Research Article
Viral Hepatitis

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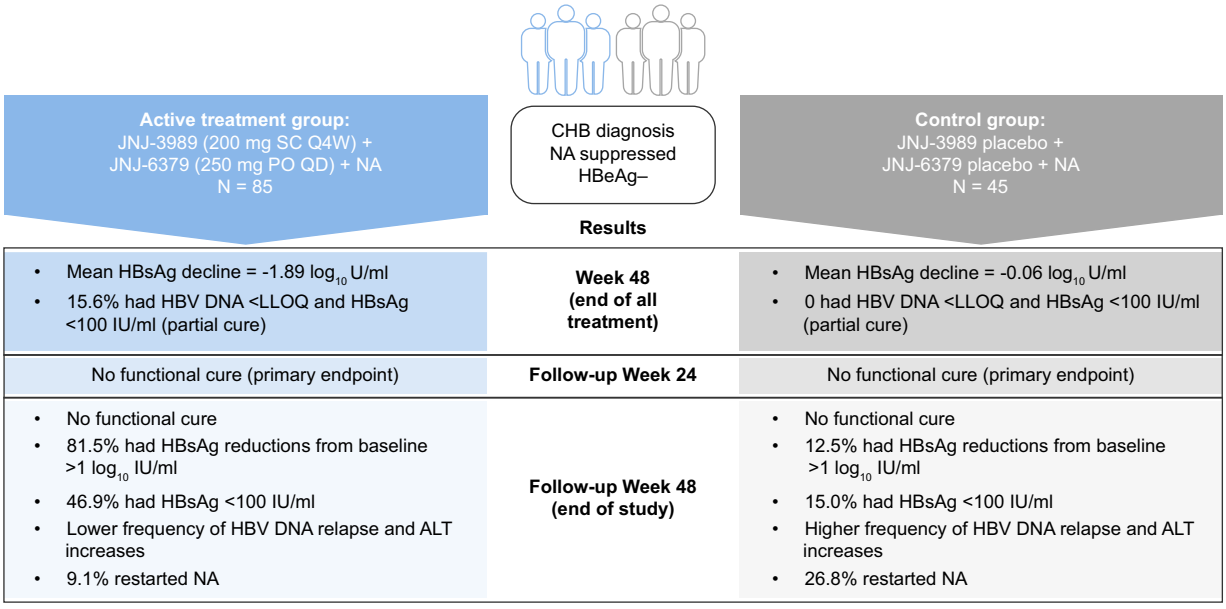
Graphical abstract



Highlights

- No functional cure achieved 24 or 48 weeks after 48 weeks of JNJ-3989 + JNJ-6379 + NA.
- All patients had pronounced declines in HBsAg after 48 weeks of JNJ-3989 + JNJ-6379 + NA.
- Maintained HBsAg declines from JNJ-3989 + JNJ-6379 + NA up to 48-weeks off-treatment.
- Pronounced HBV DNA and HBsAg suppression off-treatment after JNJ-3989 + JNJ-6379 + NA.
- JNJ-3989 + JNJ-6379 treatment was safe and well tolerated.

Impact and implications

Achieving a functional cure from chronic hepatitis B (CHB) with finite treatments is a major unmet medical need. The current study assessed the rate of functional cure and clinical outcome after controlled nucleos(t)ide analogue (NA) withdrawal in patients with low levels of HBsAg induced by 48 weeks of treatment with the small-interfering RNA JNJ-3989 and the capsid assembly modulator JNJ-6379 plus NA *vs.* patients who only received NA treatment. Though functional cure was not achieved by any patient in either arm, the 48-week treatment regimen of JNJ-3989, JNJ-6379, and NA did result in more patients achieving pronounced reductions in HBsAg, with clinically meaningful reductions maintained for up to 48 weeks off all treatments, as well as fewer off-treatment HBV DNA increases and alanine aminotransferase flares. These findings provide valuable insights for future studies investigating potential finite treatment options, while the reported efficacy and safety outcomes may be of interest to healthcare providers making treatment decisions for patients with NA-suppressed HBeAg-negative CHB.

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JNJ-73763989 and bersacapavir treatment in nucleos(t)ide analogue-suppressed patients with chronic hepatitis B: REEF-2

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Background & Aims: Functional cure for chronic hepatitis B (CHB) requires finite treatment. Two agents under investigation with the goal of achieving functional cure are the small-interfering RNA JNJ-73763989 (JNJ-3989) and the capsid assembly modulator JNJ-56136379 (JNJ-6379; bersacapavir).

Methods: REEF-2, a phase IIb, double-blind, placebo-controlled, randomized study, enrolled 130 nucleos(t)ide analogue (NA)–suppressed hepatitis B e-antigen (HBeAg)–negative patients with CHB who received JNJ-3989 (200 mg subcutaneously every 4 weeks) + JNJ-6379 (250 mg oral daily) + NA (oral daily; active arm) or placebos for JNJ-3989 and JNJ-6379 +active NA (control arm) for 48 weeks followed by 48 weeks off-treatment follow-up.

Results: At follow-up Week 24, no patients achieved the primary endpoint of functional cure (off-treatment hepatitis B surface antigen [HBsAg] seroclearance). No patients achieved functional cure at follow-up Week 48. There was a pronounced on-treatment reduction in mean HBsAg from baseline at Week 48 in the active arm *vs*. no decline in the control arm (1.89 *vs*. 0.06 $\log_{10}$ IU/ml; $p = 0.001$). At follow-up Week 48, reductions from baseline were >1 $\log_{10}$ IU/ml in 81.5% *vs*. 12.5% of patients in the active and control arms, respectively, and 38/81 (46.9%) patients in the active arm achieved HBsAg <100 IU/ml *vs*. 6/40 (15.0%) patients in the control arm. Off-treatment HBV DNA relapse and alanine aminotransferase increases were less frequent in the active arm, with 7/77 (9.1%) and 11/41 (26.8%) patients in the active and control arms, respectively, restarting NAs during follow-up.

Conclusions: Finite 48-week treatment with JNJ-3989 + JNJ-6379 + NA resulted in fewer and less severe post-treatment HBV DNA increases and alanine aminotransferase flares, and a higher proportion of patients with off-treatment HBV DNA suppression, with or without HBsAg suppression, but did not result in functional cure.

ClinicalTrials.gov Identifier: NCT04129554.

Introduction

Chronic HBV infection affects ~3.5% of the global population.[1] The current treatment options, pegylated interferon and nucleos(t)ide analogues (NAs), suppress viral replication,[2] but rarely lead to functional cure, defined as sustained off-treatment hepatitis B surface antigen (HBsAg) seroclearance.[3] Thus, the search continues for a finite treatment for chronic hepatitis B (CHB) that can result in functional cure.

Two antiviral CHB therapies under investigation are JNJ-73763989 (JNJ-3989) and JNJ-56136379 (JNJ-6379; bersacapavir). JNJ-3989 is composed of two liver-targeted small-interfering RNAs (siRNAs) administered subcutaneously (SC). JNJ-3989 engages endogenous RNA interference to cleave HBV RNA transcripts resulting in reduced levels of all HBV proteins and pregenomic RNA.[4] JNJ-6379, an orally administered capsid assembly modulator, inhibits HBV replication by interfering with capsid assembly and causing the formation of empty capsids (class capsid assembly modulator-empty)[5] that lack HBV DNA and RNA.[6,7] Both of these therapeutics have shown antiviral activity and good safety profiles in patients.[4,8,9]

The phase IIb REEF-1 study (ClinicalTrials.gov Identifier: NCT03982186) investigated 48 weeks of combination treatment with JNJ-3989 and/or JNJ-6379 with NA in hepatitis B e-antigen (HBeAg)–positive or –negative patients who were either not currently treated or NA suppressed.[10] NA treatment was discontinued at end of treatment (EOT) if

Keywords: bersacapavir; CAM; capsid assembly modulator; chronic hepatitis B; finite therapy; HBV; hepatitis B virus; JNJ-56136379; JNJ-73763989; NA cessation; siRNA.
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patients met predefined NA stopping criteria. Forty-eight weeks of treatment with JNJ-3989 dose-dependently reduced HBsAg; at EOT, nearly 75% of patients treated with the highest dose of JNJ-3989 (200 mg) reached HBsAg <100 IU/ml and 30% met NA stopping criteria.

Studies have shown that controlled NA cessation can induce HBsAg seroclearance in patients with HBeAg-negative CHB,[11,12] but the rate varies with generally higher rates in European *vs.* Asian patients.[13,14] According to the international treatment guidelines for the management of CHB by the European Association for the Study of the Liver,[15] controlled withdrawal of NA treatment can be considered in non-cirrhotic patients with long-term (≥3 years) NA suppression and HBeAg-negative CHB if appropriate follow-up is conducted.[16,17,18] Multiple cohort studies of NA withdrawal after long-term treatment suggest that low levels of HBsAg (preferentially <100 IU/ml) when NAs are discontinued are associated with higher likelihood of achieving HBsAg seroclearance and lower risk of viral and biochemical relapse.[19] The REEF-2 study assessed whether reduction of HBsAg to low levels with 48 weeks of JNJ-3989 treatment (plus viral suppression with NA and JNJ-6379), followed by NA withdrawal, leads to functional cure in the described population.

The primary objective of this study was to evaluate the efficacy of the REEF-2 treatment regimen and NA stopping as assessed by off-treatment HBsAg seroclearance 24 weeks after completion of the 48-week treatment phase. Secondary objectives included change in virologic parameters over time and evaluation of safety and tolerability.

Patients and methods

Study design and patients

REEF-2, a phase IIb, double-blind, placebo-controlled, randomized study (ClinicalTrials.gov Identifier: NCT04129554), was conducted at 33 centers in seven European countries (Belgium, France, Germany, Italy, Poland, Spain, and the United Kingdom). Non-cirrhotic patients aged 18 to 65 with HBeAg-negative CHB who were virologically suppressed with NA treatment for ≥24 months prior to screening were enrolled (Fig. S1). Eligible patients had HBsAg >100 IU/ml at screening, and HBV DNA <60 IU/ml and alanine aminotransferase (ALT) <2.0× upper limit of normal (ULN) on two measurements ≥6 months apart (one at screening).

Patients were randomized (2:1) to receive JNJ-3989 (200 mg SC injection every 4 weeks [Q4W]) + JNJ-6379 (250 mg oral tablets daily [QD]) + NA (entecavir, tenofovir alafenamide, or tenofovir disoproxil fumarate QD; active arm) or JNJ-3989 placebo (SC Q4W) + JNJ-6379 placebo (oral QD) + NA (control arm; Fig. S1). Patients received treatment for 48 weeks and then discontinued all treatments, including NAs, without the requirement to meet pre-specified criteria; this was followed by a 48-week off-treatment follow-up phase. NA retreatment criteria during follow-up were: confirmed HBeAg seroreversion, HBV DNA increase >2,000 IU/ml and ALT >5× ULN, HBV DNA increase >20,000 IU/ml. NA treatment was restarted immediately if there were signs of decreasing or impaired liver function indicated by laboratory or clinical assessments or HBV DNA >100,000 IU/ml, regardless of ALT levels (this last criterium was added during the study via protocol amendment).

This study was conducted according to ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practice. Study protocols were approved by the local independent ethics committee/institutional review board. Written informed consent was obtained from all study patients.

Endpoints and assessments

The primary endpoint was the proportion of patients who achieved functional cure, defined as HBsAg seroclearance (<lower limit of quantification [LLOQ] = 0.05 IU/ml) at follow-up Week 24, without restarting NA treatment. Secondary efficacy endpoints included the proportion of patients who achieved HBsAg seroclearance at Week 48 and follow-up Week 48 without restarting NAs, proportion of patients with HBV DNA <LLOQ (20 IU/ml) at Week 48 and <LLOQ or <2,000 IU/ml at follow-up Week 48, change from baseline over time in HBsAg, HBV DNA, and ALT, proportion of patients achieving certain thresholds of HBsAg (*e.g.*, HBsAg <100, <10, and <1, and <0.05 [seroclearance] IU/ml), and proportion of patients with clinical relapse (*i.e.*, HBV DNA >2,000 IU/ml increases with ALT flares [confirmed ALT ≥3× ULN and ≥3× nadir]).

Safety and tolerability of the study drugs were evaluated by assessments for adverse events (AEs), abnormal clinical laboratory tests, 12-lead electrocardiogram, vital signs, and physical examination. Patient safety was assured through inclusion of an independent data monitoring committee and an independent flare expert panel that reviewed and adjudicated all ALT flares.

Statistical analysis

The total planned sample size was 120 patients, with 80 and 40 allocated to the active and control arms, respectively. All efficacy data were analyzed by treatment arm (active *vs.* control), analysis phase (double-blind treatment phase *vs*. off-treatment follow-up), and over time (when applicable). The modified intent-to-treat analysis set was the primary population used for efficacy analyses and included all patients who were randomized and received ≥1 dose of study drug, excluding those impacted by the COVID-19 pandemic (*e.g.*, those who, because of COVID-19 or similar pandemic-related reasons, withdrew from the study prior to Week 72, or had no efficacy assessment for the primary endpoint). The safety population included all patients who received ≥1 dose of any study drug.

Results

Patients

NA-suppressed, HBeAg-negative patients with CHB (N = 130) were enrolled at European sites with study initiation on November 7, 2019, and study completion on June 9, 2022. Eighty-five and 45 patients were randomized to the active and control arms, respectively (Fig. 1 and Fig. S1). The modified intent-to-treat population included 128 patients, excluding two who withdrew for COVID-19–related reasons (Fig. 1). Overall, 66.9% of patients were male, 66.2% were White, 19.2% were Asian, the mean age was 46.0 years; the mean duration of NA treatment at study entry was 8.3 years (Table 1). All patients had baseline HBV DNA <LLOQ, and the mean (SD) baseline

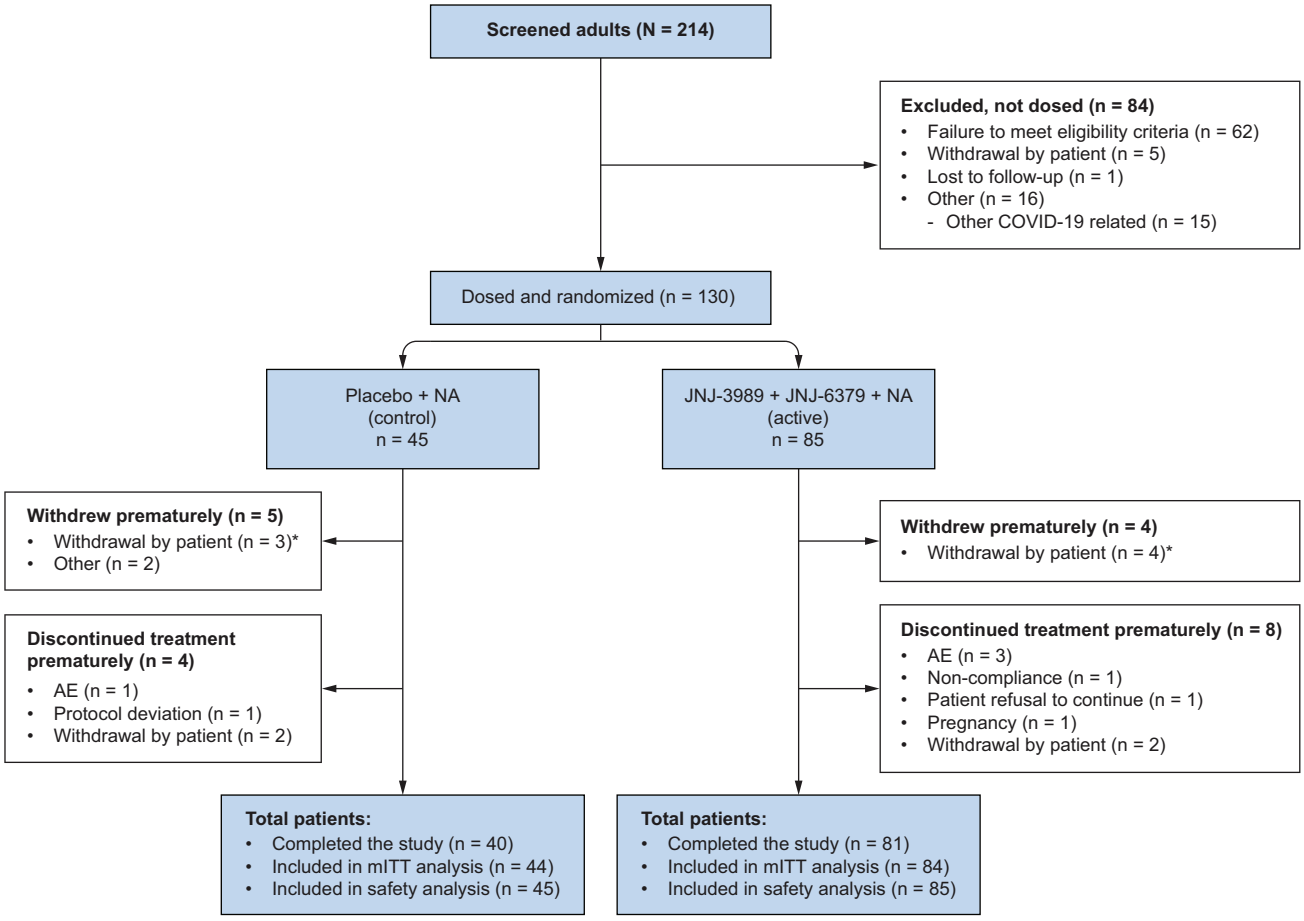

Fig. 1. Study flow diagram. *One patient's decision was COVID-19 related. The patients (one in each arm) who withdrew prematurely due to COVID-19–related reasons were excluded from the mITT analysis. AE, adverse event; JNJ-3989, JNJ-73763989; JNJ-6379, JNJ-56136379; mITT, modified intent-to-treat; NA, nucleos(t)ide analogue.

HBsAg levels for the active and control arms were 3.43 (0.53) and 3.49 (0.70) IU/ml, respectively.

Of the 130 patients enrolled, 81 (95.3%) and 40 (88.9%) in the active and control arms, respectively, completed the study (Fig. 1). Most premature study terminations were due to patient choice and only 8 (9.4%) and 4 (8.9%) patients in the active and control arms, respectively, discontinued treatment with JNJ-3989, JNJ-6379, or placebo prematurely (Fig. 1).

Efficacy

Primary endpoint

At follow-up Week 24, no patients achieved the primary endpoint of functional cure (off-treatment HBsAg seroclearance), and no patients achieved functional cure at follow-up Week 48 (end of the follow-up; Fig. 2).

HBsAg values

The secondary endpoint, mean (SE; range) HBsAg change from baseline at Week 48, was –1.89 (0.06; –3.4 to –1.0) $\log_{10}$ IU/ml in the active arm and –0.06 (0.01; –0.3 to 0.2) $\log_{10}$ IU/ml in the control arm ($p < 0.001$; Fig. 3A; Table 2; Fig. S2). Preliminary multivariate analyses of the association between baseline factors (race, age, sex, NA-treatment duration, and baseline HBsAg level) and >2 $\log_{10}$ IU/ml reduction in HBsAg from baseline at Week 48 did not identify a significant factor ($p < 0.05$), though Asian race (odds ratio [OR] [95% CI] = 2.2 [0.7–7.5]; $p = 0.189$) and higher baseline HBsAg levels (OR [95% CI] = 2.1 [0.7–5.9]; $p = 0.159$) demonstrated a trend for an association (Table S1). By follow-up Week 48, mean (SE; range) HBsAg change from baseline was –1.46 (0.07; –4.0 to –0.3) $\log_{10}$ IU/ml in the active arm and –0.49 (0.12; –4.5 to 0.1) $\log_{10}$ IU/ml in the control arm ($p < 0.001$; Fig. 3A; Table 2; Fig. S2). At Week 48, follow-up Week 24, and follow-up Week 48, 54/76 (71.1%), 53/79 (67.1%), and 38/81 (46.9%) patients in the active arm achieved HBsAg <100 IU/ml *vs.* 1/41 (2.4%), 4/39 (10.3%), and 6/40 (15.0%) patients in the control arm, respectively (Fig. 2).

Though mean HBsAg levels increased in the active arm after EOT, reductions from baseline were >1 $\log_{10}$ IU/ml in 81.5% of patients at follow-up Week 48 *vs.* 12.5% in the control arm (Fig. S2). Furthermore, 13.2% and 18.4% of patients in the active arm had declining (>0.2 $\log_{10}$ IU/ml reduction) or stable (±0.2 $\log_{10}$ IU/ml change) HBsAg levels, respectively, from Week 48 to follow-up Week 48 (Fig. S3).

One patient in the active arm achieved transient HBsAg seroclearance from follow-up Week 28 to follow-up Week 36, and one in the control arm achieved HBsAg seroclearance at

Table 1. Demographics and baseline characteristics for the ITT population.*

	Placebos + NA (control), n = 45	JNJ-3989 + JNJ-6379 + NA (active), n = 85	Total, N = 130
Sex, n (%)			
Male	29 (64.4)	58 (68.2)	87 (66.9)
Female	16 (35.6)	27 (31.8)	43 (33.1)
Age, years	47.4 (10.55)	45.3 (10.10)	46.0 (10.27)
Race, n (%)			
White	30 (66.7)	56 (65.9)	86 (66.2)
Asian	8 (17.8)	17 (20.0)	25 (19.2)
Black or African American	5 (11.1)	7 (8.2)	12 (9.2)
Not reported	1 (2.2)	4 (4.7)	5 (3.8)
Unknown	1 (2.2)	1 (1.2)	2 (1.5)
Disease characteristics			
HBsAg, $\log_{10}$ IU/ml	3.49 (0.703)	3.43 (0.530)	3.45 (0.594)
HBsAg level: <100 IU/ml, n (%)	1 (2.2)	0	1 (0.8)
HBV DNA <LLOQ, n (%)[†]	45 (100)	85 (100)	130 (100)
HBV RNA <LOD, n (%)[‡]	42 (97.7)[§]	77 (92.8)[§]	119 (94.4)[§]
HBcrAg <LLOQ, n (%)[‖]	33 (75.0)[§]	56 (65.9)	89 (69.0)[§]
ALT, U/L	23.9 (10.75)	24.2 (10.89)	24.1 (10.80)
Fibroscan score, kPa	5.02 (1.301)	5.23 (1.482)	5.16 (1.420)
Duration of NA at study entry, years	8.1 (4.48)	8.4 (4.79)	8.3 (4.67)
Stratification factors, %			
Asian *vs.* non-Asian	17.8/82.2	20.0/80.0	19.2/80.8
Type of NA: ETV *vs.* TDF/TAF[¶]	37.8/62.2	38.8/61.2	38.5/61.5
HBsAg level: <1,000 *vs.* ≥1,000 IU/ml	24.4/75.6	20.0/80.0	21.5/78.5

ALT, alanine aminotransferase; ETV, entecavir; HBcrAg, hepatitis B core-related antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; ITT, intent-to-treat; JNJ-3989, JNJ-73763989; JNJ-6379; JNJ-56136379; LLOQ, lower limit of quantification; LOD, limit of detection; NA, nucleos(t)ide analogue; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

*Values are mean (SD) unless otherwise noted.

[†]HBV DNA, LLOQ = 20 IU/ml.

[‡]HBV RNA, LOD = 2.49 $\log_{10}$ copies/ml.

[§]Number of patients in the denominator differs from ITT population.

[‖]HBcrAg, LLOQ = 3.0 $\log_{10}$ U/ml.

[¶]Two patients were on TAF.

follow-up Week 36 until the end of the study after a clinical flare (ALT and/or aspartate aminotransferase >3× ULN and >3 × nadir) and restarting NA. Two additional patients, one in each arm, became HBsAg seronegative as a result of liver transplantation that was required due to hepatocellular carcinoma on continued NAs for the active arm patient and severe HBV reactivation for the control arm patient.[20]

On-treatment response

All patients had baseline HBV DNA levels <LLOQ (20 IU/ml), which was maintained at Week 48 in 73/75 (97.3%) and 41/41 (100%) in the active and control arms, respectively (Fig. 4). There was no viral breakthrough (*i.e.*, confirmed [two consecutive visits] 1 $\log_{10}$ IU/ml increase from nadir or confirmed HBV DNA >200 IU/ml if nadir was HBV DNA <LLOQ) during the 48-week treatment phase for either arm. Mean ALT values remained near baseline levels during the treatment phase; there was a gradual increase in the active arm with 16/76 (21.1%) patients having ALT >2× their baseline value (*vs.* none in the control arm). Mean ALT levels remained in the normal range (Fig. 5).

Off-treatment response

Off-treatment clinical relapse (*i.e.*, HBV DNA >2000 IU/ml increases with ALT flares [confirmed ALT ≥3× ULN and ≥3× nadir]) were observed in 3/77 (3.9%) and 11/41 (26.8%) patients in the

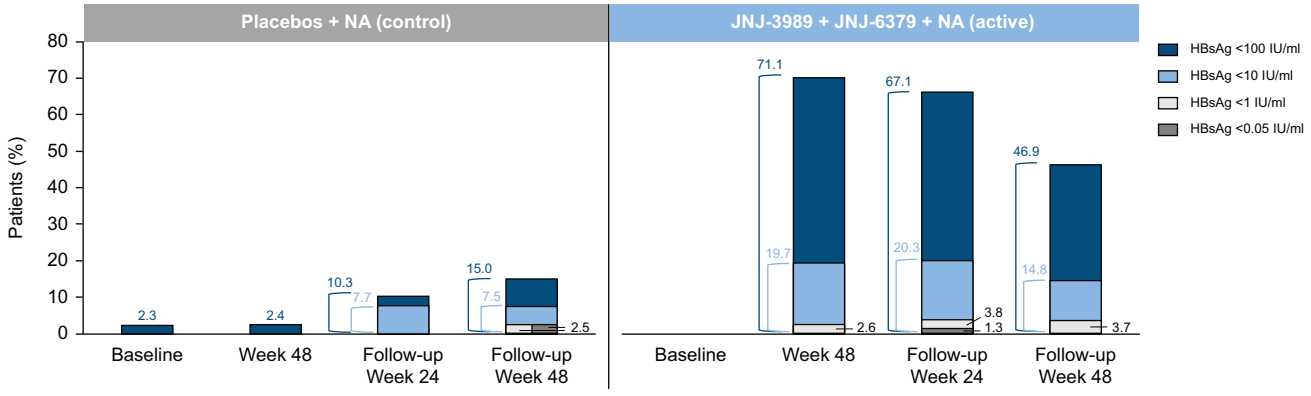

Fig. 2. Proportion of patients who met HBsAg thresholds by time point/visit. HBsAg, hepatitis B surface antigen; JNJ-3989, JNJ-73763989; JNJ-6379, JNJ-56136379; NA, nucleos(t)ide analogue.

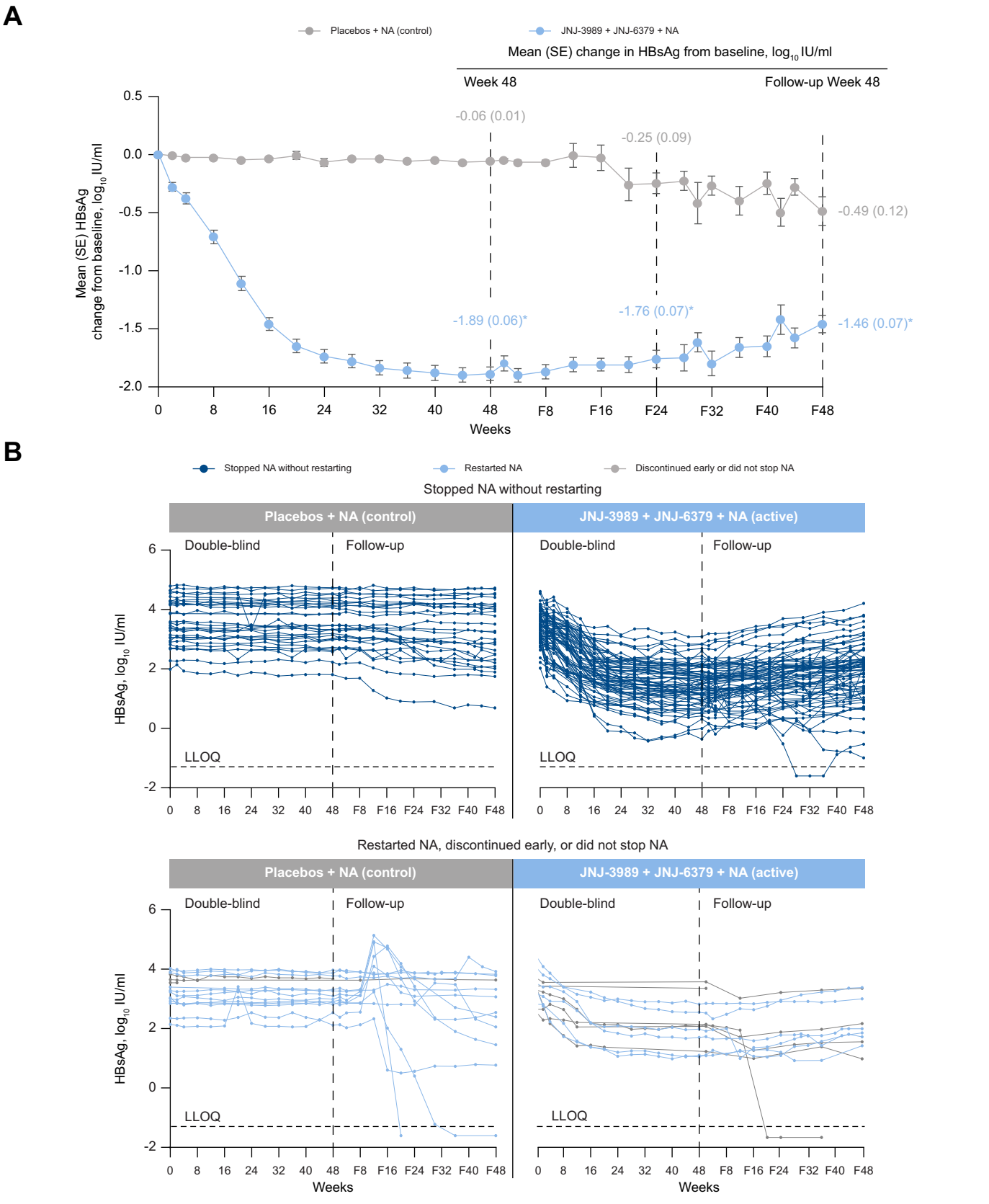

Fig. 3. Mean and individual change in HBsAg over time. *p < 0.001 between arms at each time point. Mixed model repeated measures including treatment arm, analysis time point (week), their interaction, two randomization stratification factors (race and type of NA), baseline blood marker categorical variable, and treatment arm by baseline interaction as fixed effects. F, follow-up; HBsAg, hepatitis B surface antigen; JNJ-3989, JNJ-73763989; JNJ-6379, JNJ-56136379; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogue.

Table 2. HBsAg, ALT, and HBV DNA values.*

	Placebos + NA (control) n = 45				JNJ-3989 + JNJ-6379 + NA (active) n = 85			
	Baseline	**Change from baseline at Week 48**	**Change from baseline at follow-up Week 48**		**Baseline**	**Change from baseline at Week 48**	**Change from baseline at follow-up Week 48**	
HBsAg, mean (SE), log_{10} IU/ml	3.49 (0.11)	−0.06 (0.01)	−0.49 (0.12)		3.43 (0.06)	−1.89 (0.06)†	−1.46 (0.07)†	
HBsAg	**Baseline**	**Week 48**	**Follow-up Week 48**		**Baseline**	**Week 48**	**Follow-up Week 48**	
<100 IU/ml	1/44 (2.3)	1/41 (2.4)	6/40 (15.0)		0	54/76 (71.1)	38/81 (46.9)	
<10 IU/ml	0	0	3/40 (7.5)		0	15/76 (19.7)	12/81 (14.8)	
<LLOQ‡	—	0	1/40 (2.5)		—	0	0	
≥1 log_{10} reduction from baseline	—	0	5/40 (12.5)		—	76/76 (100)	66/81 (81.5)	
≥2 log_{10} reduction from baseline	—	0	1/40 (2.5)		—	25/76 (32.9)	13/81 (16.0)	
		HBV DNA <2,000 IU/ml	**HBV DNA <LLOQ#**			**HBV DNA <2,000 IU/ml**	**HBV DNA <LLOQ#**	
Off-treatment HBV DNA at follow-up Week 48§		19/41 (46.3)‖	1/41 (2.4)‖			62/77 (80.5)¶	17/77 (22.1)¶	
		HBV DNA <2,000 IU/ml and HBsAg <100 IU/ml	**HBV DNA <LLOQ# and HBsAg <100 IU/ml**			**HBV DNA <2,000 IU/ml and HBsAg <100 IU/ml**	**HBV DNA <LLOQ# and HBsAg <100 IU/ml**	
Off-treatment HBV DNA and HBsAg at follow-up Week 48§		3/41 (7.3)‖	0‖			31/77 (40.3)¶	12/77 (15.6)¶	
		>2,000 IU/ml	**>100,000 IU/ml**			**>2,000 IU/ml**	**>100,000 IU/ml**	
Off-treatment virologic relapse** by peak HBV DNA		27/41 (65.8)	11/41 (26.8)			26/77 (33.8)	2/77 (2.6)	
ALT flare†† during follow-up		12/42 (28.6)				3/83 (3.6)		
	<3× ULN	**≥3× to <5× ULN**	**≥5× to <10× ULN**	**≥10× ULN**	**<3× ULN**	**≥3× to <5× ULN**	**≥5× to <10× ULN**	**≥10× ULN**
ALT peak level during follow-up	25/41 (61.0)	2/41 (4.9)	4/41 (9.8)	10/41 (24.3)	73/77 (94.8)	2/77 (2.6)	1/77 (1.3)	1/77 (1.3)
		>2,000 IU/ml		**>100,000 IU/ml**		**>2,000 IU/ml**		**>100,000 IU/ml**
Off-treatment clinical relapse‡‡ by peak HBV DNA		11/41 (26.8)		11/41 (26.8)		3/77 (3.9)		1/77 (1.3)
NA retreatment		12/44 (27.3)				6/84 (7.1)		

ALT, alanine aminotransferase; AST, aspartate transaminase; HBsAg, hepatitis B surface antigen; JNJ-3989, JNJ-73763989; JNJ-6379, JNJ-56136379; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogue.

*Values are n/N (%) unless otherwise stated.

†p <0.001 between arms at each time point. Mixed model repeated measures including treatment arm, analysis time point (week), their interaction, two randomization stratification factors (race and type of NA), baseline blood marker categorical variable, and treatment arm by baseline interaction as fixed effects.

‡LLOQ = −1.3 log_{10} IU/ml = 0.05 IU/ml.

§Patients with off-treatment HBV DNA suppression at follow-up Week 48. All patients who stopped NAs are included in the denominator, while the numerators include patients who remained off-treatment at follow-up Week 48 and met the thresholds for each treatment arm.

‖Of 41 patients with off-treatment data during follow-up, 12 (27.3%) restarted NA, one (2.4%) dropped out before follow-up Week 48 without restarting NAs, and 28 (68.3%) were off-treatment at follow-up Week 48.

¶Of 77 patients with off-treatment data during follow-up, six (7.8%) restarted NA, none dropped out before follow-up Week 48 without restarting NAs, and 71 (92.2%) were off-treatment at follow-up Week 48.

#LLOQ = 1.3 log_{10} IU/ml = 20 IU/ml.

**Confirmed HBV DNA >peak threshold.

††Confirmed ALT ≥3× ULN and ≥3× nadir.

‡‡Confirmed HBV DNA >peak threshold and confirmed ALT and/or AST ≥3× ULN and ≥3× nadir.

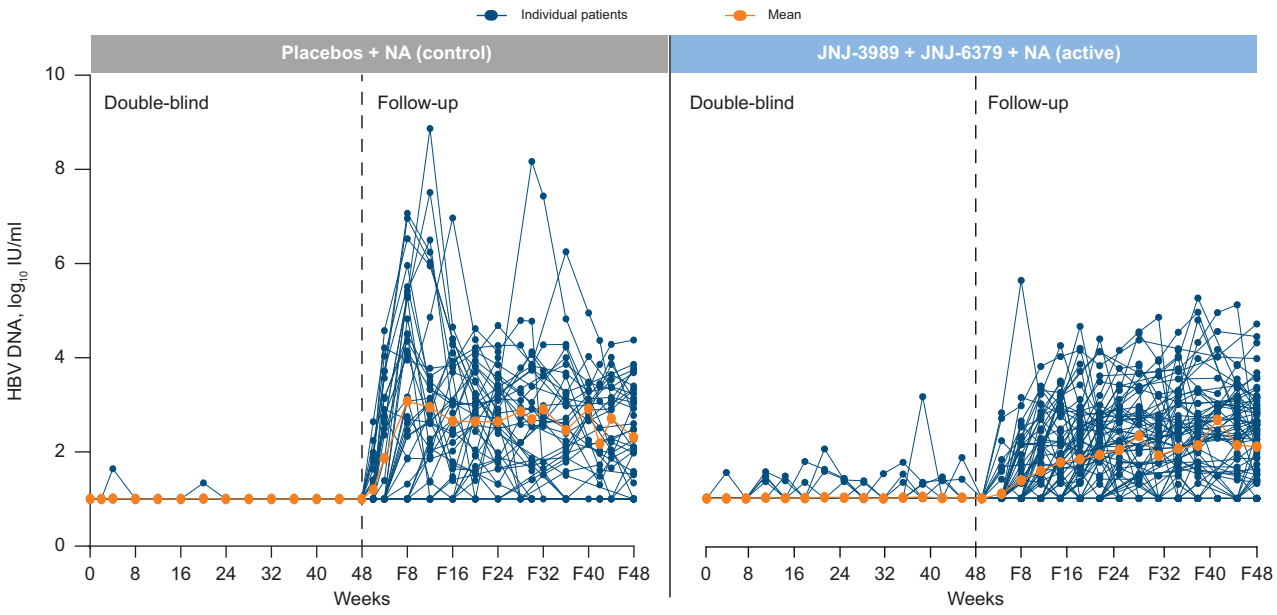

Fig. 4. HBV DNA over time in individual patients. In each figure panel, the orange line is the mean for all patients. F, follow-up; JNJ-3989, JNJ-73763989; JNJ-6379, JNJ-56136379; NA, nucleos(t)ide analogue.

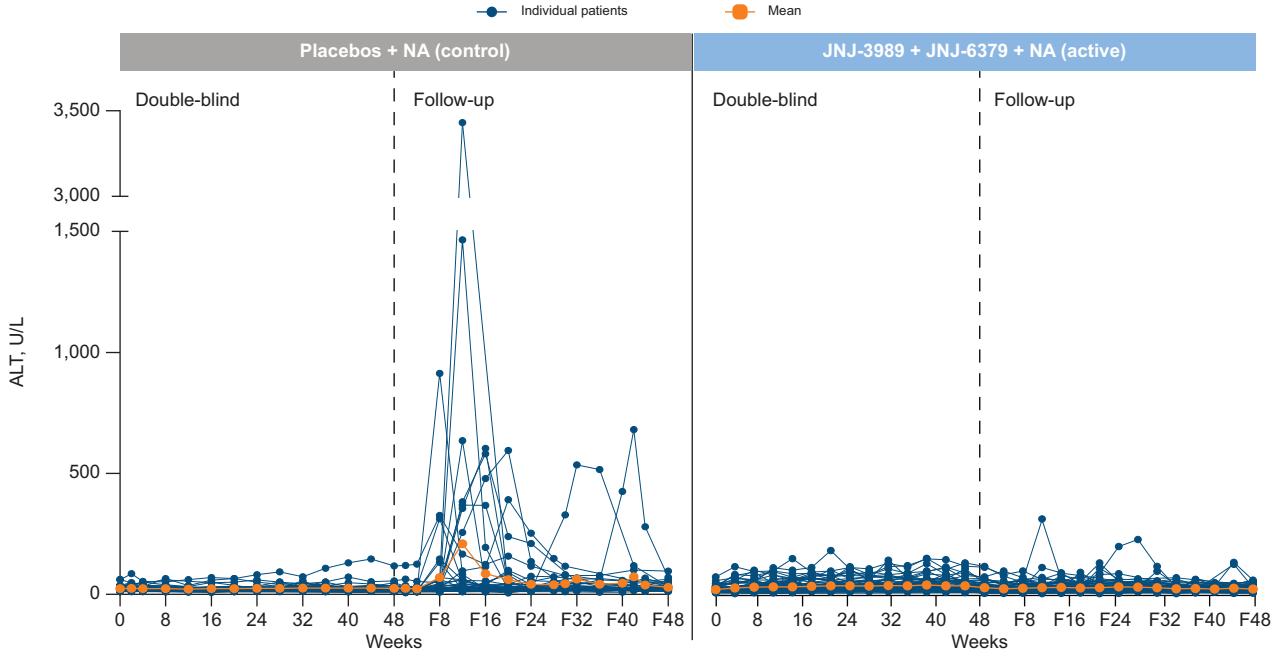

Fig. 5. ALT over time in individual patients. In each figure panel, the orange line is the mean for all patients. ALT, alanine aminotransferase; F, follow-up; JNJ-3989, JNJ-73763989; JNJ-6379, JNJ-56136379; NA, nucleos(t)ide analogue.

active and control arms, respectively. Increases in HBV DNA during follow-up correlated with ALT increases (active: $p = 0.0059$; control: $p < 0.0001$; Fig. S4), and peak HBV DNA levels >100,000 IU/ml were associated with ALT flares ≥3× ULN. In patients with virologic relapse with confirmed off-treatment peak HBV DNA >100,000 IU/ml, peak ALT >3× ULN was observed in 1/2 (50%) and 11/11 (100%) patients in the active and control arms, respectively. HBV DNA increases were less frequent and less pronounced in the active arm (peak HBV DNA >2,000 IU/ml: active = 33.8%, control = 65.8%; peak HBV DNA >100,000 IU/ml [virologic relapse]: active = 2.6%, control = 26.8%, OR [95% CI] = 9.1 [2.4–34.3], $p = 0.001$; Table S2), resulting in a substantially lower rate of ALT flares (active = 3.6%, control = 28.6%) during follow-up. Seven cases of off-treatment transient HBeAg positivity were observed, and most were in patients from the control arm who met NA retreatment criteria (Table S3). Few

Table 3. AEs during the 48-week double-blind treatment phase and 48-week off-treatment follow-up phase.

	48-week double-blind treatment phase		48-week off-treatment follow-up phase	
Patients with ≥1, n (%)	Placebos + NA (control) n = 45	JNJ-3989 + JNJ-6379 + NA (active) n = 85	Placebos + NA (control) n = 41	JNJ-3989 + JNJ-6379 + NA (active) n = 84
AEs	32 (71.1)	69 (81.2)	28 (68.3)	55 (65.5)
Related AEs	15 (33.3)	38 (44.7)	1 (2.4)	1 (1.2)
JNJ-3989/placebo	12 (26.7)	34 (40.0)	1 (2.4)	1 (1.2)
JNJ-6379/placebo	11 (24.4)	36 (42.4)	1 (2.4)	1 (1.2)
NA (ETV/TDF/TAF)	3 (6.7)	10 (11.8)	0	1 (1.2)
AEs leading to death	0	0	0	0
SAEs	1 (2.2)	2 (2.4)	3 (7.3)	2 (2.4)
Related SAEs	0	0	1 (2.4)*	0
AEs leading to discontinuation of JNJ-6379 and/or JNJ-3989	1 (2.2)	3 (3.5)	—	—
Grade 3 or 4 AEs	2 (4.4)	13 (15.3)	7 (17.1)	7 (8.3)
ALT increased	0	0	4 (9.8)	2 (2.4)
eGFR decreased†	0	6 (7.1)	0	1 (1.2)
AEs of special interest	8 (17.8)	29 (34.1)	11 (26.8)	7 (8.3)
Renal complications	5 (11.1)	21 (24.7)	0	2 (2.4)
Injection-site reactions	0	4 (4.7)	0	0
Hematologic abnormalities	2 (4.4)	2 (2.4)	1 (2.4)	2 (2.4)
ALT/AST elevations	1 (2.2)	3 (3.5)	10 (24.4)	5 (6.0)
Cholesterol increases	2 (4.4)	1 (1.2)	0	1 (1.2)
Most common AEs (≥10% of patients during the double-blind or follow-up phases)				
eGFR decrease (≥10 to <30% decline)	4 (8.9)	17 (20.0)	—	—
Headache	5 (11.1)	15 (17.6)	6 (14.6)	8 (9.5)
Arthralgia	6 (13.3)	7 (8.2)	6 (14.6)	2 (2.4)
Back pain	5 (11.1)	7 (8.2)	1 (2.4)	5 (6.0)
COVID-19	2 (4.4)	9 (10.6)	2 (4.9)	10 (11.9)
ALT increase	1 (2.2)	3 (3.5)	10 (24.4)	5 (6.0)

AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; ETV, entecavir; JNJ-3989, JNJ-73763989; JNJ-6379, JNJ-56136379; NA, nucleos(t)ide analogue; SAEs, serious adverse events; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.
*One patient experienced severe acute liver failure after stopping NAs that was considered related to study procedure.[20]
†Likely due to JNJ-6379 based on its known profile; this was reversible at the end of therapy. Most events designated by investigators as related to treatment, except for in one patient in each phase.

patients in the active arm had ALT flares during the follow-up phase with 73/77 (94.8%) having peak ALT levels <3× ULN *vs.* 25/41 (61.0%) in the control arm (Table 2). In contrast, 10/41 (24.3%) of these patients in the control arm had peak ALT levels ≥10× ULN *vs.* only 1/77 (1.3%) in the active arm (OR [95% CI] = 28.3 [3.3–245.6], $p = 0.002$; Table 2 and Table S2). Within the active arm, no significant association was observed between baseline characteristics, including race, sex, age, and NA treatment duration and HBV DNA >100,000 IU/ml (virologic relapse) or ALT ≥10× ULN (Table S4).

Seven of 77 (9.1%) patients in the active arm and 11/41 (26.8%) patients in the control arm met NA retreatment criteria at any time during follow-up (OR [95% CI] = 0.2 [0.1–0.6], $p = 0.006$; Fig. 3B; Tables S2 and S3). Of patients who met retreatment criteria, a confirmed increase in HBV DNA to >20,000 IU/ml was the most common reason patients met retreatment criteria during follow-up (active: 3/3 [100%]; control: 9/10 [90.0%]). Other reasons in the control arm included an HBV DNA increase of >2,000 IU/ml and ALT >5× ULN (6/10 [60.0%]), HBeAg seroreversion (3/10 [30.0%]), and signs of reduced liver function (1/10 [10.0%]). During follow-up, one patient in the control arm developed a serious AE (SAE) related to discontinuation of NAs. Though this patient restarted NA treatment immediately when indicated by the restarting criteria, severe HBV reactivation and acute liver failure necessitated urgent liver transplantation, which was successful.[20]

Among patients who stopped NAs, at follow-up Week 48, 17/77 (22.1%) and 1/41 (2.4%) patients in the active and control arms, respectively, had HBV DNA <LLOQ; 31/77 (40.3%) and 3/41 (7.3%) in the active and control arms, respectively, had HBV DNA <2,000 IU/ml and HBsAg <100 IU/ml; and 12/77 (15.6%) and 0 in the active and control arms, respectively, had HBV DNA <LLOQ and HBsAg <100 IU/ml, which is commonly referred to as partial cure[21] (Table 2).

Safety

Safety was evaluated as a secondary endpoint throughout the study. During the 48-week treatment phase, ≥1 AE was experienced by 69 (81.2%) patients in the active arm, 38 (44.7%) of whom had AEs related to treatment, and by 32 (71.1%) patients in the control arm, 15 (33.3%) of whom had AEs related to treatment (Table 3). During the 48-week follow-up phase, 55 (65.5%) and 28 (68.3%) patients in the active and control arms, respectively, experienced ≥1 AE. During treatment, grade 3 or 4 AEs were experienced by 13 (15.3%) and 2 (4.4%) patients in the active and control arms, respectively, most of which were grade 3 (active: 11 [12.9%]; control: 1 [2.2%]). Six (4.6%) patients had grade 3 or 4 AEs related to study treatment, all of whom belonged to the active arm. The majority of grade 3 AEs and 4/6 treatment-related grade 3 AEs during the double-blind phase were reported as reduction in estimated glomerular filtration rate based on creatinine levels. During follow-up, grade 3 or 4 AEs were experienced by seven patients from each arm, and only one patient from each arm had a grade 3 or 4 AE related to the study drug. Rates of SAEs were low for both arms during the treatment phase, occurring in two (2.4%) and one (2.2%) patient(s) in the active and control arms,

respectively, and during follow-up, occurring in two (2.4%) and three (7.3%) patients in the active and control arms, respectively. There were no deaths.

Discussion

Potential treatment regimens for CHB that aim to provide functional cure, by definition, should be finite. Different studies suggest that NA discontinuation may be a mechanism to achieve HBsAg loss in a subset of non-cirrhotic, HBeAg-negative patients who are virologically suppressed by NA treatment.[15,17,18] While factors associated with off-treatment response (and absence of relapse) are not completely established, low HBsAg levels, preferentially <100 IU/ml, at the time of NA discontinuation have been shown to be the best predictor of success (*i.e.*, HBsAg loss).[11,15] The REEF-2 study explored the effect of NA stopping in virally suppressed HBeAg-negative patients treated with NAs, with or without JNJ-3989 and JNJ-6379, to assess whether increasing the proportion of patients with HBsAg levels <100 IU/ml prior to stopping NA treatment increases the efficacy of treatment discontinuation.

The primary endpoint of the study, functional cure at follow-up Week 24, was not achieved by any patients. Based on previous NA stopping studies that included European cohorts on long-term NA treatment,[11,13,19,22] the rate of HBsAg decline and loss observed in the control arm was lower than expected; only one patient in this arm achieved HBsAg loss at follow-up Week 36 after a viral relapse with ALT flare that required NA retreatment. The limited HBsAg decline observed is likely explained by the fact that only 31.7% of patients had HBsAg <1,000 IU/ml and only one patient in the control arm had HBsAg <100 IU/ml at the time of NA stopping.[13,19,22,23] Of note, this patient had EOT HBsAg of 65 IU/ml and a 1.12 $\log_{10}$ reduction in HBsAg from EOT with relatively stable levels from follow-up Week 24 to 48.

Although functional cure was not achieved, pronounced and sustained JNJ-3989–induced declines in HBsAg levels were observed for patients in the active arm, with 71.1% of these patients achieving HBsAg <100 IU/ml at EOT, which was maintained in 46.9% of patients at follow-up Week 48. Even with this high proportion of patients in the active arm achieving HBsAg <100 IU/ml at Week 48, only one achieved transient HBsAg seroclearance during the 48-week follow-up phase. This indicates that induced reduction of HBsAg levels with an HBsAg-targeting siRNA is different from naturally achieved low HBsAg, with or without NA treatment, in terms of increasing the probability of achieving HBsAg seroclearance. While most patients in the active arm had slowly increasing HBsAg levels during follow-up, 32% showed no increase and 13% had further reductions in HBsAg after the EOT. Mean HBsAg reductions from baseline were 1.89 $\log_{10}$ at EOT and 1.46 $\log_{10}$ at the end of follow-up in the active arm, and 0.06 $\log_{10}$ and 0.49 $\log_{10}$, respectively, in the control arm. The observed reduction of HBsAg in some control arm patients and the slow increase in the active arm, with 32% of active arm patients having no increase, may be related to the immune-stimulating effect of stopping NAs.

A potential limitation of our study is the relatively short 48-week follow-up period, as HBsAg seroclearance, virolgic relapse, biochemical flares, and/or other clinical outcomes can occur over multiple years after NA cessation.[11,19,24] Additional analyses are needed to characterize the immune changes associated with the reduction of HBsAg under JNJ-3989 treatment *vs.* natural or NA treatment–associated low HBsAg levels. Another potential limitation is the length of the treatment phase (*i.e.*, 48 weeks); a longer duration of HBsAg suppression from an extended treatment period may be required to achieve functional cure. Lastly, similar to other large clinical studies in CHB, no liver biopsies were taken, and thus assessment of viral or immune changes in the liver could not be performed.

In the REEF-1 study, patients treated with JNJ-3989 and NA without JNJ-6379 had greater reductions in mean HBsAg levels than patients treated with JNJ-3989 and NA in combination with JNJ-6379.[10] The underlying mechanism of this observation is not understood, but the current study provides support for the REEF-1 findings that there is no added benefit to on-treatment HBsAg decline from adding JNJ-6379 to JNJ-3989.

A higher proportion of patients in the active *vs.* control arm reached off-treatment cutoffs for HBsAg and HBV DNA (*e.g.*, 43.7% <2,000 IU/ml + HBsAg <100 IU/ml and 16.9% HBV DNA <LLOQ + HBsAg <100 IU/ml). While functional cure is the ideal treatment goal, durable suppression of viral parameters in the absence of antiviral therapy may be an acceptable treatment goal leading to improved clinical outcomes and survival rates.[3,21]

During the follow-up phase, a greater proportion of patients in the control arm experienced off-treatment virologic and clinical relapses, with peak HBV DNA >100,000 IU/ml and peak ALT ≥10× ULN *vs.* the active arm. Consequently, more patients in the control (27.3%) *vs.* active (7.1%) arm required NA retreatment. Treatment with JNJ-3989 decreased the risk of severe off-treatment HBV DNA increases and ALT flares and increased the chance of sustained, "indolent," off-treatment HBV DNA and HBsAg suppression. Longer follow-up data are needed to confirm the sustained off-treatment response in the active arm and to assess potential late relapses and/or events of HBsAg seroclearance.

The treatment regimens in REEF-2 were safe and well-tolerated, consistent with other studies.[4,10] The rates of SAEs, laboratory abnormalities, and early treatment discontinuation were similar to those observed in the REEF-1 study arm that included JNJ-3989, JNJ-6379, and NA.[10] Similar proportions of patients from each arm of this study experienced SAEs during each phase, however, a higher rate of patients in the active arm experienced AEs and grade 3 or 4 AEs (most cases reported were grade 3 reductions of estimated glomerular filtration rate) compared with the control arm. Importantly, the higher rate of overall AEs in the active arm did not result in an increased rate of AEs leading to discontinuation of the study treatment or death. One patient in the control arm who stopped NA treatment experienced HBV DNA elevations with delayed ALT, meeting the criteria for NA retreatment at follow-up Week 11.[20] Despite initiation of NA treatment, this patient experienced sub-acute liver failure and successfully underwent liver transplantation.[20] Based on this case, the protocol-specified criteria for NA retreatment were modified to initiate NA retreatment immediately in case of HBV DNA >100,000 IU/ml, irrespective of ALT levels. With these adapted criteria, stopping NAs was generally safe. This unfavorable outcome of NA termination underscores the potential risk of this stopping NA

intervention as well as the importance of close monitoring and early retreatment.

The REEF-2 trial represents, to date, the largest prospective, randomized study on treatment discontinuation in patients with CHB with consistent management of NA retreatment according to protocol-specified criteria. The findings provide important insights for future study design with finite treatment approaches. REEF-2 recruited fully, despite the COVID-19 pandemic, and the attrition rate was very low, a testament to the patients and expert clinical sites. The lack of functional cure in this trial could potentially be attributed to the exclusion of patients with HBsAg levels <100 IU/ml at screening. Of note, although REEF-2 recruited only at European sites, 19% of the enrolled patients were Asian.

In conclusion, in the REEF-2 study, the combination of JNJ-3989 + JNJ-6379 + NA resulted in fewer and less severe post-treatment HBV DNA increases and ALT flares, *vs.* NA-only treatment, and led to sustained off-treatment HBV DNA and HBsAg suppression, but functional cure from CHB was not achieved. Combination regimens of JNJ-3989 with immunomodulators are being explored and may be necessary to achieve functional cure.

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Abbreviations

AE, adverse event; ALT, alanine aminotransferase; CHB, chronic hepatitis B; EOT, end of treatment; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; JNJ-3989, JNJ-73763989; JNJ-6379, JNJ-56136379; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogue; OR, odds ratio; Q4W, every 4 weeks; QD, daily; SAEs, serious adverse events; SC, subcutaneous; siRNA, small-interfering RNA; ULN, upper limit of normal.

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Conflicts of interest

KA received grants from Abbott and MSD; served as a consultant for Janssen, Assembly, Arbutus, Immunocore, Roche, BMS, Boehringer Ingelheim, Novartis, Shinoigi, and Sobi; served as a speaker for Gilead and Sobi; and served on a data safety monitoring or advisory board for Drug Farm, NUC-B, and Aligos. MBu received grants from Gilead and speaker fees from Gilead and AbbVie. FvB received grants/research support from BMS, Gilead, Humedics, Roche, and Janssen; received honoraria or consulting fees from AbbVie, Bayer, Gilead, Eisai, Ipsen, Janssen, MSD/Merck, Novartis, and Roche; and participated in a company-sponsored speakers bureau from AbbVie, Bayer, Gilead, Eisai, Ipsen, Janssen, MedUpdate, MSD/Merck, and Novartis. PL served on advisory boards or speaker bureaus for BMS, Roche, Gilead, GSK, AbbVie, MSD, Arrowhead, Alnylam, Janssen, Spring Bank, MYR, Eiger Biopharmaceuticals, Aligos Therapeutics, and Antios Therapeutics. EJ served as a consultant for AbbVie, Gilead, and Roche; and received speaker fees from AbbVie, MSD, and Roche. MBo served as a consultant for Janssen, Gilead, MBS Pharma, MSD, GSK, and AbbVie. TVa received grants from Gilead and BMS; served as a consultant for Janssen, Gilead, and AbbVie; and received speaker fees from Gilead. DM reports relationships with Janssen Pharmaceuticals and IQVIA. OL, TVe, TNK, CM, JJ, MBe, RK, MBi, and ILD are or were Janssen employees at the time of study conduct and may hold stock in Johnson & Johnson.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

All authors were involved in the critical revisions of the manuscript and the review of important content, were accountable for all aspects of the work (accuracy and integrity), and approved the final manuscript submitted. At least one author had access to all of the data and can vouch for the integrity of the data analyses. OL, TVe, TNK, CM, JJ, MBe, RK, MBi, and ILD designed the protocol and analyzed the data.

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.

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Supplementary data

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Author names in bold designate shared co-first authorship

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