LP4

First Clinical Experience with RNA Interference-based Triple Combination Therapy in Chronic Hepatitis B: JNJ-3989, JNJ-6379 and a Nucleos(t)ide Analogue

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Introduction

- Chronic hepatitis B (CHB) is currently treated with a nucleos(t)ide analogue (NA; entecavir [ETV], tenofovir disoproxil fumarate [TDF], or tenofovir alafenamide), and occasionally with pegylated interferon.[1,2]
- Only 0–3% of patients will achieve a functional cure, i.e. hepatitis B surface antigen (HBsAg) loss with or without anti-HBs seroconversion, following five years of NA monotherapy.[1–3]
- Hepatitis B virus (HBV) RNA transcripts are silenced by RNA interference (RNAi) therapy, and this type of therapy has demonstrated promising antiviral activity as a potential component of finite therapy for CHB[4–6]
  - The RNAi JNJ-73763989 (JNJ-3989; ARO-HBV) silences HBV RNA transcripts from host-integrated HBV DNA and episomal cccDNA
  - In part 2 of the study AROHBV1001 (NCT03365947) in CHB patients, three monthly JNJ-3989 doses (100–400 mg, one dose every 4 weeks [Q4w]) with an NA (ETV or TDF) achieved >1 $\log_{10}$ HBsAg reductions regardless of baseline hepatitis B e-antigen (HBeAg) status or prior NA therapy, reduced all measurable viral products and was well tolerated.[7]
- JNJ-56136379 (JNJ-6379), a novel, class N capsid assembly modulator (CAM-N) inducing normal empty capsid formation blocked HBV replication and de-novo cccDNA formation in preclinical models,[8] and reduced HBV DNA and HBV RNA levels over a treatment period of 28 days in CHB patients and was well tolerated.[9]
- Reported here is a cohort in study AROHBV1001 exploring the triple combination therapy of JNJ-3989, JNJ-6379 and an NA
  - We report efficacy and safety data up to Day 113 (i.e. two months post JNJ-3989 dosing, and one month post JNJ-6379 dosing).

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
  - Cohorts 1b–11 investigated dual therapy with JNJ-3989 and an NA in CHB patients.[7,10]
- In cohort 12, CHB patients who were HBeAg positive or negative, NA-experienced (regardless of HBV DNA level) or NA-naïve were enrolled and received the following triple combination treatment:
  - Three 200 mg JNJ-3989 subcutaneous doses (i.e. on Days 1, 29 and 57)
  - Oral JNJ-6379 250 mg once daily for 12 weeks (i.e. until Day 85)
  - All patients either started or continued with NA (ETV or TDF) treatment on Day 1, which continued beyond the end of JNJ-6379 dosing.
- Study visits were conducted at screening and on Days 1, 8, 15, 29, 43, 57, 85, 113, with ongoing extended follow up approximately every two months for 12 months.
- The following serum viral parameters were assessed: HBV DNA (Roche Cobas, lower limit of quantification [LLOQ] 20 IU/mL), HBV RNA (Abbott m2000, LLOQ 1.65 $\log_{10}$ U/mL), 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, including clinical laboratory assessments and adverse events (AEs), were conducted from screening through Day 113, as reported here, and will continue through the extended follow-up period.

Results

Patient Characteristics and Disposition

- Baseline characteristics are listed in **(Table 1)**.
- All patients received their planned JNJ-3989, JNJ-6379 and NA doses with no treatment discontinuations or dose adjustments.

Table 1: Baseline Characteristics and Demographics.

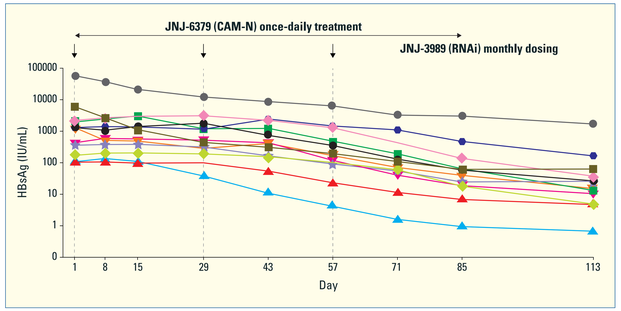
	JNJ-3989 (3 x 200 mg Q4w) + JNJ-6379 250 mg once daily + daily NA treatment N=12
Age, years; median (range)	46 (34–67)
Male, n (%)	8 (67)
Race, n (%) Asian	12 (100)
BMI, kg/m²; mean (range)	26.8 (20–36)
HBeAg positive/negative, n	4/8
NA experienced, n (%)	7 (58)
Mean (range) HBsAg on Day 1 (IU/mL)	6612 (116–62,490)

BMI: body mass index; HBeAg: hepatitis B e-antigen; HBsAg: hepatitis B surface antigen; NA: nucleos(t)ide analogue; Q4w: once every 4 weeks.

Effect of JNJ-3989, JNJ-6379 and NA Combination Therapy on HBsAg Levels

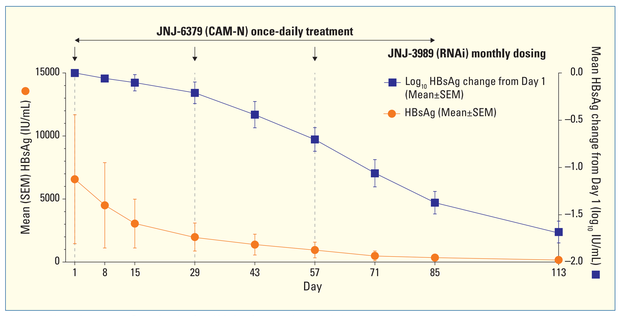
- HBsAg levels declined during treatment with the triple combination of JNJ-3989, JNJ-6379 and an NA, in all patients, irrespective of baseline HBsAg level **(Figure 1)**
  - Mean HBsAg levels and mean $\log_{10}$ HBsAg reduction from Day 1 are shown in **Figure 2**.

Figure 1: Individual Changes in HBsAg Levels over Time with JNJ-3989, JNJ-6379 and NA Treatment.



CAM-N: class N capsid assembly modulator; HBsAg: hepatitis B surface antigen; NA: nucleos(t)ide analogue; RNAi: RNA interference.

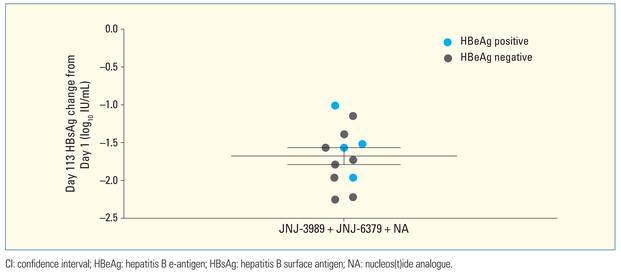
Figure 2: Mean HBsAg Levels over Time and Mean Change from Day 1 with JNJ-3989, JNJ-6379 and NA Treatment.



12 patients/time point except on Days 43 and 71 for which data for one patient are missing.
CAM-N: class N capsid assembly modulator; HBsAg: hepatitis B surface antigen; NA: nucleos(t)ide analogue; RNAi: RNA interference; SEM: standard error of the mean.

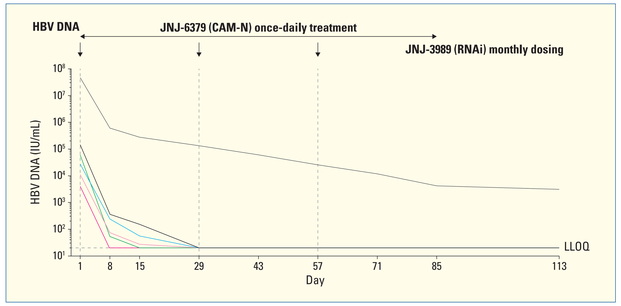
- At Day 113 (typical mean nadir after three JNJ-3989 doses, 56 days after the last dose), mean HBsAg (standard error of the mean [SEM]) $\log_{10}$ IU/mL reduction from Day 1 was 1.7 (0.11), n=12.
- **Figure 3** shows HBsAg values at Day 1 and at Day 113.
- All 12 patients in cohort 12 achieved a ≥1.0 $\log_{10}$ IU/mL reduction in HBsAg from Day 1 at the nadir, which was Day 85 for 1 patient and Day 113 for 11 patients
  - Similar responses were observed for HBeAg positive and negative patients
    - HBeAg positive (n=4): Mean nadir –1.52 $\log_{10}$ IU/mL
    - HBeAg negative (n=8): Mean nadir –1.76 $\log_{10}$ IU/mL.
- All patients had HBsAg >100 IU/mL on Day 1 and 10/12 patients achieved HBsAg <100 IU/mL after 12 weeks of therapy with JNJ-3989, JNJ-6379 and an NA.

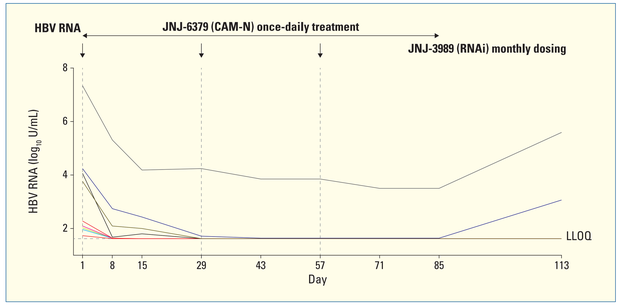
Figure 3: Mean (95% CI) and Individual HBsAg Changes from Day 1 ($\log_{10}$ IU/mL) with JNJ-3989, JNJ-6379 and NA Treatment.

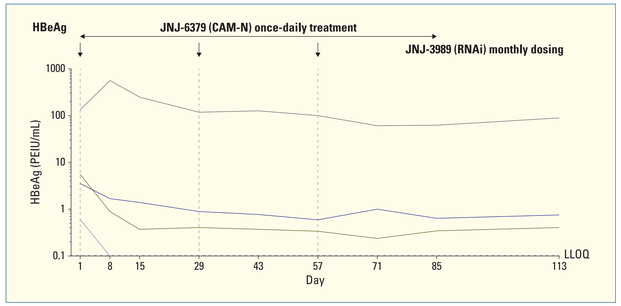


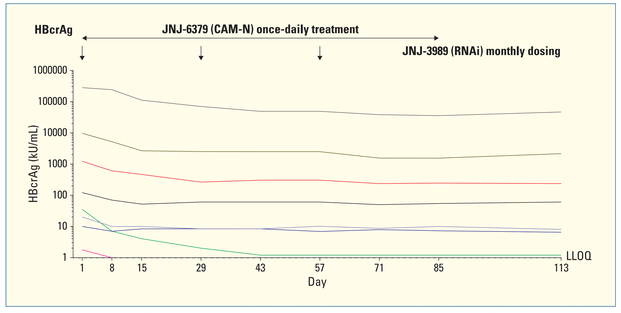
CI: confidence interval; HBeAg: hepatitis B e-antigen; HBsAg: hepatitis B surface antigen; NA: nucleos(t)ide analogue.

Figure 4: Individual Changes in HBV DNA, HBV RNA, HBeAg and HBcrAg with JNJ-3989, JNJ-6379 and NA Treatment.









Data are shown for patients with detectable parameters at baseline. CAM-N: class N capsid assembly modulator; HBeAg: hepatitis B e-antigen; HBcrAg: hepatitis B core-related antigen; LLOQ: lower limit of quantification; NA: nucleos(t)ide analogue; RNAi: RNA interference. HBV DNA LLOQ: 20 IU/mL; HBV RNA LLOQ: 1.65 log10 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

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

- **Figure 4** shows levels of viral parameters during treatment with JNJ-3989, JNJ-6379 and an NA for patients with measurable parameters on Day 1.
- All patients with >1000 IU/mL HBV DNA on Day 1 (n=6, 3.7–7.7 $\log_{10}$ IU/mL) had a rapid decline in HBV DNA **(Figure 4)**
  - One of these six patients had high HBV DNA levels on Day 1 (7.7 $\log_{10}$ IU/mL), which declined to 3.5 $\log_{10}$ IU/mL on Day 113.
- One patient had HBV DNA >LLOQ and <1000 IU/mL at baseline (33 IU/mL) and had persistently low HBV DNA levels at or just above the LLOQ (highest value was 54 IU/mL on Day 71) – these data are not included in **Figure 4**; this patient had been on NA treatment for approximately seven years prior to study start.
- Of the nine patients with quantifiable HBV RNA (Day 1, 1.75–7.5 $\log_{10}$ U/mL), six had levels <LLOQ by Day 29.
- Patients positive on Day 1 for HBeAg (n=4) or HBcrAg (n=8) had reductions in these parameters, although these reductions were generally not as pronounced as for the other parameters.

Safety and Tolerability

- Three doses of 200 mg Q4w JNJ-3989 in combination with daily 250 mg JNJ-6379 for 12 weeks and an NA daily were generally well tolerated in CHB patients as of the October 4, 2019 safety data cutoff.
- No deaths, discontinuations, serious AEs or severe AEs were reported.
- Two AEs of mild respiratory infection, not related to treatment, were reported.
- There were no clinically significant findings on vital signs, 12-lead electrocardiograms, hematology or clinical chemistry parameters
  - The only notable treatment-emergent laboratory findings were grade 1, transient isolated alanine aminotransferase elevations (n=5 patients, 57–122 U/L), which resolved with continued dosing and were potentially induced by reduction of viral parameters.

Conclusions

- This is the first study to investigate the safety and efficacy of a triple combination of an RNAi (JNJ-3989 200 mg 3x Q4w, three doses), a CAM-N (JNJ-6379 250 mg daily for 12 weeks) and an NA (daily) in patients with CHB.
- This triple combination was well tolerated, and all CHB patients achieved robust reductions in HBsAg, HBV DNA, and HBV RNA. Reductions in HBeAg and HBcrAg were generally less pronounced during the dosing period
  - All patients achieved a ≥1.0 $\log_{10}$ IU/mL (90%) reduction (nadir ranged from –1.01 to –2.26 $\log_{10}$ IU/mL) in HBsAg
  - HBsAg reductions were similar in HBeAg positive and HBeAg negative patients.
- Studies of longer duration with this triple combination are underway aimed at assessing functional cure rates in patients with CHB.

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