Short-term treatment with RNA interference therapy, JNJ-3989, results in sustained hepatitis B surface antigen suppression in patients with chronic hepatitis B receiving nucleos(t)ide analogue treatment

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JNJ-3989 and a nucleos(t)ide analogue: Mechanisms of action

- NAs inhibit viral replication but do not prevent the production of HBsAg
- Previously reported data up to Day 112 (8 weeks after the JNJ-3989 dose) showed that treatment with JNJ-3989 (100–400 mg) in combination with an NA (TDF or ETV) resulted in reductions in HBsAg, HBeAg, HBV RNA and HBcrAg, and was well tolerated in patients with CHB


cccDNA = covalently closed circular DNA; CHB, chronic hepatitis B; ETV, entecavir; HBeAg, hepatitis B e antigen; HBcrAg, hepatitis B core related antigen; HBsAg, hepatitis B surface antigen; NA = nucleos(t)ide analogue; pgRNA = pregenomic RNA; siRNA = short interfering RNA; TDF, tenofovir
AROHBV1001: Study design

Open-label part in patients with CHB, focus on cohorts receiving JNJ-3989 3 X Q4w

**Study population:**
1. CHB HBeAg-positive or -negative patients
2. NA-experienced or -naïve patients

**Dose administration:**
- Injections (sc) of JNJ-3989 were given on Days 0, 28 and 56
- Oral QD treatment with TDF or ETV was started or continued on Day 0 and was administered beyond end of JNJ-3989 treatment

**Assessments:**
1. Viral parameters from Day 0 to Day 392, i.e., 48 weeks after the last JNJ-3989 dose
2. Safety from Day 0 to Day 336, i.e., 40 weeks after the last JNJ-3989 dose

<table>
<thead>
<tr>
<th>Cohort</th>
<th>N</th>
<th>JNJ-3989 dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b</td>
<td>8</td>
<td>100 mg</td>
</tr>
<tr>
<td>3b</td>
<td>8</td>
<td>200 mg</td>
</tr>
<tr>
<td>4b</td>
<td>8</td>
<td>300 mg</td>
</tr>
<tr>
<td>5b</td>
<td>8</td>
<td>400 mg</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>300 mg</td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>300 mg</td>
</tr>
</tbody>
</table>

CHB = chronic hepatitis B; ETV = entecavir; HBeAg = hepatitis B e-antigen; NA = nucleos(t)ide analogue; Q4w = every 4 weeks; QD = once daily; sc = subcutaneous; TDF = tenofovir
AROHBV1001: Objectives of analysis

The objectives of this analysis of JNJ-3989 were to assess sustained response in HBsAg, HBV RNA, HBeAg and HBcrAg up to Day 392, 48 weeks after the last JNJ-3989 dose in patients with CHB continuing with NA treatment from Day 0 to end of study.

Patients receiving 3 doses of JNJ-3989 (Q4w) 100–400 mg and having reached Day 392 were classified as sustained responders and non-sustained responders based on HBsAg response:

**Sustained responder**
≥1 log<sub>10</sub> IU/mL reduction in HBsAg from Day 0 to Day 392

**Non-sustained responder**
<1 log<sub>10</sub> IU/mL reduction in HBsAg from Day 0 to Day 392

Patients were included in the analyses if their HBsAg was reduced by ≥1 log<sub>10</sub> IU/mL from Day 0 at any time through Day 392.

CHB = chronic hepatitis B; HBcrAg = hepatitis B core-related antigen; HBeAg = hepatitis B e-antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; IU, international units; NA = nucleos(t)ide analogue; Q4w = every 4 weeks.
AROHVBV1001: Baseline characteristics and demographics

### JNJ-3989 3 x Q4w, 100–400 mg cohort

<table>
<thead>
<tr>
<th></th>
<th>Cohort 2b 100 mg N=8</th>
<th>Cohort 3b 200 mg N=8</th>
<th>Cohort 4b 300 mg N=8</th>
<th>Cohort 5b 400 mg N=8</th>
<th>Cohort 8* 300 mg N=4</th>
<th>Cohort 9‡ 300 mg N=4</th>
<th>All patients N=40</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years; mean (range)</strong></td>
<td>51 (32.0–66.0)</td>
<td>48 (41.0–57.0)</td>
<td>52 (4.0–63.0)</td>
<td>42 (29.0–61.0)</td>
<td>37 (26.0–46.0)</td>
<td>36 (30.0–42.0)</td>
<td>45 (26.0–66.0)</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>6 (75.0)</td>
<td>5 (62.5)</td>
<td>8 (100.0)</td>
<td>6 (75.0)</td>
<td>2 (50.0)</td>
<td>2 (50.0)</td>
<td>29 (72.5)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td>8 (100.0)</td>
<td>8 (100.0)</td>
<td>5 (62.5)</td>
<td>6 (75.0)</td>
<td>3 (75.0)</td>
<td>4 (100.0)</td>
<td>34 (85.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>0</td>
<td>1 (12.5)</td>
<td>0</td>
<td>4 (100.0)</td>
<td>1 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>0</td>
<td>0</td>
<td>0 (0.0)</td>
<td>2 (25.0)</td>
<td>0</td>
<td>0</td>
<td>5 (12.5)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (100.0)</td>
<td>8 (100.0)</td>
<td>2 (25.0)</td>
<td>6 (75.0)</td>
<td>1 (25.0)</td>
<td>0</td>
<td>3 (75.0)</td>
</tr>
<tr>
<td><strong>HBeAg positive (%)</strong></td>
<td>1 (12.5)</td>
<td>1 (12.5)</td>
<td>3 (37.5)</td>
<td>1 (12.5)</td>
<td>0</td>
<td>4 (100.0)</td>
<td>14 (35.0)</td>
</tr>
<tr>
<td><strong>NA experienced, n (%)</strong></td>
<td>6 (75.0)</td>
<td>8 (100.0)</td>
<td>12 (75.0)</td>
<td>7 (87.5)</td>
<td>0</td>
<td>4 (100.0)</td>
<td>32 (80.0)</td>
</tr>
<tr>
<td><strong>Mean (SEM) HBsAg on Day 1 (IU/mL)</strong></td>
<td>3937 (2142.0)</td>
<td>3212 (2453.0)</td>
<td>9381 (8275.0)</td>
<td>4032 (1652.0)</td>
<td>137795 (8814.0)</td>
<td>7358 (2726.0)</td>
<td>18628 (10166.0)</td>
</tr>
</tbody>
</table>

*All patients in cohort 8 were HBeAg positive and NA-experienced at baseline. ‡All patients in cohort 9 were HBeAg positive and NA-naive at baseline. HBeAg = hepatitis B e-antigen; HBsAg = hepatitis B surface antigen; IU = international units; NA = nucleos(t)ide analogue; Q4w = every 4 weeks; SEM = standard error of the mean.
AROHBV1001: Effect of JNJ-3989 and NA treatment on HBsAg

Based on cohort 2b–5b, 8 and 9 data. Bold lines with circles represents mean values. Thin lines represent individual patients. Black dotted line represents change of -1 log_{10} IU/mL from Day 0 value.

HBsAg = hepatitis B surface antigen; NA, nucleos(t)ide analogue; SE, standard error

In total, **15/38 (39%) patients** who were responders throughout the study were sustained responders at Day 392

Off-treatment sustained HBsAg responders (n=15)

Off-treatment non-sustained HBsAg responders (n=23)

HBsAg non-responder (n=1)
AROHVB1001: Effect of JNJ-3989 and NA treatment on HBV RNA levels

Based on cohort 2b–5b, 8 and 9 data. Only patients with HBV RNA levels >1 log_{10} IU/mL above LLOQ were included in this analysis. Bold lines with circles represents mean values. Thin lines represent individual patients. Black dotted line represents change of –1 log_{10} IU/mL from Day 0.

HBV = hepatitis B virus; IU = international units; NA = nucleos(t)ide analogue; SE, standard error

Reductions in HBV RNA levels were generally more pronounced in HBsAg sustained responders than non-responders through to Day 392
AROHBV1001: Effect of JNJ-3989 and NA treatment on HBeAg and HBcrAg

Of the patients with quantifiable HBeAg and HBcrAg levels on Day 0, greater reductions in HBeAg and HBcrAg were seen in HBsAg sustained responders versus non-sustained responders.

Based on cohort 2b–5b, 8 and 9 data. Only patients with HBeAg and HBcrAg levels >1log_{10} IU/mL above LLOQ were included in these analyses. Bold lines with circles represent mean values. Thin lines represent individual patients. Black dotted line represents change of –1 log_{10} IU/mL from Day 0.

*patients with HBeAg seroclearance events. HBcrAg = hepatitis B core-related antigen; HBeAg = hepatitis B e-antigen; NA = nucleos(t)ide analogue; PEIU = Paul Ehrlich international units; U, units; SE standard error
AROHBV1001: Drug-related adverse events occurring through Day 336 after last JNJ-3989 dose

<table>
<thead>
<tr>
<th>Drug-related AE in ≥ 2 patients, n (%)</th>
<th>Cohort 2b N=8 100 mg</th>
<th>Cohort 3b N=8 200 mg</th>
<th>Cohort 4b N=8 300 mg</th>
<th>Cohort 5b N=8 400 mg</th>
<th>Cohort 8† N=4 300 mg</th>
<th>Cohort 9‡ N=4 300 mg</th>
<th>All arms N=40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site discoloration, injection site erythema, injection site bruising</td>
<td>0</td>
<td>0</td>
<td>2 mild (25.0)</td>
<td>2 mild (25.0)</td>
<td>2 mild (50.0)</td>
<td>1 mild (25.0)</td>
<td>7 (17.5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 mild (12.5)</td>
<td>0</td>
<td>0</td>
<td>1 mild (12.5)</td>
<td>0</td>
<td>0</td>
<td>2 (5.0)</td>
</tr>
<tr>
<td>Blood creatine kinase elevated</td>
<td>0</td>
<td>0</td>
<td>1 severe (12.5)</td>
<td>0</td>
<td>1 mild (25.0)</td>
<td>0</td>
<td>2 (5.0)</td>
</tr>
<tr>
<td>Blood bilirubin increased, hyperbilirubinemia</td>
<td>0</td>
<td>1 mild (12.5)</td>
<td>1 mild (12.5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (5.0)</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>0</td>
<td>0</td>
<td>1 mild (12.5)</td>
<td>1 mild (12.5)</td>
<td>0</td>
<td>0</td>
<td>2 (5.0)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>1 mild (12.5)</td>
<td>0</td>
<td>1 mild (12.5)</td>
<td>0</td>
<td>0</td>
<td>2 (5.0)</td>
</tr>
</tbody>
</table>

There were no new AEs drug-related reported from Day 85 through Day 392, 48 weeks after the last JNJ-3989 dose. A single AE of possibly related abnormal liver function test (peak ALT 136 U/L) was reported. There were no additional grade 3 or 4 laboratory abnormalities during the treatment phase.

Three non-drug related SAEs were reported: anxiety with depression in a single patient and menorrhagia, each requiring hospitalisation. All SAEs were resolved.

*All patients in cohort 8 were HBeAg positive and NA-experienced at baseline. †All patients in cohort 9 were HBeAg positive and NA-naïve at baseline. AE = adverse event; SAE, serious adverse event
AROHBV1001: Conclusions

For the first time in patients with CHB, siRNA therapy resulted in sustained, off-treatment $\geq 1\log_{10}$ IU/mL reductions in HBsAg through to 48 weeks after the last JNJ-3989 dose.

- Reductions in HBV RNA, HBeAg, HBcrAg were more pronounced in HBsAg sustained responders than non-responders.
- Three injections of JNJ-3989 (Q4w) were well tolerated at doses up to 400 mg and appeared to have a good long-term safety profile.

- These results support the evaluation of longer durations of treatment with JNJ-3989 + NA, with the objective of providing functional cure in patients with CHB.
  - 48-week phase 2b studies of JNJ-3989 + NA, with or without JNJ-6379 (CAM-N) are underway to assess functional cure rates in patients with CHB.

CAM-N = capsid assembly modulator class N (inducing normal empty capsid formation); CHB = chronic hepatitis B; HBcrAg = hepatitis B core-related antigen; HBeAg = hepatitis B e-antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; NA = nucleos(t)ide analogue; Q4w = every 4 weeks.
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