Establishment of High Rates of Functional cure of HBeAg negative chronic HBV with REP 2139-Mg Based Combination Therapy

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HBV infection has occurred in ~ 2 billion people:
Typically resolved and well controlled by host immunity.

Chronic HBV infection still persists in up to 350 million people. **WHY?**

**HBsAg likely prevents the establishment of immune control:**

HBsAg is the most abundant circulating viral antigen
Produced independently from virions (as subviral particles)
Largely derived from integrated HBV DNA
**Cannot be targeted by direct acting antivirals**

HBsAg is an important immune checkpoint inhibitor in chronic HBV infection
Inhibits innate and adaptive immunity
Exhausts the B- and T-cell response
HBsAg production in chronic HBV

- Infected hepatocyte
- cccDNA
- Subviral particles
- MVB
- No virus production
- "Integrated" hepatocyte
- Integrated HBV DNA
- "Subviral particles"
- Virions Filaments
- Replenishment of cccDNA
- Infection
NAPs block the release of subviral particles from infected or “integrated” hepatocytes

Circulating HBsAg can now be cleared by existing immune function
Critical elimination of HBsAg mediated immunosuppression
Functional cure can be established
Mechanism of action of REP 2139 in HBV

HBV subviral particle assembly pathway
(from cccDNA or integrated HBV DNA)
(Huovila et al, J Cell Biol 1992; 118: 1305-1320)

REP 2139 enters the ERGIC and inhibits SVP morphogenesis (host target currently unknown)

Intracellular degradation of HBsAg is enhanced

Inhibition of HBsAg secretion (from cccDNA or integrated HBV DNA) is accompanied by declines in intracellular HBsAg

Blanchet et al., Antiviral Res 2019; 164: 87-105
REP 401 Study
Clearing HBsAg to improve immunological recovery

TDF 300mg PO qD
Pegasys 180ug SC qW
NAPs: REP 2139-Mg or REP 2165-Mg 250mg IV qW
REP 2165 = REP 2139 variant with improved tissue clearance

Roehl et al., Mol Ther Nuc Acids 2017; 8: 1-12
REP 401 on-treatment HBsAg response

LLOQ = lower limit of quantification (0.05 IU/mL)
TND = HBsAg not detected (0.00 IU/mL)

REP 2139-Mg = REP 2165-Mg
4/40 non-responders
8/40 HBsAg > 1 log reduction but > 1 IU/mL
28/40 HBsAg < 1 IU/mL
24/40 HBsAg loss (≤ 0.05 IU/mL)

Standard of care only
< 1 log reduction in HBsAg
HBsAg > 1 log reduction but > 1 IU/mL
HBsAg < 1 IU/mL

February 23, 2019
REP 401 on-treatment anti-HBs response

Prot. Imm. = threshold for protective immunity (10 mIU / mL)
absent = no significant anti-HBs present (≤ 0.1 mIU / mL)

Anti-HBs dramatically increased with the introduction of pegIFN
(but only in patients with HBsAg declines to < 1 IU/mL)
REP 401 on-treatment HBV DNA response

TDF-induced HBV DNA declines unaffected during therapy (no negative drug-drug interactions)

LLOQ = lower limit of quantification (10 IU/mL)
TND = HBV DNA PCR product not detected in assay
Clearance of infected / integrated hepatocytes

Transaminase flares occur in 38/40 patients

Appear to be immune-mediated:

- Timing correlated with antiviral response
- Strength correlated with HBsAg response
- All self-resolving either during therapy or follow-up
- Liver function is continually normal throughout (bilirubin, albumin, INR)
- Otherwise asymptomatic

Correlated with the establishment functional control
REP 401
Antiviral performance during therapy and follow-up

34/40 patients have completed treatment and ≥ 24 weeks of treatment-free follow-up

HBsAg (IU/mL)

Baseline EOT FW24 FW48

0% (0/40) 60% (24/40*) 53% (18/34) 50% (8/16)

HBsAg loss (≤ 0.05 IU/mL)

Anti-HBs (mIU/mL)

Baseline EOT FW24 FW48

5% (2/40) 60% (24/40*) 59% (20/34) 56% (9/16)

HBsAg seroconversion (Anti-HBs ≥ 10 mIU/mL)

HBV DNA (IU/mL)

Baseline EOT FW24 FW48

0% (0/40) 55% (22/40*) 50% (17/34) 62% (10/16)

HBV DNA target not detected

0% 45% 38% 31%

* 3 patients withdrew from therapy early for personal reasons

EOT = end of treatment

HBV DNA LLOQ to 2000 IU/mL
**REP 401**
Liver status during treatment and follow-up

### ALT (U/L)

- **Baseline**: 47% (19/40)
- **EOT**: 32% (13/40*)
- **FW24**: 91% (31/34)
- **FW48**: 94% (15/16)

Normal ALT (≤ 50 U/L)

### Median hepatic stiffness (kPa)

- **Baseline**: 52% (21/40)
- **EOT**: 22% (9/40*)
- **FW24**: 62% (21/34)
- **FW48**: 81% (13/16**)

Median hepatic stiffness consistent with F0 (≤ 7 kPa)

* Improvement in liver function during follow-up

** Significant improvement compared to baseline

* 3 patients withdrew from therapy early for personal reasons

** 2 FW48 fibroscan results still pending
# Interim REP 401 response summary

<table>
<thead>
<tr>
<th>Patients entered into trial</th>
<th>40</th>
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<tbody>
<tr>
<td>End of treatment HBsAg response</td>
<td></td>
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<tr>
<td>&gt; 1 log from baseline</td>
<td>36</td>
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<tr>
<td>&lt; 1 IU/mL</td>
<td>27</td>
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<tr>
<td>≤ 0.05 IU/mL</td>
<td>24</td>
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<tr>
<th>Patients currently completed treatment and ≥ 24 weeks of follow-up</th>
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<tr>
<td>Inactive HBV (HBV DNA ≤ 2000 IU/mL, normal ALT)</td>
<td>44%</td>
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<td>Functional cure (HBsAg and HBV DNA target not detected)</td>
<td>41%</td>
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<td>Clinical benefit, no therapy required (Low risk of progression, reduced risk of HCC)</td>
<td>85%</td>
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Transition of REP 2139-Mg to subcutaneous dosing
• REP 2139-Mg is already optimized for SC administration
• REP 2139-Mg SC formulation is administered via IV in the REP 401 protocol

Initiation of phase IIA triple combination trial in the US
• In collaboration with the ACTG (DAIDS / NIH)
• Will use same regimen as in the REP 401 trial (NUCs + pegIFN + REP 2139-Mg)

Assessing other immunotherapies
• PegIFN is much better tolerated in HBV than in HCV but results in loss of T-cells during therapy
  
  Marcellin et al., Liv Int 2008; 28: 477-485
  Micco et al., J Hepatol 2013; 58: 225-233

• Functional cure rates may improve with other immunotherapies
  • Thymosin alpha 1 (T-cell agonist)
  • TLR / RIG-I agonists
  • Therapeutic vaccines
A collaborative effort!

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<th>Clinical evaluations:</th>
<th>Dhaka, Bangladesh</th>
<th>Chișinău, Moldova</th>
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