Immunotherapeutics in the Treatment of Chronic Hepatitis B

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HBV Forum & ICE-HBV
Therapeutic Vaccines Webinar

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## FOCUS ON LIVER AND METABOLIC DISEASES

<table>
<thead>
<tr>
<th>PRODUCT NAME</th>
<th>PRECLINICAL</th>
<th>PHASE 1</th>
<th>PHASE II</th>
<th>PHASE III</th>
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<tr>
<td>Pemvidutide</td>
<td>NASH</td>
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<td>Readouts on Phase 1 NAFLD and T2DM studies H1 2022</td>
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<td>Pemvidutide</td>
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<td>US IND filing Q4 2021, with trial initiation expected Q1 2022</td>
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<td>HepTcell™</td>
<td>Chronic Hepatitis B</td>
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<td>In Phase 2, data readout expected H2 2022</td>
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</table>
CURRENT HBV THERAPEUTICS DO NOT LEAD TO FUNCTIONAL CURE
Immune activation will be required for significant impact

- Current antivirals prevent disease progression but rarely clear chronic infection
- Newer direct-acting antivirals unlikely to result in immune reactivation alone
- Breaking T cell immune tolerance is key to functional cure
- Immunotherapy is designed to “wake up” dormant T-cells to eliminate infection
GOAL OF IMMUNOTHERAPY IN CHB

Limitations of prior immunotherapeutic approaches

• Many therapeutic vaccines have failed
  - Limited to or biased towards Surface Antigen-specific tolerance barrier
  - Vaccine based on full length antigens - T cell responses bias towards less-conserved domains
  - Weak immunogens/vaccine formulation

• Non-specific immunomodulators (checkpoint inhibitors or TLR agonists) carry risk of off-target effects

IMMUNE RESOLUTION OF CHB
Importance of core and polymerase as target antigens

- T cell responses against HBsAg are strongly affected by duration of exposure
- T cell responses against core and polymerase are dominant in chronic resolved infection
- Baseline T cell responses against core and polymerase are associated with virological control following NA discontinuation

Le Bert Gastroenterology 2020; Garcia-López J Hepatol. 2021, Rivino J Clin Invest. 2018
HEPTCELL IMMUNOTHERAPEUTIC TECHNOLOGY
Long synthetic peptides to promote CD4+ and CD8+ T cell responses

- 30 to 40 a.a. long peptides manufactured by solid phase synthesis
- Contain CD4+ and CD8+ T cell epitopes to overcome HLA restriction
- Fluorocarbon moiety promotes micelle formation and improves immunogenicity
- Robust immunogenicity observed with this peptide platform in young and older adults

HEPTCELL PRECLINICAL ACTIVITY

Broad cross-genotype coverage

HepTcell covers 4 predominant HBV genotypes and all other genotypes by homology

- Most individual peptide components of HepTcell can cross-react with multiple HBV genotypes
- Collectively, the peptides in HepTcell cross-react with genotypes A-D
- Based on HBV homology, HepTcell expected to cross-react with all HBV genotypes
HEPTCELL: PHASE 1 SAFETY AND IMMUNOGENICITY STUDY
Study in subjects chronically infected with HBV

Population (n=60)
- 18-65 yo with eAg negative chronic HBV for ≥ 2 years
- Tenofovir or entecavir for ≥ 2 years
- HBV DNA <50 IU/ml for ≥ 1 year
- No history of cirrhosis and current Fibroscan < 11.5 kPa

Treatment
- 3 double blind dose escalating cohorts enrolled from sites in UK and Korea
- Low (150 µg) or high dose (500 µg) peptides, with or without IC31, c/w IC31 or saline
- 3 IM injections 28 days apart, followed by 6-month observation

Endpoints
- Safety: Routine labs, AEs, injection site assessment
- Cultured IFN-Ɣ Elispot
- qHBsAg
HEPTCELL: PHASE 1 SAFETY AND IMMUNOGENICITY STUDY

Safety

- 1 SAE (infectious colitis between dose 2 and 3) in High + IC31 subject
- No autoimmune events
- No hepatitis flares
- No trends in other AEs
- Injection site reactions were self-limited and mild-moderate except for one patient with severe tenderness in the low + IC31 group

<table>
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<tr>
<th>Investigator Assessed Injection Site Reactions</th>
<th>Low (N=10)</th>
<th>Low + IC31 (N=10)</th>
<th>High (N=10)</th>
<th>High + IC31 (N=11)</th>
<th>IC31 (N=10)</th>
<th>Placebo (N =10)</th>
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<tr>
<td>Any Reaction (%)</td>
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<td>60</td>
<td>50</td>
<td>46</td>
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<tr>
<td>Burning (%)</td>
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<td>20</td>
<td>0</td>
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<td>10</td>
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<td>10</td>
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<td>Swelling (%)</td>
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<tr>
<td>Pain (%)</td>
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<td>30</td>
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<td>Tenderness (%)</td>
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<td>40</td>
<td>50</td>
<td>10</td>
<td>0</td>
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</tbody>
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HEPTCELL: PHASE 1 SAFETY AND IMMUNOGENICITY STUDY
Robust IFN-γ ELISpot Responses that Increase over Time

Change from Baseline, Day 85

Change from Baseline over Successive Administrations

Predominant response to HBV polymerase
HEPTCELL – PHASE 2 CLINICAL TRIAL
Multinational, multicenter trial of HepTcell in inactive chronic hepatitis B (CHB)

- Patients with inactive CHB and HBsAg levels ≤ 100 IU/mL is a subpopulation that might demonstrate a response to immunotherapy
- Virologic response appears to be more likely to occur with a longer duration of immunotherapy
- 80 patients with HBeAg negative inactive CHB and HBsAg ≤ 100 IU/mL randomized 1:1 to HepTcell or placebo administered every 4 weeks for 24 weeks
- Follow-up at 48 weeks after the last dose will assess the safety and durability of response
- Efficacy endpoints
  - **Primary**: proportion of patients with 1.0-log reduction in HBsAg from baseline at Week 24
  - **Secondary**: HBsAg clearance, changes from baseline in HBsAg, HBV DNA, HBcrAg, pg-RNA at Week 24
- Data readout expected in H2 2022
HEPTCELL – KEY COMPONENT OF COMBINATION APPROACH
Combination with novel direct-acting antivirals for improved activity

Chronic HBV Treatment Schedule

DIRECT ACTING ANTIVIRALS
Suppress HBV DNA/viral antigens to reduce virus-induced immune dysregulation
Target ≤100 IU/mL HBsAg

HEPTCELL
Break T cell tolerance and reprogram HBV-specific immune responses

FUNCTIONAL CURE
Loss of HBV DNA and HBsAg
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