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

M. Bazinet[1], V. Pântea[2], V. Cebotarescu[2], L. Cojuhari[3], P. Jimbei[3] and A. Vaillant[1]

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

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Abstract LO2

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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

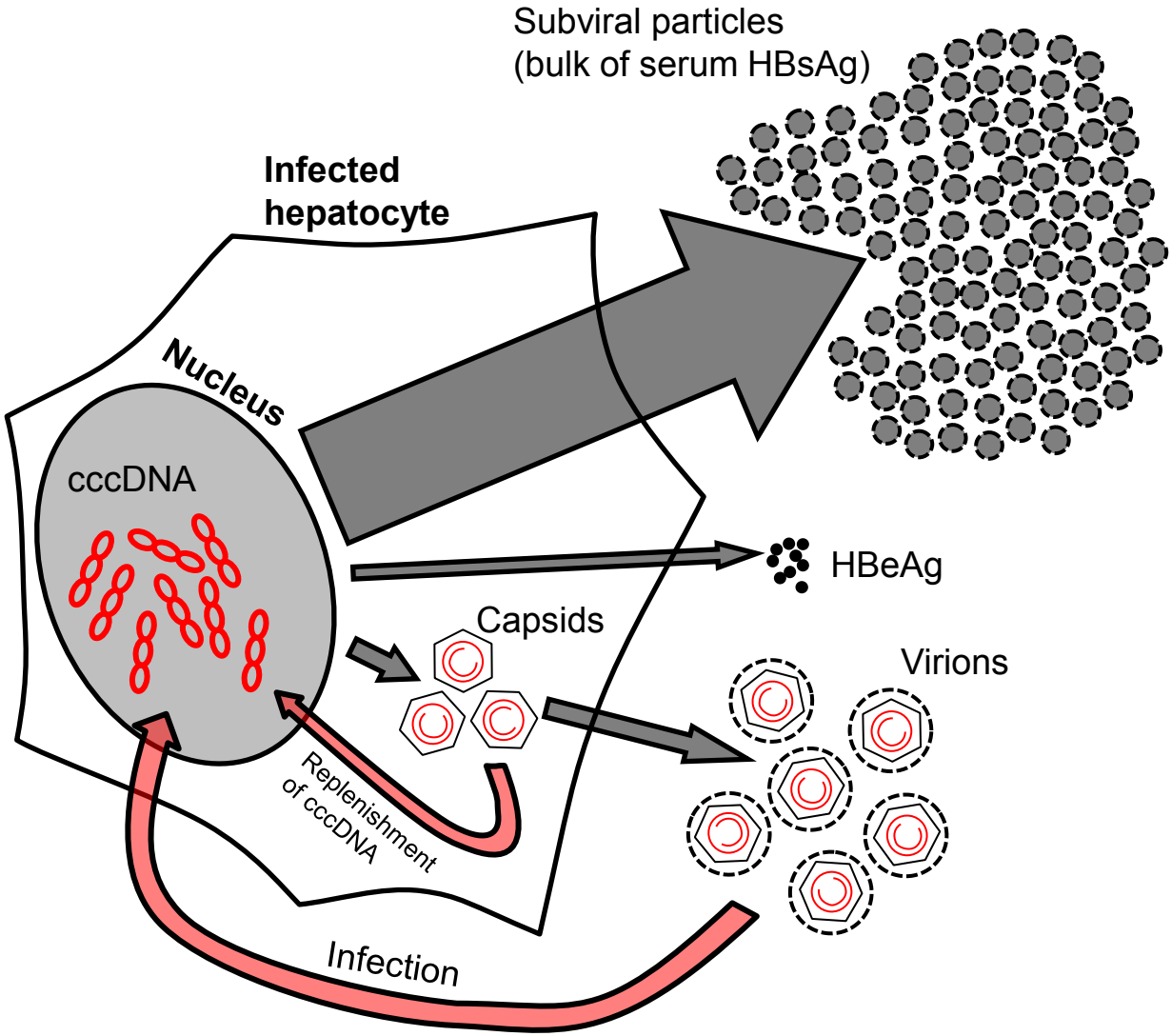
- HBsAg is a critical component of the HDV life cycle:

    - 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)

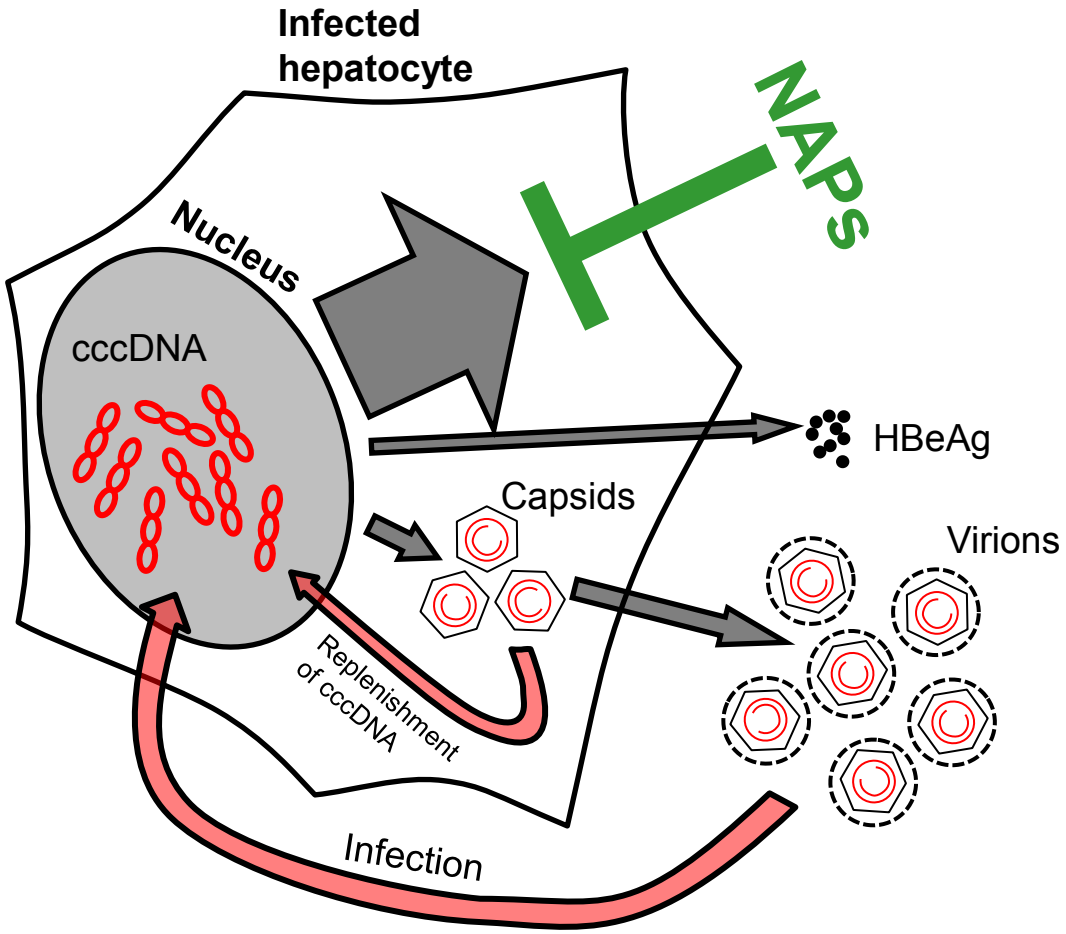
Nucleic Acid Polymers (NAPs) in HBV therapy

- 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



Particle production in HBV infection



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

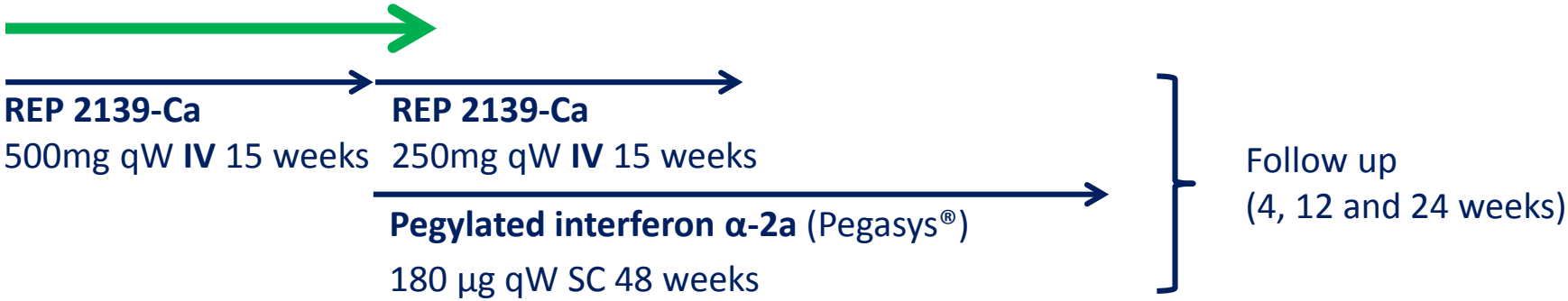
12 patients enrolled with HBV / HDV co-infection at the start of treatment:

- Anti-HDAg+
- Serum HBsAg > 1000 U / ml
- HBeAg-
- compensated liver disease
- mild to moderate fibrosis, non cirrhotic.

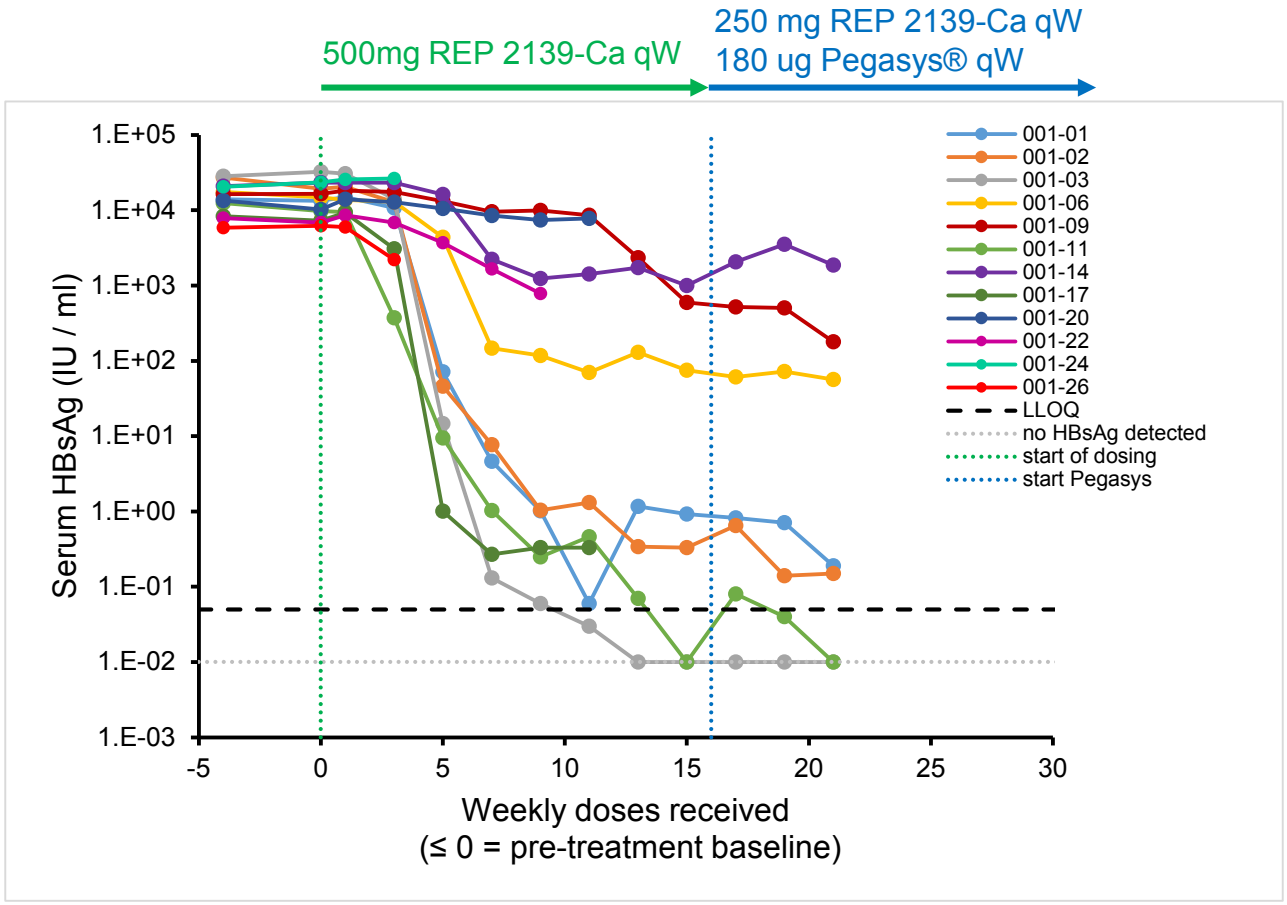
Viremia monitored at University of Duisburg-Essen, Germany:

- Abbott PCR (HBV DNA)
- Abbott Architect (HBsAg and anti-HBs)
- Robogene RT-PCR (HDV RNA)
- Diasorin (anti-HDAg)

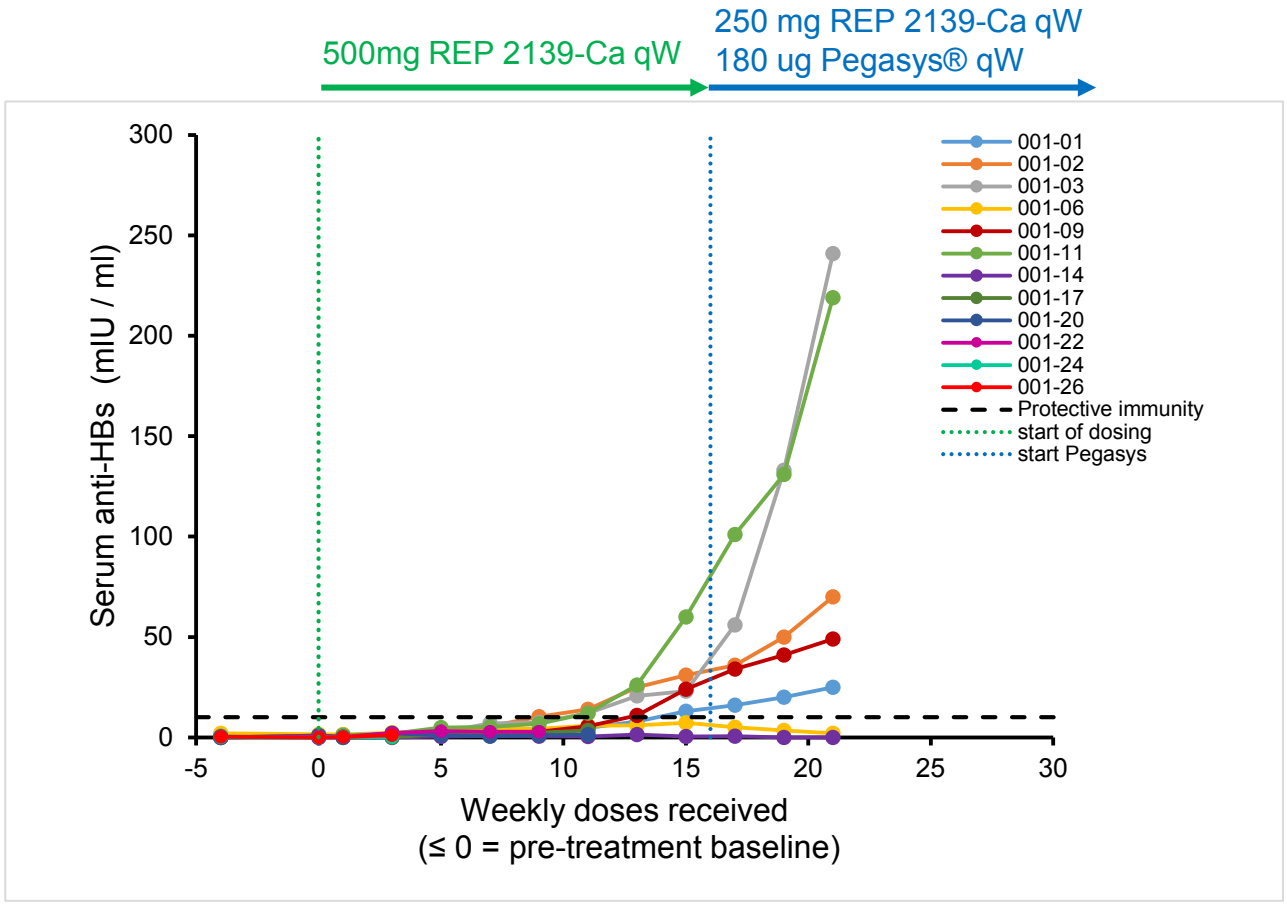
REP 301 Trial Design



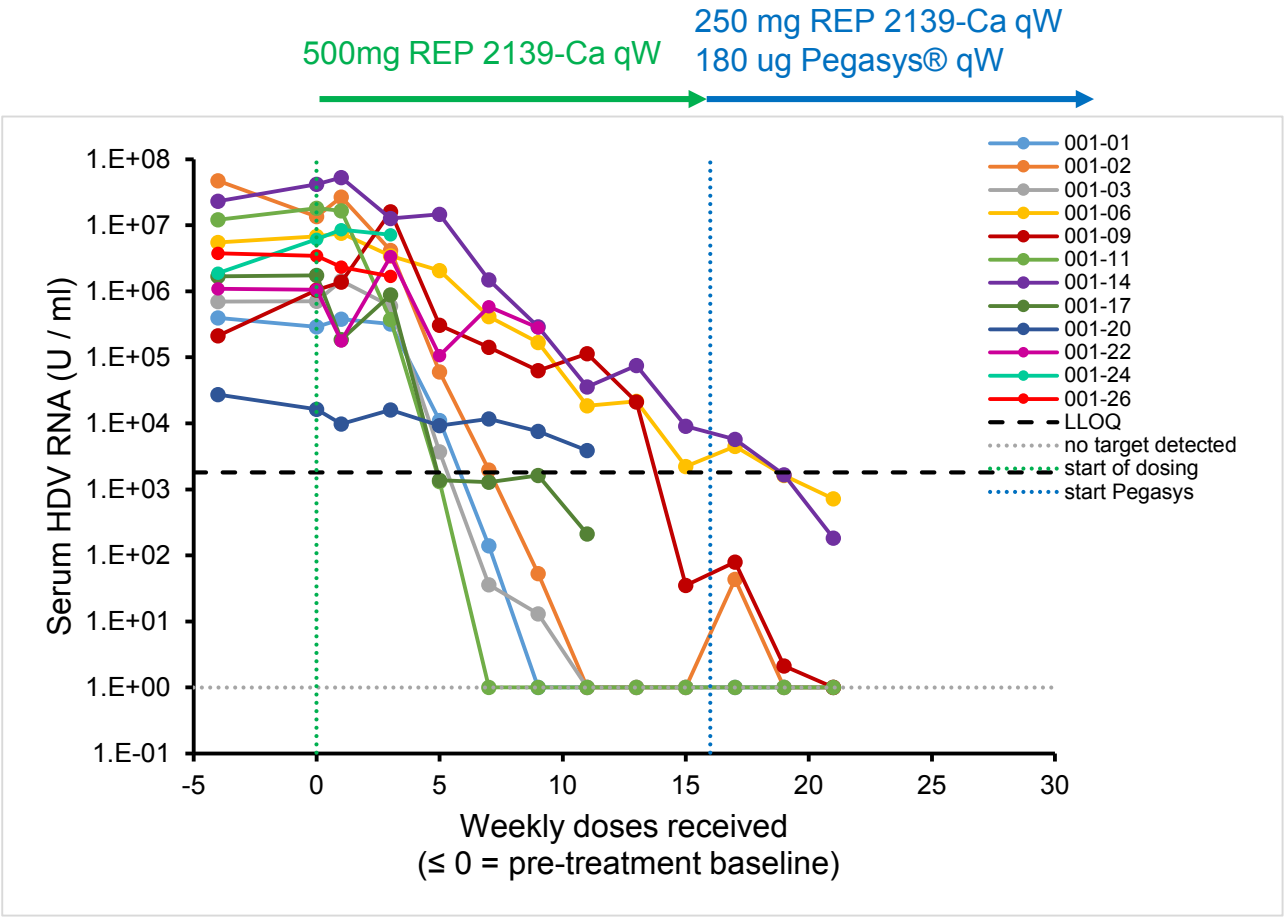
Interim REP 301 Efficacy Data (serum HBsAg)



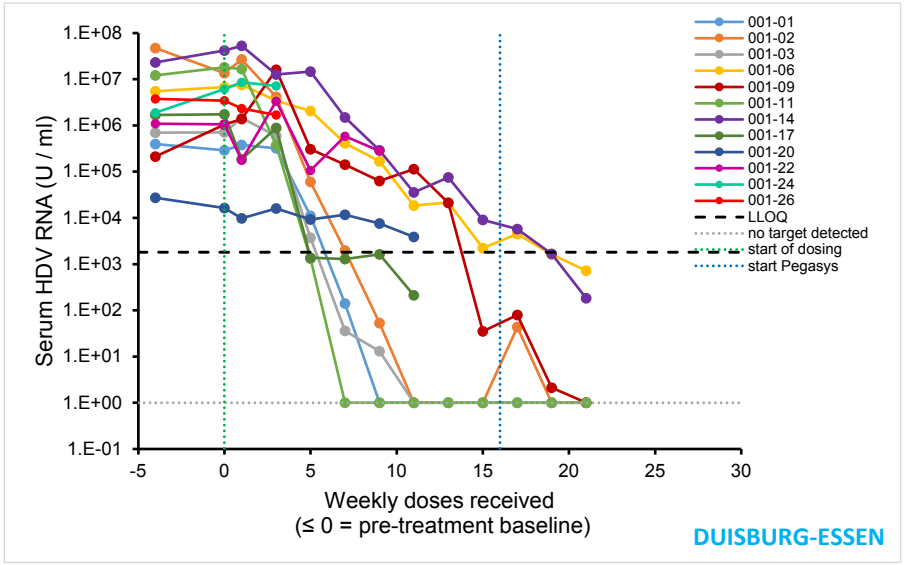
Interim REP 301 Efficacy Data (serum anti-HBs)

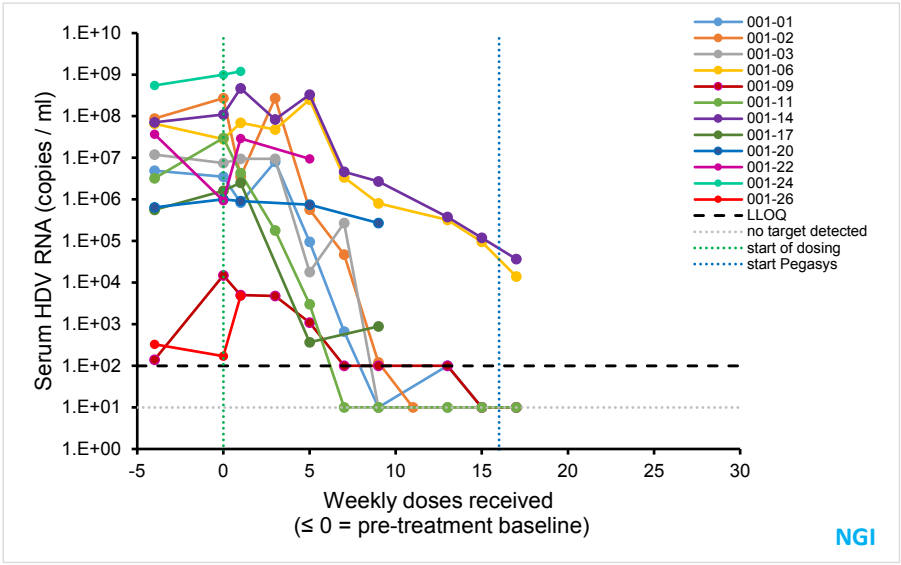


Interim REP 301 Efficacy Data (serum HDV RNA)



Validation of REP 301 HDV RNA
(conducted at National Genetics Institute, USA)

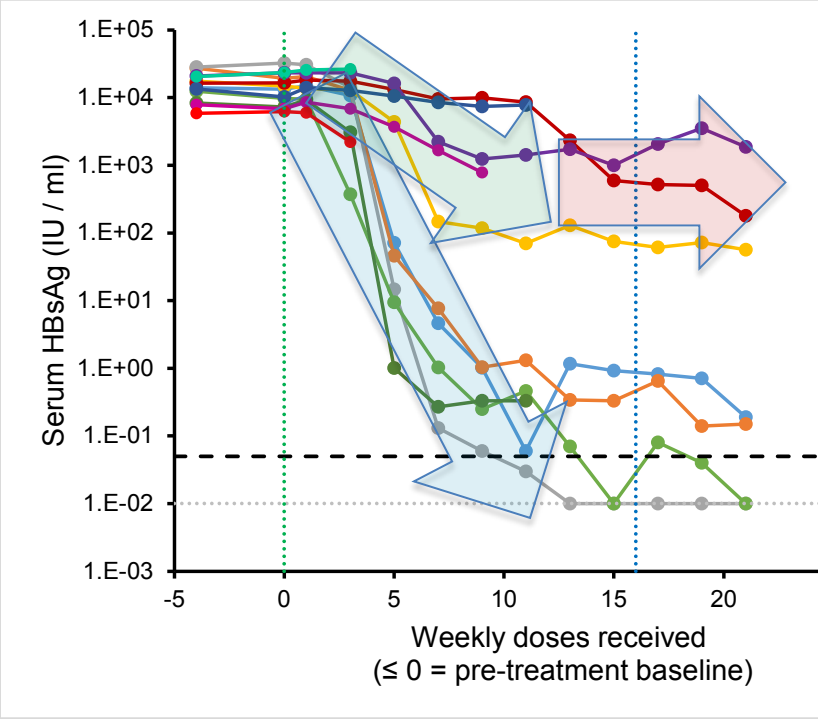




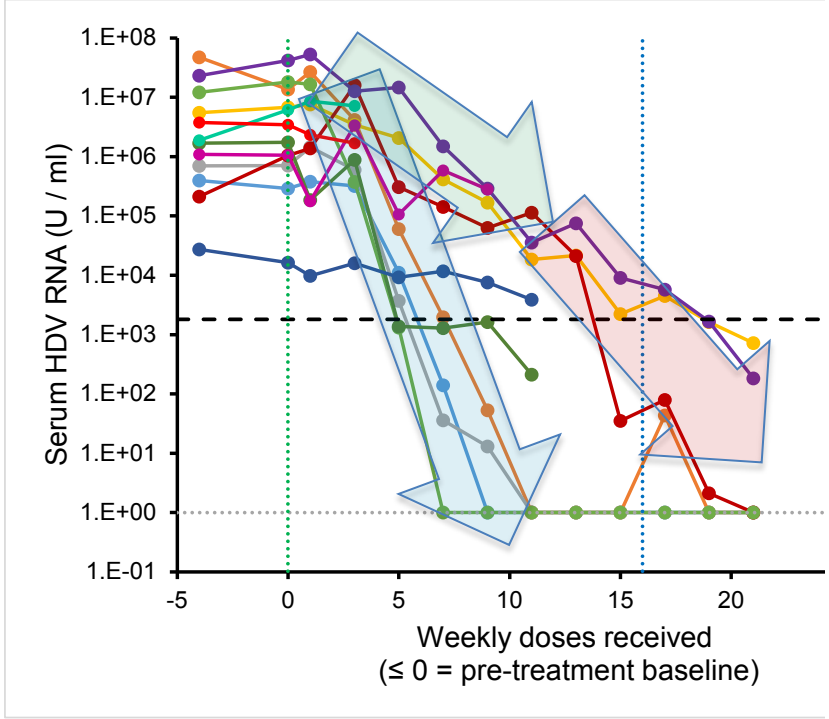
Performed on frozen samples sent from trial site.
Primers optimized from HDV GT1 sequence

HBsAg versus HDV RNA response

HBsAg



HDV RNA



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 (infrequenty requiring supportive treatment)
    - attributed to the presence of phthalate plasticisers in IV tubing
  - Clinical serology monitored weekly with no clinically significant findings

Summary

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.

Acknowledgements

Validation of HDV RNA test results was performed at the National Genetics Institute, Los Angeles, USA

Dr. Jeffrey Albrecht
Dr. Peter Schmid

Related EASL 2015 presentations on NAPs

Topic	Abstract Number	Time / Date Session
HBV in vitro activity of NAPs	P0556	April 23 12:00 – 13:00 HBV: Oral ePoster 1
HBV RNA post-trial analysis (REP 102 protocol)	O114	April 25 12:00 – 12:15 Viral Hepatitis B & D: Clinical
Serum cytokine post-trial analysis (REP 102 protocol)	P0659 (ePoster Tour C-12)	April 25 12:30 – 13:00 Viral hepatitis: Hepatitis B & D - Clinical
HBV in vivo activity of NAPs	P0542	April 25 13:00 – 14:00 Molecular and cellular biology: Oral ePoster 1
HDV in vitro activity of NAPs	LP26 (ePoster Tour A-13)	April 25 15:30 – 16:00 Hall B Late Breaker E-posters

Presentations can be downloaded after the conference at www.replicor.com
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