Update on the safety and efficacy of REP 2139 monotherapy and subsequent combination therapy with pegylated interferon alpha-2a in chronic HBV / HDV co-infection in Caucasian patients

M. Bazinet[1], V. Pântea[2], V. Cebotarescu[2], L. Cojuhari[3], P. Jimbei[3] J. Albrecht[4], P. Schmid[4], H. Karimzadeh[5], M. Roggendorf[5] 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.
4. National Genetics Institute, Los Angeles, USA
5. Institute for Virology, Technische Universität München, Munich, Germany

Annual Meeting of the American Association for Study of Liver Diseases
November 15, 2015

AASLD THE LIVER MEETING 2015 SAN FRANCISCO

replicor

Therapy for HBV / HDV co-infection

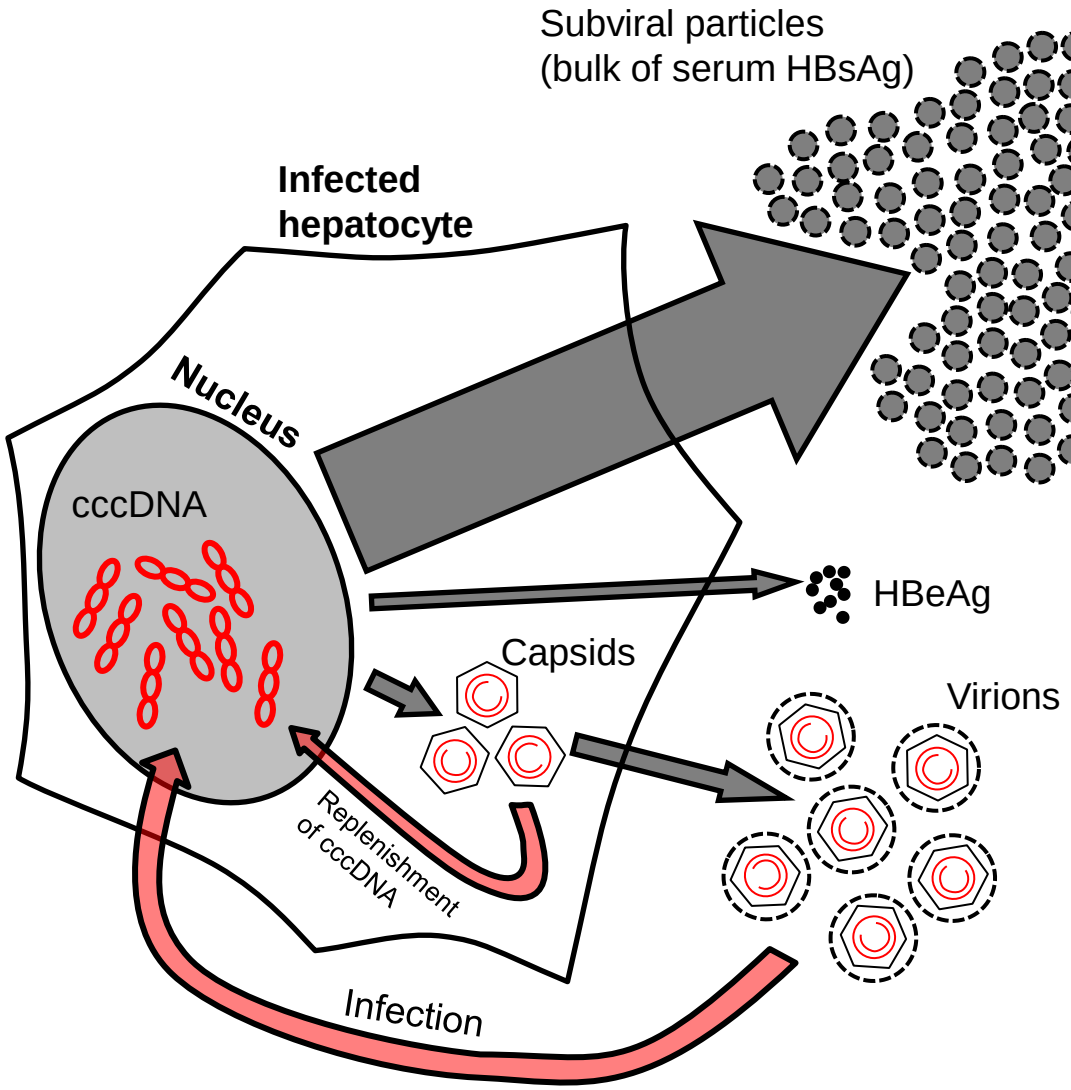
- 15-20 million patients are affected by HBV / HDV co-infection
- Most aggressive form of viral hepatitis with the fastest progression to cirrhosis.

- 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:

    - HBsAg not produced by HDV but is required for its assembly
        - HDV infection only occurs with HBV infection
    - 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

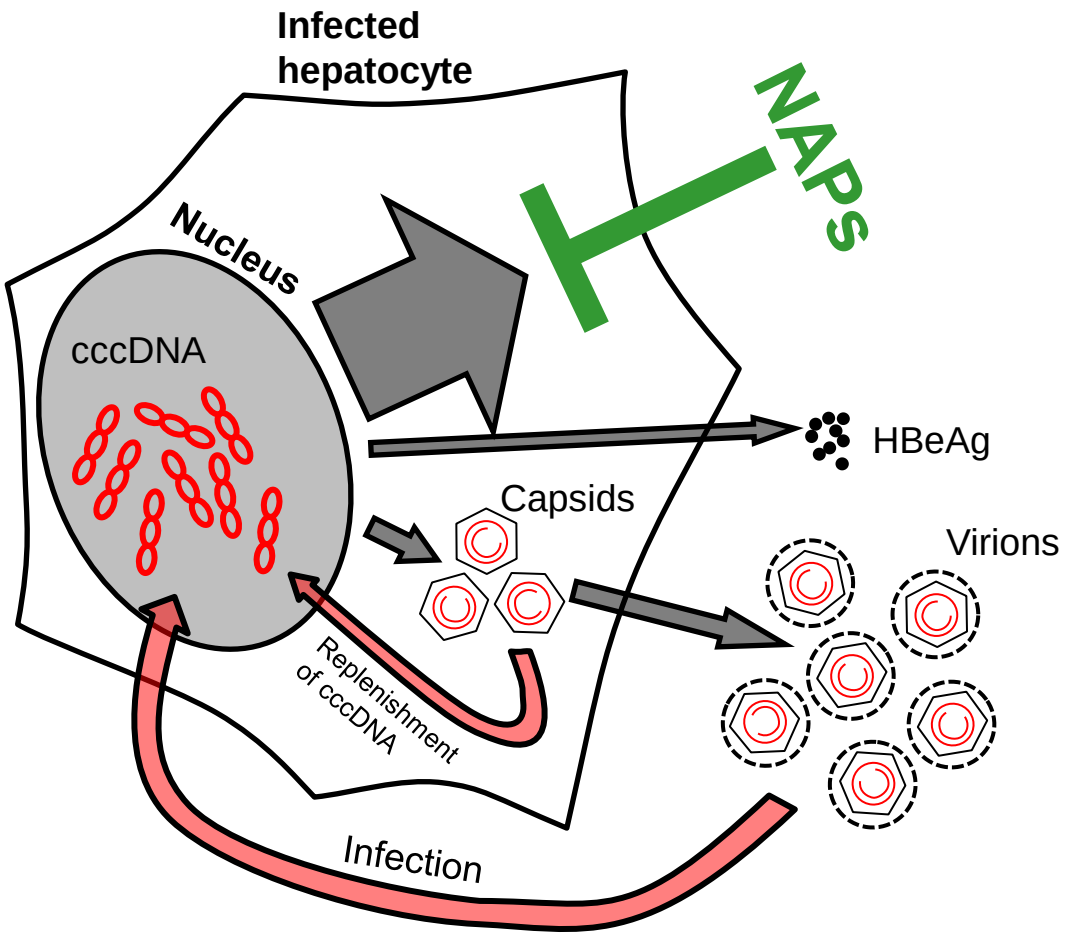


HBsAg is the key:

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

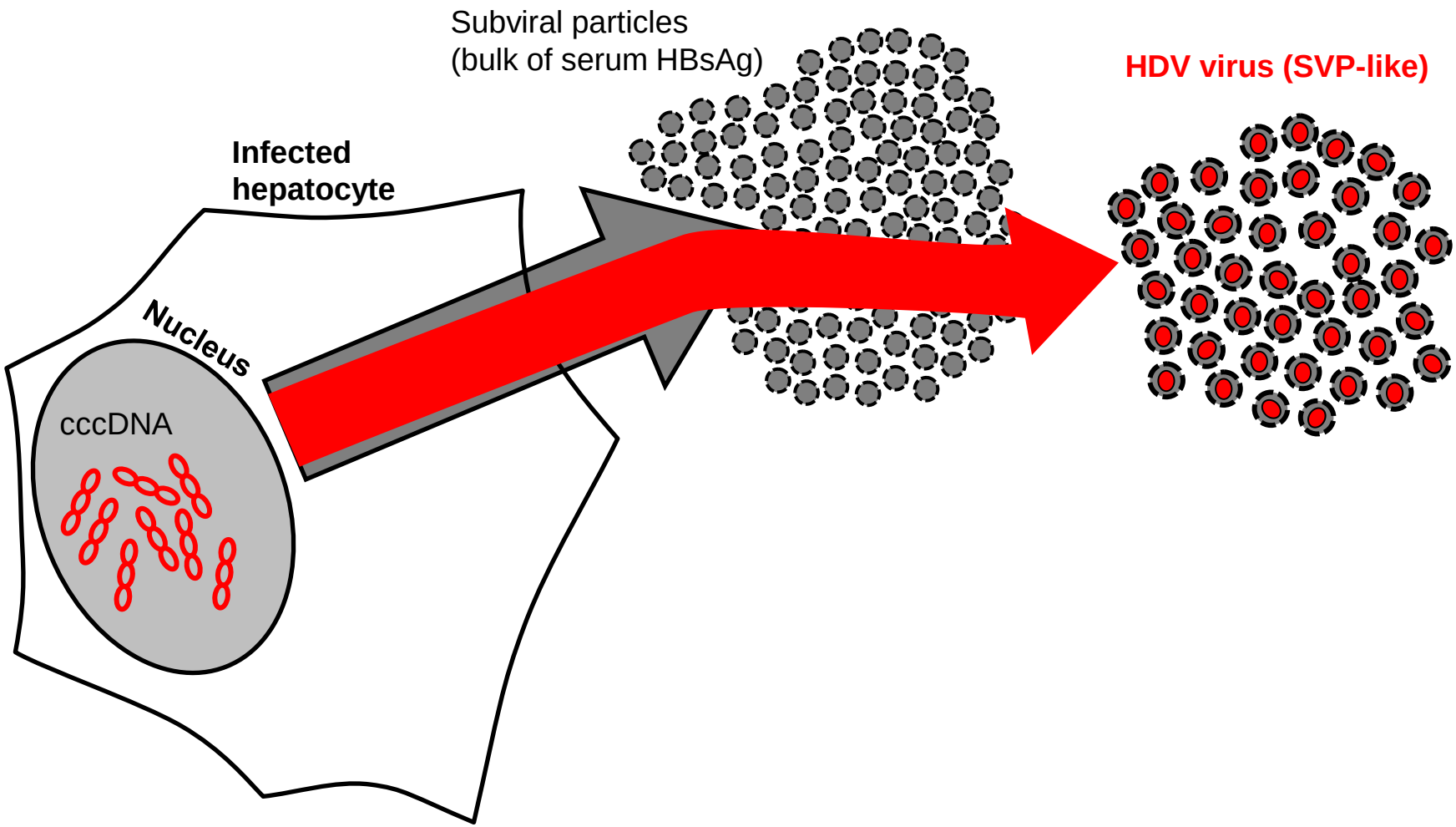
HBsAg removal will likely be essential to achieve high rates of functional cure

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
CRO monitored trial compliant with EU GCP
Clinicaltrials.org # NCT02233075

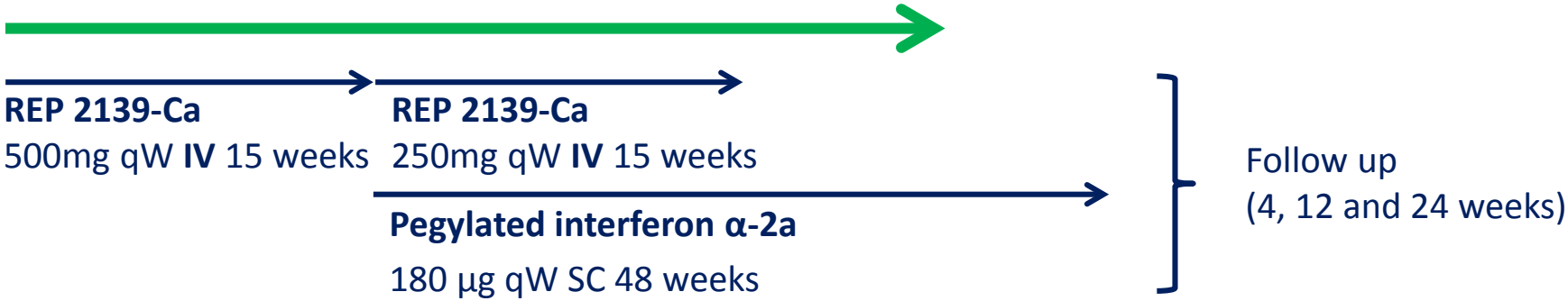
12 patients enrolled with HBV / HDV co-infection at the start of treatment:

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

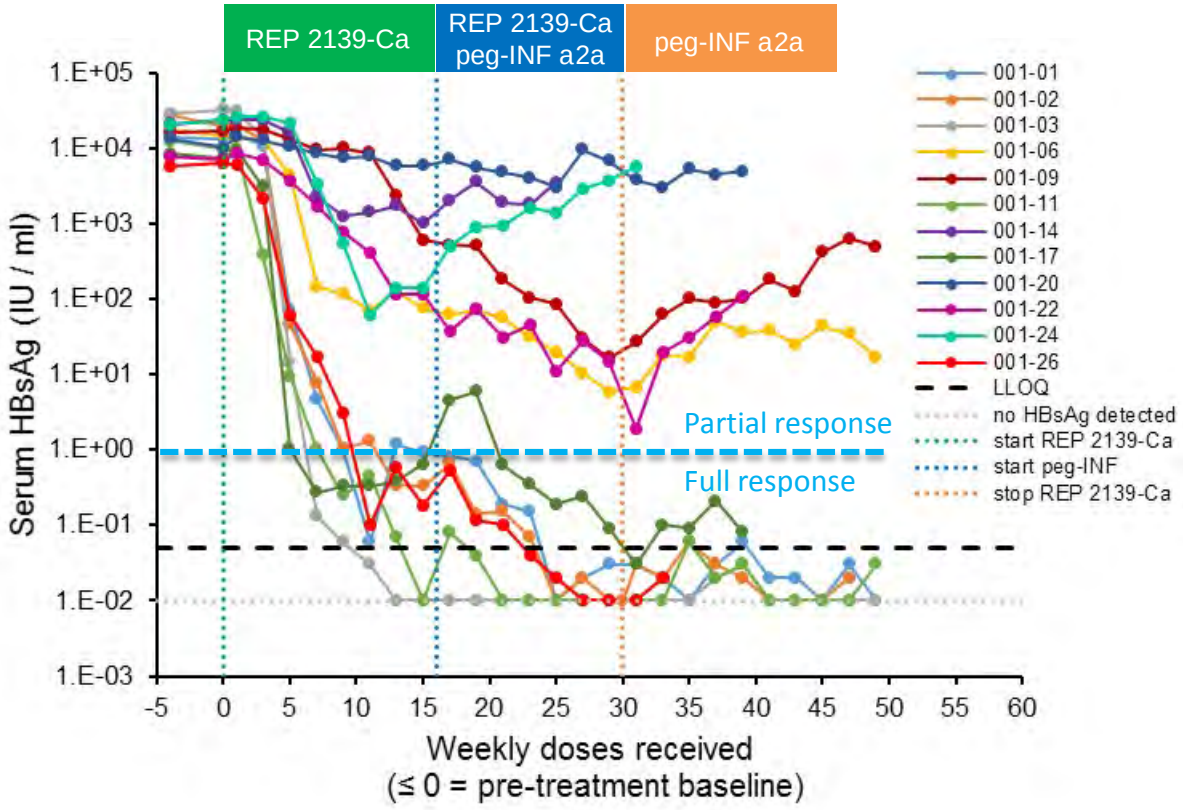
Viremia monitored at University of Duisburg-Essen, Germany:

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

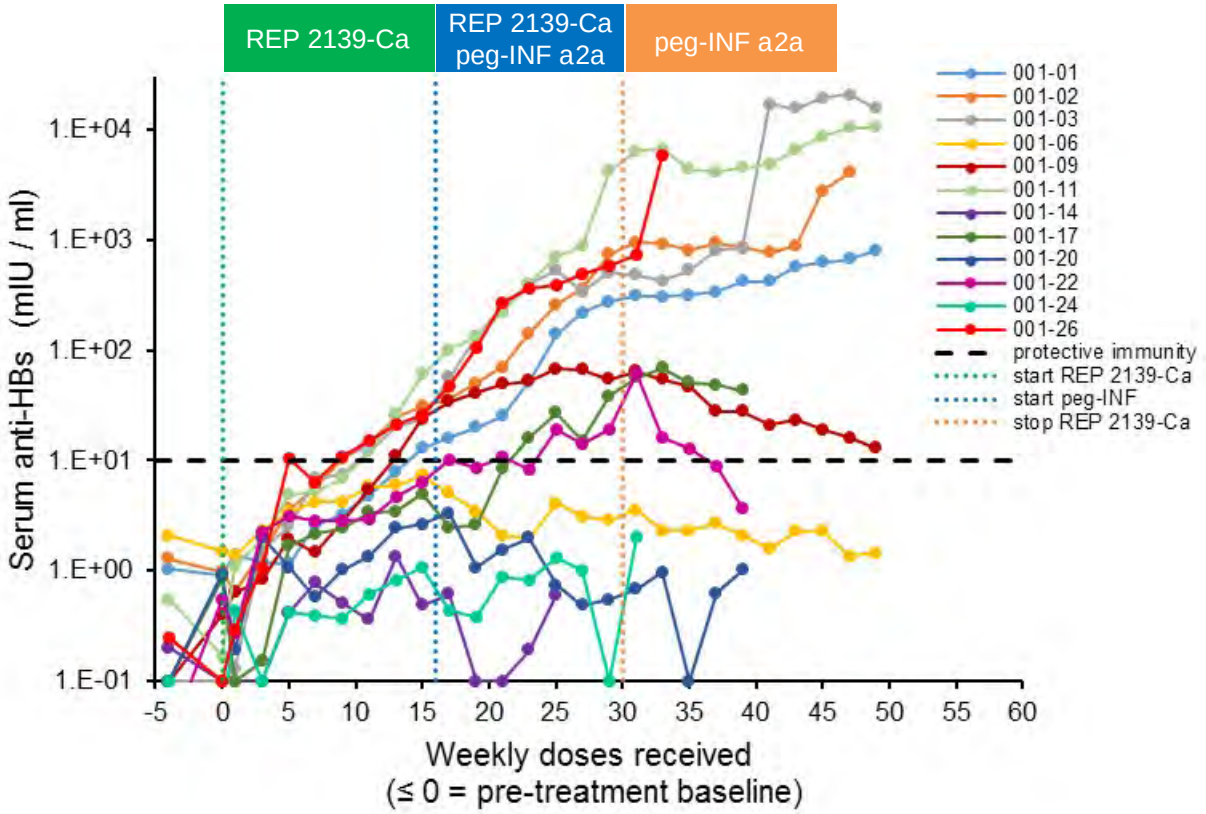
REP 301 Trial Design



Interim REP 301 Efficacy Data (serum HBsAg)



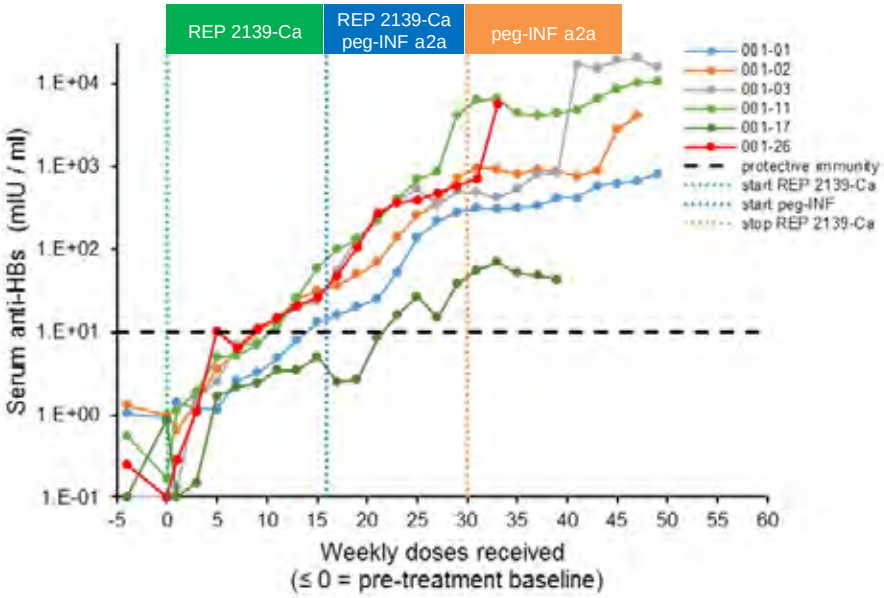
Interim REP 301 Efficacy Data (serum anti-HBs)



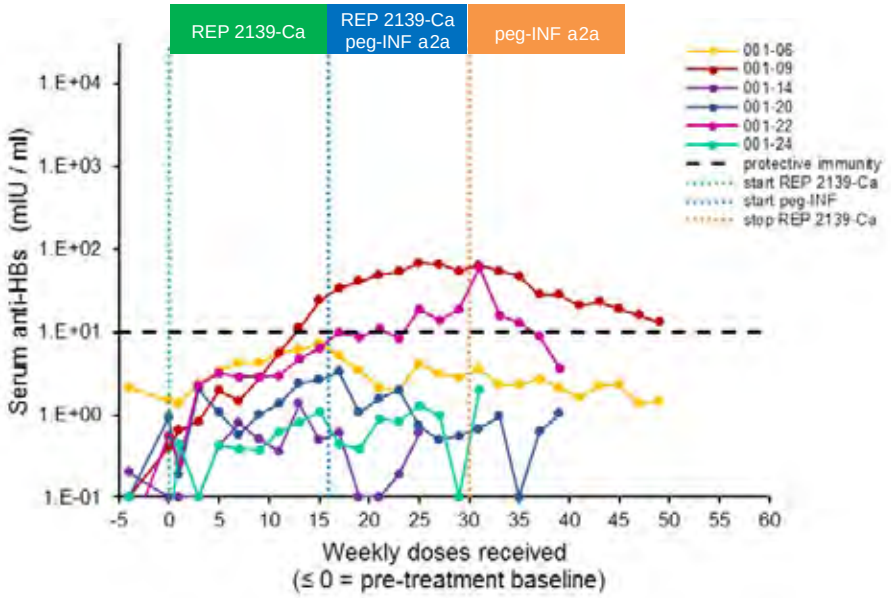
Increased anti-HBs titers are correlated with the onset of peg-INF therapy

Anti-HBs response versus HBsAg response

HBsAg full response
(HBsAg < 1 IU / ml)

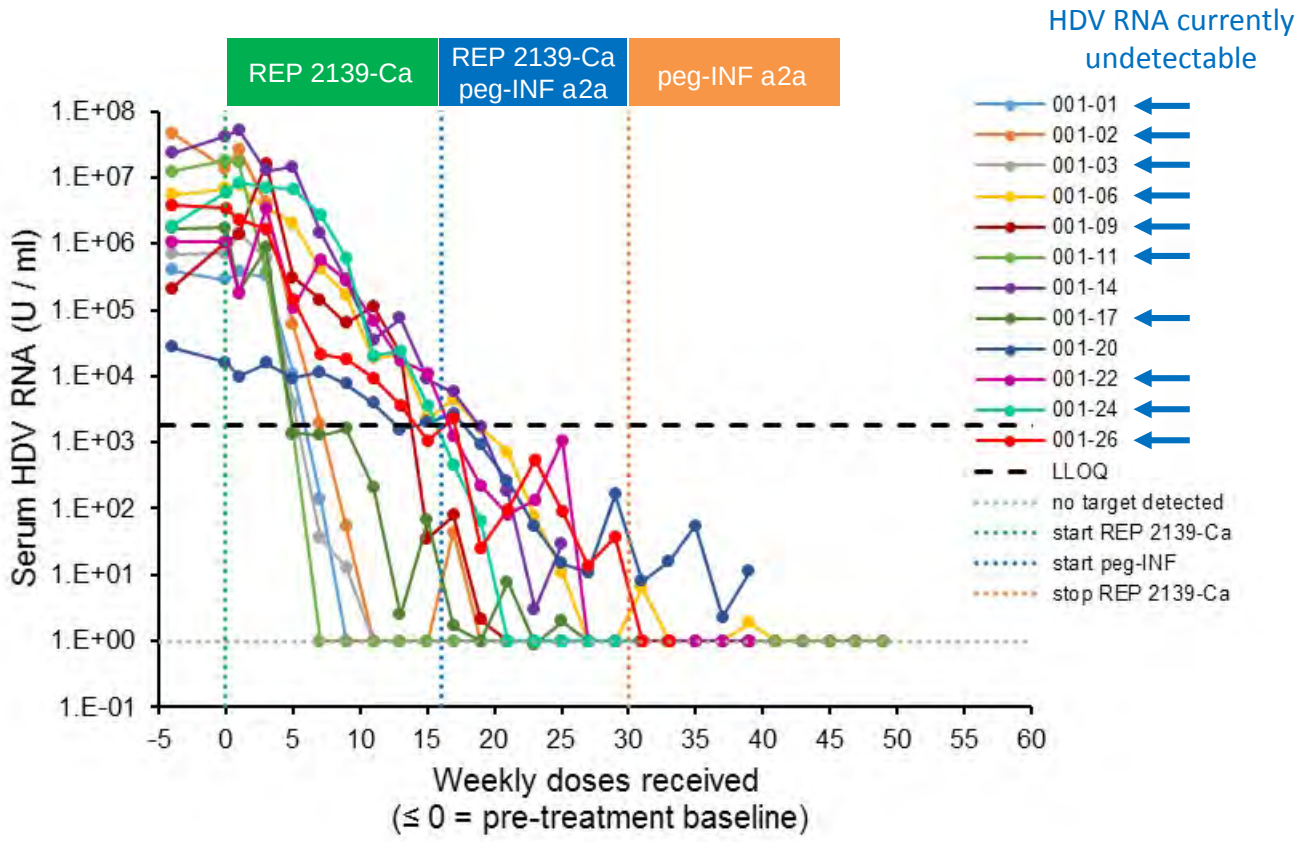


HBsAg partial response
(HBsAg > 1 IU / ml)



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)

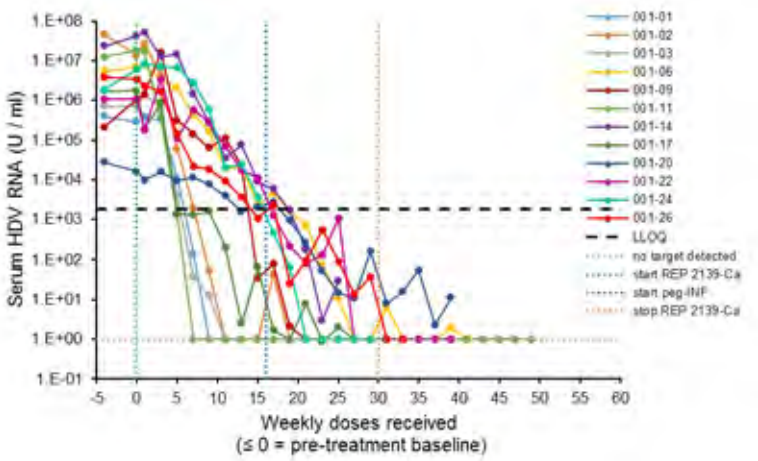


10 / 12 patients currently have no detectable HDV RNA

A distinct antiviral activity of NAPs against HDV is likely present

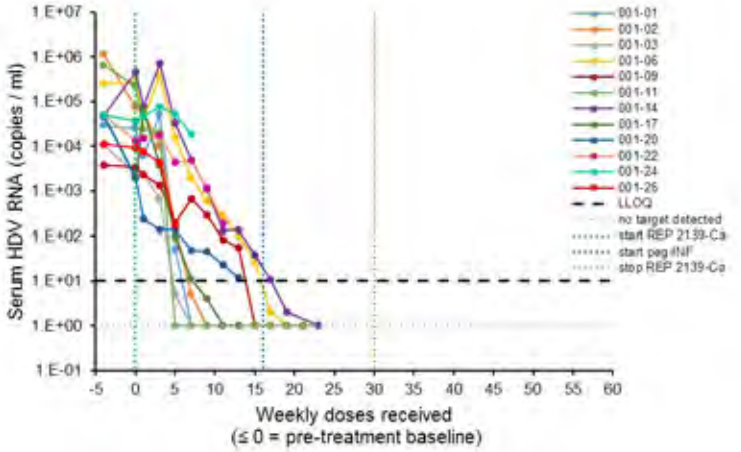
Validation of HDV RNA response

University of Duisburg - Essen

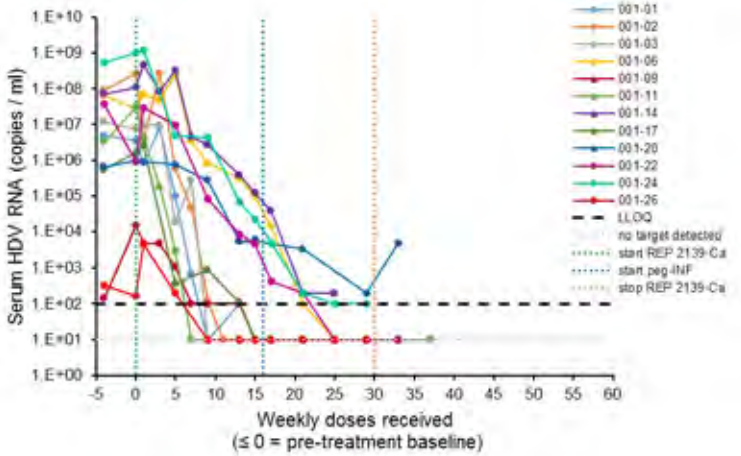


HDV RNA clearance validated in three independent labs

Technical University of Munich



National Genetics Institute

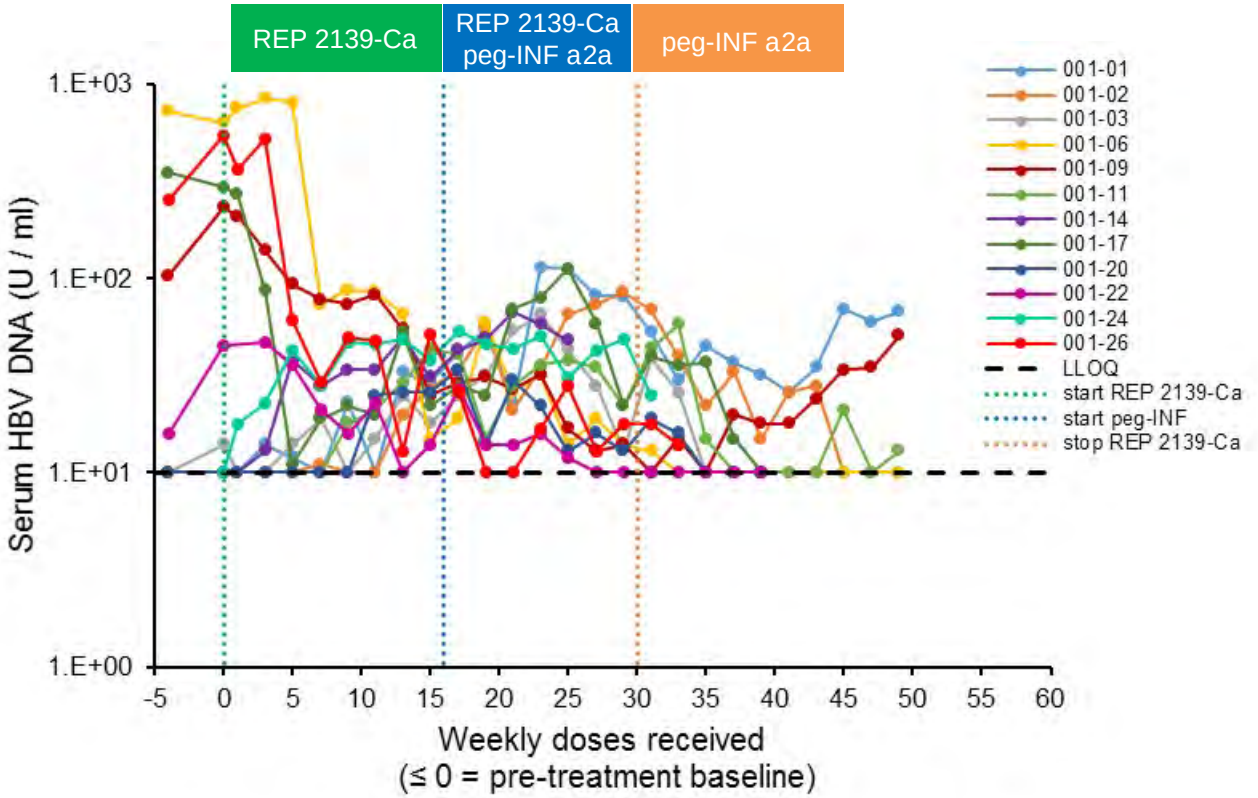


Repression of HBV by HDV

Serum HBV DNA is repressed in patients with chronic HDV co-infection while serum HBsAg persists.

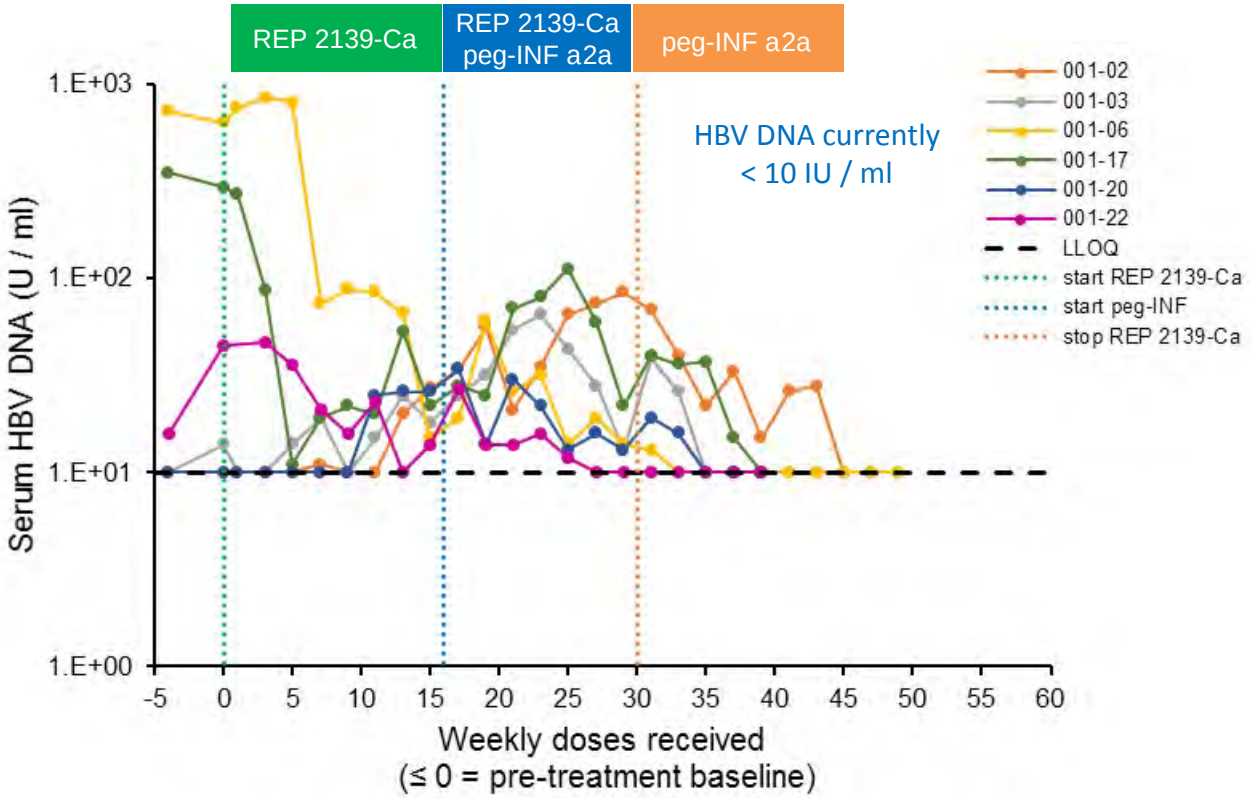
Some aspect of HDV lifecycle interferes with production of HBV virions (mechanism currently unknown)

Interim REP 301 Efficacy Data (serum HBV DNA)



De-repression of HBV DNA consistent with impairment of HDV replication

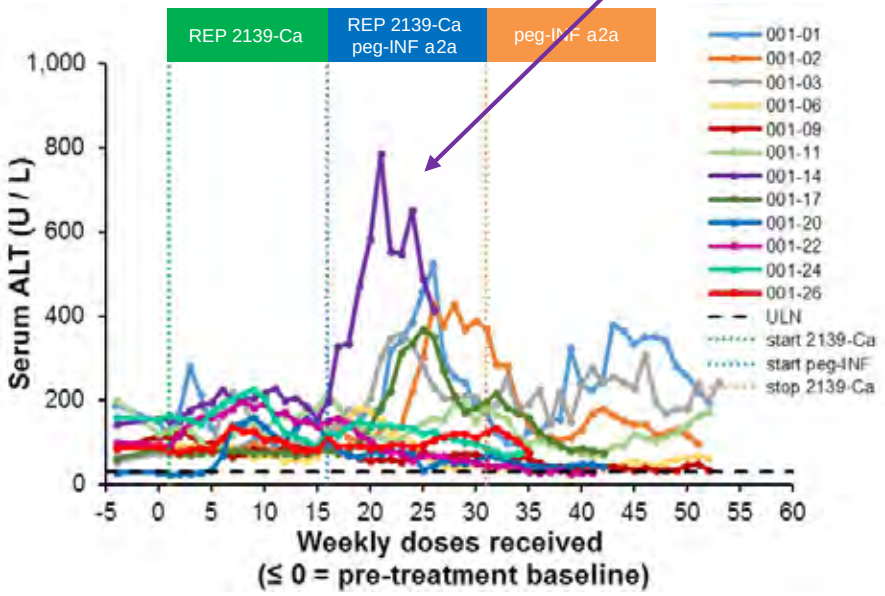
Interim REP 301 Efficacy Data (serum HBV DNA)

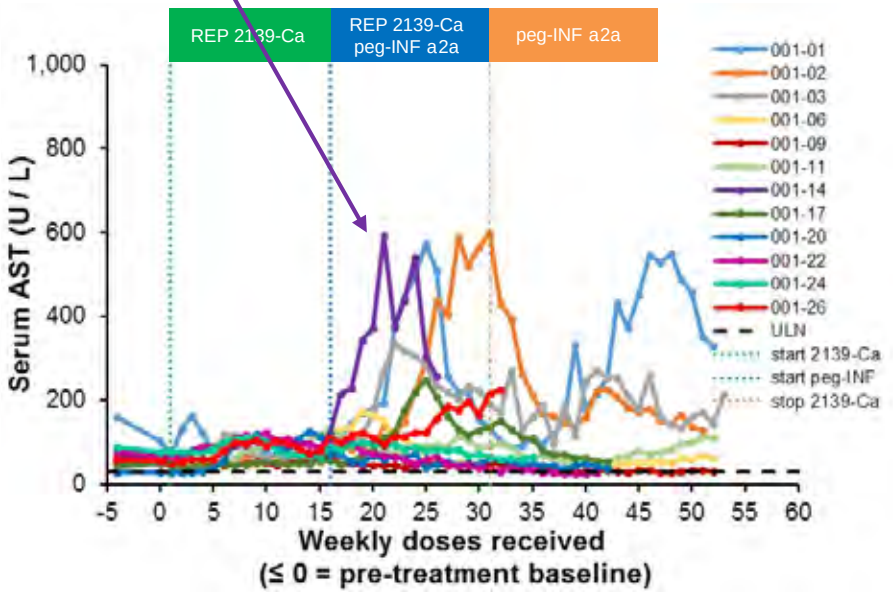


Serum HBV DNA reduced to < 10 IU / ml in 6 patients after starting peg-INF therapy

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

Treatment halted in 001-14 (bilirubin > 2X ULN, related to addition of peg-INF)

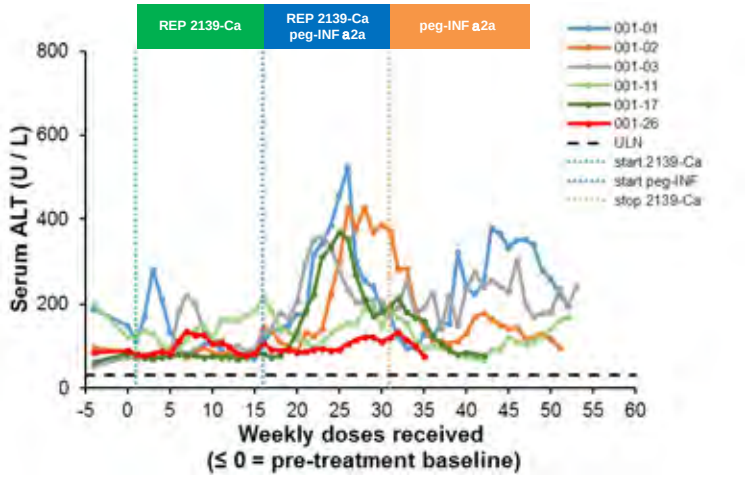


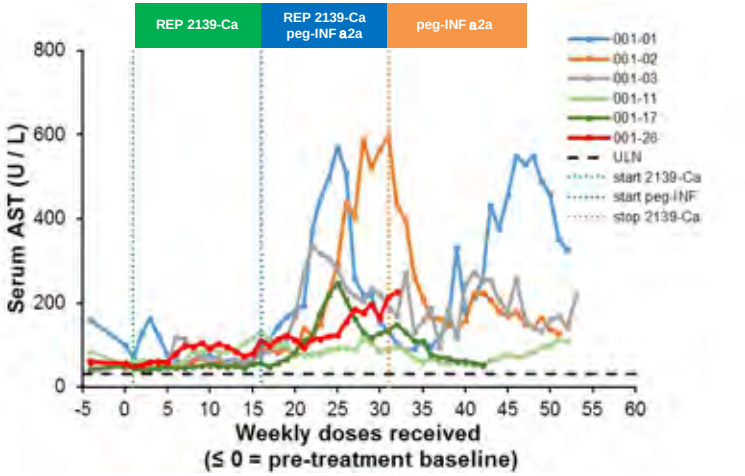


Liver flares are correlated with the onset of peg-INF therapy

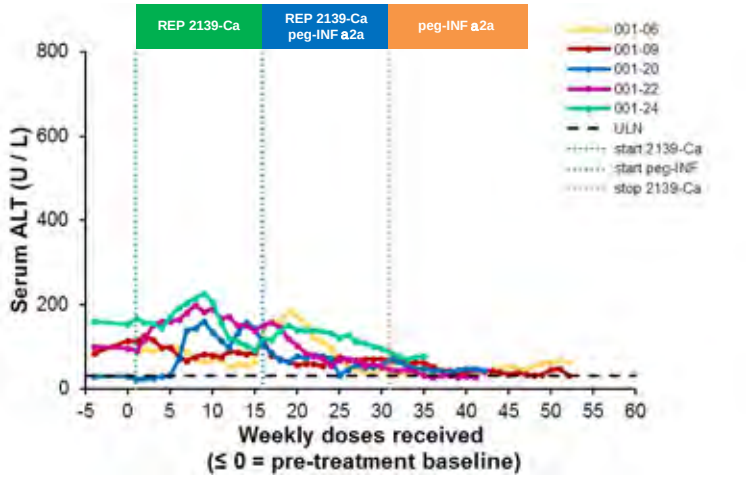
Serum ALT / AST response versus HBsAg response

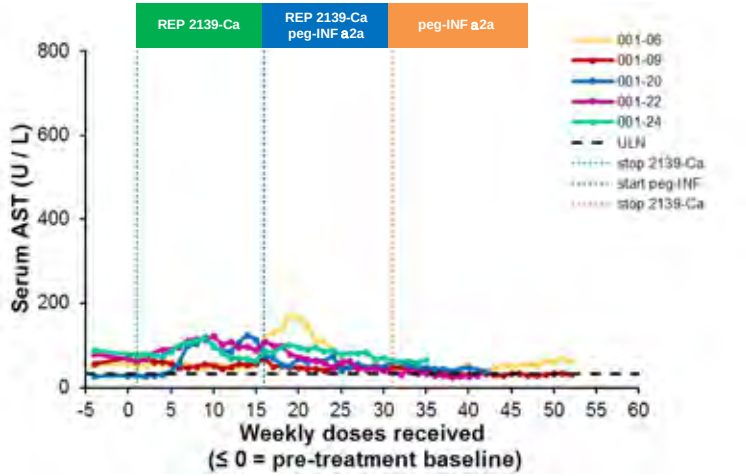
HBsAg full response (HBsAg < 1 IU / ml)





HBsAg partial response (HBsAg > 1 IU / ml)





Liver flares are correlated with serum HBsAg < 1 IU / ml at the start of peg-INF therapy

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
  - No clinically significant findings in clinical serology
- With the addition of peg-INF α2a to REP 2139-Ca therapy:
  - Asymptomatic reductions in platelet and white blood cell counts which stabilize after 5-10 weeks with continued peg-INF α2a exposure
  - ALT / AST flares: limited to patients with serum HBsAg < 1 IU / ml
  - No other signs of liver dysfunction (except bilirubin elevation in one patient)

Summary

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

Pharmacologic effect of NAPs on serum HBsAg observed in Asian patients in previous trials is replicated in Caucasian patients.

REP 2139-Ca is well tolerated.

Increased anti-HBs production and/or liver flares 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.