RNA Interference (RNAi) in Chronic Hepatitis B (CHB): Data from Phase 2 Study with JNJ-3989

**INTRODUCTION**

RNAi with JNJ-3989 (formerly ARO-HBV) shows promise in CHB by silencing HBV RNA from cccDNA and integrated HBV DNA, reducing all viral products, including HBsAg.

**OBJECTIVES**

AROHBV1001 is a double blind, single dose escalating study in healthy volunteers (NHV) and open label, multi-dose escalating study in patients with chronic HBV infection (CHB, NCT03365947). Objectives are:

- Safety and tolerability of JNJ-3989 in NHV and CHB.
- Single dose pharmacokinetics of JNJ-3989 in NHV.
- Reduction of HBsAg from day 1 to post-dose nadir in CHB.
- Multiple additional exploratory objectives.

**RESULTS**

**Safety and Tolerability**

- No dose related pattern of adverse changes in safety and tolerability of JNJ-3989 were observed.
- Safety and tolerability of JNJ-3989 in NHV from Day 1 to the study and NUC naïve CHB patients started daily NUC on day 1.
- Viral DNA (LLOQ 20 IU/mL), viral RNA (LLOQ 1.65 Log U/mL) and antigens (qHBsAg (LLOQ 0.05 IU/mL), qHBeAg (LLOQ 0.01 PEIU/mL), qHBcAg (LLOQ 1 kU/mL)) were measured periodically.

**Mean Log HBsAg change from day 1**

- Individual changes in HBV DNA, HBeAg, HBcrAg and HBV RNA

**Baseline Demographics in CHB Patients**

<table>
<thead>
<tr>
<th>Cohort Code</th>
<th>Cohort 2b 100 mg</th>
<th>Cohort 3b 200 mg</th>
<th>Cohort 4b 300 mg</th>
<th>Cohort 5b 400 mg</th>
<th>Cohort 8 300 mg</th>
<th>Cohort 9 300 mg</th>
<th>Total</th>
<th>NADIR Log HBsAg reduction by patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number CHB in cohort</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>24</td>
<td>All patients received 3 monthly doses of JNJ-3989 and had 16 weeks of HBsAg data</td>
</tr>
<tr>
<td>HBsAg pos / HBsAg 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>11 / 13</td>
<td>Range of HBsAg NADIR: -1.3 to -3.8 Log10</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>18</td>
<td>Mean Log HBsAg NADIR: -2.0 Log10</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>3 / 1 / 0</td>
<td>4 / 0 / 0</td>
<td>23 / 1 / 0</td>
<td><strong>Mean HBsAg positive (n=11): -2.5 Log10</strong></td>
<td></td>
</tr>
<tr>
<td>Gender (M/F/Unknown)</td>
<td>2 / 0 / 2</td>
<td>0 / 0 / 2</td>
<td>0 / 0 / 2</td>
<td>8 / 0 / 4</td>
<td>2 / 2 / 0</td>
<td>2 / 2 / 0</td>
<td>9 / 10 / 4</td>
<td><strong>Mean HBsAg negative (n=13): -1.8 Log10</strong></td>
</tr>
<tr>
<td>Mean baseline HBsAg (SEM) (IU/mL)</td>
<td>(2540) 659</td>
<td>732</td>
<td>1,128</td>
<td>137,795</td>
<td>7,358</td>
<td>26,159</td>
<td><strong>Mean HBeAg positive (n=11): -2.5 Log10</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Mean HBeAg negative (n=13): -1.8 Log10 | **Individual changes in HBV DNA, HBeAg, HBcrAg and HBV RNA**

- Colors below indicate cohorts as follows: Red (C2b), orange (C3b), purple (C4b), green (C5b), black (C8), brown (C9), HBsAg (solid line), HBsAg- (dashed line)

**CONCLUSIONS**

- JNJ-3989 administered subcutaneously appears to be well tolerated at monthly doses up to 400 mg.
- Monthly RNAi effectively reduced all measurable viral products. Strong HBsAg responses were observed in all HBV patients.
- HBsAg positive CHB patients showed a moderately larger HBsAg reduction than HBsAg negative patients.
- No dose related pattern of adverse changes in laboratory values (e.g. ALT, AST, total bilirubin, creatinine).
- AE at injection site (rash, erythema, bruising/hematoma, tenderness) reported with approximately 12% of injections, all of which were mild.
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