HBsAg and HDV RNA Reduction with REP 2139-Ca and PEG-IFN Alpha 2a in Chronic HBV / HDV Infection.

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Disclosures

M. Bazinet, A. Vaillant: Shareholder and Employee of Replicor Inc.
M. Roggendorf: Member, Replicor SAB
H. Karimzadeh: Paid consultant of Replicor

All other authors have nothing to disclose.

Therapy for HBV / HDV co-infection

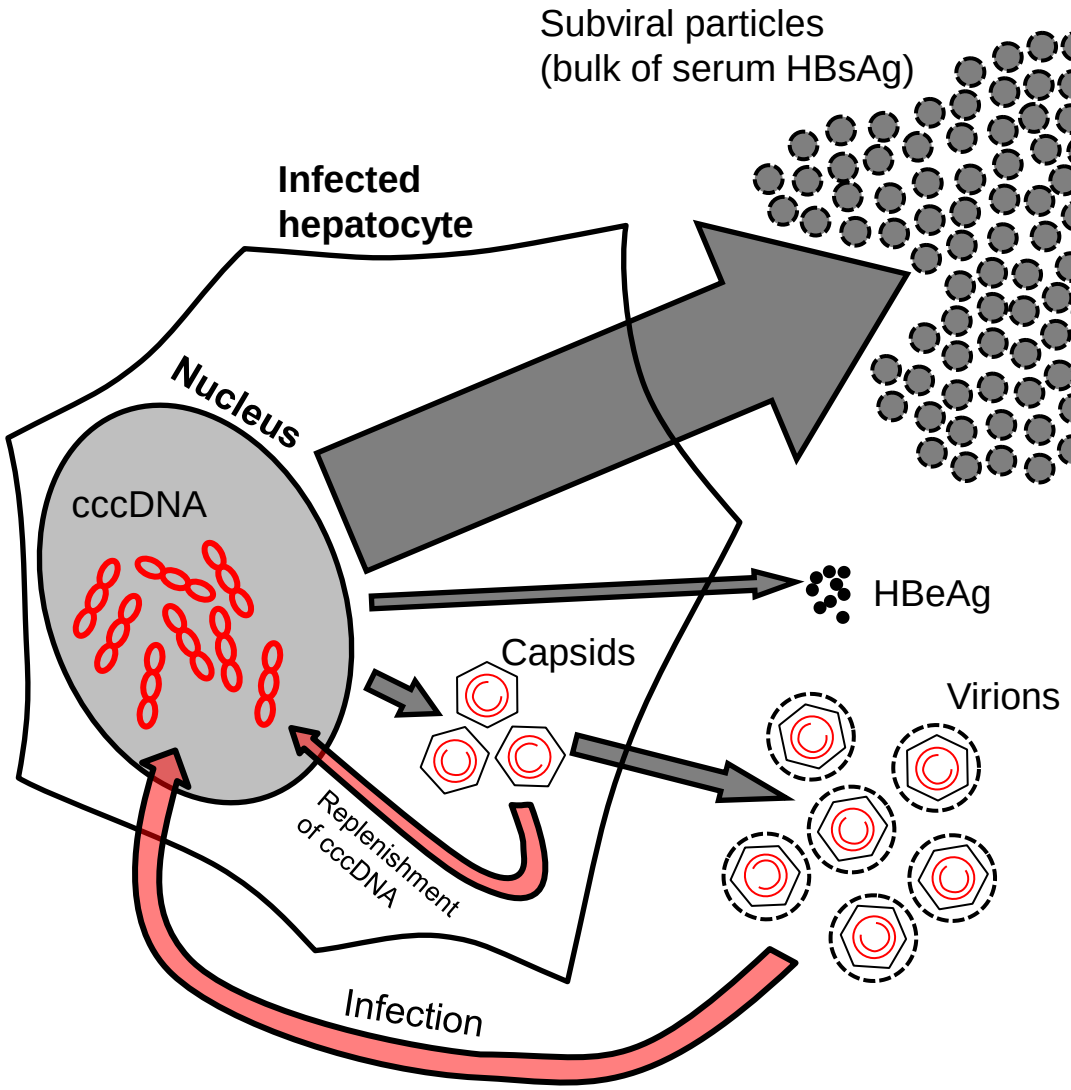
- 15-20 million patients are affected by HBV / HDV co-infection
- Most aggressive form of viral hepatitis with the fastest progression to cirrhosis.

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

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

    - HDV assembly may be linked to the assembly of HBV subviral particles (Bonino et al., 1986 J. Virol. 58: 954-950)

Particle production in HBV infection

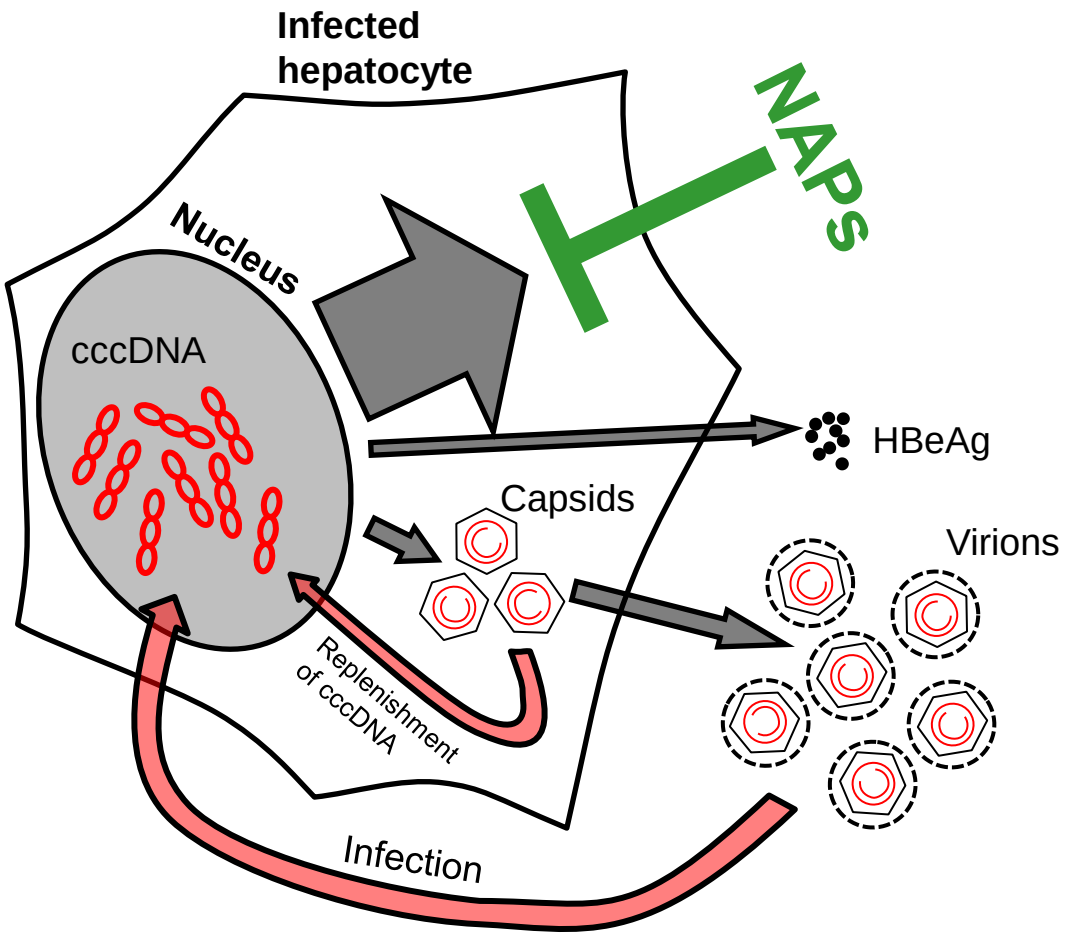


HBsAg is the key:

Sequesters anti-HBs
Suppresses innate immunity
Suppresses T-cell proliferation
Suppresses cytokine signaling
Suppresses immunotherapy

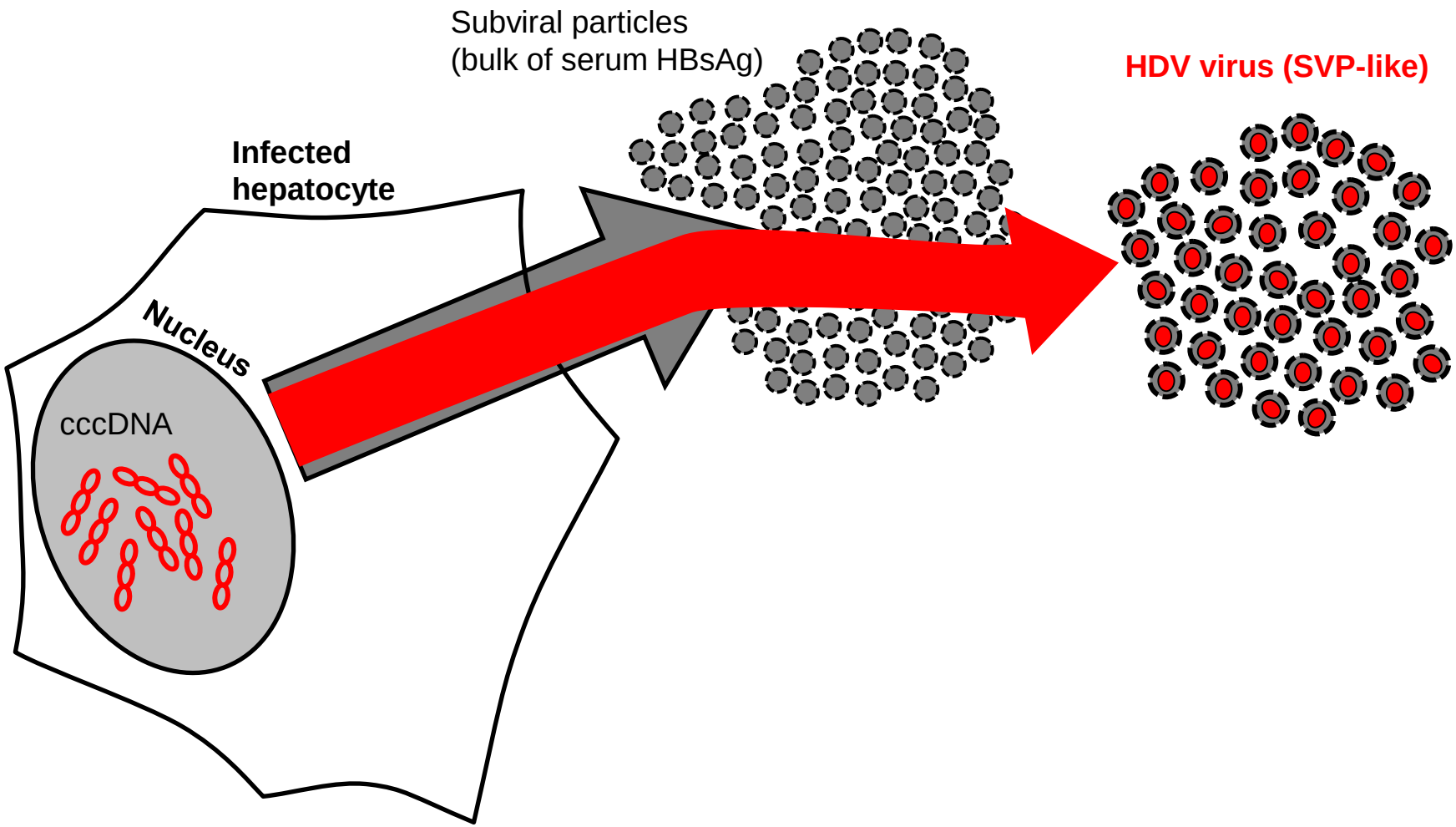
HBsAg removal will likely be essential to achieve high rates of functional cure

Particle production in HBV infection



Virions are not directly targeted by NAPs

Potential NAP effect in HDV



(Bonino et al., 1986 J. Virol. 58: 954-950)

REP 2139-Ca + peg-INF in HBV / HDV co-infection (REP 301)

Caucasian patients treated in Chisinau, Moldova
Clinicaltrials.org # NCT02233075

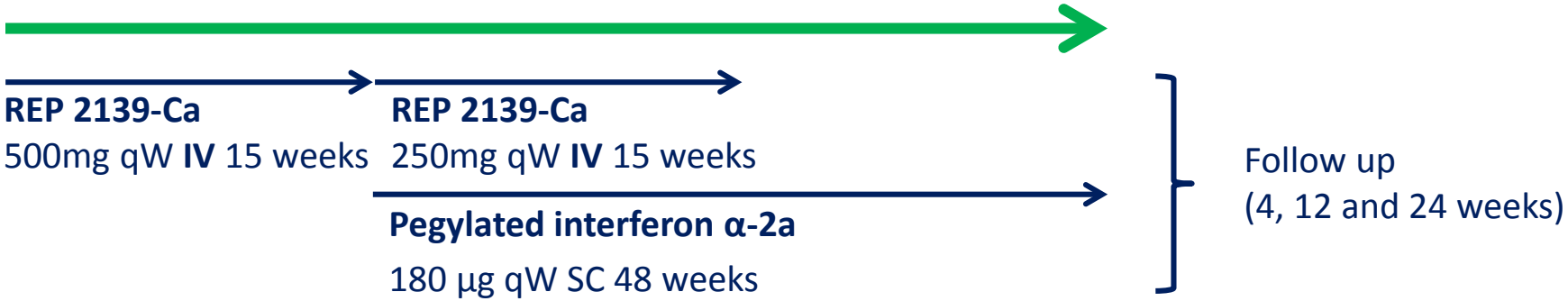
12 patients enrolled with HBV / HDV co-infection at the start of treatment:

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

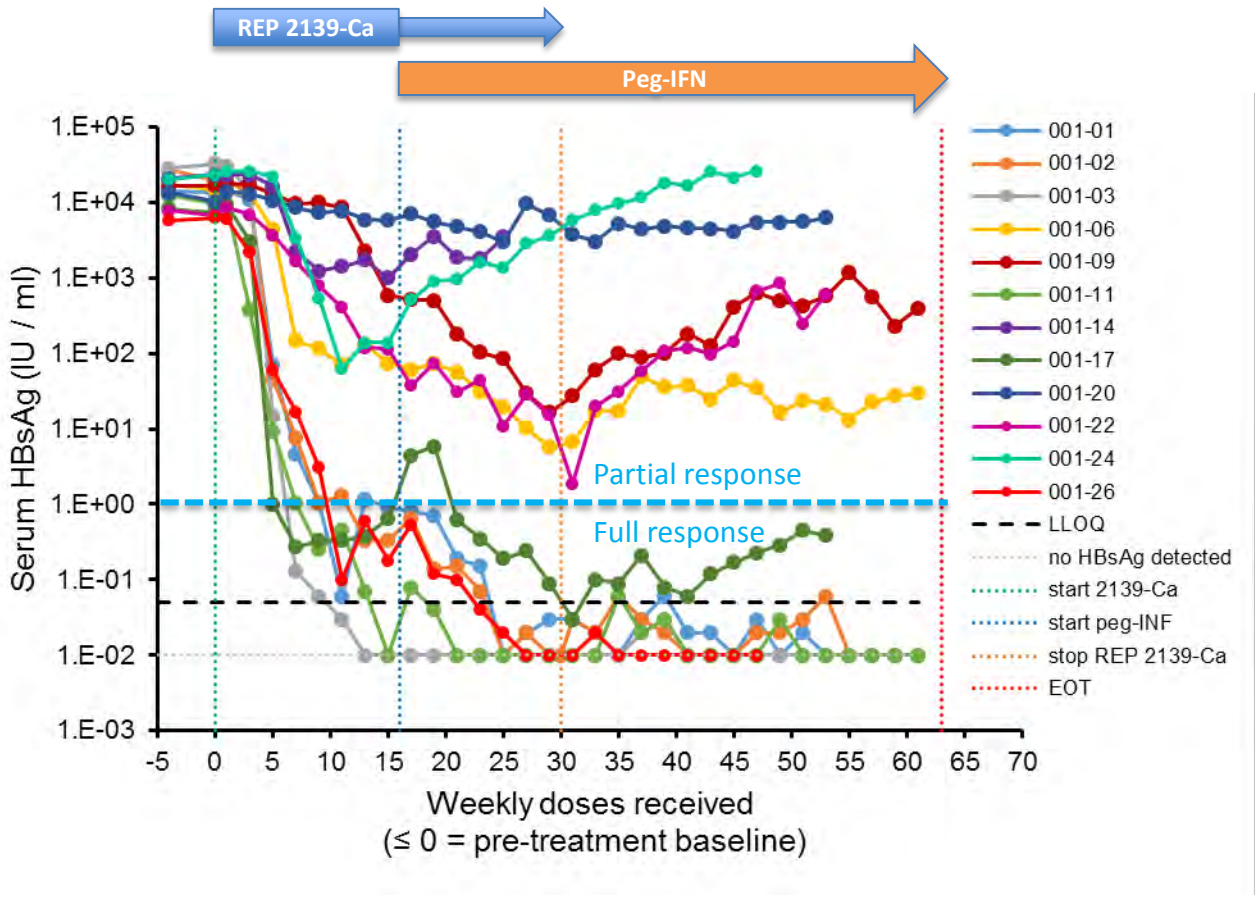
Viremia monitored at University of Duisburg-Essen, Germany:

- Abbott PCR (HBV DNA)
- Abbott Architect Quantitative (HBsAg and anti-HBs)
- Robogene RT-PCR (HDV RNA) – validated at two external sites
- Diasorin (anti-HDAg)

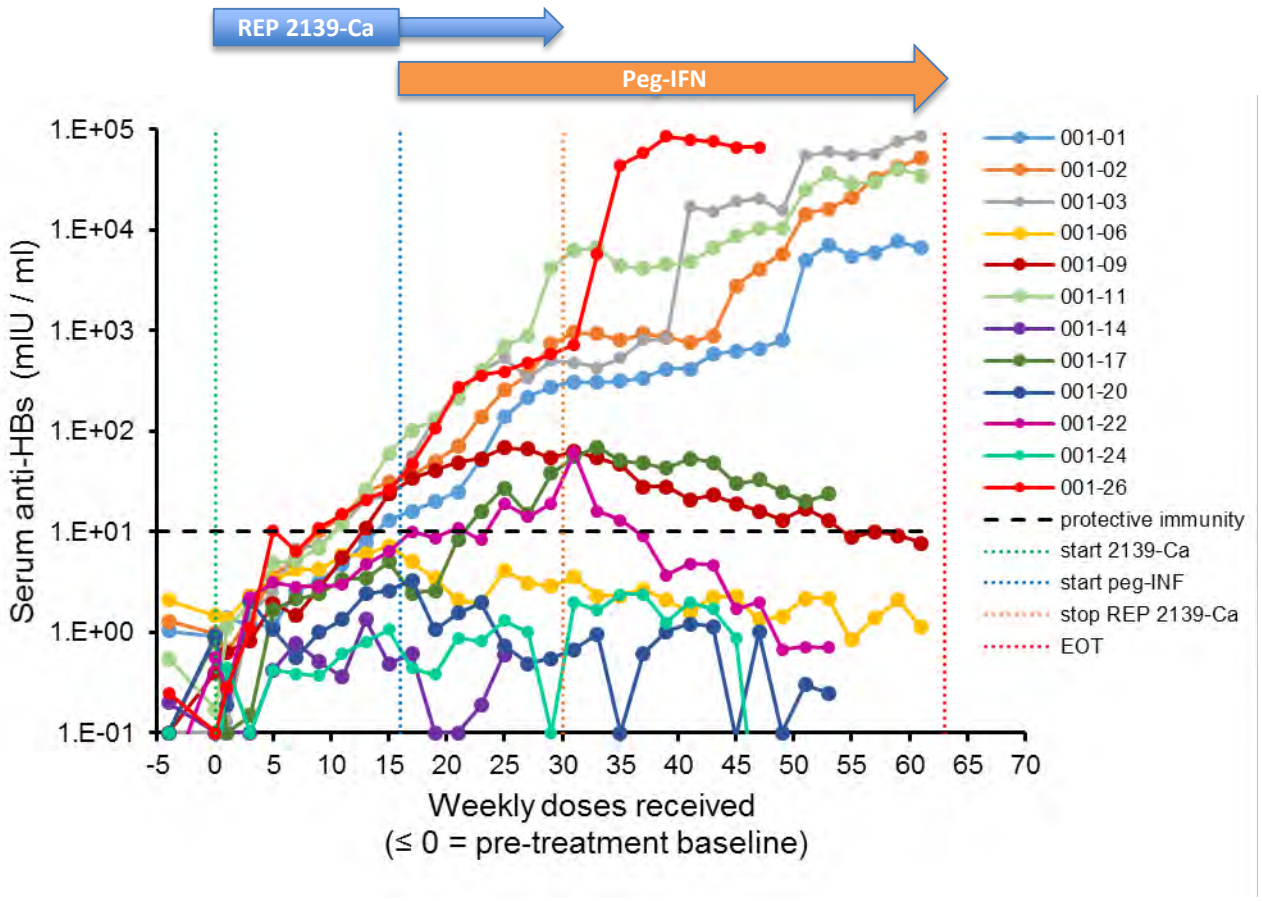
REP 301 Trial Design



Interim REP 301 Efficacy Data (serum HBsAg)



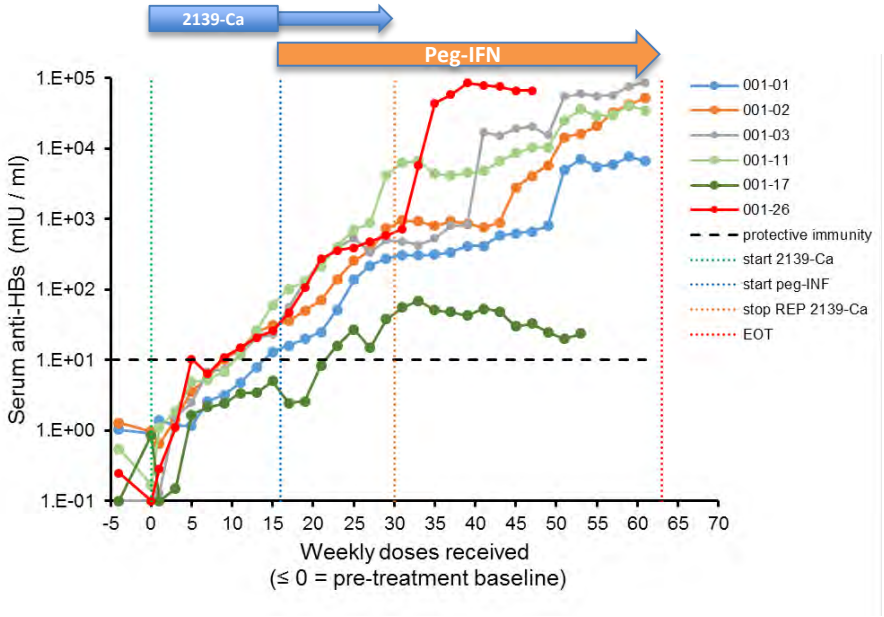
Interim REP 301 Efficacy Data (serum anti-HBs)



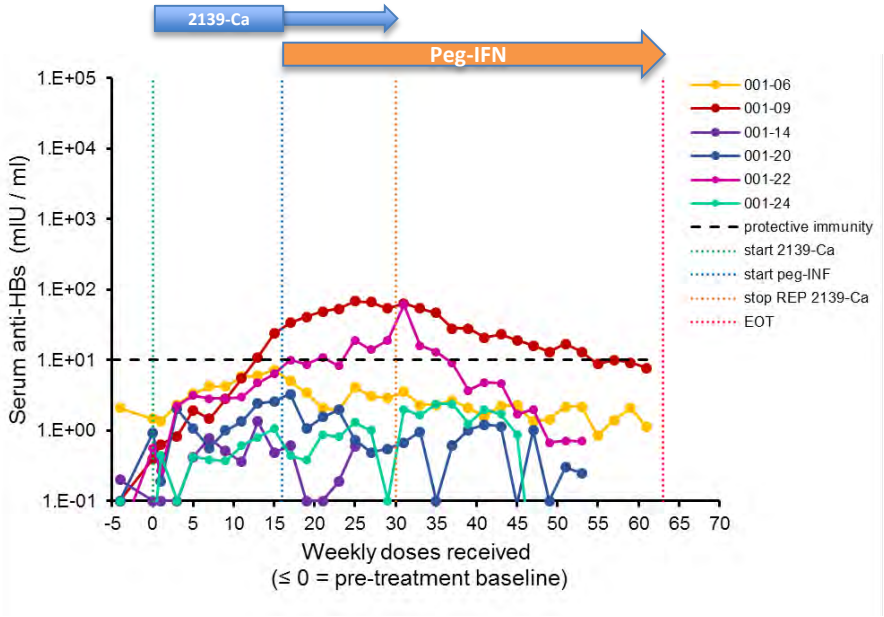
Increased anti-HBs titers are correlated with the onset of peg-INF therapy

Anti-HBs response versus HBsAg response

HBsAg full response (HBsAg < 1 IU / ml)

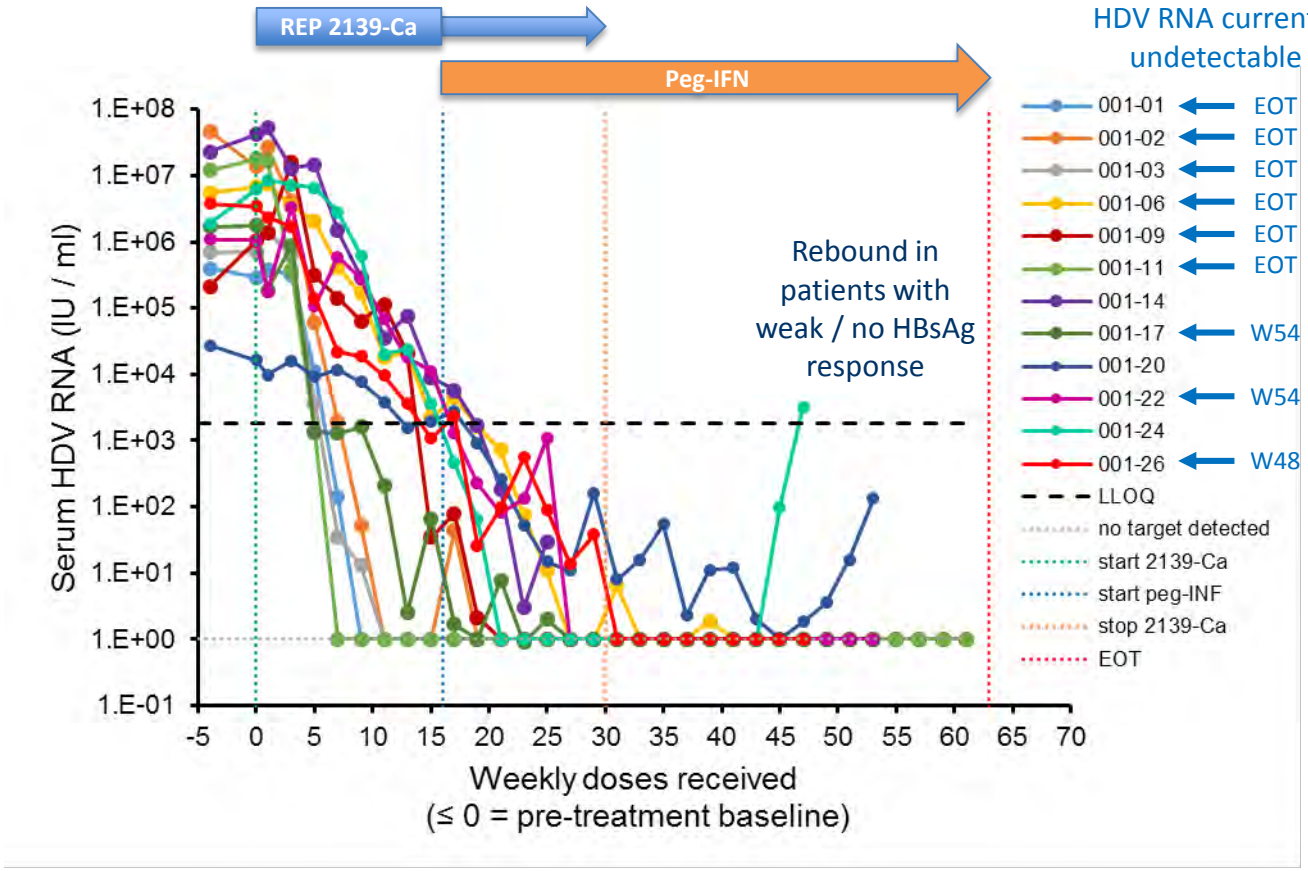


HBsAg partial response (HBsAg > 1 IU / ml)



Increased anti-HBs titers are correlated with serum HBsAg < 1 IU / ml at the start of peg-INF therapy

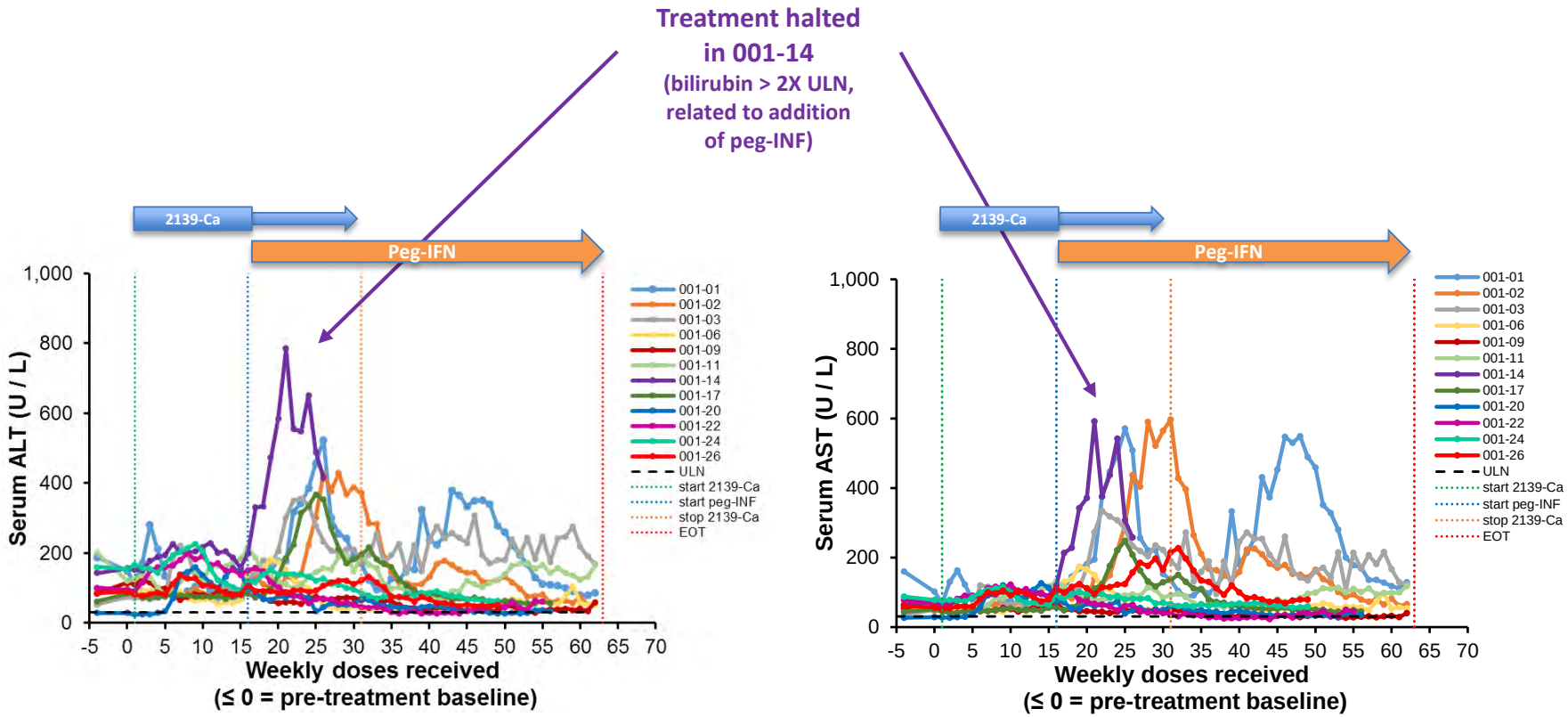
Interim REP 301 Efficacy Data (serum HDV RNA)



9 / 12 patients currently have no detectable HDV RNA

A distinct antiviral activity of NAPs against HDV is likely present

Interim REP 301 Liver Response Data (serum ALT / AST)



Liver flares are correlated with the onset of peg-INF therapy

Updated REP 2139-Ca safety profile in the REP 301 protocol

- REP 2139-Ca mono-therapy exposure:
  - Infusion AEs (grade 1-2 fever, redness itchiness, asthenia or headache):
    - Attributed to the presence of phthalate plasticisers in IV tubing
    - Self-resolve after infusion
    - Acclimation with continued therapy
  - Mild, asymptomatic reductions in hemoglobin (2/12 patients), platelets and white blood cell counts develop during the last half of monotherapy exposure.
- With the addition of peg-INF α2a to REP 2139-Ca therapy:
  - Reductions in hemoglobin, platelet and white blood cell counts are stable but maintenance has required reduced peg-INF α2a dosing / supportive therapy in 5 patients.
  - ALT / AST flares: limited to start of peg-IFN α2a exposure and appear self resolving
  - No other signs of liver dysfunction (except bilirubin elevation in one patient after peg-IFN a2a exposure).

Summary

REP 2139-Ca is able to simultaneously reduce HBsAg and HDV RNA in patients with chronic HBV / HDV co-infection.

Increased anti-HBs production correlated with the start of peg-INF α2a exposure appears to be related to the extent of clearance of serum HBsAg.

Longer combination treatment with immunotherapy will likely result in a higher proportion of patients with a full HBsAg response (< 1 IU / ml).

NAP-based antiviral therapy may become an important new treatment option for patients with HBV / HDV co-infection.