New Directions Towards a Functional Cure for Chronic Hepatitis B

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A Large Unmet Medical Need in Hepatitis B

- Most common chronic viral infection in the world with ~257 MM chronic carriers
- US 1.2M, EU 14M (G5 2.8M), Japan 1M, China >100M
  - HBV prevalence >> HCV prevalence
- 10th leading cause of death WW (789K deaths/year)
- Despite available therapies, between 1990-2010 mortality associated to liver cancer or cirrhosis increased by 62% and 29%, respectively
Goals of a Finite Treatment Regimen

Durable Post-Treatment Response

Functional Cure
- HBsAg seroclearance with or without anti-HBs antibodies (HBV DNA undetectable, HBeAg seroconversion, normal ALT)

Partial Cure
- Undetectable HBV DNA, HBeAg seroconversion, normal ALT and low HBsAg (<1,000 IU/mL)
Standard of Care Has a Low Cure Rate

Rate of New Infections >> Rate of Clearance of Infected Hepatocytes

Adapted from Zoulim, EASL 2016
Janssen Hepatitis B Strategy

Build a Portfolio of Diverse Mechanisms of Action Agents

**Intensify Antiviral Treatment**

- Reduce cccDNA Formation & Virus Production
- Silence/Eliminate cccDNA

**Boost Immune Response**

- Boost Effective HBV Specific T-cell Responses
- Boost Innate Immunity

Launch successive waves of combination treatment to increase rate of functional cure
Wide Breadth of HBV Targets and Approaches

- Oligonucleotides
- Nucleotides
- Gene editing approaches
- Capsids, Class I
- Capsids, Class II
- Entry inhibitors
- Therapeutic vaccine
- cccDNA inhibitors
- Checkpoint Inhibitors
- HBx
- sAg secretion inhibitors
- TLR agonists
- RIG-I agonist
- Epigenetic modulators

Multiple Approaches in Pursuit Across the Global HBV Community
Combinations are Key

Novel MOA’s with SOC may block replication and cccDNA replenishment.

Rate of Clearance of Infected Hepatocytes >> Rate of New Infections

Adapted from Zoulim, EASL 2016
Capsid Assembly Modulators (CAMs)

Backbone of an Effective anti-HBV Strategy

**CAMs Influence Assembly Kinetics**

*Induce two types of empty capsids in vitro*

- Class I - Normal geometry & size
- Class II - Abnormal geometry & size

**CAM “Primary” Mechanism**

<table>
<thead>
<tr>
<th></th>
<th>AL-3778</th>
<th>JNJ-379</th>
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</thead>
<tbody>
<tr>
<td>PHH HBV DNA</td>
<td>1400/&gt;5000</td>
<td>118/347</td>
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**CAM “Secondary” Mechanism**

<table>
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<tbody>
<tr>
<td>PHH intracellular HBV RNA</td>
<td>&gt;5000/&gt;5000</td>
<td>604/2698</td>
</tr>
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- **Nucleos(t)ide analog**
  - NA

- **Dane particle**
  - (Infectious DNA containing)

- **RNA containing particle**
  - (pgRNA, spliced RNA)

- **Subviral particles**
  - (HBsAg)
CAMs Inhibit Production of HBV DNA and RNA Containing Particles

Primary Mechanism - Late Step in Viral Lifecycle

Nucleos(t)ides analogs do not inhibit the production of RNA containing particles
CAMs Inhibit cccDNA Formation in PHH

Secondary Mechanism - Early Step in Viral Lifecycle

Dose-dependent inhibition of cccDNA formation in presence of JNJ-379 when added together with viral inoculum

No inhibition of cccDNA formation observed with nucleos(t)ide analogs

Berke, JM et al. AASLD 2016
A World of Capsid Assembly Modulators
Advancing in Clinical Development

- **Arbutus**
  - AB-423 Phase 1a completed
  - AB-506 Preclinical

- **Assembly**
  - ABI-H0731 Phase 1b
  - ABI-H2158 Preclinical

- **Chromix**
  - Preclinical

- **Enanta**
  - Preclinical

- **HEC Pharma**
  - GLS4JHS Phase 2 (Class 2 CAM)

- **Janssen**
  - AL-3778 Phase 1b completed, high dose, delivered BID
  - **JNJ-379 Phase 1b in progress, low dose, QD schedule**
  - JNJ-440 Preclinical, anticipate Q12018 first-in-human

- **Roche**
  - RG7902 Phase 1

- **Qilu**
  - QL-007 Phase 1
  - QL-0A6A Preclinical
JNJ-379: Ongoing Phase 1b Study

Treatment-Naïve HBeAg (+/-) CHB Patients

- **Session 8** (100 mg D1, 25 mg ≥D2, QD)
  - Completed

- **Session 9** (75 mg, QD)
  - Completed

- **Session 11** APAC (75 mg, QD)
  - Enrollment ongoing
  - In Asian patients

- **Session 10** (150 mg, QD)
  - Fully enrolled

- **Optional Session A** (>200 mg, QD)
  - Pending results from Session 10

n=12
(9 active/3 placebo)

28 days treatment
(8 weeks follow-up)

Zoulim et al., LB-15, AASLD 2017
JNJ-379: Phase 1b HBV DNA Viral Kinetics

Demonstration of Excellent Potency in Phase 1b

Mean (± SD) changes from baseline in HBV DNA (log_{10} IU/mL) over time during the 4-week treatment for Sessions 8 and 9 of study 56136379HPB1001 Part II

Dose
- Pooled placebo (N=8)
- JNJ-379 25mg QD (N=8) *
- JNJ-379 75mg QD (N=8)

* and *** refer respectively to 1 and 3 patients with HBV DNA <LLOQ of the HBV DNA assay

#100mg loading dose on day 1, 25mg QD thereafter

Significant reductions also observed in HBV RNA

Zoulim et. al., LB-15, AASLD 2017
JNJ-379 Monotherapy Clinical Summary
25 and 75 mg QD Dosing Cohorts

• Generally safe and well tolerated
  – Safety profile was similar between doses and placebo
  – There were no SAEs or AEs leading to discontinuation or deaths
  – All AEs and laboratory abnormalities resolved over time

• Antiviral activity
  – Significant decrease in HBV DNA
  – Substantial reduction in HBV RNA levels

• No relevant changes in HBsAg and HBeAg levels
  – Based on MOA, greater than 4 weeks of treatment will likely be needed to see antigen decreases

• Based on the promising data obtained to date, JNJ-379 Phase 2 combination studies are planned for early 2018
Janssen in Hepatitis B

New Directions Towards a Functional Cure

• Janssen has a strong commitment to the development of novel, finite combination treatment regimens with the potential to provide a functional cure for HBV infected patients

• Our current pipeline contains multiple assets in clinical development and we are continuing to advance additional preclinical assets
  – JNJ-379 Phase 2 combination studies planned for early 2018
  – Advancing additional approaches with other MOAs

• We are pursuing a strategy designed to demonstrate target engagement with our assets in Phase 1 and rapidly advance them into Phase 2 combination studies that can advance our ability to develop a more effective treatment regimen for HBV infected patients