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]) in combination with an NA (ETV or TDF) achieved >1 log10 HBsAg reductions regardless of baseline hepatitis B e-antigen (HBeAg) status or prior NA therapy, reduced all measurable viral markers, and improved liver histology.

• The RNAi JNJ-73763989 (JNJ-3989; ARO-HBV) silences HBV RNA transcripts from host-integrated HBV DNA and viral particles.

• Artsynova (JNJ-6379) is a class N capsid assembly modulator that blocks HBV capsid formation to prevent production of new virions.

• The triple combination therapy of JNJ-3989, JNJ-6379, and TDF/ETV by monthly dosing of JNJ-3989 (RNAi) 3 x 200 mg and JNJ-6379 250 mg achieved >1 log10 HBsAg reductions regardless of baseline HBeAg status or prior NA therapy, reduced all measurable viral markers, and improved liver histology.

Methods

• JNJ-3989 is a double-blind, single ascending dose study in healthy volunteers (n=12) and an open-label, multiple ascending dose study in CHB patients (n=252) across the efficacy and safety of JNJ-3989.

• Cohorts 1–11 investigated dual therapy with JNJ-3989 and TDF or ETV (Table 1).

• In cohort 12, CHB patients who were HBsAg positive or negative and HBV RNA positive or negative (HBeAg with 20 IU/mL) were included and received no previous triple combination treatment.

• Three 285 mg JNJ-3989 autologous (i.e., 136.5, 210, and 285), one 200 mg JNJ-3989 dosing on Day 1, and two 200 mg dosing on Day 8.

• All patients either started or continued with NA (ETV or TDF) treatment on Day 1, which continued beyond the end of JNJ-3989 dosing.

• Study visits were conducted on screening and on Days 1, 5, 12, 20, 42, 65, 119, and 221, with ongoing extended follow-up approximately every two months for 12 months.

• The following were monitored: HBV DNA (PCR-based, upper limit of quantification [ULOQ] 20,000 IU/mL), HBV RNA (RT-qPCR, ULOQ 1900 IU/mL), ALT, AST, HBsAg, HBcAg, HBcrAg, HBV DNA LLOQ, HBV RNA LLOQ, HBV DNA LLOQ, HBV RNA LLOQ, HBcrAg LLOQ, and vaccinia virus–encoded antigen.

• Safety assessments, including clinical laboratory measurements and adverse events (AEs), were conducted from screening through Day 221, as are repairs, and will continue through the extended follow-up period.

Results

Patient Characteristics and Disposition

• Baseline characteristics are listed in Table 1.

• All patients received planned JNJ-3989, JNJ-6379 and NA dosing with no treatment discontinuations or dose adjustments.

Table 1: Baseline Characteristics and Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>JNJ-3989 n=11</th>
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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 NA in all patients, irrespective of HBeAg status (Figure 1).

• Mean HBsAg levels and mean log10 HBsAg reduction from Day 1 are shown in Figure 2.

• 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 NA.

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

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

Figure 3: Mean HBsAg changes from Day 1 with JNJ-3989, JNJ-6379 and NA Treatment.

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