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
• <u>NCT patients must:</u> (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).

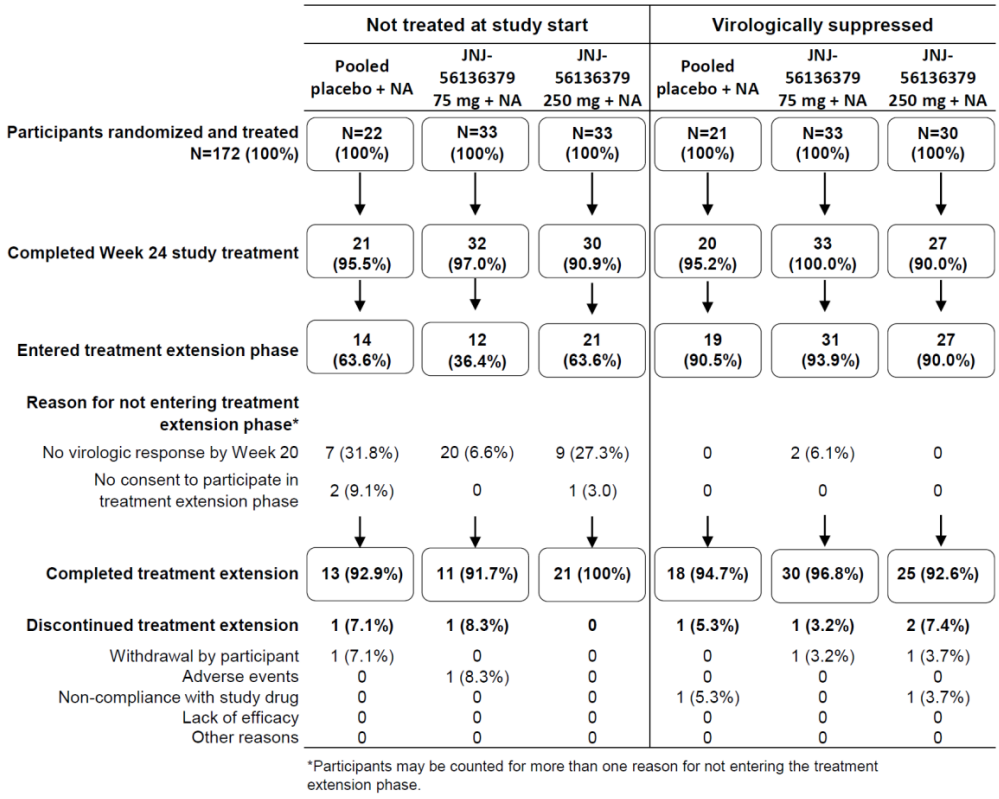
[b]Treatment in 75- and 250-mg JNJ-56136379 monotherapy arms was changed during the study to NA and JNJ-56136379+NA, respectively.

[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.



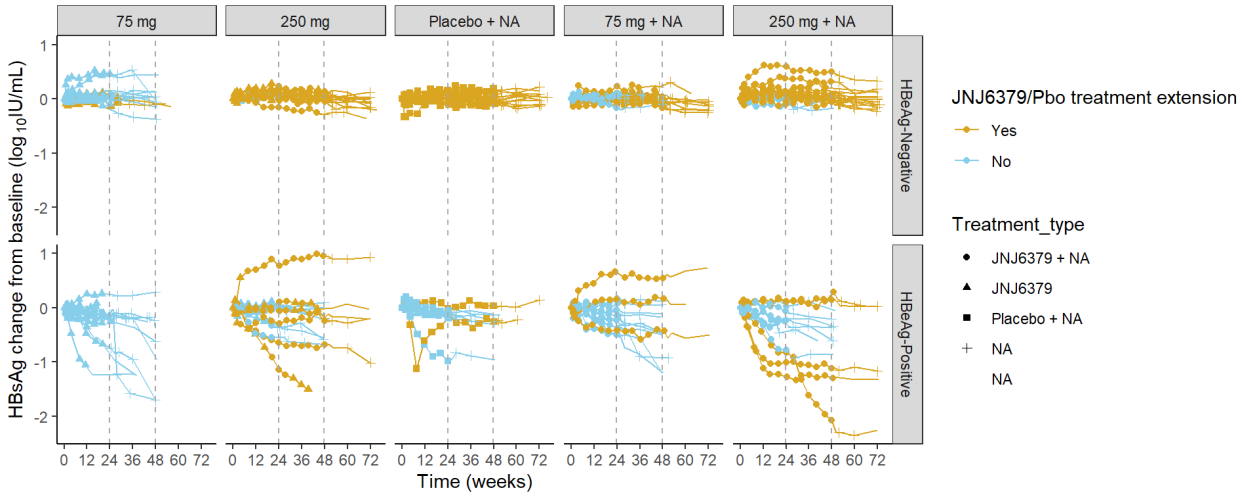
*Participants may be counted for more than one reason for not entering the treatment extension phase.

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.

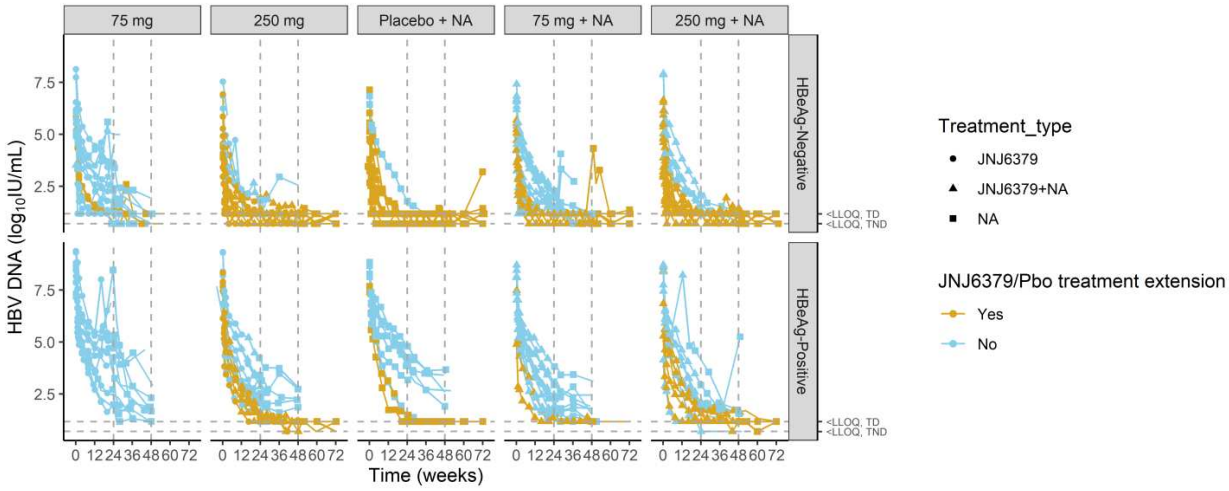
Dotted vertical lines indicate the end of the treatment phase at Week 24 and the end of extended treatment phase at Week 48. Treatment in the 75- and 250-mg JNJ-56136379 monotherapy arms was changed during the study to NA and JNJ-56136379+NA, respectively.



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.

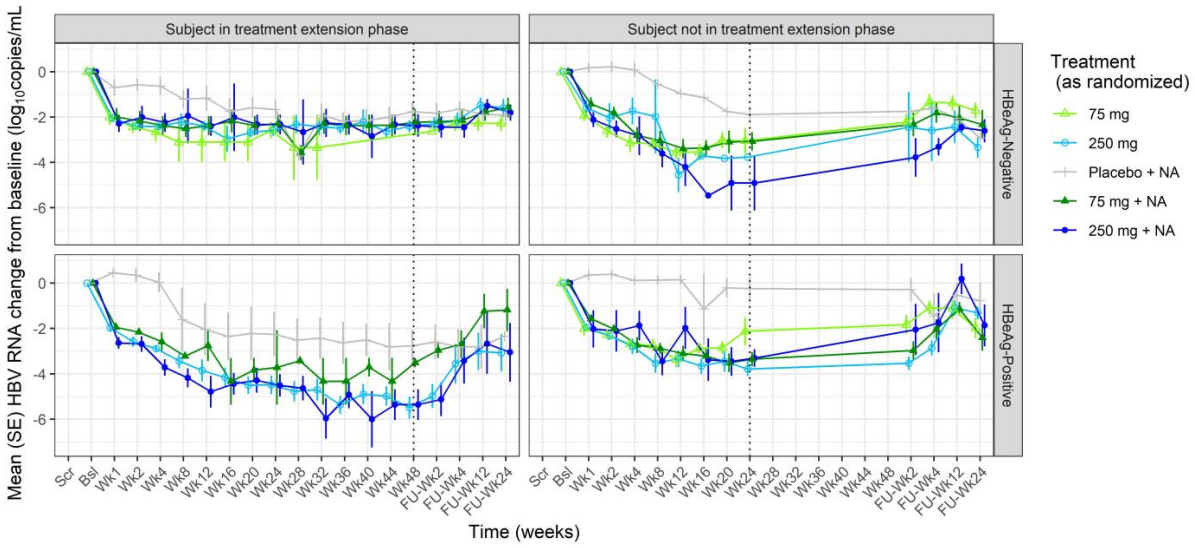
Online supplemental figure S3. HBV DNA and HBV RNA by HBeAg status.

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.

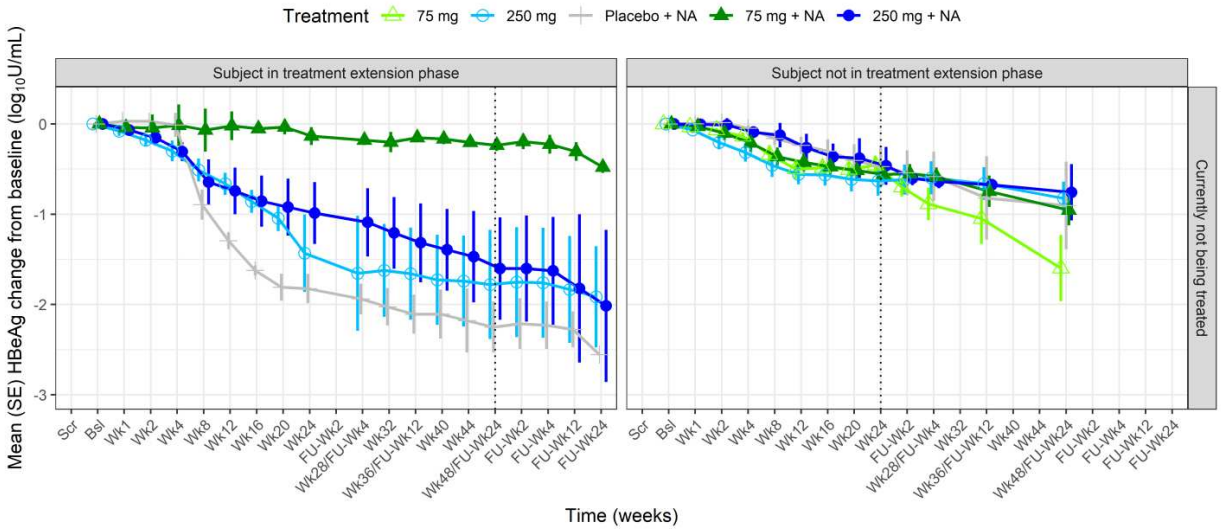


HBV RNA assessed using a quantitative reverse transcription polymerase chain reaction assay. Not detected HBV RNA values were imputed by a value of 5 copies/mL. Dotted vertical lines indicate the end of the treatment phase at Week 24 and the end of extended treatment phase at Week 48. Treatment in the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

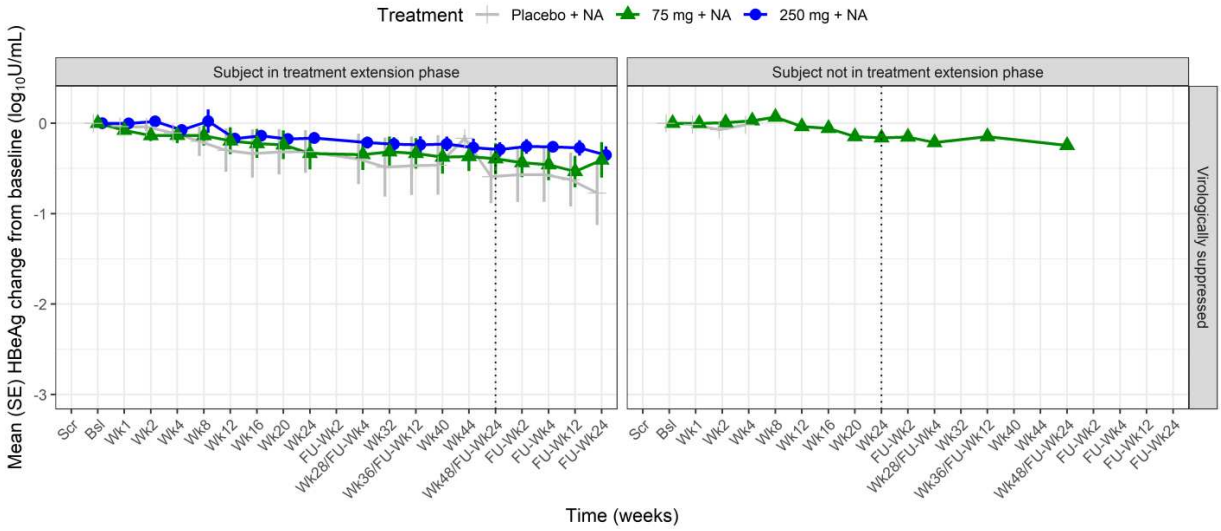
Abbreviations: Bsl, baseline visit; FU, follow up; HBV, hepatitis B virus; HBeAg, hepatitis B e-antigen; NA, nucleos(t)ide analogue; NCT, not treated at study start; Scr, screening visit; SE, standard error; Wk, Week.

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

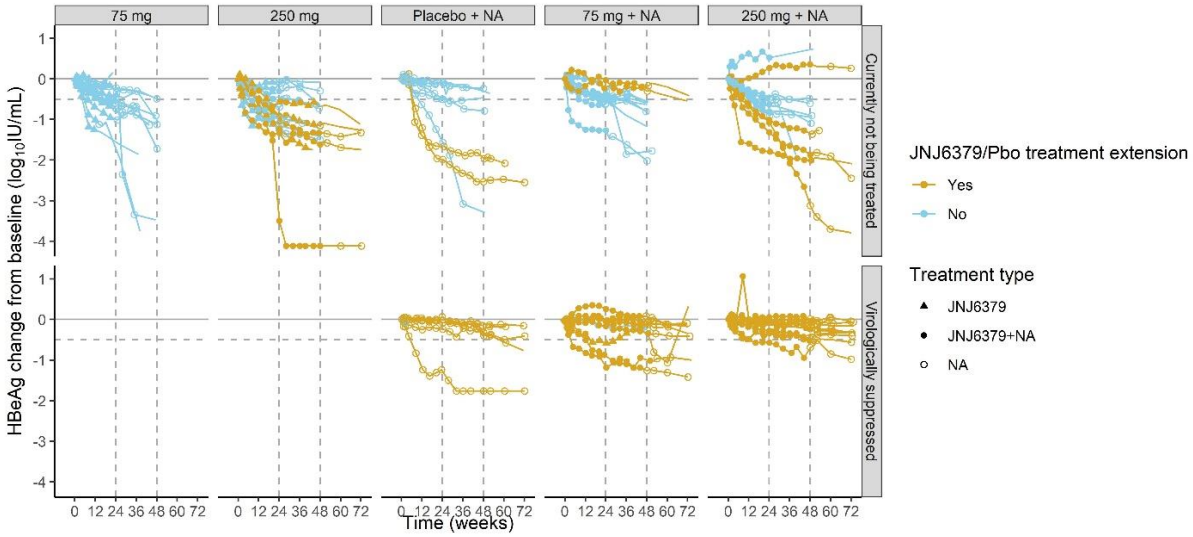
A) Per treatment extension including monotherapies arms in NCT patients.



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.

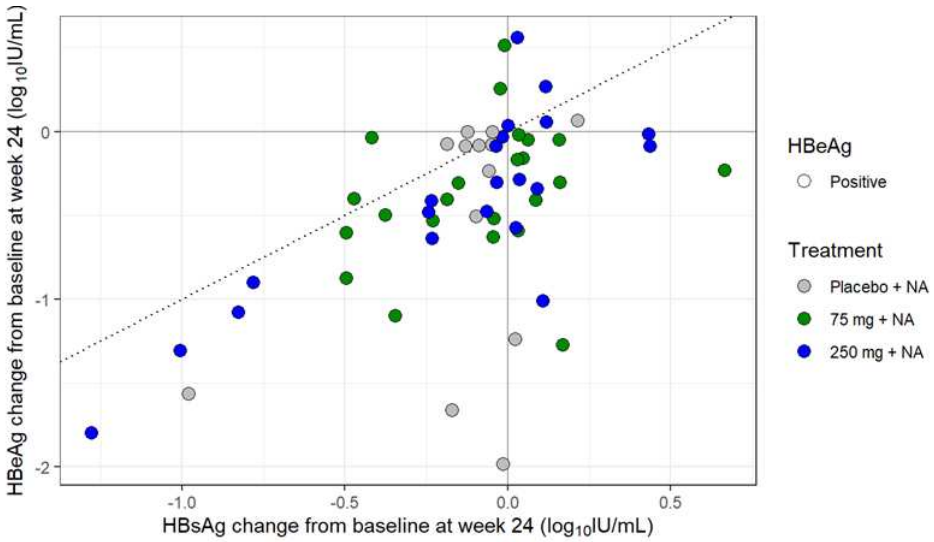
HBeAg assessed using an Abbott Architect™ assay; HBeAg LLOQ: 0.11 IU/mL and ULOQ: 1,400 IU/mL; HBeAg values >ULOQ (1,400 IU/mL) were imputed with 1,540 IU/mL.

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

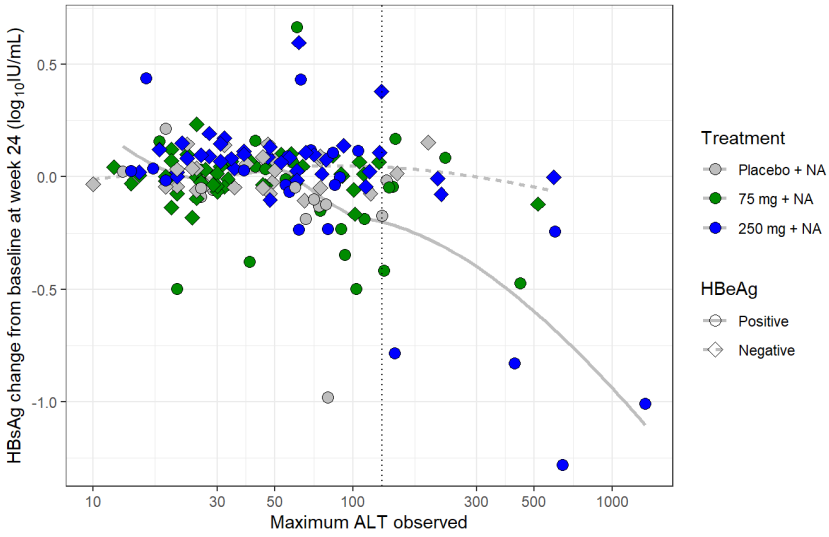
Abbreviations: Bsl, baseline visit; FU, follow up; HBeAg, hepatitis B e-antigen; IU, international unit; JNJ6379, JNJ-56136379; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogue; NCT, not treated at study start; Scr, screening visit; SE, standard error; VS, virologically suppressed; ULOQ,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



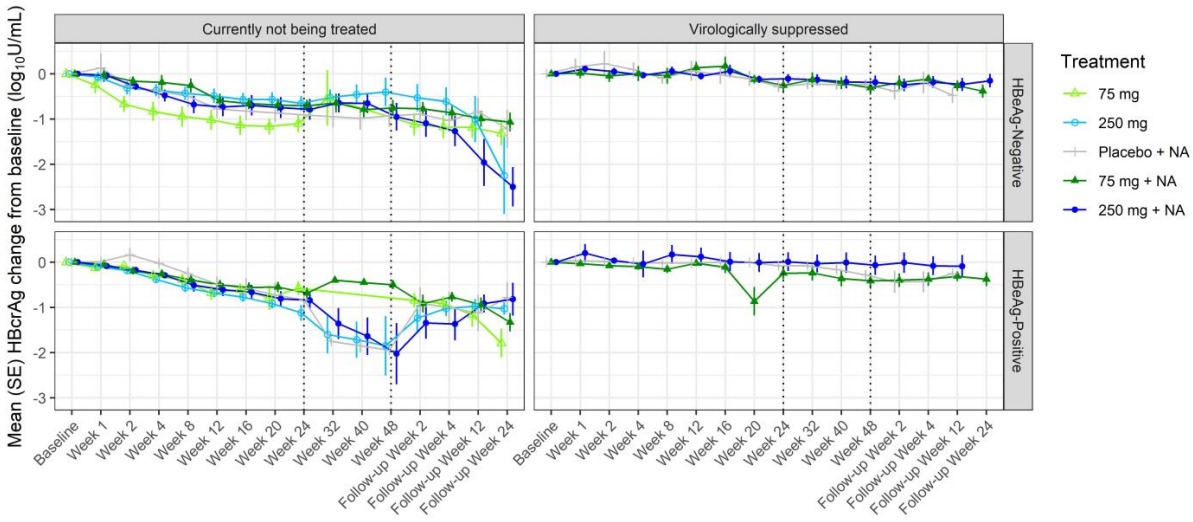
B) Correlation (pooled placebo/JNJ-56136379+NA treatment arms) of change from baseline in HBsAg at Week 24 and maximum observed ALT (until Week 24) in all patients.



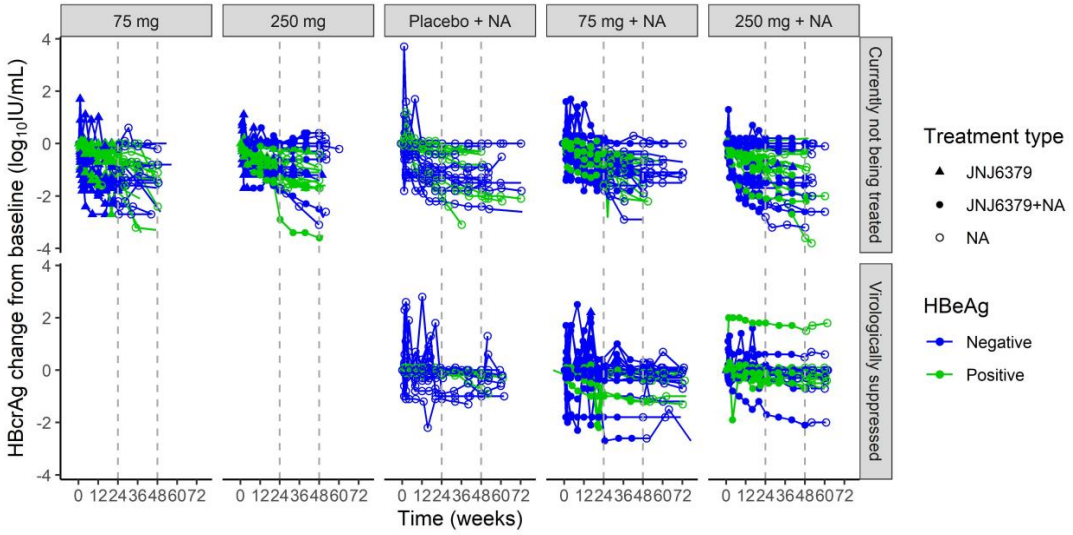
Abbreviations: ALT, alanine aminotransferase; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; IU, international unit; NA, nucleos(t)ide analogue; NCT, not treated at study start; VS, virologically suppressed.

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.

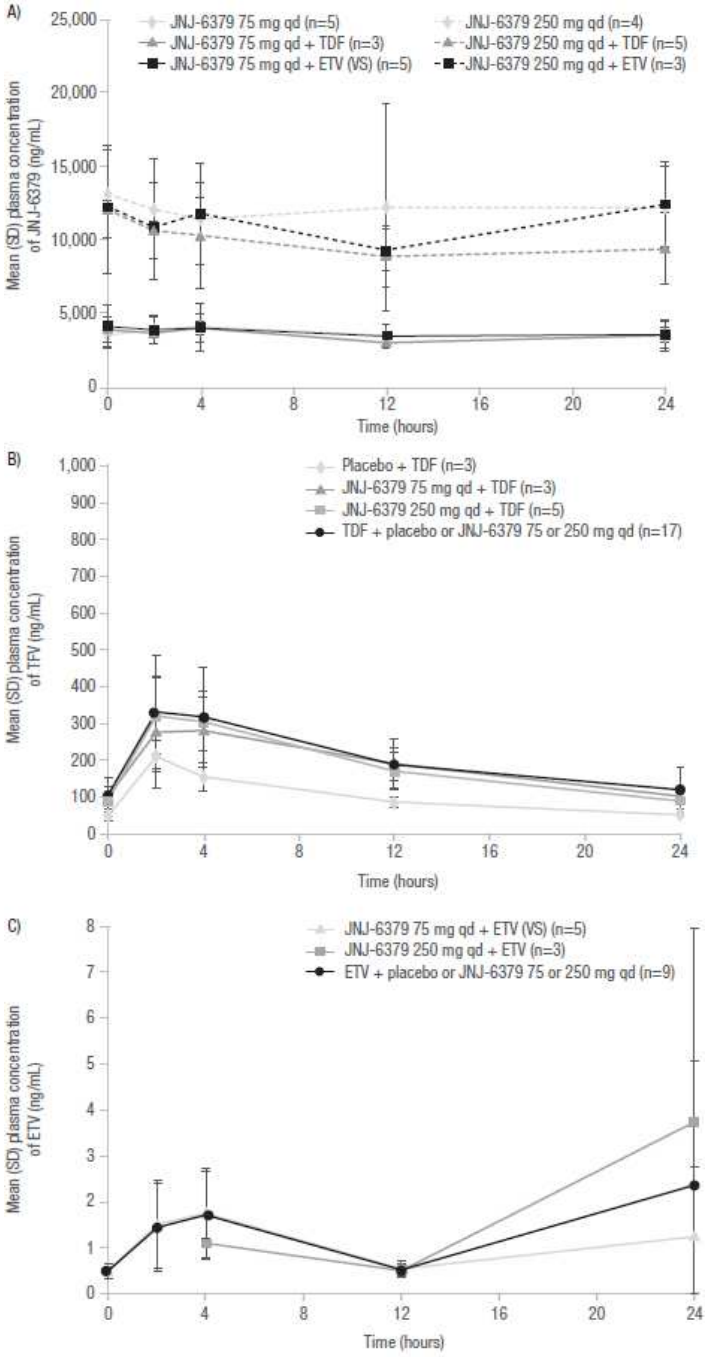
Abbreviations: FU, follow up; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e-antigen; IU, international unit; JNJ6379, JNJ-56136379; NA, nucleos(t)ide analogue.

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.

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