Short term RNA interference (RNAi) therapy in chronic hepatitis B (CHB) using JNJ-3989 brings majority of patients to HBsAg <100 IU/ml threshold

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Simplified theory of an HBV RNAi therapeutic

1. “HBsAg Theory”
   - Reducing HBsAg enables host immune system de-repression and long term control of virus

2. Destabilizing Viral Function
   - Silencing all antigens and reducing pgRNA could destabilize normal viral function
   - Enable host immune system de-repression and long term control of virus

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JNJ-3989 (ARO-HBV): Key design elements

- Addresses full HBV transcriptome
  - Two hepatocyte targeted RNAi molecules
  - Works for cccDNA and integrated-derived transcripts
  - Previously shown to reduce HBV DNA, HBV RNA, HBsAg, HBeAg, & HBcrAg \(^1,2\)
- Multiple triggers to avoid resistance development and increase coverage of viral genomes

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1 Gane et al. 2018 Hepatology 68:6 LB-25  
2 Gane et al. 2019 APASL Abstract 638
Study design AROHBV1001

- AROHBV1001 is a double blind, single dose escalating study in healthy volunteers and open label, multi-dose escalating study in patients with CHB

- The ongoing phase 2 portion of AROHBV1001 assesses 3 subcutaneous doses of JNJ-3989 administered weekly to monthly in HBeAg positive or negative CHB patients concomitantly with ETV or TDF

- This interim analysis reports reductions in HBsAg levels and safety in initial CHB cohorts
  - Reductions in HBsAg below certain thresholds in patients that had 24 weeks or more of HBsAg assay results (n=40)
  - Effect of more frequent dosing (every other week or weekly) vs. monthly dosing (n=40)
  - Safety and tolerability (includes all CHB patients in cohorts 2b-11, n=56)
### Baseline characteristics of CHB patients with ≥ 24 weeks of results available

<table>
<thead>
<tr>
<th>Cohort</th>
<th>2b</th>
<th>3b</th>
<th>4b</th>
<th>5b</th>
<th>8</th>
<th>9</th>
<th>6</th>
<th>7</th>
<th>10</th>
<th>11</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg)</td>
<td>100</td>
<td>200</td>
<td>300</td>
<td>400</td>
<td>300</td>
<td>300</td>
<td>100</td>
<td>100</td>
<td>200</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>Dosing frequency</td>
<td>Q4w x 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Q2w x 3</td>
<td></td>
<td>Q1w x 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number CHB in cohort</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>40</td>
</tr>
<tr>
<td>HBeAg pos / HBeAg neg</td>
<td>1/3</td>
<td>0/4</td>
<td>1/3</td>
<td>1/3</td>
<td>4/0</td>
<td>4/0</td>
<td>0/4</td>
<td>1/3</td>
<td>1/3</td>
<td>0/4</td>
<td>13/27</td>
</tr>
<tr>
<td>NUC experienced</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>Race (Asian/Pacific Islander/Other)</td>
<td>4/0/0</td>
<td>4/0/0</td>
<td>4/0/0</td>
<td>4/0/0</td>
<td>3/1/0</td>
<td>4/0/0</td>
<td>3/1/0</td>
<td>1/3/0</td>
<td>4/0/0</td>
<td>3/0/1</td>
<td>34/5/1</td>
</tr>
<tr>
<td>Genotype (B/C/D/Unknown)</td>
<td>2/0/0/2</td>
<td>0/0/0/4</td>
<td>0/0/0/4</td>
<td>0/0/0/4</td>
<td>2/2/0/0</td>
<td>0/0/0/4</td>
<td>0/0/0/4</td>
<td>2/1/0/1</td>
<td>1/0/1/2</td>
<td>7/3/1/29</td>
<td>16,435 (10,120)</td>
</tr>
<tr>
<td>Mean baseline HBsAg (SEM) [IU/mL]</td>
<td>2,808 (2,540)</td>
<td>659 (310)</td>
<td>732 (295)</td>
<td>1,128 (625)</td>
<td>137,795 (88,141)</td>
<td>7,358 (2,726)</td>
<td>1,115 (795)</td>
<td>1,573 (429)</td>
<td>7,613 (7,068)</td>
<td>3,564 (1,843)</td>
<td></td>
</tr>
</tbody>
</table>

- Monthly dosing
- Mostly HBeAg negative
- Mostly NUC experienced
- Monthly dosing
- HBeAg positive
- Nuc experienced or naïve
- Shorter dosing intervals
- Every other week or weekly
- Mostly HBeAg negative
- Mostly NUC experienced

• Mean Baseline HBsAg

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Safety and Tolerability

• 168 total doses administered to 56 CHB patients (cohorts 2b through 11)

• No drug related SAEs reported
  • Unrelated SAE of menorrhagia
  • Unrelated SAE of anxiety/depression

• All patients received all 3 scheduled doses; No dropouts

• No dose related pattern of adverse changes in laboratory values (e.g. ALT, AST, total bilirubin, creatinine)

• 17 total AEs at injection site (10% injections) reported (e.g. erythema, tenderness, bruising), all mild

Data as of 3/8/2019
Adverse Events mostly mild without dose related pattern

### AEs reported in ≥ 2 CHB patients

<table>
<thead>
<tr>
<th>AE Reported Terms</th>
<th>Cohort 2b Open Label n = 8</th>
<th>Cohort 3b Open Label n = 8</th>
<th>Cohort 4b Open Label n = 8</th>
<th>Cohort 5b Open Label n = 8</th>
<th>Cohort 6 Open Label n = 4</th>
<th>Cohort 7 Open Label n = 4</th>
<th>Cohort 8 Open Label n = 4</th>
<th>Cohort 9 Open Label n = 4</th>
<th>Cohort 10 Open Label n = 4</th>
<th>Cohort 11 Open Label n = 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sore Throat, URTI</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>Injection Site Erythema/Redness, Very mild Erythema, Injection Site Rash, Injection Site Hematoma/Brusing, IS Pain</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>12</td>
<td></td>
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<tr>
<td>Headache</td>
<td>2</td>
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<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>6</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Raised or Elevation in Creatine Kinase</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td></td>
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</tr>
<tr>
<td>Lower Back Ache/Pain</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
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<td>4</td>
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<tr>
<td>Acne, Facial Acne</td>
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<tr>
<td>Bronchitis, Viral Bronchitis</td>
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<tr>
<td>Diarrhea, Intermittent Diarrhea</td>
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<tr>
<td>Pain in abdomen, Intermittent Right Upper Quadrant Pain</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Insect Bites ankles, Flea Bites neck</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Dizzy, Light headedness</td>
<td>1</td>
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<tr>
<td>Hot flush</td>
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<tr>
<td>Presence of calcium oxalate crystals in urine</td>
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<tr>
<td>Dry cough</td>
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<tr>
<td>Elevated Blood Pressure, Worsening Hypertension</td>
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<td>2</td>
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<tr>
<td><strong>Other all single occurring terms:</strong></td>
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<td><strong>64 Total</strong></td>
</tr>
</tbody>
</table>

(as of 3/8/2019)
All patients receiving 3 monthly doses have achieved > 1 log reduction in HBsAg

- NADIR in HBsAg is reached around 4 months post start of therapy
- Duration of pharmacologic effect persisted for > 4 months after last dose

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(as of 2/28/2019)
Shorter dosing intervals do not accelerate HBsAg decline

**Monthly dosing intervals**

Mean HBsAg reductions from baseline

- 100 mg (C2b)
- 200 mg (C3b)
- 300 mg (C4b)
- 400 mg (C5b)
- 300 mg E+, NUC naive (C8)
- 300 mg E+, NUC exp (C9)

**Shorter dosing intervals**

Mean HBsAg reductions from baseline

- 100 mg q2w x 3 (C6)
- 100 mg q1w x 3 (C7)
- 200 mg q1w x 3 (C10)
- 300 mg q1w x 3 (C11)

• Similar NADIR to monthly doses

• All HBsAg patients responded regardless of HBeAg status or previous NUC experience
  
  • Mean NADIR HBeAg negative (n=27): -1.82 Log10 IU/mL ± 0.09
  
  • Mean NADIR HBeAg positive (n=13): -2.28 Log10 IU/mL ± 0.21
  
  • 100% (40 of 40) had ≥ 1.0 Log10 IU/mL HBsAg reduction

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Topic of discussion: Is on-treatment HBsAg level important for HBsAg seroclearance?

HBsAg levels of <100 IU/mL and HBsAg reduction of > 1 Log10 IU/mL have been associated with increased probability of HBsAg seroclearance after cessation of NUCs in HBeAg negative patients.¹

¹ Jeng et al. 2018 Hepatology 68:425-434
Distribution of quantitative HBsAg pre and post 3 doses of JNJ-3989

Baseline
Median: 1263 IU/mL
Min: 7.0 IU/mL
Max: 392,800 IU/mL

NADIR
Median: 14.5 IU/mL
Min: 0.05 IU/mL
Max: 8950 IU/mL

Red Points: HBeAg positive patients
Black Points: HBeAg negative patients

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Most patients (88%) achieve HBsAg ≤ 100 IU/mL after 3 doses of JNJ-3989

<table>
<thead>
<tr>
<th>Baseline HBsAg</th>
<th>Threshold</th>
<th>N</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;1000 IU/mL</td>
<td>21 of 40</td>
<td>51%</td>
</tr>
<tr>
<td></td>
<td>&gt;100 IU/mL</td>
<td>37 of 40</td>
<td>93%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NADIR HBsAg</th>
<th>Threshold</th>
<th>N</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤100 IU/mL</td>
<td>35 of 40</td>
<td>88%</td>
</tr>
<tr>
<td></td>
<td>≤10 IU/mL</td>
<td>17 of 40</td>
<td>43%</td>
</tr>
<tr>
<td></td>
<td>≤1 IU/mL</td>
<td>5 of 40</td>
<td>13%</td>
</tr>
</tbody>
</table>

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HBeAg positive patient with post-treatment antigen elevations followed by host response

- Male patient on ETV for 11 years and continued ETV throughout study
  - HBV DNA BLOQ throughout the study
- Patient received 400mg JNJ-3989 q4w x 3
- 3.0 Log10 HBsAg reduction from baseline with recovery beginning 2 mos after last dose
- 2.0 Log10 HBV RNA reduction to LLOQ
- 1.0 Log10 HBcAg and 0.8 Log10 HBeAg reduction
- HBsAg decrease 6 months after last dose following attempted viral return consistent with increased host control of HBV virus (0.054 IU/mL) at 8 months

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Summary and Conclusions

• JNJ-3989 (formerly ARO-HBV) administered subcutaneously was well tolerated at doses up to 400 mg

• RNAi with JNJ-3989 reduced all measurable viral products, including HBsAg in HBeAg positive or HBeAg negative patients

• JNJ-3989 rapidly reduces HBsAg to thresholds possibly associated with improved chances of HBsAg seroclearance in many patients, even after only 3 doses
  • 88% of patients achieved HBsAg <100 IU/mL
  • 100% of patients achieved ≥ 1.0 Log10 IU/mL HBsAg reduction

JNJ-3989 exhibits characteristics desirable for a cornerstone therapy in finite regimens aimed at HBsAg seroclearance in patients with chronic hepatitis B infection
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