siRNA Based Therapy for Chronic Hepatitis B Treatment

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On behalf of the JNJ-3989 / JNJ-6379 Compound Development Team
Introduction

• Role of HBsAg reduction in...
  • Functional cure in the natural course of the disease
  • Functional cure with long term NA treatment / the Stop Nuc concept
  • Functional cure with finite treatment regimens

• Concept of HBsAg reduction as precondition of an improved host immune control
  • HBsAg is well described as immune suppressant
  • what is the role of HBsAg from integrated DNA?

• JNJ-3989 (AROHBV) in combination with NA has demonstrated potent reduction of HBsAg and all HBV transcripts: HBeAg, HBcrAg, RNA, and DNA
JNJ-3989 (AROHBV): 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 development of resistance and increase coverage of viral genomes

\(^1\) Gane et al. 2018 Hepatology 68:6 LB-25 \(^2\) Gane et al. 2019 APASL Abstract 638
## 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>Q2w x 3</td>
<td>Q1w x 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></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>0/0/0/4</td>
<td>0/0/0/4</td>
<td>2/1/0/1</td>
<td>1/0/1/2</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>16,435 (10,120)</td>
</tr>
</tbody>
</table>

- Monthly dosing
- 13/16 HBeAg negative
- 14/16 NA experienced
- Monthly dosing
- HBeAg positive
- 4/8 NA exp.
- Shorter dosing intervals: Every other week or weekly
- 14/16 HBeAg negative
- 12/16 NA experienced

Yuen MF et al. ILC 12 April 2019, PS-080
All patients receiving 3 monthly doses of JNJ-3989 have achieved > 1 log reduction in HBsAg

- NADIR in HBsAg is reached around 2 months after last injection
- Duration of pharmacologic effect persisted for > 4 months after last dose

Yuen MF et al. ILC 12 April 2019, PS-080
Shorter dosing intervals of JNJ-3989 do not accelerate HBsAg decline

- All patients experienced HBsAg decline regardless of HBeAg status or previous NUC experience
  - Mean (SEM) NADIR HBeAg negative (n=27): \(-1.82 \log_{10} \text{IU/mL} \pm 0.09\)
  - Mean (SEM) NADIR HBeAg positive (n=13): \(-2.28 \log_{10} \text{IU/mL} \pm 0.21\)
  - 100% (40 of 40) had \(\geq 1.0 \log_{10} \text{IU/mL}\) HBsAg reduction

Yuen MF et al. ILC 12 April 2019, PS-080
Distribution of HBsAg at Baseline and at Nadir following 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

Yuen MF et al. ILC 12 April 2019, PS-080
Most patients (88%) achieve HBsAg ≤ 100 IU/mL after 3 doses of JNJ-3989

<table>
<thead>
<tr>
<th>Baseline HBsAg</th>
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</thead>
<tbody>
<tr>
<td>Threshold</td>
<td>N</td>
<td>Percent</td>
</tr>
<tr>
<td>&gt;1000 IU/mL</td>
<td>21 of 40</td>
<td>51%</td>
</tr>
<tr>
<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></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold</td>
<td>N</td>
<td>Percent</td>
</tr>
<tr>
<td>≤100 IU/mL</td>
<td>35 of 40</td>
<td>88%</td>
</tr>
<tr>
<td>≤10 IU/mL</td>
<td>17 of 40</td>
<td>43%</td>
</tr>
<tr>
<td>≤1 IU/mL</td>
<td>5 of 40</td>
<td>13%</td>
</tr>
</tbody>
</table>

Yuen MF et al. ILC 12 April 2019, PS-080
Two JNJ-3989 posters presented at AASLD 2019

- Dose selection of JNJ-3989 - additional cohorts with lower doses:

  Dose Response with the RNA Interference Therapy JNJ-3989 Combined with Nucleos(t)ide Analogue Treatment in Expanded Cohorts of Patients with Chronic Hepatitis B

  Gane, E. et al. Poster 0696
  Presented 8 Nov. 2019 at The Liver Meeting

  Combination of JNJ-3989 with JNJ-6379 (CAM-N) - 12 week combination cohort:

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

  Yuen, MF. et al. LB-Poster 4
  Presented 11 Nov. 2019 at The Liver Meeting
JNJ-3989 – next steps

Longer treatment and combination - 48 weeks in the ongoing ph2b study REEF-1:

Clinical Protocol

A Phase 2b, Multicenter, Double-blind, Active-controlled, Randomized Study to Investigate the Efficacy and Safety of Different Combination Regimens Including JNJ-73763989 and/or JNJ-56136379 for the Treatment of Chronic Hepatitis B Virus Infection

The REEF-1 Study

Protocol 73763989HPB2001; Phase 2b

ClinTrials.gov: NCT03982186
Combination Treatment

Inhibition at multiple steps & removing immune inhibitory viral antigens

JNJ-6379 “Primary” mechanism (“empty capsid” formation)

JNJ-6379 “Secondary” mechanism (de novo cccDNA formation)

Nucleos(t)ide Analogues

Dane particle (infectious DNA containing)

RNA containing particle (pgRNA, spliced RNA)

JNJ-3989 (degrades all viral RNAs)

Subviral particles (HBsAg)

Antigen reduction might restore immune response

HBV (HBsAg) antigen reduction: Potential restoration of immune response

AND

Complete inhibition of viral replication: Intensified viral suppression/cccDNA depletion
Capsid Assembly Modulators (CAMs)

Also known as: Core protein allostERIC modulator (CpAM), core (protein) inhibitor or capsid assembly effector/inhibitor

Proposal for a new nomenclature

Class N - Normal geometry & size
Class A - Abnormal geometry & size
Summary and Conclusions

- Three subcutaneous injections of JNJ-3989 were 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.
- In majority of patients 3 doses of JNJ-3989 rapidly reduces HBsAg to thresholds possibly associated with improved chances of HBsAg seroclearance:
  - 88% of patients achieved HBsAg <100 IU/mL
  - 100% of patients achieved ≥ 1.0 Log10 IU/mL HBsAg reduction
- HBsAg responses to JNJ-3989 in different populations are consistent with its ability to silence HBV RNA from cccDNA and host-integrated viral DNA.
- Overall JNJ-3989 demonstrated anti-HBV characteristics desirable for an RNAi therapy.
- Studies of longer duration are underway, including triple combinations aimed at functional cure in CHB patients.