HBV Novel Therapies

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CONFLICT OF INTEREST

I have financial relationships to disclose within the past 12 months relevant to my presentation:

Consultant and Speaker Bureau
Abbvie, BMS, Gilead, Merck/MSD, Roche
Achievements and ongoing challenges Hepatitis B

- Suppression of HBV replication
- Decrease hepatic inflammation and fibrosis
- Prevent/reduce complications of cirrhosis, reduction of HCCs
- Very good safety (10yrs)

Hepatitis B treatment NA or PEG-IFN

No HBV cure

References:
Definition of HBV cure:
what do we want to achieve?

Serum

Therapy

HBsAg

HBVDNA

cccDNA

Liver

Time

+/- Anti-HBsAb

Partial Cure

Functional Cure

Complete Cure

Sterilizing Cure

Lok et al, Hepatitis B Cure: From Discovery to Regulatory Approval; Hepatology / J Hepatol joint publication; 2017
Pathogenesis of HBV-related Liver Disease

HBV is not a cytopathic virus
Liver injury is immune mediated

Host immune response vs. HBV replication
HBV Life Cycle and Antiviral Targets

Lok A et al. J Hepatol 2017
HBV Life Cycle and Antiviral Targets

Lok A et al. J Hepatol 2017
Model for HBV entry in hepatocytes and development of entry inhibitors

Entry inhibitors
- Myrcludex (pre-S1 peptide)
  - Blank et al, J Hepatol 2016
  - Bogomolov et al, J Hepatol 2016
- Ezetimibe
  - Lucifora, Antiviral Res 2013
- Proanthocyanidin
  - Tsukuda, Hepatology 2017
- Cyclosporin analogues
  - Shimura, J Hepatol 2017

Li et al, elife 2012; Urban et al, Gastroenterology 2014
HBV Serum DNA-levels decline during Myrcludex B treatment

⇒ HBV DNA levels decline significantly during Myrcludex B treatment in all groups.
⇒ Pronounced effects by > 1log in 6/8 patients were observed in the 10 mg dosing group.
⇒ 7/40 showed > 1log HBV reduction in lower dosing groups.

S Urban, AASLD 2014
HBV-HDV entry Inhibitor Myrcludex B for the Treatment of Hepatitis Delta

Primary endpoint: 2 log HDV RNA decline or undetectable at week 24

- Asymptomatic bile acid increase  (based on mode of action of NTCP block)
- ALT-decline in all dose groups
- HBsAg levels remained stable

** p < 0.001

Wedemeyer H et al. ILC 2018; PO
Prolonged RNAi therapy with ARC-520 in treatment-naïve, HBeAg positive and negative patients with chronic HBV results in significant reductions of HBsAg.

**Immediate reductions in HBsAg in HBeAg+ patients:**
Mean max $-2.2 \text{ Log10}$; max observed $-3.1 \text{ Log10}$

**Lower reductions in HBsAg in HBeAg− patients:**
Mean max $-0.7 \text{ Log10}$; max observed $-1.4 \text{ Log10}$

7/8 patients reported at least one mild AE.

Multiple doses of ARC-520 resulted in additional reductions in all markers.

Reduction in HBeAg+ patients greater than in HBeAg− patients.

Difference reflects reductions in HBsAg from cccDNA in HBeAg+ patients vs. integrated DNA in HBeAg−.

Yuen MF, et al. EASL 2017, Amsterdam. #PS-045
HBV Life Cycle and Antiviral Targets

Compounds in evaluation
BAY41-4109
HAP-12
AT-130
NVR3-778
JNJ-379
ABI-H0731
ABI-H0808
GLS4JHS
HAP_R01
SBA_R01
AB-423

Lok A et al. J Hepatol 2017
Interfer HBV capsid assembly by destabilizing core particle assembly or disrupting existing capsides.

Additive effect with the NVR 3-778 + PegIFN combination on HBV DNA reduction (1.97 log IU/mL)
No changes in HBsAg levels
Safety, pharmacokinetics and antiviral activity of novel capsid assembly modulator JNJ-6379 in treatment-naive chronic hepatitis B patients without cirrhosis

"Primary" mechanism
Interference with capsid assembly kinetics, preventing encapsidation of (pg)RNA and blocking HBV replication

"Secondary" mechanism
Inhibition of the de-novo formation of cccDNA, potentially by interfering with the capsid disassembly process

Part 2: Chronic Hepatitis B patients receiving JNJ-6379 or placebo

<table>
<thead>
<tr>
<th>Session 8*</th>
<th>100 mg</th>
<th>75 mg</th>
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<tbody>
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<td>(8 drug; 4 placebo)</td>
<td>QD</td>
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<th>Session 10</th>
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<th>Option A</th>
<th>250 mg</th>
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<tr>
<td>(9 drug; 3 placebo)</td>
<td>QD</td>
</tr>
</tbody>
</table>

Dosing period (days): 0-28

Zoulim F et al. IILC 2018; LBO-004
Safety, pharmacokinetics and antiviral activity of novel capsid assembly modulator JNJ-6379 in treatment-naive chronic hepatitis B patients without cirrhosis

- A Phase IIa study has begun in treatment-naïve and virologically-suppressed CHB patients (NCT03361955)

HBV DNA undetectable: 38% of cases 75 mg and 38% of 150mg
HBV RNA undetectable: 75-80% cases with same doses
No Changes in HBsAg levels

Safety profile was good

Zoulim F et al. IILC 2018; LBO-004
HBV Life Cycle and Antiviral Targets

1. Entry
   - Entry inhibitors
   - Inhibitors of rcDNA to cccDNA conversion
   - Targeting HBx

2. Trafficking
   - Targeting cccDNA degradation - Epigenetic regulation

3. cccDNA formation
   - cccDNA transcription

4. cccDNA transcription
   - HBx regulates factors
   - Host factors
   - mRNAs
     - 0.7 kb
     - 2.4 kb
     - 2.1 kb
     - 3.5 kb
   - pgRNA
   - Pol
   - Core
   - RNA+
   - RNA-
   - DNA-
   - DNA+
   - Nucleocapsid formation
   - pgRNA packaging

5. Translation
   - Interferons

6. Nucleocapsid formation
   - pgRNA packaging
   - Nucleocapsid assembly modulators

7. DNA synthesis
   - Polymerase inhibitors

8. Trafficking
   - Assembly and secretion inhibitors
   - Cyclophilin inhibitors

9. Regulation of host genes by viral proteins

Integration

RC DNA

dsiDNA

Genomic DNA

Integration

Hepatocyte

Lok A et al. J Hepatol 2017
Nucleic acid polymers (NAPs)

Nucleic Acid Polymers (NAP) have entry and post-entry antiviral effects in HBV infection *in vitro*  Noordeen, F et al. AAC. 2013
REP 2139 or REP 2165 in combination with TDF and PEG IFN alpha2a in treatment naïve HBeAg negative

REP 2139-Mg or REP 2165-Mg used in combination with TDF and peg-IFN alpha-2a in treatment-naïve Caucasian patients with chronic HBeAg-negative HBV

Serum HBsAg (A), anti-HBs (B), and HBV DNA (C) dynamics in the REP 401 protocol

Bazinet M, et al. EASL 2017, Amsterdam. #THU-154
Stimulation Of Innate Immunity: Oral Toll-Like Receptor-7 Agonist GS-9620 in Patients with Chronic HBV Infection

Gane et al, Journal of Hepatology, 2015

<table>
<thead>
<tr>
<th>n (%)</th>
<th>HBsAg ≤5000 IU/mL</th>
<th>HBsAg &gt;5000 IU/mL</th>
<th>HBsAg ≤5000 IU/mL</th>
<th>HBsAg &gt;5000 IU/mL</th>
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<tbody>
<tr>
<td>Responders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ISG15 &gt;2-fold change)</td>
<td>28 (60)</td>
<td>8 (35)</td>
<td>10 (83)</td>
<td>8 (62)</td>
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<tr>
<td>Nonresponders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ISG15 ≤2-fold change)</td>
<td>19 (40)</td>
<td>15 (65)</td>
<td>2 (17)</td>
<td>5 (38)</td>
</tr>
</tbody>
</table>
Stimulation of IFN gene agonists: RNA Sensor RIG-I Dually Functions as an Innate Sensor and Direct Antiviral Factor for HBV

- RIG-I senses the HBV genotype A, B, and C for the induction of type III IFNs
- The 5'-ε region of HBV pgRNA is a key element for the RIG-I mediated recognition
- RIG-I counteracts the interaction of HBV P with pgRNA to suppress viral replication
- Type III IFNs are predominantly induced in human hepatocytes during HBV infection
Effects of SB9200 (Inarigivir) therapy on immune responses in patients with chronic hepatitis B

- 20 non-cirrhotic HBV subjects per cohort
- Randomized 4:1 SB 9200 vs placebo

Virological markers (log10 D1 to W12)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Study arm</th>
<th>HBV DNA response</th>
<th>HBV RNA response</th>
<th>HBsAg response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1 and 2, n=38</td>
<td>SB9200 (n=30)</td>
<td>-0.66</td>
<td>-0.8</td>
<td>-0.18</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=8)</td>
<td>0.33</td>
<td>1.0</td>
<td>-0.18</td>
</tr>
<tr>
<td>Difference: SB9200 vs placebo</td>
<td>1 log HBV DNA reduction with SB9200</td>
<td>1.8 log HBV RNA reduction with SB9200</td>
<td>No effect</td>
<td></td>
</tr>
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</table>

Anti-HBs Activity Biomarkers (to W12)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Study arm</th>
<th>CP</th>
<th>‘masked’ anti-HBs</th>
<th>CP AND ‘masked’ anti-HBs</th>
<th>CP AND HBV DNA response (&gt;0.5log)</th>
<th>CP AND HBV RNA response (&gt;0.5log)</th>
<th>‘masked’ anti-HBs AND HBV DNA response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1 and 2, n=38</td>
<td>SB9200 (n=30)</td>
<td>10 (33%)</td>
<td>9 (30%)</td>
<td>3 (30%), n=10</td>
<td>6 (60%), n=10</td>
<td>6 (67%), n=9</td>
<td>9 (100%), n=9</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=8)</td>
<td>1 (12%)</td>
<td>2 (25%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Difference: SB9200 vs placebo</td>
<td>Enhanced with SB9200</td>
<td>No effect</td>
<td>Enhanced with SB9200</td>
<td>Enhanced with SB9200</td>
<td>Enhanced with SB9200</td>
<td>Enhanced with SB9200</td>
<td>Enhanced with SB9200</td>
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Walsh R et al. ILC 2018; PS-160
Blockage of Immunosuppressive Pathway
A phase 1 study evaluating anti-PD-1 treatment with or without GS-4774 in HBeAg-negative chronic hepatitis B patients

- Single dose PD-1 ab ± GS-4774 well tolerated
- Modest reduction of HBsAg in all treatment arms
Therapeutic Vaccine
GS-4774 combined with TDF in patients with chronic hepatitis B

- GS-4774 is a heat-inactivated, yeast-based T-cell vaccine
  - Recombinant protein containing HBV core, surface, and X proteins
- Phase 2 study

11 patients had >0.5 Log$_{10}$ reductions in HBsAg at Week 24 (11 in GS-4774 versus 0 in TDF) and 18 at week 48
No patients achieved HBsAg loss by Week 48
Higher baseline ALT, HLA DRB 15:02, and baseline HBeAg-positive status appear associated with HBsAg decline
An approach to curing HBV might require combination therapy

- **Nucleos(t)ide Analogue**
  - To control viral replication and cccDNA re-amplification

- **Immune activator**
  - To activate or restore HBV targeting immune response

- **HBV antigen inhibition**
  - To inhibit HBV life cycle (entry or cell-spread, capsid, viral proteine secretion)

- **cccDNA inhibitor**
  - To deplete or perturb cccDNA

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**Functional Cure**

**Complete Cure**