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Dose Response with the RNA Interference Therapy JNJ-3989 Combined with Nucleos(t)ide Analogue Treatment in Expanded Cohorts of Patients with Chronic Hepatitis B

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Introduction

- Current therapies for chronic hepatitis B (CHB) include either a nucleos(t)ide analogue (NA; tenofovir disoproxil [TDF], tenofovir alafenamide, or entecavir [ETV]) or sometimes pegylated interferon.[1,2]
- After five years on NA monotherapy, only 0–3% of patients will achieve a functional cure, defined clinically as hepatitis B surface antigen (HBsAg) loss with or without anti-HBs seroconversion.[1–3]
- RNA interference (RNAi) therapy silences HBV RNA transcripts thereby reducing levels of HBsAg and all other viral products and has demonstrated promising activity as a potential component of finite therapy for CHB patients.[4–6]
- JNJ-73763989 (JNJ-3989; ARO-HBV) was designed to silence HBV RNA transcripts from episomal cccDNA and host-integrated HBV DNA.
- In part 2 of the study AROHBV1001 (NCT03365947)[7] in CHB patients, JNJ-3989 reduced serum HBsAg levels by ≥1 $\log_{10}$ IU/mL in all patients receiving three JNJ-3989 doses (100–400 mg, one every 4 weeks [Q4w]) with an NA (TDF or ETV), regardless of baseline hepatitis B e-antigen (HBeAg) status or prior NA therapy experience.[7]
- Given the lack of a dose response with 100–400 mg Q4w JNJ-3989,[7] cohorts 2b–5b (**Table 1**) were expanded from four to eight patients, and two lower dose cohorts 1b and 1c (25 and 50 mg Q4w, respectively) were added to the AROHBV1001 study.
- Efficacy and safety data up to Day 113 are presented (i.e. two months post-JNJ-3989 dosing) for cohorts 2b–5b (100–400 mg Q4w JNJ-3989), and cohorts 1b and 1c (25 mg and 50 mg Q4w JNJ-3989) (**Table 1**) (except for the nadir HBsAg data which were selected from all of the available follow-up data).

Methods

- AROHBV1001 is a double-blind, single-ascending dose study in healthy volunteers (part 1) and an open-label, multiple-ascending dose study in CHB patients (part 2) to assess the efficacy and safety of JNJ-3989 (**Table 1**).
- In cohorts 1b, 1c and 2b–5b of AROHBV1001, HBeAg positive or negative, NA-experienced or -naïve CHB patients were enrolled and received three subcutaneous JNJ-3989 doses of 25, 50, 100, 200, 300 or 400 mg Q4w on Days 1, 27 and 57 (**Table 1**).
- All patients either started (NA-naïve) or continued (NA-experienced) with daily NA (TDF or ETV) treatment on Day 1 and continued beyond the end of JNJ-3989 dosing.
- Study visits were at screening and on Days 1, 8, 15, 29, 43, 57, 85, 113, then extended follow up approximately every 2 months after Day 113 for 12 months.
- Serum viral parameters were assessed, i.e. HBV DNA (Roche Cobas, lower limit of quantification [LLOQ] 20 IU/mL), HBV RNA (Abbott m2000, LLOQ 1.65 $\log_{10}$ U/mL[4]), HBsAg (Roche Elecsys, LLOQ 0.05 IU/mL), HBeAg (Diasorin Liaison, values below 0.11 PEIU/ML are reported as not detected), and hepatitis B core-related antigen, (HBcrAg, Fujirebio Lumipulse, LLOQ 1 kU/mL).
- Safety assessments included clinical laboratory assessments and adverse events (AEs) assessed from screening through Day 113, as reported here, and through the extended follow-up period.

Table 1. Design of Part 2 MAD Open-Label Study in CHB Patients.

Cohort	N=	CHB HBeAg pos/neg NA exp/naive	CHB HBeAg pos NA naive	CHB HBeAg pos NA exp
1b	8	3 x 25 mg Q4w		
1c	8	3 x 50 mg Q4w		
2b	8	3 x 100 mg Q4w		
3b	8	3 x 200 mg Q4w		
4b	8	3 x 300 mg Q4w		
5b	8	3 x 400 mg Q4w		
6	4	3 x 100 mg Q2w		
7	4	3 x 100 mg Qw		
8	4		3 x 300 mg Q4w	
9	4			3 x 300 mg Q4w
10	4	3 x 200 mg Qw		
11	4	3 x 300 mg Qw		
12	12	3 x 200 mg Q4w + JNJ-6379 QD for 12 weeks		

These results are being presented here

CHB: chronic hepatitis B; exp: experienced; HBeAg: hepatitis B e-antigen; JNJ-6379: JNJ-56136379, a novel, class N capsid assembly modulator inducing normal empty capsid formation; MAD: multiple-ascending doses; neg: negative; pos: positive; Qw: weekly; Q2w: every 2 weeks; Q4w: every 4 weeks.

Results

Patient Characteristics and Disposition

- Baseline characteristics were generally well balanced across the cohorts (**Table 2**)
  - Most patients were NA-experienced (40/48, 83%).
- All patients received their planned JNJ-3989 doses with no treatment discontinuations.

Table 2: Baseline Demographics.

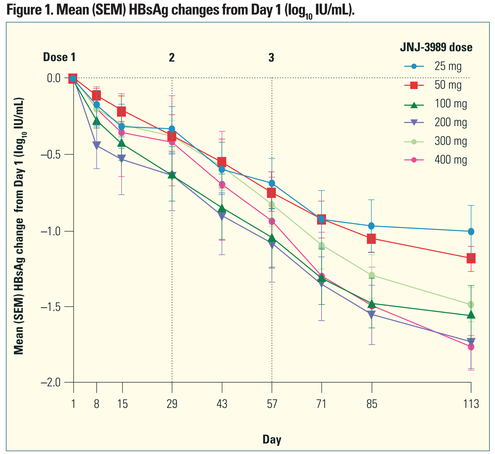
	JNJ-3989 3x Q4w, cohort, dose						
	1b	1c	2b	3b	4b	5b	All patients
	25 mg N=8	50 mg N=8	100 mg N=8	200 mg N=8	300 mg N=8	400 mg N=8	N=48
Age, years; mean (range)	43 (31–52)	48 (36–58)	51 (32–66)	48 (41–57)	52 (40–63)	42 (29–61)	47 (29–66)
Male, n (%)	5 (63)	6 (75)	6 (75)	5 (63)	8 (100)	6 (75)	36 (75)
Race, n (%)							
Asian	6 (75)	5 (63)	8 (100)	8 (100)	5 (63)	6 (75)	38 (79)
White	0	0	0	0	1 (13)	0	1 (2)
Native Hawaiian/other Pacific Islander	1 (13)	1 (13)	0	0	2 (25)	0	4 (8)
Black/AA	1 (13)	0	0	0	0	0	1 (2)
Other	0	2 (25)	0	0	0	2 (25)	4 (8)
BMI, kg/m²; mean (range)	27 (20–44)	26 (18–40)	24 (22–29)	25 (19–32)	27 (21–36)	25 (21–36)	26 (18–44)
HBeAg positive/ negative, n	2/6	3/5	1/7	1/7	3/5	1/7	11/37
NA experienced, n (%)	4 (50)	7 (88)	6 (75)	8 (100)	8 (100)	7 (88)	40 (83)
Mean (SEM) HBsAg on Day 1 (IU/mL)	6477 (2876)	4595 (1986)	3937 (2142)	3212 (2453)	9381 (8275)	4032 (1652)	5272 (1558)

AA: African American; BMI: body mass index; HBeAg: hepatitis B e-antigen; HBsAg: hepatitis B surface antigen; NA: nucleos(t)ide analogue; Q4w: every 4 weeks; SEM: standard error of the mean.

Effect of JNJ-3989 on HBsAg Levels

- JNJ-3989 reduced HBsAg levels at all doses evaluated (**Figure 1**).
- At Day 113 (typical mean nadir after three doses, 56 days after last dose), mean HBsAg (SEM) $\log_{10}$ IU/mL reduction from Day 1 was 1.00 (0.18) with 25 mg JNJ-3989, 1.18 (0.08) with 50 mg, 1.54 (0.18) with 100 mg, 1.71 (0.15) with 200 mg, 1.48 (0.11) with 300 mg and 1.75 (0.16) with 400 mg JNJ-3989.

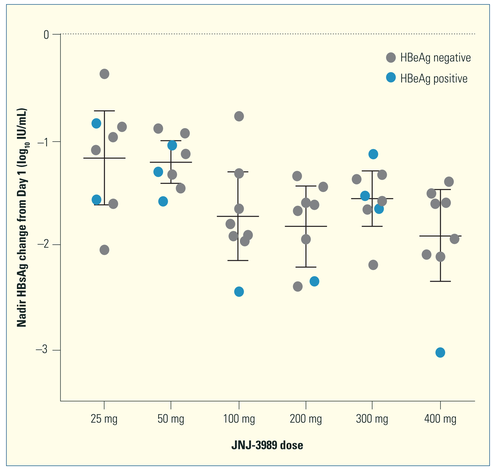
Figure 1. Mean (SEM) HBsAg changes from Day 1 ($\log_{10}$ IU/mL).



Eight patients/group/time point except for 200 mg group which had seven patients at Days 29, 43, 57, 71, 85 and 113.
For one patient with HBsAg <0.05 IU/mL, data were imputed at LLOQ/2.
HBsAg: hepatitis B surface antigen; SEM: standard error of the mean; LLOQ: lower limit of quantification.

- **Figure 2** shows changes in HBsAg levels at Day 113 compared with Day 1.
- The proportion of patients with Day 113 data who achieved ≥1.0 $\log_{10}$ reduction in HBsAg from Day 1 at nadir was 4/8 (25 mg JNJ-3989), 6/8 (50 mg), 7/8 (100 mg), 8/8 (200 mg), 8/8 (300 mg), and 8/8 (400 mg)
  - Similar responses were observed for HBeAg positive and negative patients
    - HBeAg positive (n=11): Mean nadir –1.52 $\log_{10}$ IU/mL
    - HBeAg negative (n=37): Mean nadir –1.62 $\log_{10}$ IU/mL.
  - One patient receiving 200 mg JNJ-3989 had undetectable HBsAg at Day 113, and achieved 1.6 $\log_{10}$ IU/mL reduction on Day 15 prior to HBsAg seroclearance.
- For patients with HBsAg >100 IU/mL (Day 1) and with Day 113 data, 2/7 (25 mg), 3/8 (50 mg), 5/7 (100 mg), 5/6 (200 mg), 6/8 (300 mg) and 5/7 (400 mg) achieved HBsAg <100 IU/mL with JNJ-3989 treatment.

Figure 2. Mean (95% CI) and Individual HBsAg changes from Day 1 ($\log_{10}$ IU/mL).



Patients had variable follow-up times, the nadir HBsAg changes from Day 1 are from all of the available patient data.
CI: confidence interval; HBeAg: hepatitis B e-antigen; HBsAg: hepatitis B surface antigen.

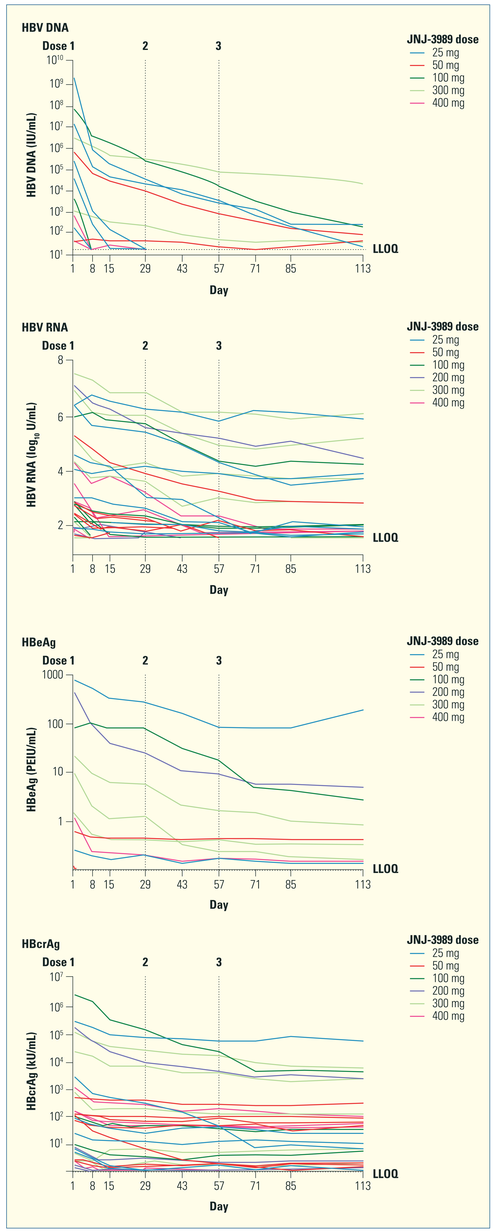
Individual Changes in HBV DNA, HBV RNA, HBeAg, and HBcrAg

- For patients with measurable parameters on Day 1, patients had a robust decline in HBV DNA and HBV RNA levels, and reductions in HBeAg and HBcrAg were less pronounced with JNJ-3989 treatment (**Figure 3**).

Safety and Tolerability

- Safety data for Cohorts 1b to 5b through Day 113 showed that three monthly doses of JNJ-3989 at 25–400 mg in combination with an NA were generally well tolerated in CHB patients (**Table 3**).
- Three non-drug related serious AEs were reported (anxiety with depression in a single patient and menorrhagia, each requiring hospitalization).
- The most commonly reported AEs at least possibly drug related consisted of various AEs at the injection site (e.g, discoloration, erythema, bruising, rash), which were all mild and reported in five patients.
- There were no reports of thrombocytopenia and one report of possibly drug-related Stage 1 acute kidney injury with creatinine increase (from 1.10 mg/dL Day 1 pre-dose to a peak of 1.55 mg/dL on Day 8 and return to 1.06 mg/dL on Day 15), which was treatment emergent but likely due to creatine supplementation and did not lead to treatment interruption or adjustment.
- A single AE reported of mild, possibly related, abnormal liver function tests (peak alanine aminotransferase [ALT] 136 U/L) was reported, representing the highest treatment-emergent ALT elevation in cohorts 1b to 5b through Day 113 (end of study)
  - There were no cases of simultaneous elevations of ALT >3x upper limit of normal and total bilirubin >2x upper limit of normal.

Figure 3. Individual Changes in HBV DNA, HBV RNA, HBeAg and HBcrAg with JNJ-3989 and NA Treatment.



Data are shown for patients with detectable parameters at baseline.
HBeAg: hepatitis B e-antigen; HBcrAg: hepatitis B core-related antigen; LLOQ: lower limit of quantification.
HBV DNA LLOQ: 20 IU/mL; HBV RNA LLOQ: 1.65 $\log_{10}$ U/mL; HBeAg LLOQ: 0.01 PEIU/mL (values below 0.11 PEIU/mL are reported as not detected) and HBcrAg LLOQ: 1 kU/mL.

Table 3: Adverse Events Possibly or Probably Drug Related Occurring up to and Including Day 113.

Possibly or probably drug-related AEs in ≥2 patients[a], n	JNJ-3989 3x Q4w, cohort, dose						
	1b	1c	2b	3b	4b	5b	All patients
	25 mg N=8	50 mg N=8	100 mg N=8	200 mg N=8	300 mg N=8	400 mg N=8	N=48
Injection site discoloration, injection site erythema, injection site bruising	1 Mild	0	0	0	2 Mild	2 Mild	5
Fatigue	1 Mild	0	1 Mild	0	0	1 Mild	3
Blood creatine phosphokinase elevated	1 Mild	0	0	0	1 Severe	0	2
Hot flush, flushing	0	1 Mild	0	0	0	1 Mild	2
Blood bilirubin increased, hyperbilirubinemia	0	0	0	1 Mild	1 Mild	0	2
Pruritus	1 Mild	0	1 Mild	0	0	0	2

[a]MedDRA preferred term aggregated based on similarity.
AE: adverse event; Q4w: every 4 weeks.

Conclusions

- In this study in CHB patients, JNJ-3989 in combination with an NA had strong activity against HBsAg, HBV DNA and HBV RNA. Reductions in HBeAg and HBcrAg were generally less pronounced
  - HBsAg reductions were similar in HBeAg positive and HBeAg negative patients
  - Expanded cohorts with 100–400 mg JNJ-3989 confirmed previous findings that HBsAg declines were similar with these doses[7]; 97% (31/32) of these patients achieved a ≥1.0 $\log_{10}$ (90%) reduction in HBsAg
  - The 25 mg and 50 mg JNJ-3989 doses were active in reducing HBsAg, and appeared less effective than higher doses
  - HBsAg responses with JNJ-3989 are consistent with its ability to silence HBV RNA from cccDNA and host-integrated viral DNA (which is a major source of HBsAg in certain CHB populations[5])
  - JNJ-3989 was well tolerated at doses up to 400 mg Q4w for three doses.
- Overall, JNJ-3989 demonstrated anti-HBV characteristics desirable for an RNAi therapy. Studies of longer duration are underway, including triple combinations aimed at functional cure in CHB patients.

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