arms, the mean age was 39.7 years, 70% were men, 49% were Asian and 44% White and 37% were HBeAg positive. A numerically higher proportion of patients received TDF than ETV (69% vs 31%).

Mean (SD) HBsAg levels at baseline were 0.5 $\log_{10}$ IU/mL higher in NCT than VS patients (table 1) and highest in NCT patients who are HBeAg positive (4.40 (0.68) $\log_{10}$ IU/mL). Mean (SD) HBeAg baseline levels (in patients who are HBeAg

Table 1 Baseline demographics and disease characteristics

	Pooled placebo+NA N=43		JNJ-56136379 75 mg open label N=28	JNJ-56136379 75 mg+NA N=66		JNJ-56136379 250 mg open label N=32	JNJ-56136379 250 mg+NA N=63	
Age, years, mean (SD)	41.6 (9.5)		39.2 (12.1)	40.3 (11.1)		37.7 (10.9)	40.5 (11.0)	
Males, n (%)	29 (67)		19 (68)	46 (70)		18 (56)	50 (79)	
Race, n (%)*								
Asian	18 (43)		11 (41)	35 (53)		16 (50)	30 (48)	
White	23 (55)		11 (41)	26 (39)		15 (47)	30 (48)	
Other[†]	1 (2)		5 (19)	5 (8)		1 (3)	3 (5)	
	NCT (n=22)	**VS (n=21)**	**NCT (n=28)**	**NCT (n=33)**	**VS (n=33)**	**NCT (n=32)**	**NCT (n=33)**	**VS (n=30)**
ALT, U/L, mean (SD)	68.8 (37.7)	26.0 (13.8)	78.3 (55.6)	82.8 (88.0)	25.5 (11.4)	75.4 (56.0)	86.5 (93.1)	25.8 (16.4)
FibroScan liver stiffness measurement at screening, kPa, mean (SD)[‡]	6.11 (1.37)	5.13 (1.23)	5.75 (1.15)	5.58 (1.29)	5.05 (1.28)	5.95 (1.33)	5.63 (1.10)	4.93 (1.50)
HBeAg-positive, n (%)	8 (36)	6 (29)	12 (43)	12 (36)	9 (27)	14 (44)	13 (39)	10 (33)
HBV DNA, $\log_{10}$ IU/mL, mean (SD)[§]	6.11 (2.02)	0.94 (0.26)	6.84 (1.56)	6.25 (1.56)	0.92 (0.26)	6.16 (1.88)	6.02 (2.00)	0.93 (0.28)
HBV RNA, $\log_{10}$ copies/mL, mean (SD)[§]	4.67 (2.41)	1.87 (1.84)	5.60 (1.74)	4.64 (2.00)	1.70 (1.40)	5.10 (1.89)	4.44 (2.14)	1.70 (1.54)
HBsAg, $\log_{10}$ IU/mL, mean (SD)	4.05 (0.65)	3.58 (0.44)	4.00 (0.71)	3.97 (0.69)	3.48 (0.61)	4.13 (0.53)	3.98 (0.66)	3.49 (0.53)
HBV genotype, n (%)[¶]								
A	3 (15)	1 (8)	2 (8)	2 (7)	0	5 (19)	5 (19)	1 (6)
B	2 (10)	1 (8)	6 (25)	8 (29)	1 (10)	4 (15)	4 (15)	2 (13)
C	4 (20)	3 (25)	2 (8)	3 (11)	1 (10)	7 (26)	3 (12)	4 (25)
D	11 (55)	2 (17)	9 (38)	12 (43)	0	10 (37)	13 (50)	1 (6)
E, F, H, unknown	0	5 (42)	5 (21)	3 (11)	8 (80)	1 (4)	1 (4)	8 (50)

*n=42 for the pooled placebo+NA arm, n=27 for JNJ-56136379 75 mg open label arm.
†Black or African American, Native Hawaiian or Other Pacific Islander.
‡n=21, 21, 25, 32, 32, 29, 32 and 30 in the respective subgroups.
§DNA and RNA values in the VS subpopulation are mostly 'imputed' since values were below the LLOQ or target not detected, respectively. For HBV RNA: n=21, 21, 26, 28, 32, 28, 27 and 29 in the respective subgroups.
¶Genotype data in NCT patients were determined using LiPA and/or sequence-based genotype assays. Genotype data in VS patients were based on historical data provided by the investigator. n=20, 12, 24, 28, 10, 27, 26 and 16 in the respective subgroups.
ALT, alanine aminotransferase; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IU, international unit; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogue; NCT, not currently treated at study start; VS, virologically suppressed.

positive) were higher in NCT patients (2.33 (1.03) $\log_{10}$ IU/mL) than VS patients (0.39 (0.74) $\log_{10}$ IU/mL) in the combined JNJ-56136379 treatment arms. For NCT patients who are HBeAg positive, the mean (SD) baseline HBV DNA level was 7.86 (1.05) $\log_{10}$ IU/mL and 5.24 (1.32) $\log_{10}$ IU/mL for NCT patients who are HBeAg negative in the combined JNJ-56136379 treatment arms. Most VS patients (93% to 95%) had HBV DNA<lower limit of quantification (LLOQ) (20 IU/mL) at baseline. Overall, the mean baseline HBV RNA levels were comparable across arms, and higher in NCT than VS patients (table 1).

Overall, 122/129 (95%) patients receiving JNJ-56136379+NA and 41/43 (95%) receiving placebo+NA completed Week 24 study treatment; 91/129 (71%) and 33/43 (77%), respectively, entered the 24-week treatment extension phase (figure 2), which included 47/88 (53%) NCT patients and 77/84 (92%) VS patients (online supplemental figure S1). Most patients who entered the 24-week treatment extension phase completed the extension (figure 2). No patients met the treatment completion criteria at Week 48.

Antiviral efficacy

Primary endpoint

In NCT patients who are HBeAg positive, JNJ-56136379 75 mg and 250 mg+NA resulted in a mean (SE) HBsAg decline from baseline at Week 24 of 0.14 (0.10) and 0.41 (0.15) $\log_{10}$ IU/mL, respectively, versus 0.25 (0.11) for placebo+NA (table 2; figure 3A; figure 4; online supplemental figure S2). The proportion of NCT patients who are HBeAg positive with >0.3 $\log_{10}$ IU/mL reduction (corresponding to a 50% reduction) in HBsAg from baseline was 4/12 (33%) (JNJ-56136379 75 mg+NA), 5/11 (45%) (JNJ-56136379 250 mg+NA) and 2/8 (25%) (placebo+NA) (table 2). In NCT patients who are HBeAg negative and VS (HBeAg positive or negative) patients, there was no relevant effect of JNJ-56136379 75 mg and 250 mg+NA or placebo+NA on mean HBsAg levels (figure 3A).

Secondary exploratory endpoints during 24 weeks of combination treatment

HBV DNA

Change from baseline in HBV DNA levels was assessed in NCT patients (VS patients typically had levels <LLOQ at baseline). In NCT patients who are HBeAg positive (mean baseline HBV DNA levels, 7.65–8.24 $\log_{10}$ IU/mL), there were pronounced declines in mean (SE) HBV DNA at Week 24 of 5.53 (0.23) and 5.88 (0.34) $\log_{10}$ IU/mL for JNJ-56136379 75 mg and 250 mg+NA, respectively, and 5.21 (0.42) $\log_{10}$ IU/mL for placebo+NA (table 2; figure 5A; online supplemental figure S3A). In NCT patients who are HBeAg negative, interpretation of mean (SE) HBV DNA decline was confounded due to many patients (n=22/89 (25%)) with HBV DNA levels <LLOQ from Week 4 onwards (online supplemental table S3).

Table 2 Summary of antiviral efficacy at Week 24 (pooled placebo/JNJ-56136379+NA treatment arms)

	Pooled placebo+NA N=43				JNJ-56136379 75 mg+NA N=66				JNJ-56136379 250 mg+NA N=63			
Population	NCT (n=22)		VS (n=21)		NCT (n=33)		VS (n=33)		NCT (n=33)		VS (n=30)	
HBeAg status	+ (n=8)	− (n=14)	+ (n=6)	− (n=15)	+ (n=12)	− (n=21)	+ (n=9)	− (n=24)	+ (n=13)	− (n=20)	+ (n=10)	− (n=20)
HBsAg, log_{10} IU/mL												
Change from baseline at Week 24, mean (SE)	−0.25 (0.11)	0.02 (0.02)	0.01 (0.06)	0.02 (0.02)	−0.14 (0.10)	0.04 (0.02)	−0.06 (0.08)	−0.02 (0.01)	−0.41 (0.15)	0.09 (0.04)	0.11 (0.06)	0.09 (0.01)
Patients with >0.3 log_{10} decline, n (%)	2/8 (25)	0/13 (0)	0/5 (0)	0/15 (0)	4/12 (33)	0/21 (0)	2/9 (22)	0/24 (0)	5/11 (45)	0/19 (0)	0/10 (0)	0/19 (0)
Patients with >0.5 log_{10} decline, n (%)	1/8 (13)	0/13 (0)	0/5 (0)	0/15 (0)	1/12 (8)	0/21 (0)	0/9 (0)	0/24 (0)	4/11 (36)	0/19 (0)	0/10 (0)	0/19 (0)
HBV DNA, log_{10} IU/mL												
Change from baseline at Week 24, mean (SE)	−5.21 (0.42)	−3.62 (0.36)	−0.05 (0.11)	−0.03 (0.06)	−5.53 (0.23)	−4.08 (0.21)	0 (0.11)	0.02 (0.07)	−5.88 (0.34)	−3.69 (0.35)	0.02 (0.08)	−0.02 (0.06)
Patients with HBV DNA<LLOQ, n (%) at Week 24	1/8 (13)	12/13 (92)	5/5 (100)	15/15 (100)	0/12 (0)	14/21 (67)	9/9 (100)	22/24 (92)	4/11 (36)	16/19 (84)	9/10 (90)	19/19 (100)
HBV RNA, log_{10} copies/mL												
Change from baseline at Week 24, mean (SE)	−0.74 (0.52)	−1.69 (0.39)	−0.69 (0.56)	0.22 (0.15)	−3.41 (0.33)	−2.70 (0.29)	−2.63 (0.52)	−0.45 (0.18)	−3.85 (0.35)	−2.73 (0.46)	−2.94 (0.61)	−0.13 (0.13)
Patients with HBV RNA TND at baseline, n (%)	0/8	3/14 (21)	1/6 (17)*	13/15 (87)*	0/12	2/21 (10)	1/8 (13)*	18/24 (75)*	0/13	4/20 (20)	2/9 (22)*	19/20 (95)*
Patients with HBV RNA TND at Week 24, n (%)	0/8	9/13 (69)	1/5 (20)	10/15 (67)	3/12 (25)	16/21 (76)	9/9 (100)	24/24 (100)	4/11 (36)	19/19 (100)	10/10 (100)	18/18 (100)
HBeAg, log_{10} IU/mL												
Change from baseline at Week 24, mean (SE)	−0.81 (0.28)	Not applicable	−0.31 (0.24)	Not applicable	−0.49 (0.09)	Not applicable	−0.32 (0.16)	Not applicable	−0.70 (0.20)	Not applicable	−0.16 (0.06)	Not applicable
Patients with >0.3 log_{10} decline, n (%)	5/8 (63)	Not applicable	1/5 (20)	Not applicable	10/12 (83)	Not applicable	3/9 (33)	Not applicable	9/11 (82)	Not applicable	3/10 (30)	Not applicable
Patients with >0.5 log_{10} decline, n (%)	5/8 (63)	Not applicable	1/5 (20)	Not applicable	5/12 (42)	Not applicable	3/9 (33)	Not applicable	7/11 (64)	Not applicable	1/10 (10)	Not applicable
Patients with >1.0 log_{10} decline, n (%)	3/8 (38)	Not applicable	1/5 (20)	Not applicable	1/12 (8)	Not applicable	1/9 (11)	Not applicable	4/11 (36)	Not applicable	0/10 (0)	Not applicable
HBcrAg, log_{10} U/mL												
Change from baseline at Week 24, mean (SE)	−0.84 (0.27)	−0.91 (0.21)	−0.08 (0.04)	−0.28 (0.12)	−0.68 (0.12)	−0.70 (0.13)	−0.24 (0.13)	−0.25 (0.14)	−0.85 (0.18)	−0.78 (0.23)	0.01 (0.21)	−0.11 (0.10)
Patients with HBcrAg <LLOQ at baseline, n (%)	0/8	3/14 (21)	0/6	4/15 (27)	0/12	2/21 (10)	0/9	7/24 (29)	0/13	5/20 (25)	0/10	9/20 (45)
Patients with >0.3 log_{10} decline, n (%)	5/8 (63)	9/13 (69)	0/5	4/15 (27)	10/12 (83)	14/21 (67)	2/9 (22)	4/24 (17)	9/11 (82)	8/19 (42)	3/10 (30)	1/19 (5)
Patients with >0.5 log_{10} decline, n (%)	4/8 (50)	8/13 (62)	0/5	4/15 (27)	7/12 (58)	11/21 (52)	2/9 (22)	3/24 (13)	8/11 (73)	8/19 (42)	0/10	1/19 (5)
Patients with >1.0 log_{10} decline, n (%)	0/8	8/13 (62)	0/5	7/15 (47)	0/12	4/21 (19)	0/9	9/24 (38)	0/11	6/19 (32)	0/10	9/19 (47)

*Seven patients in the placebo+NA group, 13 patients in the JNJ-56136379 75 mg+NA group and eight patients in the JNJ-56136379 250 mg+NA group had HBV RNA detectable at baseline, and 1/7 (14%), 13/13 (100%) and 8/8 (100%), respectively, were TND at Week 24. HBsAg values >ULOQ were set to 5.1 log_{10} IU/mL; HBV DNA values <LLOQ (20 IU/mL) target detected or target not detected were imputed respectively with 15 IU/mL or 5 IU/mL; not detected HBV RNA values were imputed by a value of 5 copies/mL; HBeAg values >ULOQ (1400 IU/mL) were imputed with 1540 IU/mL.
−, negative; +, positive; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IU, international unit; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogue; NCT, not currently treated at study start; TND, target not detected; ULOQ, upper limit of quantification; VS, virologically suppressed.

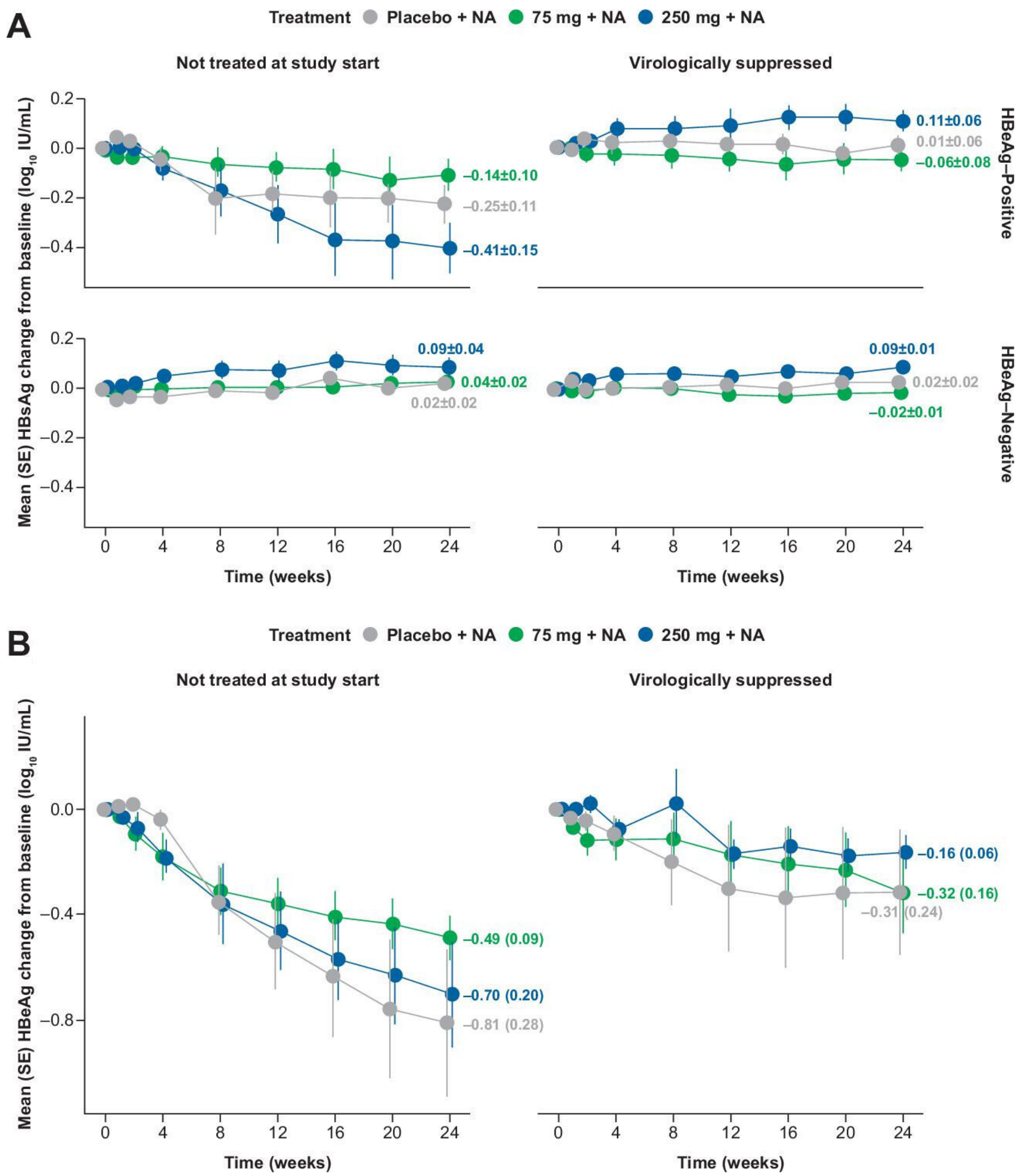


Figure 3 Mean (SE) change from baseline in HBsAg over 24 weeks of treatment. (A) Mean (SE) change from baseline in HBsAg over 24 weeks of treatment (pooled placebo/JNJ-56136379+NA treatment arms) in NCT and VS patients by HBeAg status. HBsAg assessed using an Abbott Architect assay; HBsAg lower limit of quantification: 0.05 IU/mL and ULOQ: >249 750 000 IU/mL. HBsAg values >ULOQ were set to 5.1 $\log_{10}$ IU/mL. (B) Mean (SE) change from baseline in HBeAg over 24 weeks of treatment in patients who are HBeAg positive (pooled placebo/JNJ-56136379+NA treatment arms) by prior treatment. HBeAg assessed using an Abbott Architect assay; HBeAg lower limit of quantification: 0.11 IU/mL and ULOQ: 1400 IU/mL; HBeAg values >ULOQ (1400 IU/mL) were imputed with 1540 IU/mL. HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; IU, international unit; NA, nucleos(t)ide analogue; NCT, not currently treated at study start; ULOQ, upper limit of quantification; VS, virologically suppressed.

HBeAg

In NCT patients who are HBeAg positive, JNJ-56136379 75 mg and 250 mg+NA resulted in mean (SE) HBeAg declines from baseline of 0.49 (0.09) and 0.70 (0.20) $\log_{10}$ IU/mL, respectively, versus 0.81 (0.28) for placebo+NA at Week 24 (table 2; figure 3B; online supplemental figure S4). For VS patients who are HBeAg positive, mean reductions in HBeAg levels were smaller. In patients who are HBeAg positive, the proportion with a >0.3 $\log_{10}$ IU/mL reduction in HBeAg from baseline at Week 24 for NCT patients was higher in the combined JNJ-56136379+NA treatments arms than for placebo+NA (19/23 (83%) vs 5/8 (63%), respectively) and also in VS patients (6/19 (32%) vs 1/5 (20%), respectively) suggesting a trend of more consistent declines across patients (table 2).

Observed declines in HBeAg at Week 24 mostly correlated with declines in HBsAg and early on-treatment isolated alanine aminotransferase (ALT) elevations (ALT flares) (figure 3; online supplemental figure S5). Maximal individual HBsAg and HBeAg reductions were 1.28 and 1.8 $\log_{10}$ IU/mL at Week 24, respectively, in the JNJ-56136379+NA groups and occurred in the patients with the most pronounced HBV DNA declines at Week 24.

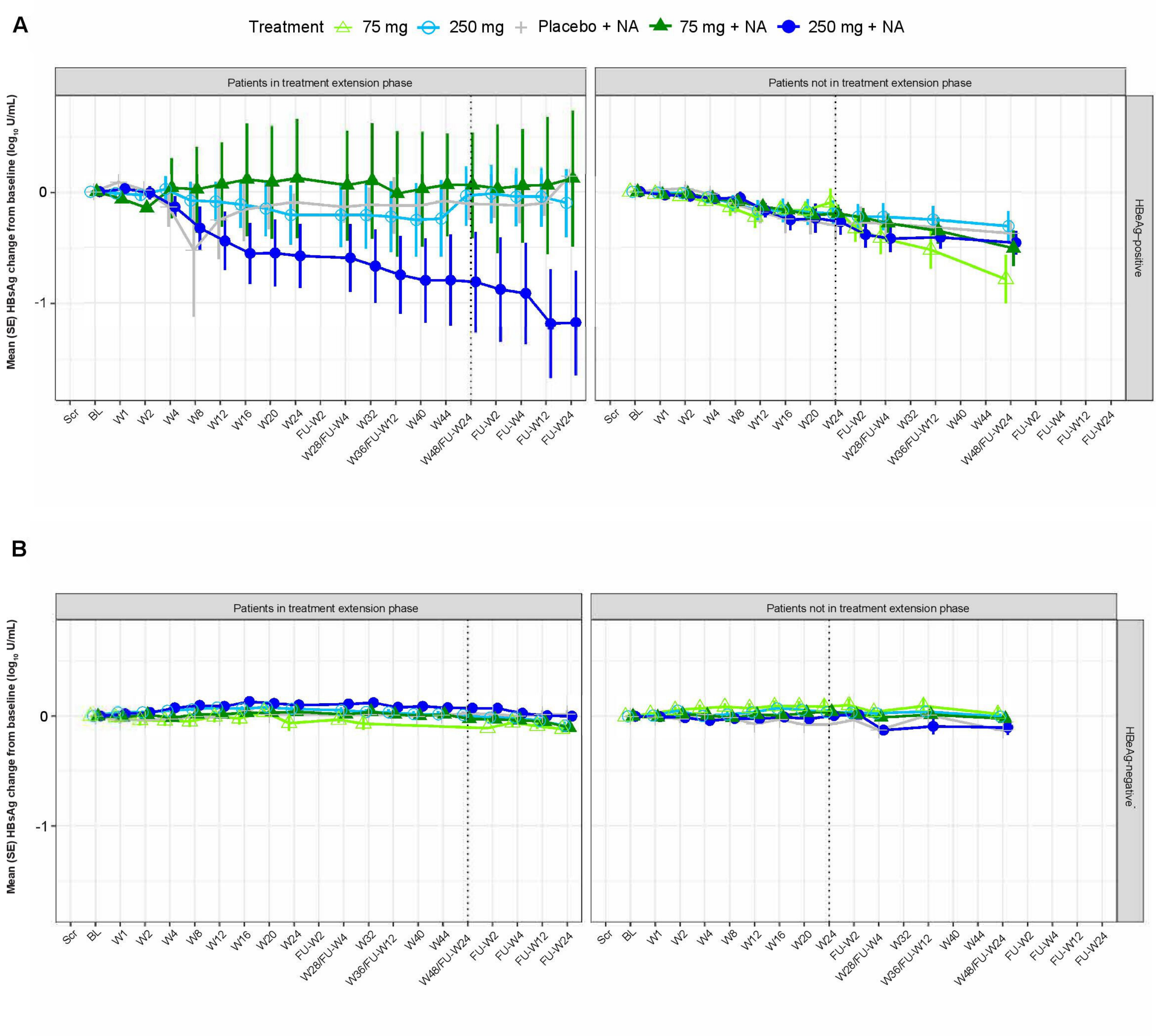


Figure 4 Change from baseline in HBsAg throughout the study in NCT patients, by HBeAg status. (A) Per treatment extension including monotherapy arms in patients who are HBeAg positive and (B) per treatment extension including monotherapy arms in patients who are HBeAg negative. HBsAg assessed using an Abbott Architect assay; HBsAg lower limit of quantification: 0.05 IU/mL and ULOQ: >249 750 000 IU/mL. HBsAg values >ULOQ were set to 5.1 log_{10} IU/mL. Dotted vertical lines indicate the end of the treatment phase at Week 24 and the end of extended treatment phase at Week 48. Treatment in the 75 mg and 250 mg JNJ-56136379 monotherapy arms was changed during the study to NA and JNJ-56136379+NA, respectively. BL, baseline visit; FU, follow-up; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; IU, international unit; NA, nucleos(t)ide analogue; NCT, not currently treated at study start; Scr, screening visit; ULOQ, upper limit of quantification; W, Week.

HBV RNA

In NCT and VS patients, reductions from baseline in mean HBV RNA levels were observed for the JNJ-56136379+NA combination arms (table 2 and figure 5B). In NCT patients, JNJ-56136379 75 mg and 250 mg+NA showed a pronounced decline at Week 24 in mean (SE) HBV RNA (2.96 (0.23) and 3.15 (0.33) log_{10} copies/mL, respectively) versus placebo+NA (1.33 (0.32) log_{10} copies/mL). HBV RNA was target not detected at Week 24 in 19/33 (58%), 23/30 (77%) and 9/21 (43%) patients, respectively (table 2). All VS patients with detectable HBV RNA at baseline treated with JNJ-56136379+NA achieved HBV RNA target not detected at Week 24 (21/21; 100%) vs 1/7 (14%) for placebo+NA patients (table 2).

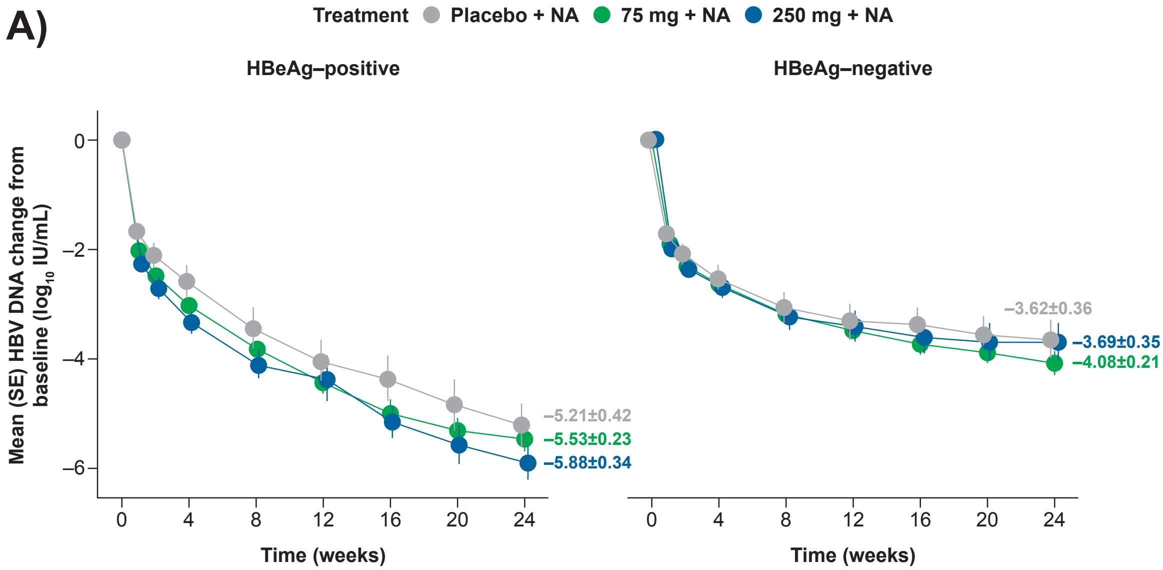
HBcrAg

No clear differences in hepatitis B core-related antigen (HBcrAg) changes from baseline were observed between the treatment arms (table 2; online supplemental figure S6).

Efficacy post-Week 24 of treatment

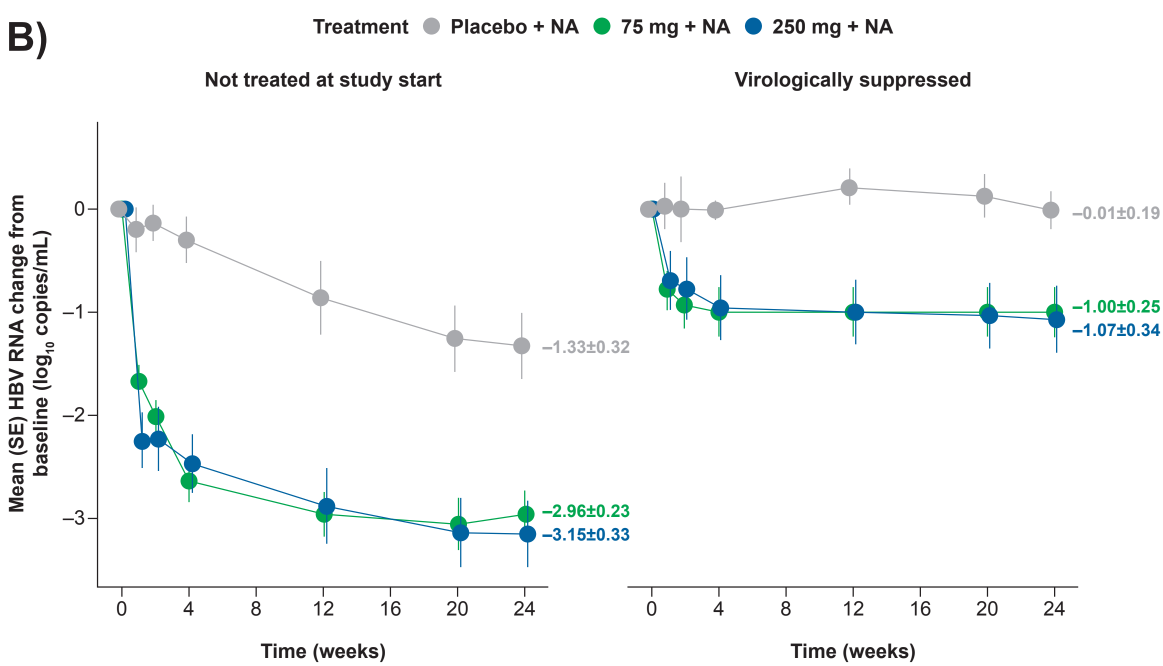
Treatment extension with JNJ-56136379 beyond Week 24 had limited additional effect on viral markers (online supplemental table S4). HBsAg and HBeAg declines predominantly occurred early during treatment, but some NCT patients who are HBeAg positive in the JNJ-56136379 250 mg+NA arm

A)



Patients with HBV DNA <LLOQ at Week 24, n (%)	JNJ-56136379 75 mg + NA	JNJ-56136379 250 mg + NA	Placebo + NA
HBeAg–positive	0/12	4/11 (36)	1/8 (13)
HBeAg–negative	14/21 (67)	16/19 (84)	12/13 (92)

B)



Patients with HBV RNA TND at Week 24, n (%)	JNJ-56136379 75 mg + NA		JNJ-56136379 250 mg + NA		Placebo + NA	
	NCT	VS	NCT	VS	NCT	VS
HBeAg–positive	3/12 (25)	9/9 (100)	4/11 (36)	10/10 (100)	0/8	1/5 (20)
HBeAg–negative	16/21 (76)	24/24 (100)	19/19 (100)	18/18 (100)	9/13 (69)	10/15 (67)

Figure 5 Mean change from baseline in HBV DNA and HBV RNA over 24 weeks of treatment (pooled placebo/JNJ-56136379+NA treatment arms). (A) Mean change in HBV DNA in NCT patients by HBeAg status. HBV DNA assessed using Roche COBAS HBV DNA assay; HBV DNA values below the LLOQ (20 IU/mL) target detected or target not detected were imputed respectively with 15 IU/mL or 5 IU/mL. Mean baseline HBV DNA levels by treatment group and by HBeAg status are shown in online supplemental table S2. (B) Mean change in HBV RNA in patients who are HBeAg positive and HBeAg negative by prior treatment. HBV RNA assessed using a quantitative reverse transcription PCR assay. Not detected HBV RNA values were imputed by a value of 5 copies/mL. HBeAg, hepatitis B e-antigen; HBV, hepatitis B virus; IU, international unit; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogue; NCT, not currently treated at study start; PCR, polymerase chain reaction; TND, target not detected; VS, virologically suppressed.

had continued HBsAg declines after Week 24 (figure 4; online supplemental figure S2).

None of the patients achieved HBsAg seroclearance and/or seroconversion through Week 48. Two patients achieved HBeAg seroclearance and seroconversion at Week 48 (one VS patient receiving placebo+NA and one NCT patient in the JNJ-56136379 250 mg monotherapy arm). The patient in the JNJ-56136379 250 mg monotherapy arm also had an HBsAg reduction of 0.6 $\log_{10}$ IU/mL at Week 24 with maximal reduction of 1.0 $\log_{10}$ at the last study visit. The patient in the placebo+NA arm with HBeAg seroclearance did not experience any HBsAg reduction.

HBV RNA levels generally increased in patients who stopped JNJ-56136379 treatment at Week 24 or 48 (online supplemental figure S3B). However, kinetics of HBV RNA differed between populations. Some NCT patients who are HBeAg negative reached a new plateau (≈1 $\log_{10}$ lower than baseline) in HBV RNA levels, which was maintained during NA treatment in the follow-up period.

ALT normalisation from baseline over time

Most NCT patients with baseline ALT>upper limit of normal (ULN) in the pooled JNJ-56136379 arms and placebo+NA arm achieved ALT normalisation at the end of treatment (Week 24 and/or 48). Of the nine VS patients with baseline ALT>ULN in the pooled JNJ-56136379 arms, four (44%) achieved ALT normalisation versus one (33%) in the pooled placebo+NA arm.

Viral breakthrough

Viral breakthrough (confirmed >1 $\log_{10}$ IU/mL increase in HBV DNA from nadir) occurred in 5/28 patients receiving JNJ-56136379 75 mg monotherapy between Weeks 16 and 20. All five patients had emerging resistant variant T33N (JNJ-56136379-fold change (FC) in EC_{50}: 85 as site-directed mutant in in vitro replication assay). NA treatment was initiated in two patients resulting in HBV DNA suppression. The other three patients discontinued the study without follow-up data available. One patient in the JNJ-56136379 75 mg monotherapy arm experienced a viral breakthrough at Week 32, with emerging F23Y mutation (FC=5.2) and was switched to NA treatment with subsequent DNA decline.

One patient receiving JNJ-56136379 250 mg monotherapy with no HBV DNA response up to Week 4 experienced a viral breakthrough at Week 8 with no emerging variants. Following viral breakthrough, NA treatment was added for all patients receiving JNJ-56136379. There were no cases of viral breakthrough in the JNJ-56136379 75 mg+NA or 250 mg+NA treatment arms until Week 24. One patient receiving JNJ-56136379 75 mg+NA experienced a viral breakthrough at Week 48 due to lack of adherence.

Seven patients (six JNJ-56136379±NA and one placebo) experienced a viral breakthrough during the NA-only treatment in the follow-up phase. Of seven patients with a viral breakthrough, three continued ongoing NA treatment and showed subsequent declines in HBV DNA. For the remaining four patients, the time of a viral breakthrough was the last available follow-up time point. No patients had emerging NA-resistance variants. One patient, who received ETV during NA-only follow-up, had documented prior failure to lamivudine and telbivudine and had the M204I lamivudine/telbivudine resistance mutation. Patients with a viral breakthrough and follow-up data available continued NA treatment with subsequent HBV declines.

Safety

Most treatment-emergent AEs were Grade 1 or 2. Three patients discontinued treatment due to AEs (table 3), one in the pooled placebo+NA arm with abdominal discomfort/gastrointestinal upset, one in the JNJ-56136379 75 mg+NA arm with streptococcal toxic shock syndrome, acute cardiac failure, myocarditis and muscle necrosis and one with weight loss in the JNJ-56136379 250 mg open-label arm. Seventeen patients had ≥Grade 3 AEs (13 (7%) in the pooled JNJ-56136379 treatment versus four (9%) in the pooled placebo+NA arms), most commonly increased ALT and aspartate aminotransferase (AST) (six (3%) and five (3%) patients, respectively) in the pooled JNJ-56136379 treatment arms versus no patients in the pooled placebo+NA arm (table 3). None of the eight reported SAEs were considered related to study treatment (table 3).

Creatine phosphokinase elevation was reported as an AE in seven (4%) patients in the pooled JNJ-56136379 treatment arms and two (5%) patients in the placebo+NA arm. One patient who received JNJ-56136379 75 mg+NA and one patient who received placebo+NA reported a Grade 3 and Grade 2 AE of creatine phosphokinase elevation, respectively. All other AEs of creatine phosphokinase elevation were Grade 1; cases resolved without discontinuation of treatment.

ALT elevations occurred in seven patients in the JNJ-56136379 treatment arms, including one patient in the JNJ-56136379 75 mg+NA arm (Grade 4), two in the JNJ-56136379 250 mg monotherapy arm (Grade 3) and four in the JNJ-56136379 250 mg+NA arm (Grade 4: n=2; Grade 2: n=1; Grade 1: n=1). These ALT elevations normalised on continued treatment and did not lead to liver failure. No Grade 3 or 4 ALT and AST elevations were observed in the pooled placebo+NA arm (online supplemental table S5). In the pooled JNJ-56136379 treatment arms, transient ALT elevations of Grade 3 were observed in 10 (5%) patients and of Grade 4 in five (3%) patients. Transient AST elevations of Grade 3 were observed in three (2%) patients and of Grade 4 in two (1%) patients.

There were two patients with peak ALT >1000 U/L (1340 and 1086 U/L) from the JNJ-56136379 250 mg+NA and JNJ-56136379 75 mg open-label arms, respectively. An additional 10 patients had peak ALT values between 300–1000 U/L (JNJ-56136379 75 mg open-label: n=2; JNJ-56136379 250 mg open-label: n=3; JNJ-56136379 75 mg+NA: n=1; JNJ-56136379 250 mg+NA: n=4). Most ALT flares occurred around Weeks 1 and 2, and time until resolution was typically between 2 and 3 weeks while treatment was continued.

Patients with estimated glomerular filtration rate based on serum creatinine ($eGFR_{cr}$) >60 mL/min/1.73 m² (lower limit of Grade 2) or higher were included in the study and sometimes declined to <60 mL/min/1.73 m², classified as Grade 3 decreases. An on-treatment decline in $eGFR_{cr}$ was observed early after JNJ-56136379±NA treatment initiation with rapid increase during the follow-up phase. Figure 6 shows fluctuations in $eGFR_{cr}$ over time, by type of NA. The reductions appeared to be more pronounced in patients receiving JNJ-56136379 250 mg±NA versus JNJ-56136379 75 mg±NA. A higher proportion of patients in the JNJ-56136379 250 mg±NA group had treatment emergent Grade 3 $eGFR_{cr}$ during study treatment (online supplemental

Table 3 Summary of reported treatment-emergent AEs (all patients receiving ≥1 dose of the study drug)

	Pooled placebo+NA N=43	JNJ-56136379 75 mg open label* N=28	JNJ-56136379 75 mg+NA N=66	JNJ-56136379 250 mg open label* N=32	JNJ-56136379 250 mg+NA N=63
Patients with ≥1 AE, n (%)	34 (79)	18 (64)	55 (83)	25 (78)	54 (86)
Most common AEs, any grade (≥5% of the patients in the combined JNJ-56136379 treatment arms)					
Headache	3 (7)	3 (11)	11 (17)	6 (19)	14 (22)
Upper respiratory tract infection	1 (2)	2 (7)	9 (14)	4 (13)	4 (6)
Nasopharyngitis	8 (19)	1 (4)	7 (11)	2 (6)	8 (13)
Fatigue	4 (9)	2 (7)	8 (12)	2 (6)	5 (8)
Back pain	0	2 (7)	5 (8)	3 (9)	3 (5)
Increased ALT	1 (2)	0	2 (3)	3 (9)	6 (10)
Nausea	3 (7)	2 (7)	2 (3)	2 (6)	5 (8)
Upper abdominal pain	1 (2)	1 (4)	3 (5)	2 (6)	4 (6)
Diarrhoea	1 (2)	2 (7)	3 (5)	1 (3)	4 (6)
Dizziness	0	1 (4)	3 (5)	4 (13)	2 (3)
Worst reported grade of AE, n (%)					
Grade 1	17 (40)	14 (50)	37 (56)	18 (56)	32 (51)
Grade 2	13 (30)	4 (14)	14 (21)	3 (9)	16 (25)
Grade 3 or 4	4 (9)	0	4 (6)	3 (9)	6 (10)
Most common Grade 3 or 4 AEs (≥2 patients in the combined JNJ-56136379 treatment arms)					
Increased ALT	0	0	2 (3)	2 (6)	2 (3)
Increased AST	0	0	2 (3)	1 (3)	2 (3)
Patients with ≥1 SAE,† n (%)	1 (2)	0	3 (5)	0	4 (6)
Patients with AEs leading to discontinuation,‡ n (%)	1 (2)	0	1 (2)	1 (3)	0

*Treatment in 75 mg and 250 mg JNJ-56136379 monotherapy arms were changed during the study to NA and JNJ-56136379+NA, respectively.
†SAEs (none related to study drugs) were colitis (n=1, placebo+NA); streptococcal toxic shock syndrome, acute cardiac failure, myocarditis, muscle necrosis (n=1), post-traumatic neck syndrome (n=1) and lymphadenitis (n=1) (JNJ-56136379 75 mg+NA) and appendicitis, ligament rupture, ovarian haemorrhage and intervertebral disc protrusion (each n=1; JNJ-56136379 250 mg+NA).
‡AEs leading to treatment discontinuation were abdominal discomfort/gastrointestinal upset (n=1, placebo+NA), streptococcal toxic shock syndrome, acute cardiac failure, myocarditis and muscle necrosis (n=1; JNJ-56136379 75 mg+NA) and abnormal weight loss (JNJ-56136379 250 mg open label).
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NA, nucleos(t)ide analogue; SAE, serious AE.

table S5). The decline in $eGFR_{cr}$ was observed at the first assessment after starting JNJ-56136379. The decline in $eGFR_{cr}$ stabilised at subsequent assessments, and there was a rapid increase in $eGFR_{cr}$. A conclusion cannot be drawn regarding the type of NA and impact on $eGFR_{cr}$ given the small sample size of patients receiving ETV.

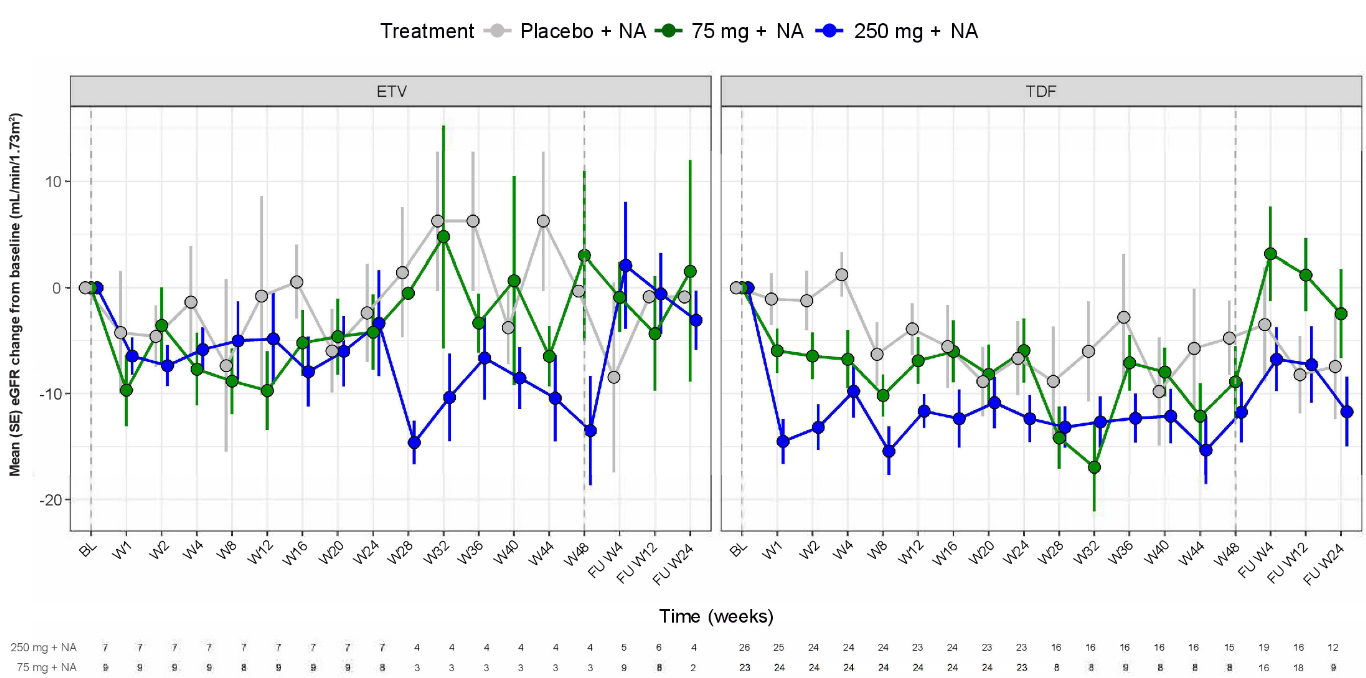


Figure 6 Mean change from baseline in $eGFR_{cr}$ throughout the study in NCT patients, by type of NA. Monotherapy treatment arms are not shown as no NA was given from the start of treatment. Dotted vertical line indicates the end of the extended treatment phase at Week 48. BL, baseline visit; $eGFR_{cr}$, estimated glomerular filtration rate based on serum creatinine; ETV, entecavir; FU, follow-up; NA, nucleos(t)ide analogue; NCT, not currently treated at study start; TDF, tenofovir disoproxil fumarate; W, Week.

Pharmacokinetics

After repeated qd dosing with JNJ-56136379 75 mg and 250 mg up to 24 weeks, observed plasma concentrations were dose proportional and within the range predicted from the population PK model (online supplemental figure S7A). The PK data were well described using a two compartmental model (central and peripheral distribution volume). Body weight was retained as a covariate to explain the volumes, including sex-specific reference weights, but age was not retained as a covariate in the model. An evaluation of the PK data from JNJ-56136379 indicated that the initial population PK model (using the same approach for body weight and the same parameters) generally well described the JNJ-56136379 concentrations observed in this study for both the 75 mg and 250 mg doses in the initial and extension treatment phases. No additional effects of race (Asian vs non-Asian) were observed.

Comparing plasma concentrations and PK parameters between the JNJ-56136379 monotherapy arms and combination arms with an NA, a PK drug-drug interaction between TDF and JNJ-56136379 was apparent. At Day 84, tenofovir disoproxil fumarate analyte (TFV) exposure was higher for both arms containing JNJ-56136379 versus placebo (online supplemental figure S7B).

In comparison with arms receiving placebo at Week 12, for all arms receiving JNJ-56136379 75 mg and 250 mg, respectively, the geometric mean ratios of TFV maximum plasma concentrations (C_{max}) were 142.81% and 165.02%, TFV included pre-dose plasma concentrations (C_{trough}) were 149.21% and 171.74% and TFV area under the plasma concentration-time curve from time 0 to τ hours post-dose (AUCτ) were 189.55% and 195.06%. Drug-drug interactions between ETV and JNJ-56136379 were not apparent (online supplemental figure S7C).

DISCUSSION

While the primary endpoint of >1 $\log_{10}$ IU/mL mean decline in HBsAg of the active versus control was not achieved, this study demonstrated that JNJ-56136379 75 mg and 250 mg qd administered in combination with TDF or ETV led to substantial reductions in HBV DNA and HBV RNA, up to Week 48, and had favourable safety and tolerability profiles. For NCT patients who are HBeAg positive, a trend of a greater, yet small HBsAg decline and more consistent, yet limited, decline in HBeAg levels was observed in the JNJ-56136379 250 mg+NA group versus the placebo+NA group.

Mean HBV DNA declines after 24 weeks in NCT patients who are HBeAg positive receiving JNJ-56136379 75 mg or 250 mg+NA were 5.53 and 5.88 $\log_{10}$ IU/mL, respectively, compared with 5.21 $\log_{10}$ IU/mL in the placebo+NA group, suggesting an incremental benefit of combining JNJ-56136379 with an NA based on enhanced viral suppression.

As reported previously, JNJ-56136379 showed potent reductions of serum HBV RNA. In NCT patients, a greater mean HBV RNA decline was observed in the JNJ-56136379 75 mg+NA and 250 mg+NA groups versus placebo+NA (2.96 and 3.15 versus 1.33 $\log_{10}$ copies/mL) at Week 24. In VS patients, mean HBV RNA declines appeared lower than in NCT patients due to low baseline HBV RNA levels and the high proportion of patients with already undetectable HBV RNA at baseline. Serum HBV RNA has recently been suggested as a measure for cccDNA transcriptional activity.[21] However, its use as a marker for cccDNA is limited in the setting of CAM treatment given their direct effect (primary MoA), preventing pgRNA encapsidation and thereby, release of HBV RNA–containing particles; thus, in the setting of CAM administration, serum HBV RNA is primarily the reflection of target engagement.[6 11 20 22] A rebound in HBV RNA after stopping JNJ-56136379 under continued NA treatment was observed, suggesting mainly a direct effect on HBV RNA release.

HBcrAg and HBeAg are derived from cccDNA and considered surrogate markers for cccDNA transcriptional activity.[23 24] If a possible effect of JNJ-56136379+NA treatment on cccDNA occurred, it may be reflected in HBeAg and HBcrAg levels. In the present study, compared with NA only, JNJ-56136379+NA had limited additional effects on HBeAg (such as more patients with >0.3 log decline), which may be due to effects on cccDNA or direct effects of the CAM-N on HBeAg secretion.[25] However, no relevant effect on HBcrAg levels was noted.

As a viral breakthrough associated with resistant variants was observed in the JNJ-56136379 monotherapy arm, JNJ-56136379 will not be developed further. These data imply that the risk of viral resistance and breakthrough should be considered for the drug class of CAMs in general. The JNJ-56136379 emerging variant was detectable as the dominant variant until the last visit with sequence data available. The analysis of persistence of CAM-related variants after stopping JNJ-56136379 is hampered by the fact that either NA rescue treatment was started in most patients resulting in subsequent HBV DNA declines or the patients were lost to follow-up. No cases of viral breakthrough were observed in the JNJ-56136379+NA combination arms through Week 24, although one patient receiving JNJ-56136379 75 mg+NA experienced viral breakthrough at Week 48, likely due to adherence issues.

JNJ-56136379 was well tolerated, where most treatment-emergent AEs were Grade 1 or 2; no study treatment-related SAEs were observed. Transient Grade 3 and 4 ALT/AST elevations without signs of impaired liver function were observed in the JNJ-56136379+NA arm. ALT/AST elevations normalised on continued treatment. ALT flares were primarily observed in NCT patients who are HBeAg positive and were often associated with decreases in viral parameters. Isolated and transient treatment-emergent ALT and AST increases have been observed during treatment with NAs,[26] mainly in patients who are HBeAg positive.[13 15 16 18 19 27]

JNJ-56136379±NA treatment caused a transient decrease in $eGFR_{cr}$, with an increase during the follow-up phase. The increase in plasma creatinine that occurred shortly after treatment initiation with JNJ-56136379 suggests a renal transporter effect of JNJ-56136379 at the proximal tubular level, leading to decreased tubular excretion of creatinine and lower $eGFR_{cr}$ values.

Plasma levels of JNJ-56136379 were dose-proportional as reported previously.[10 12] There was no evidence of a drug-drug interaction between JNJ-56136379 and ETV. TFV exposure was twofold higher in combination with JNJ-56136379 versus with placebo. Although these changes were not considered clinically relevant, the clinical impact of longer treatment exposure to a combination regimen of JNJ-56136379 and TDF is unknown. Therefore, further studies are needed to evaluate if the increase in TFV exposure is unique to co-administration with JNJ-56136379 or if similar increases are observed for the CAM class.

Strengths of the study were the comprehensive design that included a blinded comparison of active versus placebo, NCT and VS patients, HBeAg-positive and -negative patients, relevant numbers of Asian patients and patients from China, monotherapy and combination treatment, two doses of study drug and a response guided longer treatment period to better characterise antiviral activity. Limitations included the low power to fully assess the primary and secondary endpoints in patient subgroups and the initial treatment extension criteria with a stringent threshold for HBV DNA at 24 weeks, which may have excluded patients who could have responded with further treatment.

In conclusion, treatment with JNJ-56136379 in combination with an NA in patients with CHB showed pronounced reductions in HBV DNA and HBV RNA. Limited effects of JNJ-56136379 on HBsAg and HBeAg levels were observed. Both doses of JNJ-56136379 in combination with an NA were well tolerated over a prolonged treatment period and demonstrated target engagement. While JNJ-56136379 in combination with an NA did not show a clear benefit over NA monotherapy, several other CAMs of different classes and chemotypes, with improved preclinical characteristics are in discovery and in clinical development. The results of these studies will inform on the role of CAMs in future combination regimens for the treatment of HBV.

Author affiliations
[1]Toronto General Hospital, Toronto, Ontario, Canada
[2]Erasmus Medical Center, Rotterdam, Zuid-Holland, The Netherlands
[3]Nanfang Hospital, Southern Medical University, Guangzhou, China
[4]Université de Paris Cité, INSERM UMR1149, Hôpital Beaujon AP-HP, Clichy, France
[5]The Chinese University of Hong Kong, Hong Kong SAR, China
[6]Hospices Civils de Lyon and Lyon University & INSERM U1052-Cancer Research Institute of Lyon, Lyon, France
[7]Department of Gastroenterology and Hepatology, Kumamoto University, Kumamoto, Japan
[8]Faculty of Health Sciences in Bytom, Medical University of Silesia, Katowice, Poland
[9]ID Care, Hillsborough, New Jersey, USA
[10]ZNA Jan Palfijn, CPU, Antwerp, Belgium
[11]Hospital Universitario Vall d'Hebrón and CIBERHED del Instituto Carlos III, Barcelona, Spain
[12]Division of Gastroenterology and Hepatology, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[13]Department of Pathophysiology and Transplantation, CRC 'A. M. and A. Migliavacca' Center for Liver Disease, University of Milan, Milan, Italy
[14]Janssen Pharmaceutica NV, Beerse, Belgium
[15]Janssen Pharmaceuticals R&D, Titusville, New Jersey, USA

Acknowledgements The authors would like to thank the patients and their families, the study investigators and site staff and all the members of the JNJ-56136379 Compound Development and Operations Teams for conducting this study and other Janssen staff members for their important contributions to the manuscript. Medical writing support for the development of this manuscript was provided by Ian Woolveridge of Ashfield MedComms, an Ashfield Health company, and Jessica Swanner, PhD, of Lumanity Communications Inc., and was funded by Janssen.

Contributors HLAJ, JH, TA, HLYC, FZ, YT, EJ, RGN, SB, MBu and PL contributed to the conduct of the studies as investigators and to the interpretation of the data. OL, TV, JV, WT, MBe, RK, MBi and US contributed to the design and conduct of the study, analysis and interpretation of the data. All authors were involved in manuscript development, review and revision, interpretation of data and have read and approved the final version to be submitted. All authors satisfy the criteria for authorship as established by the ICMJE. All authors had access to the study data and reviewed and approved the final manuscript. MBi served as the guarantor of the study.

Funding This study was sponsored by Janssen (award/grant number: not applicable).

Competing interests HLAJ received grants from AbbVie, Arbutus, Gilead Sciences, Janssen and Roche, and is a consultant for Arbutus, Arena, Enyo Pharma, Gilead Sciences, GlaxoSmithKline, Janssen, Merck, Roche, Vir Biotechnology and Viroclinics. JH declares no conflicts of interest. TA has received grants and served as a speaker and clinical investigator for AbbVie, Antios Therapeutics, Enyo Pharma, Eiger BioPharmaceuticals, Gilead Sciences, Janssen, Merck and Roche. HLYC is an advisor for AbbVie, Aligos, Arbutus, Gilead Sciences, Hepion, Janssen, Merck, Roche, Vir Biotechnology, Vaccitech and VenatoRx, and served as a speaker for Gilead Sciences, Mylan and Roche. FZ has participated in advisory committees or review panels for Janssen, Gilead Sciences, AbbVie, Arbutus, Transgene, Contravir, Myrpharma, Spring Bank, Aligos and Assembly, received grant/research support from Roche and Sanofi/Evotec, and speaking and teaching support from Gilead Sciences. YT received lecture fees from Fujirebio, Sysymex and Gilead Sciences, consigned/joint research expenses from Fujifilim, Janssen, Gilead Sciences, GlaxoSmithKline and Stanford Junior University, and has participated in advisory boards for Gilead Sciences and GlaxoSmithKline. EJ has served as a speaker and clinical investigator for AbbVie, Bristol Myers Squibb, Gilead Sciences, Janssen, Merck and Roche. RGN has received grant/clinical research support from Janssen, Assembly, AbbVie, Alkermes, Gilead Sciences, Merck and ViiV, and has participated in speaker panels for Gilead Sciences, Merck, Insemed and ViiV. SB has participated in advisory committees or review panels for AbbVie, Gilead Sciences and Merck, and has received speaking and teaching support from AbbVie, Bristol Myers Squibb and Gilead Sciences. MBu has participated in advisory committees or review panels for Arbutus, Gilead Sciences, Janssen, Merck, Roche and Spring Bank Board, board membership for AbbVie, received grant/research support from Gilead Sciences and Janssen, and speaking and teaching support from Gilead Sciences, Janssen and Bristol Myers Squibb. PL has participated in advisory boards/speaker bureaus for Bristol Myers Squibb, Roche, Gilead Sciences, GlaxoSmithKline, AbbVie, Merck, Arrowhead, Alnylam, Janssen, Spring Bank Board, Myrpharma and Eiger. OL, TV, JV, WT, MBe, RK, MBi and US are all employees of Janssen Pharmaceuticals and Johnson & Johnson stockholders.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the relevant local institutional review boards/ethics committees. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

ORCID iDs
Jinlin Hou http://orcid.org/0000-0001-8230-8583
Tarik Asselah http://orcid.org/0000-0002-0024-0595
Fabien Zoulim http://orcid.org/0000-0002-2245-0083
Pietro Lampertico http://orcid.org/0000-0002-1026-7476
Michael Biermer http://orcid.org/0000-0001-6993-8206

REFERENCES

1 World Health Organization. *Hepatitis B*, July 27, 2021.
2 Lok AS, Zoulim F, Dusheiko G, *et al*. Hepatitis B cure: from discovery to regulatory approval. *Hepatology* 2017;66:1296–313.
3 Terrault NA, Lok ASF, McMahon BJ, *et al*. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018;67:1560–99.
4 European Association for the Study of the Liver. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017;67:370–98.
5 Asselah T, Loureiro D, Boyer N, *et al*. Targets and future direct-acting antiviral approaches to achieve hepatitis B virus cure. *Lancet Gastroenterol Hepatol* 2019;4:883–92.
6 Fanning GC, Zoulim F, Hou J, *et al*. Therapeutic strategies for hepatitis B virus infection: towards a cure. *Nat Rev Drug Discov* 2019;18:827–44.
7 Wu D, Ning Q. Toward a cure for hepatitis B virus infection: combination therapy involving viral suppression and immune modulation and long-term outcome. *J Infect Dis* 2017;216:S771–7.
8 Tout I, Loureiro D, Mansouri A, *et al*. Hepatitis B surface antigen seroclearance: immune mechanisms, clinical impact, importance for drug development. *J Hepatol* 2020;73:409–22.
9 Berke JM, Dehertogh P, Vergauwen K, *et al*. Capsid assembly modulators have a dual mechanism of action in primary human hepatocytes infected with hepatitis B virus. *Antimicrob Agents Chemother* 2017;61. doi:10.1128/AAC.00560-17. [Epub ahead of print: 25 July 2017].

10 Vandenbossche J, Jessner W, van den Boer M, *et al*. Pharmacokinetics, safety and tolerability of JNJ-56136379, a novel hepatitis B virus capsid assembly modulator, in healthy subjects. *Adv Ther* 2019;36:2450–62.
11 Berke JM, Dehertogh P, Vergauwen K, *et al*. Antiviral properties and mechanism of action studies of the hepatitis B virus capsid assembly modulator JNJ-56136379. *Antimicrob Agents Chemother* 2020;64. doi:10.1128/AAC.02439-19. [Epub ahead of print: 21 Apr 2020].
12 Zoulim F, Lenz O, Vandenbossche JJ, *et al*. JNJ-56136379, an HBV capsid assembly modulator, is well-tolerated and has antiviral activity in a phase 1 study of patients with chronic infection. *Gastroenterology* 2020;159:521–33.
13 Gane EJ, Schwabe C, Lenz O. JNJ-64530440 (JNJ-0440), a novel class N capsid assembly modulator (CAM-N): safety, tolerability, pharmacokinetics (PK), and antiviral activity of multiple ascending doses in patients (PTS) with chronic hepatitis B (CHB). *Hepatology* 2019;70.
14 Sulkowski MS, Agarwal K, Fung SK, *et al*. Continued therapy with ABI-H0731 + NrtI results in sequential reduction/loss of HBV DNA, HBV RNA, HBeAg, HBcrAg and HBsAg in HBeA-positive patients. *Hepatology* 2019;70:LP1.
15 Yuen M-F, Agarwal K, Gane EJ, *et al*. Safety, pharmacokinetics, and antiviral effects of ABI-H0731, a hepatitis B virus core inhibitor: a randomised, placebo-controlled phase 1 trial. *Lancet Gastroenterol Hepatol* 2020;5:152–66.
16 Gane E, Liu A, Yuen M-F, *et al*. RO7049389, a core protein allosteric modulator, demonstrates robust anti-HBV activity in chronic hepatitis B patients and is safe and well tolerated. *J Hepatol* 2018;68:S101.
17 Feng S, Gane E, Schwabe C, *et al*. A five-in-one first-in-human study to assess safety, tolerability, and pharmacokinetics of RO7049389, an inhibitor of hepatitis B virus capsid assembly, after single and multiple ascending doses in healthy participants. *Antimicrob Agents Chemother* 2020;64. doi:10.1128/AAC.01323-20. [Epub ahead of print: 20 Oct 2020].
18 Zhao N, Jia B, Zhao H, *et al*. A first-in-human trial of GLS4, a novel inhibitor of hepatitis B virus capsid assembly, following single- and multiple-ascending-oral-dose studies with or without ritonavir in healthy adult volunteers. *Antimicrob Agents Chemother* 2019;64. doi:10.1128/AAC.01686-19. [Epub ahead of print: 20 Dec 2019].
19 Zhang H, Wang F, Zhu X, *et al*. Antiviral activity and pharmacokinetics of the hepatitis B virus (HBV) capsid assembly modulator GLS4 in patients with chronic HBV infection. *Clin Infect Dis* 2021;73:175–82.
20 Lam AM, Ren S, Espiritu C, *et al*. Hepatitis B virus capsid assembly modulators, but not nucleoside analogs, inhibit the production of extracellular pregenomic RNA and spliced RNA variants. *Antimicrob Agents Chemother* 2017;61.
21 Giersch K, Allweiss L, Volz T, *et al*. Serum HBV pgRNA as a clinical marker for cccDNA activity. *J Hepatol* 2017;66:460–2.
22 Feld JJ, Colledge D, Sozzi V, *et al*. The phenylpropenamide derivative AT-130 blocks HBV replication at the level of viral RNA packaging. *Antiviral Res* 2007;76:168–77.
23 Chen E-Q, Feng S, Wang M-L, *et al*. Serum hepatitis B core-related antigen is a satisfactory surrogate marker of intrahepatic covalently closed circular DNA in chronic hepatitis B. *Sci Rep* 2017;7:173.
24 Testoni B, Lebossé F, Scholtes C, *et al*. Serum hepatitis B core-related antigen (HBcrAg) correlates with covalently closed circular DNA transcriptional activity in chronic hepatitis B patients. *J Hepatol* 2019;70:615–25.
25 Lahlali T, Berke JM, Vergauwen K, *et al*. Novel potent capsid assembly modulators regulate multiple steps of the hepatitis B virus life cycle. *Antimicrob Agents Chemother* 2018;62. doi:10.1128/AAC.00835-18. [Epub ahead of print: 24 Sept 2018].
26 Chang M-L, Liaw Y-F. Hepatitis B flares in chronic hepatitis B: pathogenesis, natural course, and management. *J Hepatol* 2014;61:1407–17.
27 Jacobson IM, Ma X, Nguyen T. Analysis of the longer-term safety profile of the hepatitis B virus core inhibitor ABI-H0731 in an open-label extension study. *Hepatology* 2020;72:820.

SUPPLEMENTAL MATERIAL

Online Supplemental Methods

Patient population

Not currently treated (NCT) patients were hepatitis B e-antigen (HBeAg)-positive with hepatitis B virus (HBV) DNA ≥20,000 IU/mL or HBeAg-negative with HBV DNA >2,000 IU/mL, and alanine aminotransferase (ALT) > upper limit of normal (ULN) but ≤5x ULN at screening. Virologically suppressed (VS) patients had received the same nucleos(t)ide analogue (NA) treatment (entecavir [ETV] or tenofovir disoproxil fumarate [TDF]) and dose for ≥12 months prior to screening and had HBV DNA <60 IU/mL at screening and ≥6 months prior, and ALT ≤2x ULN at screening. Fibrosis was evaluated (to exclude cirrhosis). Patients had to have a liver biopsy result within 1 year classified as Metavir F0–F2 or a liver stiffness measurement <8.0 kPa (FibroScan™) within 6 months prior to screening or at the time of screening.

Endpoints

Other secondary endpoints included the proportion of patients with ALT improvement and normalization; the proportion of patients with virological breakthrough; changes in the HBV genome sequence; pharmacokinetics (PK); safety and tolerability, including adverse events (AEs) and clinical laboratory tests. Exploratory endpoints included changes from baseline in HBV RNA and hepatitis B core-related antigen (HBcrAg) levels. For the extended treatment phase (48 weeks), additional endpoints included: the proportions of patients meeting treatment completion criteria (Figure 1 footnote), and with sustained reduction/suppression and/or seroclearance, considering hepatitis B surface antigen (HBsAg), HBeAg, HBV DNA, and ALT levels during follow-up.

Study evaluations

Qualitative and quantitative HBsAg and HBeAg levels were assessed in real-time at a central laboratory using Abbott Architect™ assays (Abbott Laboratories), with a lower limit of quantification (LLOQ) of 0.05 IU/mL and 0.11 IU/mL, respectively. Values greater than the upper limit of quantification (ULOQ) were set to (ULOQ+[ULOQ/10]) IU/mL for HBsAg and HBeAg.

HBV DNA and HBV RNA levels were quantified at a central laboratory. HBV DNA was measured in real-time using a COBAS® TaqMan® HBV DNA assay (Roche), with a LLOQ of 20 IU/mL. HBV DNA <LLOQ was imputed as 15 IU/mL [1.18 $\log_{10}$ IU/mL]. HBV RNA was measured using a validated quantitative reverse-transcription polymerase chain reaction assay targeting the 3' region of the genome (DDL Diagnostic Laboratory, Rijswijk, Netherlands) similar to an assay described previously[1] with a limit of detection (LOD) of 2.49 $\log_{10}$ copies/mL and an LLOQ of 4.04 $\log_{10}$ copies/mL. Samples not detected by the HBV RNA assay were imputed with 5 copies/mL (0.69 $\log_{10}$ copies/mL). RNA values down to LOD were considered quantitative for analysis purposes (RNA being exploratory endpoint).

HBcrAg was assessed using the Lumipulse platform (Fujirebio, Malvern, PA), which detects HBeAg, HBcrAg, and p22cr protein with an LLOQ of 3.0 $\log_{10}$ U/mL. HBcrAg levels <3.0 $\log_{10}$ U/mL were imputed with 2.7 $\log_{10}$ U/mL. Anti-HBsAg and anti-HBeAg antibodies were determined using chemiluminescence immunoassays and/or enzyme-linked immunosorbent assay–based assay. Per protocol, JNJ-56136379 was discontinued in CHB patients who had (1) viral breakthrough (confirmed on-treatment HBV DNA increase by >1 $\log_{10}$ IU/mL from nadir level or HBV DNA >200 IU/mL if previously HBV DNA <LLOQ) or (2) confirmed non-response (<1 $\log_{10}$ IU/mL decline in HBV DNA from baseline at Week 4 and 8).

AEs and SAEs were coded according to Medical Dictionary for Regulatory Activities terms (version 21.0). Clinical laboratory tests included hematology, blood biochemistry, blood coagulation and urinalysis. Laboratory abnormalities could also be reported as AEs by the investigators.

The viral sequence analysis focused on 15 HBV core protein amino acid (aa) positions of interest, associated with *in vitro* resistance to JNJ-56136379 and/or other CAMs.[2] Baseline aa polymorphisms were defined as differences versus the universal HBV genotype (GT)-A reference sequence (NCBI ID X02763) if the sequence frequency of the variant was ≥15%. Treatment-emergent substitutions were defined as aa variants not present at baseline (read frequency <1%) and detected post-baseline with a read frequency ≥15%. The impact of aa substitutions on JNJ-56136379 *in vitro* activity was assessed in a transient replication assay using site-directed mutations in a GT-D backbone.[2]

Statistical analyses

The adequacy of the sample size for the different parts of the study was assessed by evaluating the performance of the analysis of the primary endpoint comparing JNJ-56136379+NA with placebo+NA (Week 24). Power was assessed using simulations (10,000 replicates per scenario) for the placebo+NA and JNJ-56136379+NA arms. Descriptive statistics included n, mean, standard deviation [SD], coefficient of variation, geometric mean, median, minimum, and maximum. PK parameters included predose plasma concentrations (C_{trough}), multiple dose maximum plasma concentrations (C_{max}), area under the plasma concentration-time curve from time 0 to τ hours post dose (AUC_{τ}), and the urine PK parameter, renal clearance (CL_R). An existing population PK model was used to verify observations versus predictions. The 1 $\log_{10}$ was used based on Bayesian analyses using historic data of meta-analyses of HBsAg responses to current standard of care in literature. In addition, analyses suggested that mean 1 $\log_{10}$ differences versus NA might have a chance to increase HBsAg loss.[3,4]

Online supplemental tables

Online supplemental table S1. Study eligibility criteria.

Inclusion criteria	**Exclusion criteria**
• 18–70 years of age, inclusive	• Positive for anti-HBsAg antibodies
• BMI 18.0–35.0 kg/m^2, inclusive	• Current HAV infection (confirmed by hepatitis A antibody IgM), HDV infection (confirmed by HDV antibody), HEV infection (confirmed by hepatitis E antibody IgM)
• Documented CHB infection (1) Serum HBsAg-positive at screening and serum HBsAg- or HBV DNA-positive ≥6 months prior to screening (2) Serum IgM anti-HBc antibody negative at screening	• HIV-1 or HIV-2 infection (confirmed by antibodies) at screening
• 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[5,6] measurement <8.0 kPa within 6 months prior to screening or at the time of screening	• History of or current HCV infection (confirmed by HCV antibody)
• Provide written informed consent to participate	• 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
• NCT patients must: (1) not have received any CHB treatment at screening, i.e., 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	• Evidence of hepatic decompensation at any time point prior to or at the time of screening: (1) Direct bilirubin >1.2x ULN; OR (2) INR >1.5x ULN; OR (3) serum albumin < LLN; OR (4) documented history or current evidence of

intake of study drugs); AND (2) 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 (3) have HBsAg >250 IU/mL at screening; AND (4) must have ALT >ULN and ≤5 x ULN at screening, determined in the central laboratory	variceal bleeding, ascites, or hepatic encephalopathy
• <u>VS patients must:</u> (1) have been 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 (2) been on the same NA treatment (ETV or TDF) and the same dose for ≥12 months prior to screening; AND (3) have had HBsAg >250 IU/mL at screening; AND (4) have had ALT ≤2x ULN at screening	• Evidence of liver disease of non-HBV etiology. This included but was 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
• Female patients must either have been not of childbearing age, or of childbearing age and: (1) had a negative highly sensitive serum pregnancy test (β-human chorionic gonadotropin) at screening (2) were practicing a highly effective, preferably user-independent method of contraception (failure rate of <1% per year when used consistently and correctly) and agreed to remain on a highly effective method while receiving study treatment and until 90 days after the last dose of JNJ-56136379	• 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 patient may still be eligible if HCC has been ruled out by a more specific imaging procedure (contrast enhanced ultrasound, CT, or MRI)
• Male patients must have agreed: (1) to comply with contraceptive measures until at least 90 days after the last dose of JNJ-56136379	• One or more of the following laboratory abnormalities at screening: (1) any laboratory abnormality > Grade 1 (as defined by the DAIDS Toxicity Grading Scale),

(2) not to donate sperm during the study and for at least 90 days after receiving the last dose of JNJ-56136379	with the exception of ALT/AST, considered to be clinically significant by the investigator at screening (2) alpha-fetoprotein outside the normal range
	• Known allergies, hypersensitivity, or intolerance to JNJ-56136379 or its excipients
	• Contraindications to the use of ETV or TDF, per local prescribing information
	• 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
	• Had major surgery (requiring general anesthesia) within 12 weeks prior to screening, or who had not fully recovered from surgery, or had surgery planned during study treatment, or within 12 weeks after the last dose of study drug
	• Received an organ transplant

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CHB, chronic hepatitis B; DAIDS, Division of AIDS; ETV, entecavir; HAV, hepatitis A virus; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; HIV, human immunodeficiency virus; IgM, immunoglobulin M; INR, international normalized ratio; IU, international unit; LLN, lower limit of normal; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.

Online supplemental table S2. Baseline disease characteristics in NCT patients by HBeAg status.

	NCT, HBeAg+			NCT, HBeAg–		
	Pooled placebo+NA N=8	**JNJ-56136379 75-mg+NA N=12**	**JNJ-56136379 250-mg+NA N=13**	**Pooled placebo+NA N=14**	**JNJ-56136379 75-mg+NA N=21**	**JNJ-56136379 250-mg+NA N=20**
ALT, U/L, mean (SD)	66.6 (19.4)	94.9 (53.4)	101.6 (137.5)	70.0 (45.7)	76.0 (103.4)	76.6 (49.1)
HBsAg, log_{10} IU/mL, mean (SD)	4.53 (0.61)	4.26 (0.91)	4.40 (0.68)	3.79 (0.56)	3.81 (0.51)	3.71 (0.52)
HBV DNA, log_{10} IU/mL, mean (SD)	8.24 (0.52)	7.72 (1.01)	7.65 (1.43)	4.89 (1.42)	5.40 (1.14)	4.97 (1.57)
HBV RNA, log_{10} copies/mL, mean (SD)	7.11 (0.70)	6.63 (1.27)	6.07 (1.66)	3.39 (1.85)	3.76 (1.52)	3.46 (1.94)
HBcrAg, log_{10} IU/mL, mean (SD)	8.48 (0.37)	7.93 (0.89)	7.73 (1.22)	4.31 (1.38)	4.66 (1.25)	4.37 (1.39)
HBV genotype, n (%)[a]						
A	0	1 (8)	2 (15)	3 (21)	1 (5)	3 (15)
B	1 (13)	6 (50)	2 (15)	1 (7)	5 (24)	3 (15)
C	4 (50)	2 (17)	4 (31)	2 (14)	3 (14)	5 (25)
D	3 (38)	2 (17)	5 (39)	8 (57)	10 (48)	8 (40)
E, F, H	0	1 (8)	0	0	2 (10)	1 (5)

[a]Genotype data were determined using LiPA and/or sequence-based genotype assays.

Online supplemental table S3. HBV DNA in NCT patients.

	Pooled Placebo+NA N=22		**JNJ-56136379 75-mg open label N=28**		**JNJ-56136379 75-mg+NA N=33**		**JNJ-56136379 250-mg open label N=32**		**JNJ-56136379 250-mg+NA N=33**	
HBeAg status	**+ (n=8)**	**− (n=14)**	**+ (n=12)**	**− (n=16)**	**+ (n=12)**	**− (n=21)**	**+ (n=14)**	**− (n=18)**	**+ (n=13)**	**− (n=20)**
HBV DNA <LLOQ, n (%)										
Baseline	0/8	0/14	0/12	0/16	0/12	0/21	0/14	0/18	0/13	0/20
Week 4	0/8	5/14 (36)	0/12	1/16 (6)	0/12	3/21 (14)	0/14	6/17 (35)	0/12	7/20 (35)
Week 12	0/8	9/13 (69)	0/11	3/15 (20)	0/12	9/21 (43)	0/14	9/15 (60)	2/12 (17)	11/19 (58)
Week 24	1/8 (13)	12/13 (92)	0/8	4/14 (29)	0/12	14/21 (67)	4/14 (29)	13/16 (81)	4/11 (36)	16/19 (84)

HBV DNA assessed using Roche COBAS HBV DNA assay; HBV DNA values below the lower limit of quantification (LLOQ; 20 IU/mL) target detected or target not detected were imputed respectively with 15 IU/mL or 5 IU/mL.

Abbreviations: −, negative; +, positive; HBeAg, hepatitis B e-antigen; HBV, hepatitis B virus; LLOQ, lower limit of detection; NA, nucleos(t)ide analogue; NCT, not treated at study start.

Online supplemental table S4. Summary of antiviral efficacy at Week 48.[a]

	Pooled placebo+NA N=43				**JNJ-56136379 75-mg+NA N=66**				**JNJ-56136379 250-mg open label N=32**		**JNJ-56136379 250-mg+NA N=63**			
Population	**NCT (n=22)**		**VS (n=21)**		**NCT (n=33)**		**VS (n=33)**		**NCT (n=32)**		**NCT (n=33)**		**VS (n=30)**	
HBeAg status	**+ (n=2)**	**– (n=11)**	**+ (n=5)**	**– (n=13)**	**+ (n=2)**	**– (n=9)**	**+ (n=8)**	**– (n=21)**	**+ (n=5)**	**– (n=13)**	**+ (n=5)**	**– (n=14)**	**+ (n=9)**	**– (n=15)**
HBsAg, log_{10} IU/mL														
Change from baseline at Week 48, mean (SE)	-0.11 (0.15)	0.03 (0.03)	0.04 (0.06)	0.01 0.02)	0.06 (0.48)	-0.02 (0.03)	-0.08 (0.09)	-0.04 0.02)	-0.04 (0.27)	0.01 (0.03)	-0.81 (0.45)	0.08 (0.04)	0.05 (0.07)	0.03 (0.02)
Patients with >0.3 log_{10} decline, n (%)	0/2 (0)	0/11 (0)	0/5 (0)	0/13 (0)	1/2 (50)	0/9 (0)	2/8 (25)	0/21 (0)	1/5 (20)	0/13 (0)	3/5 (60)	0/14 (0)	0/9 (0)	0/15 (0)
Patients with >0.5 log_{10} decline, n (%)	0/2 (0)	0/11 (0)	0/5 (0)	0/13 (0)	0/2 (0)	0/9 (0)	1/8 (12)	0/21 (0)	1/5 (20)	0/13 (0)	3/5 (60)	0/14 (0)	0/9 (0)	0/15 (0)
HBV DNA, log_{10} IU/mL														
Change from baseline at Week 48, mean (SE)	-6.36 (0.14)	-3.65 (0.40)	0.04 (0.12)	0 (0.11)	-5.01 (1.3)	-3.71 (0.55)	0 (0.13)	-0.01 (0.07)	-6.41 (0.41)	-3.31 (0.28)	-6.02 (0.60)	-3.52 (0.33)	-0.23 (0.09)	-0.05 (0.05)
Patients with HBV DNA <LLOQ, n (%) at Week 48	2/2 (100)	11/11 (100)	5/5 (100)	13/13 (100)	2/2 (100)	8/9 (89)	8/8 (100)	21/21 (100)	5/5 (100)	13/13 (100)	4/5 (80)	13/14 (93)	9/9 (100)	15/15 (100)
HBV RNA, log_{10} copies/mL														
Change from baseline at Week 48, mean (SE)	–2.76 (0.68)	–1.75 (0.41)	–0.39 (0.27)	0.47 (0.28)	–3.51 (0.21)	–2.23 (0.57)	–2.74 (0.58)	–0.36 (0.17)	–5.49 (0.49)	–2.40 (0.27)	–5.36 (0.68)	–2.37 (0.50)	–3.31 (0.55)	–0.16 (0.16)

Patients with HBV RNA TND at baseline, n (%)	0/8	3/14 (21)	1/6 (17)	13/15 (87)	0/12	2/21 (10)	1/8 (13)	18/24 (75)	0/14	0/18	0/13	4/20 (20)	2/9 (22)	19/20 (95)
Patients with HBV RNA TND at Week 48, n (%)	0/2	6/11 (55)	0/5	8/13 (62)	1/2 (50)	8/9 (89)	8/8 (100)	20/21 (95)	5/5 (100)	11/13 (85)	5/5 (100)	13/14 (93)	9/9 (100)	15/15 (100)
HBeAg, log_{10} IU/mL														
Change from baseline at Week 48, mean (SE)	−2.25 (0.28)	Not applicable	−0.59 (0.30)	Not applicable	−0.24 (0.06)	Not applicable	−0.39 (0.17)	Not applicable	−1.78 (0.60)	Not applicable	−1.60 (0.57)	Not applicable	−0.29 (0.08)	Not applicable
Patients with >0.3 log_{10} decline, n (%)	2/2 (100)	Not applicable	4/5 (80)	Not applicable	0/2 (0)	Not applicable	4/8 (50)	Not applicable	5/5 (100)	Not applicable	4/5 (80)	Not applicable	4/9 (44)	Not applicable
Patients with >0.5 log_{10} decline, n (%)	2/2 (100)	Not applicable	1/5 (20)	Not applicable	0/2 (0)	Not applicable	2/8 (25)	Not applicable	5/5 (100)	Not applicable	4/5 (80)	Not applicable	2/9 (22)	Not applicable
Patients with >1.0 log_{10} decline, n (%)	2/2 (100)	Not applicable	1/5 (20)	Not applicable	0/2 (0)	Not applicable	2/8 (25)	Not applicable	4/5 (80)	Not applicable	4/5 (80)	Not applicable	0/9 (0)	Not applicable
HBcrAg, log_{10} U/mL														
Change from baseline at Week 48, mean (SE)	−1.95 (0.05)	−0.93 (0.25)	−0.28 (0.11)	−0.23 (0.10)	−0.50 (0.10)	−0.76 (0.18)	−0.41 (0.18)	−0.31 (0.15)	−1.85 (0.66)	−0.40 (0.31)	−2.03 (0.68)	-0.95 (0.31)	−0.07 (0.21)	−0.19 (0.15)
Patients with HBcrAg <LLOQ at baseline, n (%)	0/8	3/14 (21)	0/6	4/15 (27)	0/12	2/21 (10)	0/9	7/24 (29)	0/14	2/18 (11)	0/13	5/20 (25)	0/10	9/20 (45)
Patients with >0.3 log_{10} decline, n (%)	2/2 (100)	7/11 (64)	1/5 (20)	3/13 (23)	2/2 (100)	7/9 (78)	3/8 (38)	4/21 (19)	4/4 (100)	3/9 (33)	3/4 (75)	5/10 (50)	3/9 (33)	2/15 (13)
Patients with >0.5 log_{10} decline, n (%)	2/2 (100)	7/11 (64)	1/5 (20)	2/13 (15)	1/2 (50)	6/9 (67)	2/8 (25)	3/21 (14)	3/4 (75)	3/9 (33)	3/4 (75)	5/10 (50)	2/9 (22)	2/15 (13)
Patients with >1.0 log_{10} decline, n (%)	0/2	5/11 (46)	0/5	4/13 (31)	0/2	3/9 (33)	0/8	7/21 (33)	0/4	2/9 (22)	0/4	5/10 (50)	0/9	8/15 (53)

[a]No data to report for JNJ-56136379 75 mg open label arm as no patients reached Week 48 in that treatment arm.

n is the number of patients who continued on JNJ-56136379 until Week 48.

HBsAg values >ULOQ were set to 5.1 log_{10} IU/mL; HBV DNA values <LLOQ (20 IU/mL) target detected or target not detected were imputed respectively with 15 IU/mL or 5 IU/mL; Not detected HBV RNA values were imputed by a value of 5 copies/mL; HBeAg values >ULOQ (1,400 IU/mL) were imputed with 1,540 IU/mL.

Abbreviations: −, negative; +, positive; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IU, international unit; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogue; NCT, not treated at study start; SE, standard error; TND, target not detected; ULOQ, upper limit of quantification; VS, virologically suppressed.

Online supplemental table S5. Grade 3 or 4 treatment-emergent laboratory abnormalities occurring in ≥2 patients in the combined JNJ-56136379 treatment arms, receiving ≥1 dose of study drug.[a]

		Pooled placebo+NA N=43	JNJ-56136379 75-mg open label[b] N=28	JNJ-56136379 75-mg+NA N=66	JNJ-56136379 250-mg open label[b] N=32	JNJ-56136379 250-mg+NA N=63
Incidence, n (%)						
Increased ALT[c]	Grade 3	0	2 (7)	1 (2)	5 (16)	2 (3)
	Grade 4	0	0	1 (2)	1 (3)	3 (5)
Increased AST[c]	Grade 3	0	0	1 (2)	0	2 (3)
	Grade 4	0	0	0	0	2 (3)
Decreased $eGFR_{cr}$	Grade 3	5 (12)	1 (4)	10 (15)	7 (22)	23 (37)
	Grade 4	0	1 (4)	0	0	0
Increased creatine phosphokinase	Grade 3	0	0	4 (6)	0	2 (3)
	Grade 4	0	0	1 (2)	0	2 (3)

[a]Laboratory abnormalities were transient (Large fluctuations in $eGFR_{cr}$ occurred. Patients with $eGFR_{cr}$ 60 mL/min/1.73 m² [lower limit of Grade 2] were included in the study and sometimes dipped to <60 mL/min/1.73 m². Grade 3 creatine phosphokinase increases were isolated and in many cases were linked to strenuous exercise).

[b]Treatment in 75- and 250-mg JNJ-56136379 monotherapy arms was changed during the study to NA and JNJ-56136379+NA, respectively.

[c]ALT/AST elevations were not associated with bilirubin increases.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; $eGFR_{cr}$, estimated glomerular filtration rate based on serum creatinine; NA, nucleos(t)ide analogue.

Supplemental Figures

Online supplemental figure S1. Patient disposition in NCT and VS.

	Not treated at study start			Virologically suppressed		
	Pooled placebo + NA	JNJ-56136379 75 mg + NA	JNJ-56136379 250 mg + NA	Pooled placebo + NA	JNJ-56136379 75 mg + NA	JNJ-56136379 250 mg + NA
Participants randomized and treated N=172 (100%)	**N=22 (100%)**	**N=33 (100%)**	**N=33 (100%)**	**N=21 (100%)**	**N=33 (100%)**	**N=30 (100%)**
Completed Week 24 study treatment	**21 (95.5%)**	**32 (97.0%)**	**30 (90.9%)**	**20 (95.2%)**	**33 (100.0%)**	**27 (90.0%)**
Entered treatment extension phase	**14 (63.6%)**	**12 (36.4%)**	**21 (63.6%)**	**19 (90.5%)**	**31 (93.9%)**	**27 (90.0%)**
Reason for not entering treatment extension phase*						
No virologic response by Week 20	7 (31.8%)	20 (6.6%)	9 (27.3%)	0	2 (6.1%)	0
No consent to participate in treatment extension phase	2 (9.1%)	0	1 (3.0)	0	0	0
Completed treatment extension	**13 (92.9%)**	**11 (91.7%)**	**21 (100%)**	**18 (94.7%)**	**30 (96.8%)**	**25 (92.6%)**
Discontinued treatment extension	**1 (7.1%)**	**1 (8.3%)**	**0**	**1 (5.3%)**	**1 (3.2%)**	**2 (7.4%)**
Withdrawal by participant	1 (7.1%)	0	0	0	1 (3.2%)	1 (3.7%)
Adverse events	0	1 (8.3%)	0	0	0	0
Non-compliance with study drug	0	0	0	1 (5.3%)	0	1 (3.7%)
Lack of efficacy	0	0	0	0	0	0
Other reasons	0	0	0	0	0	0

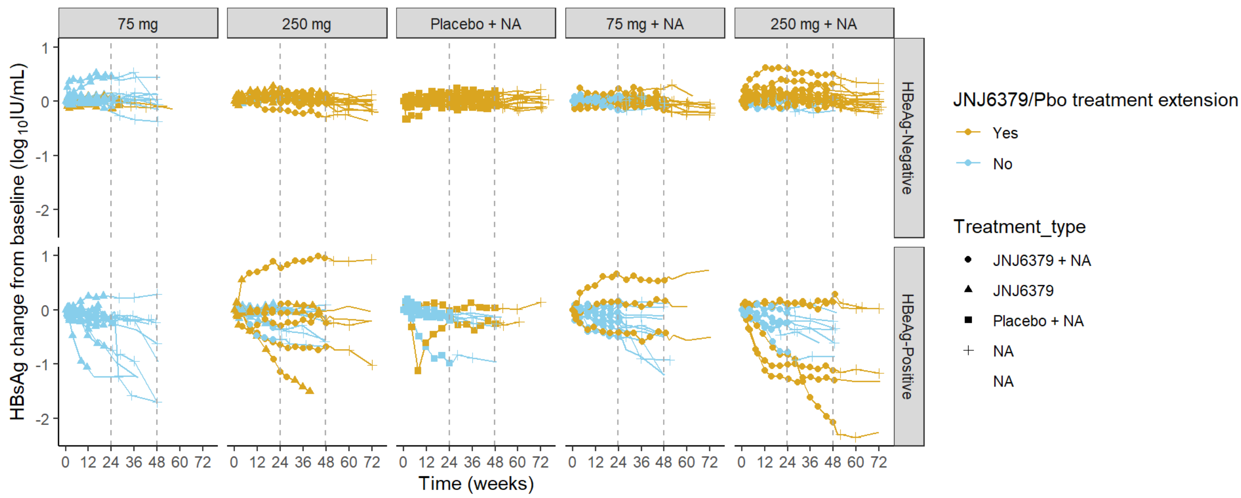
*Participants may be counted for more than one reason for not entering the treatment extension phase.

The majority of patients were assessed with the initial extension criteria (<20 IU/mL).

Online supplemental figure S2. Individual changes from baseline in HBsAg per treatment extension.

Individual profiles indicate if a patient has met the treatment extension criteria and continued JNJ-56136379/placebo treatment to Week 48 (golden lines) or stopped JNJ-56136379/placebo at or before Week 24 (blue lines). HBsAg assessed using an Abbott Architect™ assay; HBsAg LLOQ: 0.05 IU/mL and ULOQ: >249,750,000 IU/mL. HBsAg values >ULOQ were set to 5.1 log_{10} IU/mL.

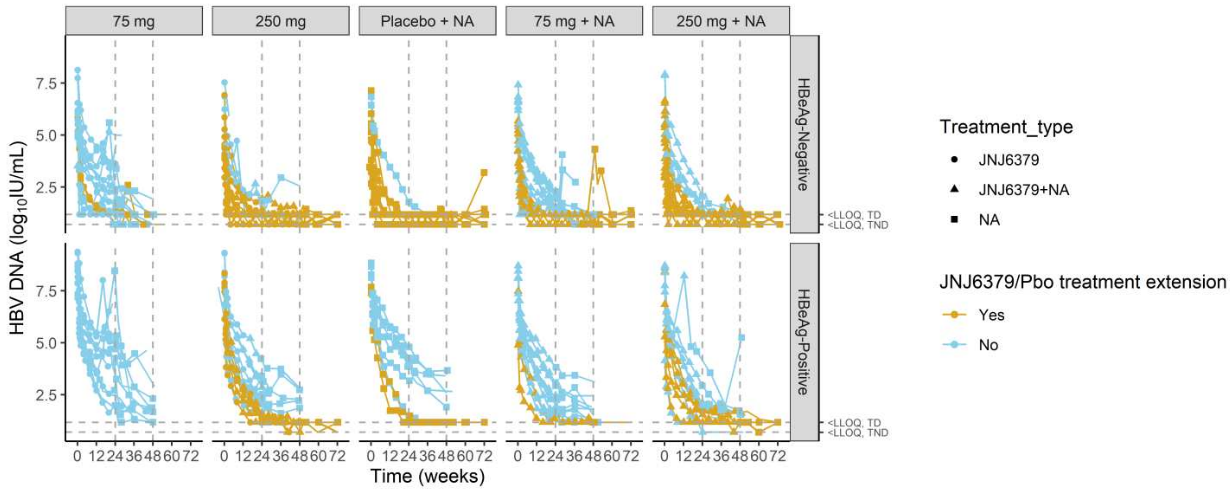
Dotted vertical lines indicate the end of the treatment phase at Week 24 and the end of extended treatment phase at Week 48. Treatment in the 75- and 250-mg JNJ-56136379 monotherapy arms was changed during the study to NA and JNJ-56136379+NA, respectively.



Abbreviations: HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; IU, international unit; JNJ6379, JNJ-56136379; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogue; Pbo, placebo; ULOQ, upper limit of quantification.

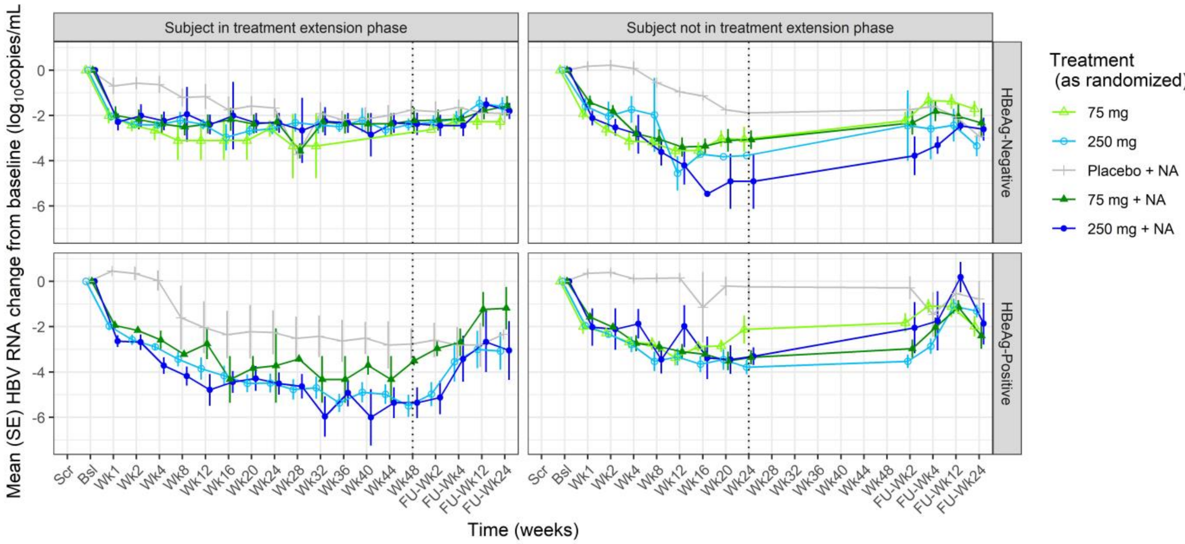
Online supplemental figure S3. HBV DNA and HBV RNA by HBeAg status.

A) HBV DNA profiles in NCT patients per treatment extension, by HBeAg status.



Individual profiles indicate if a patient has met the treatment extension criteria and continued JNJ-56136379/placebo treatment to Week 48 (golden lines) or stopped JNJ-56136379/placebo at or before Week 24 (blue lines). HBV DNA assessed using Roche COBAS HBV DNA assay; HBV DNA values below the lower limit of quantification (LLOQ) (20 IU/mL) target detected (TD) or target not detected (TND) were imputed respectively with 15 IU/mL or 5 IU/mL. Mean baseline HBV DNA levels by treatment group and by HBeAg status are shown in online supplemental table S2.

B) Mean change from baseline in HBV RNA throughout the study in NCT patients, by HBeAg status.

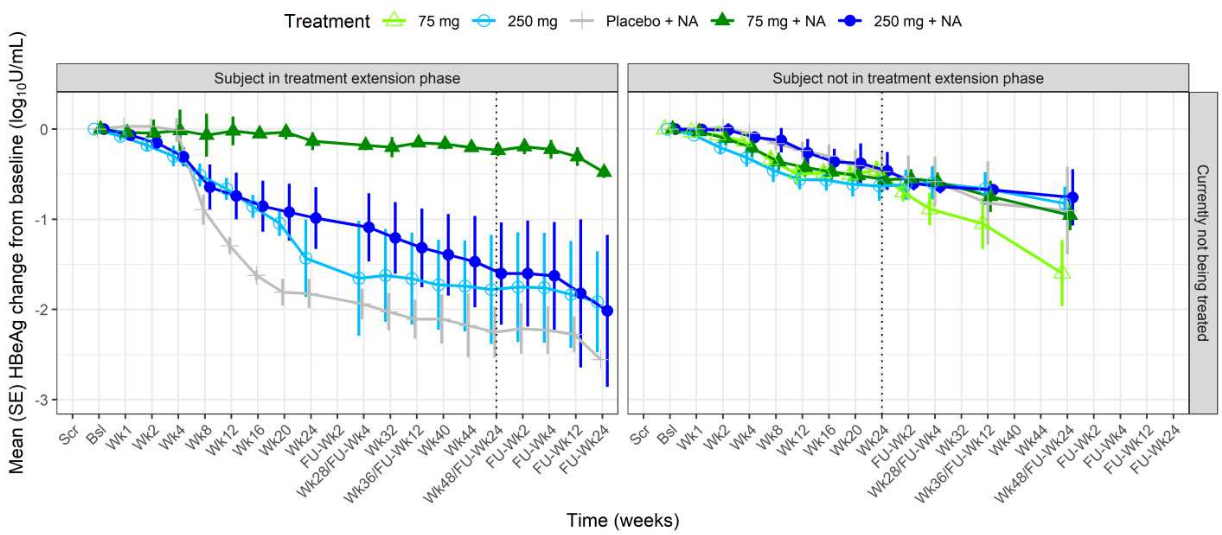


HBV RNA assessed using a quantitative reverse transcription polymerase chain reaction assay. Not detected HBV RNA values were imputed by a value of 5 copies/mL. Dotted vertical lines indicate the end of the treatment phase at Week 24 and the end of extended treatment phase at Week 48. Treatment in the 75- and 250-mg JNJ-56136379 monotherapy arms was changed during the study to NA and JNJ-56136379+NA, respectively.

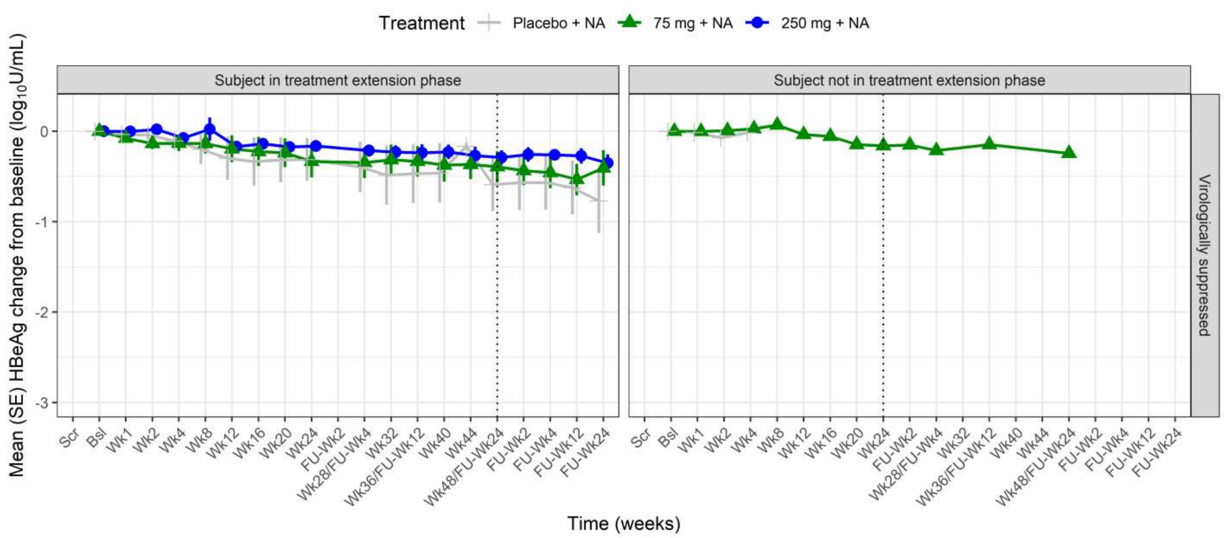
Abbreviations: Bsl, baseline visit; FU, follow up; HBV, hepatitis B virus; HBeAg, hepatitis B e-antigen; NA, nucleos(t)ide analogue; NCT, not treated at study start; Scr, screening visit; SE, standard error; Wk, Week.

Online supplemental figure S4. Change from baseline in HBeAg throughout the study in HBeAg-positive patients, by prior treatment.

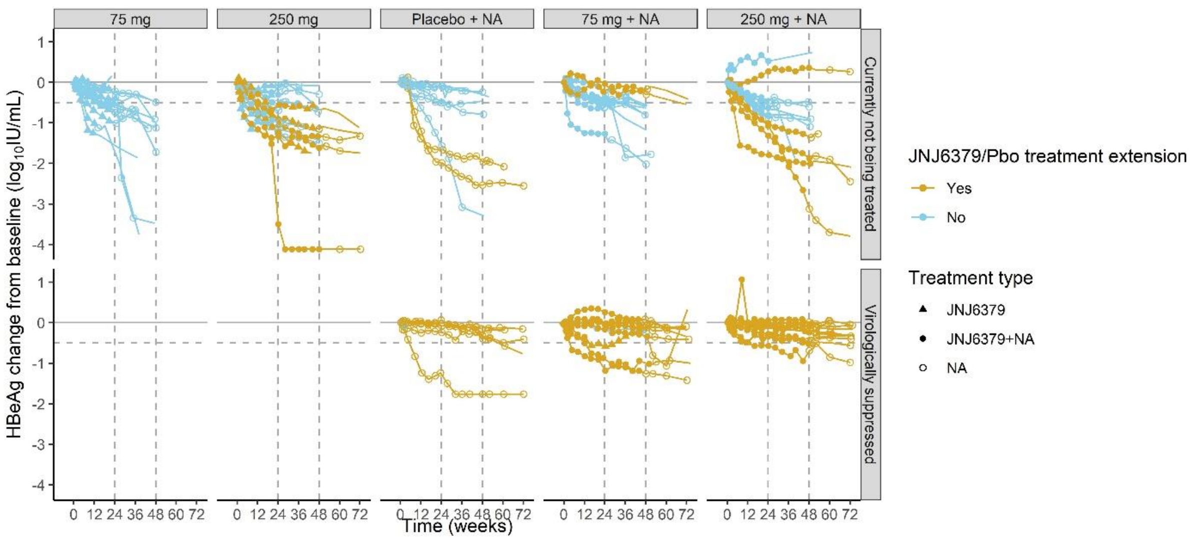
A) Per treatment extension including monotherapies arms in NCT patients.



B) Per treatment extension including monotherapies arms in VS patients.



C) Individual changes from baseline in HBeAg per treatment extension.



Individual profiles indicate if a patient has met the treatment extension criteria and continued JNJ-56136379/placebo treatment to Week 48 (golden lines) or stopped JNJ-56136379/placebo at or before Week 24 (blue lines). Treatment in 75- and 250-mg JNJ-56136379 monotherapy arms was changed during the study to NA and JNJ-56136379+NA, respectively. Dashed horizontal lines represent decline of 0.5 $\log_{10}$ IU/mL.

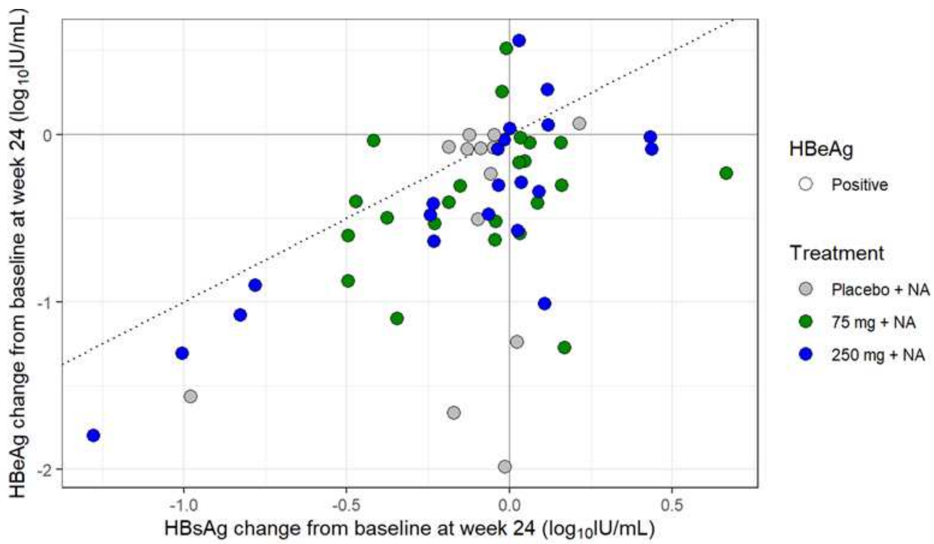
HBeAg assessed using an Abbott Architect™ assay; HBeAg LLOQ: 0.11 IU/mL and ULOQ: 1,400 IU/mL; HBeAg values >ULOQ (1,400 IU/mL) were imputed with 1,540 IU/mL.

Dotted vertical lines indicate the end of the treatment phase at Week 24 and the end of extended treatment phase at Week 48.

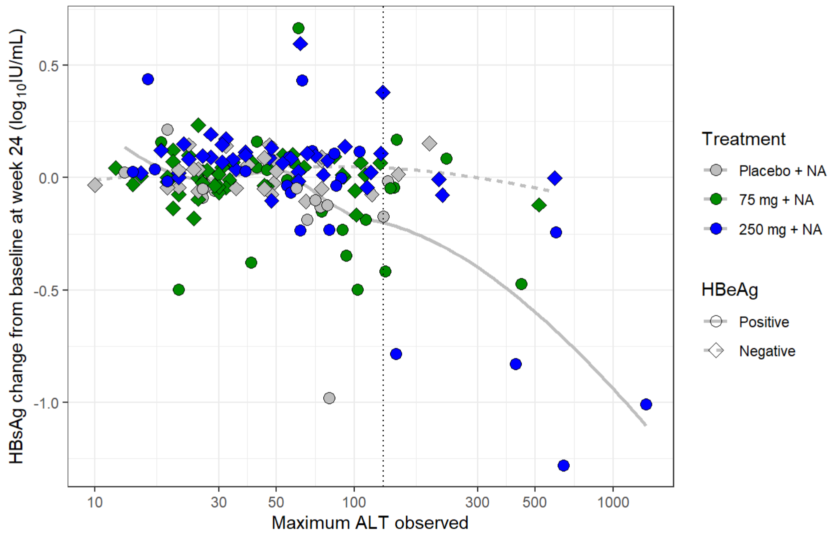
Abbreviations: Bsl, baseline visit; FU, follow up; HBeAg, hepatitis B e-antigen; IU, international unit; JNJ6379, JNJ-56136379; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogue; NCT, not treated at study start; Scr, screening visit; SE, standard error; VS, virologically suppressed; ULOQ, upper limit of quantification; Wk, Week.

Online supplemental figure S5.

A) Correlation (pooled placebo/JNJ-56136379+NA treatment arms) of change from baseline in HBeAg and HBsAg at Week 24 in NCT and VS HBeAg-positive patients.



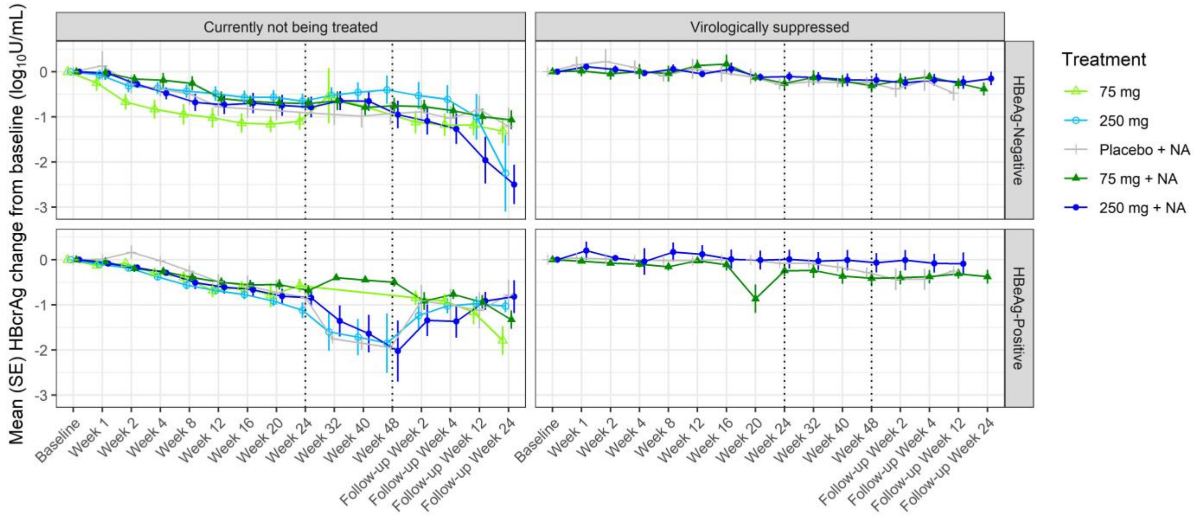
B) Correlation (pooled placebo/JNJ-56136379+NA treatment arms) of change from baseline in HBsAg at Week 24 and maximum observed ALT (until Week 24) in all patients.



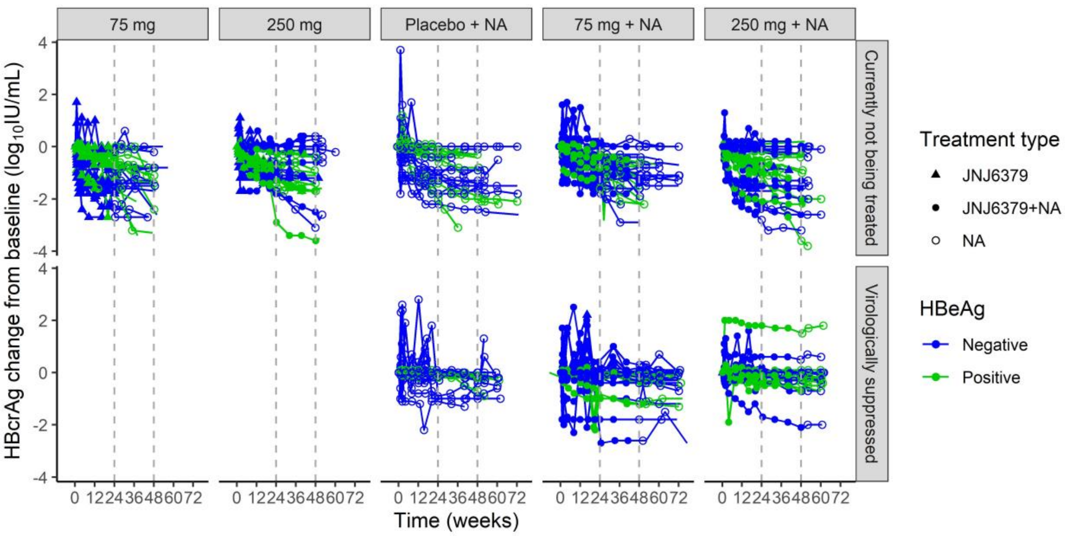
Abbreviations: ALT, alanine aminotransferase; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; IU, international unit; NA, nucleos(t)ide analogue; NCT, not treated at study start; VS, virologically suppressed.

Online supplemental figure S6. Change from baseline in HBcrAg throughout the study, by prior treatment and by HBeAg status.

A) Mean change from baseline in HBcrAg throughout the study, by prior treatment and HBeAg status.



B) Individual changes from baseline in HBcrAg.



Dotted vertical lines indicate the end of the treatment phase at Week 24 and the end of extended treatment phase at Week 48.

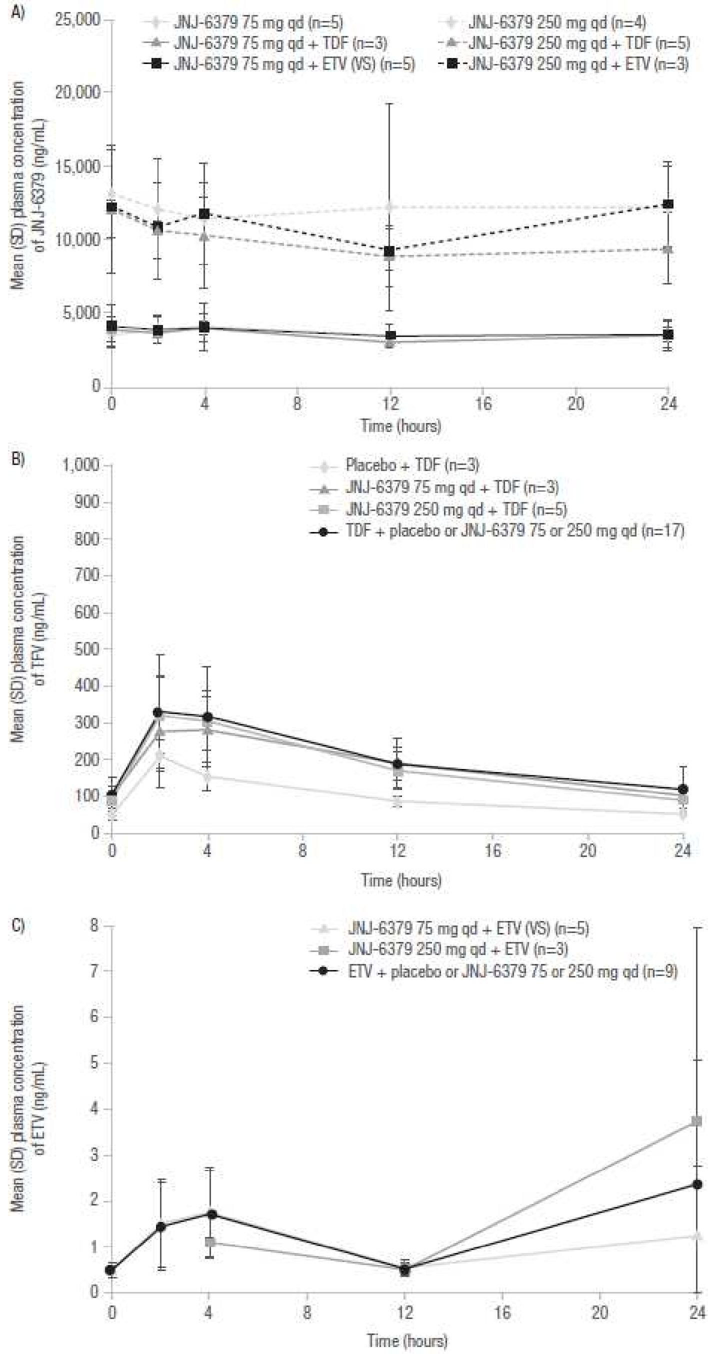
Abbreviations: FU, follow up; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e-antigen; IU, international unit; JNJ6379, JNJ-56136379; NA, nucleos(t)ide analogue.

Online supplemental figure S7. Plasma concentration-time profiles of JNJ-56136379, TFV, and ETV.

A) Linear mean (SD) plasma concentration-time profiles of JNJ-56136379 after administration of JNJ-56136379 alone at 75- or 250-mg qd and in combination with 300-mg qd TDF or 0.5-mg qd ETV in NCT and VS suppressed patients at Day 84.

B) Linear mean (SD) plasma concentration-time profiles of TFV after administration of JNJ-56136379 at 75- and 250-mg qd or placebo in combination with 300-mg TDF qd in NCT patients at Day 84.

C) Linear mean (SD) plasma concentration-time profiles of ETV after administration of JNJ-56136379 alone at 75- and 250-mg qd or placebo and in combination with 0.5-mg qd ETV in NCT and VS patients at Day 84.



ETV, entecavir; NCT, not currently treated at study start; qd, once daily; SD, standard deviation; TDF, tenofovir disoproxil fumarate; TFV, tenofovir analyte; VS, virologically suppressed.

REFERENCES

1 van Bömmel F, Bartens A, Mysickova A, Hofmann J, Krüger DH, Berg T*, et al.* Serum hepatitis B virus RNA levels as an early predictor of hepatitis B envelope antigen seroconversion during treatment with polymerase inhibitors. Hepatology 2015;**61**:66-76.

2 Verbinnen T, Tan Y, Wang G, Dehertogh P, Vergauwen K, Neefs JM*, et al.* Anti-HBV activity of the HBV capsid assembly modulator JNJ-56136379 across full-length genotype A-H clinical isolates and core site-directed mutants in vitro. J Antimicrob Chemother 2020;**75**:2526-34.

3 Slaets L, De Ridder F, Lenz O, Beumont M, Meyvisch P, Verbinnen T. Systematic review with meta-analysis: hepatitis B surface antigen decline and seroclearance in chronic hepatitis B patients on nucleos(t)ide analogues or pegylated interferon therapy. GastroHep 2020;**2**:106-16.

4 De Ridder F, Sonneveld MJ, Lenz O, Janssen HLA, Talloen W, Hansen BE. Mean HBsAg decline at week 24 of PEG-IFN-based treatment predicts subsequent rate of HBsAg clearance - suggesting a valuable endpoint for early development HBV trials. J Viral Hepat 2021;**28**:1563-9.

5 Marcellin P, Ziol M, Bedossa P, Douvin C, Poupon R, de Ledinghen V*, et al.* Non-invasive assessment of liver fibrosis by stiffness measurement in patients with chronic hepatitis B. Liver Int 2009;**29**:242-7.

6 Poynard T, Vergniol J, Ngo Y, Foucher J, Thibault V, Munteanu M*, et al.* Staging chronic hepatitis B into seven categories, defining inactive carriers and assessing treatment impact using a fibrosis biomarker (FibroTest(R)) and elastography (FibroScan(R)). J Hepatol 2014;**61**:994-1003.