Significant Reduction of HBsAg and HDV RNA by the Nucleic Acid Polymer REP 2139 in Caucasian Patients with Chronic HBV / HDV Co-infection

M. Bazinet¹, V. Pântea², V. Cebotarescu², L. Cojuhari³, P. Jimbei³ and A. Vaillant¹

1. Replicor Inc., Montreal, Canada.
2. Department of Infectious Diseases, Nicolae Testemițanu State University of Medicine and Pharmacy, Chișițnău, Republic of Moldova.
3. Toma Ciorbă Infectious Clinical Hospital, Chișițnău, Republic of Moldova.

50th Annual Meeting of the European Association for the Study of the Liver
Vienna, Austria
April 25 2015

Abstract LO2
Disclosures

Michel Bazinet, Andrew Vaillant: Shareholders and Employees of Replicor Inc.

All other authors have nothing to disclose.
Therapy for HBV / HDV co-infection

- 15-20 million patients are affected by HBV / HDV co-infection
- Most aggressive form of viral hepatitis with the fastest progression to cirrhosis.

- No approved therapy:
  - Interferon-based treatment can infrequently achieve functional cures with long exposure

- HBsAg is a critical component of the HDV life cycle:
  - HBsAg not produced by HDV but required for its assembly
    - HDV infection only occurs with HBV infection
  - Both HBV and HDV have the same entry mechanisms (due to shared HBsAg function in both viral envelopes).
  - HDV assembly may be linked to the assembly of HBV subviral particles (Bonino et al., 1986 J. Virol. 58: 954-950)
Nucleic Acid Polymers (NAPs) in HBV therapy

- Two antiviral mechanisms HBV infection:
  - block HBV entry
  - post entry activity: blocks subviral particle (SVP) formation
    - leads to clearance of serum HBsAg in patients
  - production of virions is not targeted by NAPs
Particle production in HBV infection

- Infected hepatocyte
- Nucleus
- cccDNA
  - Replenishment of cccDNA
- Infected
- Subviral particles (bulk of serum HBsAg)
- Capsids
- HBeAg
- Virions
Particle production in HBV infection

Infected hepatocyte

Nucleus

cccDNA

Replenishment of cccDNA

Infection

NAPs

HBeAg

Capsids

Virions
Nucleic Acid Polymers (NAPs) in HDV therapy

• The hypothesis for NAP effect in HBV / HDV co-infection:
  • NAPs may block HDV entry and or the production of HDV derived from a SVP-related assembly mechanism
  • “liberated” anti-HBs may directly target HDV
REP 2139-Ca + Pegasys® in HBV / HDV co-infection (REP 301)

Caucasian patients treated in Chisinau, Moldova
CRO monitored trial compliant with EU GCP
Clinicaltrials # NCT02233075

12 patients enrolled with HBV / HDV co-infection at the start of treatment:
• Anti-HDAg+
• Serum HBsAg > 1000 U / ml
• HBeAg-
• compensated liver disease
• mild to moderate fibrosis, non cirrhotic.

Viremia monitored at University of Duisburg-Essen, Germany:
• Abbott PCR (HBV DNA)
• Abbott Architect (HBsAg and anti-HBs)
• Robogene RT-PCR (HDV RNA)
• Diasorin (anti-HDAg)
REP 301 Trial Design

REP 2139-Ca
500mg qW IV 15 weeks

REP 2139-Ca
250mg qW IV 15 weeks

Pegylated interferon α-2a (Pegasys®)
180 μg qW SC 48 weeks

Follow up (4, 12 and 24 weeks)
Interim REP 301 Efficacy Data (serum HBsAg)

Weekly doses received
(≤ 0 = pre-treatment baseline)

- 500mg REP 2139-Ca qW
- 250 mg REP 2139-Ca qW
- 180 ug Pegasys® qW

Serum HBsAg (IU / ml)

001-01
001-02
001-03
001-06
001-09
001-11
001-14
001-17
001-20
001-22
001-24
001-26
LLOQ
no HBsAg detected
start of dosing
start Pegasys
Interim REP 301 Efficacy Data (serum anti-HBs)

500mg REP 2139-Ca qW
250 mg REP 2139-Ca qW
180 ug Pegasys® qW

Serum anti-HBs (mIU/ml)

Weekly doses received
(≤ 0 = pre-treatment baseline)
Interim REP 301 Efficacy Data (serum HDV RNA)

- **500mg REP 2139-Ca qW**
- **250 mg REP 2139-Ca qW**
- **180 ug Pegasys® qW**

**Weekly doses received**

- ≤ 0 = pre-treatment baseline

**Serum HDV RNA (U / ml)**

- LLOQ: no target detected
- Start of dosing
- Start Pegasys
Validation of REP 301 HDV RNA
(conducted at National Genetics Institute, USA)

Performed on frozen samples sent from trial site.
Primers optimized from HDV GT1 sequence
HBsAg versus HDV RNA response

Multiple antiviral effects may be present
REP 2139-Ca safety profile in the REP 301 protocol

- Preliminary safety analysis from REP 2139-Ca mono-therapy exposure (prior to Pegasys® combination therapy):
  - All AEs are grade 1-2 (fever, redness or headache) and are associated with IV infusion:
    - typically become less frequent as dosing regimen progresses
    - self-resolve after completion of IV infusion (infrequently requiring supportive treatment)
    - attributed to the presence of phthalate plasticisers in IV tubing
  - Clinical serology monitored weekly with no clinically significant findings
REP 2139-Ca is able to simultaneously reduce HBsAg and HDV RNA in patients with chronic HBV / HDV co-infection.

Pharmacologic effect on serum HBsAg observed in Asian patients is replicated in Caucasian patients.

NAP therapy is well tolerated.

Antiviral effect may be derived from entry and post-entry mechanisms.

Combination exposure with Pegasys® may provide an additional productive antiviral response.

NAP-based antiviral therapy may become an important new treatment option for patients with HBV / HDV co-infection.
Validation of HDV RNA test results was performed at the National Genetics Institute, Los Angeles, USA

Dr. Jeffrey Albrecht
Dr. Peter Schmid
<table>
<thead>
<tr>
<th>Topic</th>
<th>Abstract Number</th>
<th>Time / Date</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV in vitro activity of NAPs</td>
<td>P0556</td>
<td>April 23 12:00 – 13:00</td>
<td>HBV: Oral ePoster 1</td>
</tr>
<tr>
<td>HBV RNA post-trial analysis</td>
<td>O114</td>
<td>April 25 12:00 – 12:15</td>
<td>Viral Hepatitis B &amp; D: Clinical</td>
</tr>
<tr>
<td>Serum cytokine post-trial analysis</td>
<td>P0659</td>
<td>April 25 12:30 – 13:00</td>
<td>Viral hepatitis: Hepatitis B &amp; D - Clinical</td>
</tr>
<tr>
<td></td>
<td>(ePoster Tour C-12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV in vivo activity of NAPs</td>
<td>P0542</td>
<td>April 25 13:00 – 14:00</td>
<td>Molecular and cellular biology: Oral ePoster 1</td>
</tr>
<tr>
<td>HDV in vitro activity of NAPs</td>
<td>LP26</td>
<td>April 25 15:30 – 16:00</td>
<td>Hall B Late Breaker E-posters</td>
</tr>
<tr>
<td></td>
<td>(ePoster Tour A-13)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Presentations can be downloaded after the conference at [www.rePLICOR.com](http://www.rePLICOR.com) (Science / Conference Presentations section)