

SERUM HBV-RNA LEVELS DECLINE SIGNIFICANTLY IN CHRONIC HEPATITIS B PATIENTS DOSED WITH THE NUCLEIC-ACID POLYMER REP 2139-Ca

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Disclosures

- **Hendrik W. Reesink – Consulting / Research Support :**
Abbvie, BMS, Boehringer Ingelheim, Gilead, GSK, Janssen-Cilag, Merck/MSD, PRA-International, Regulus, Replicor, Roche, R-Pharm, Santaris.
- **Andrew Vaillant, Michel Bazinet – Stockholders (shareholder) and Employees:**
REPLICor Inc.
- **The following people have nothing to disclose:**
Louis Jansen, Femke Stelma, Karel van Dort, Neeltje Kootstra, Mamun Al-Mahtab.

Introduction

Chronic Hepatitis B Treatment

Available therapies for patients with chronic hepatitis B¹:

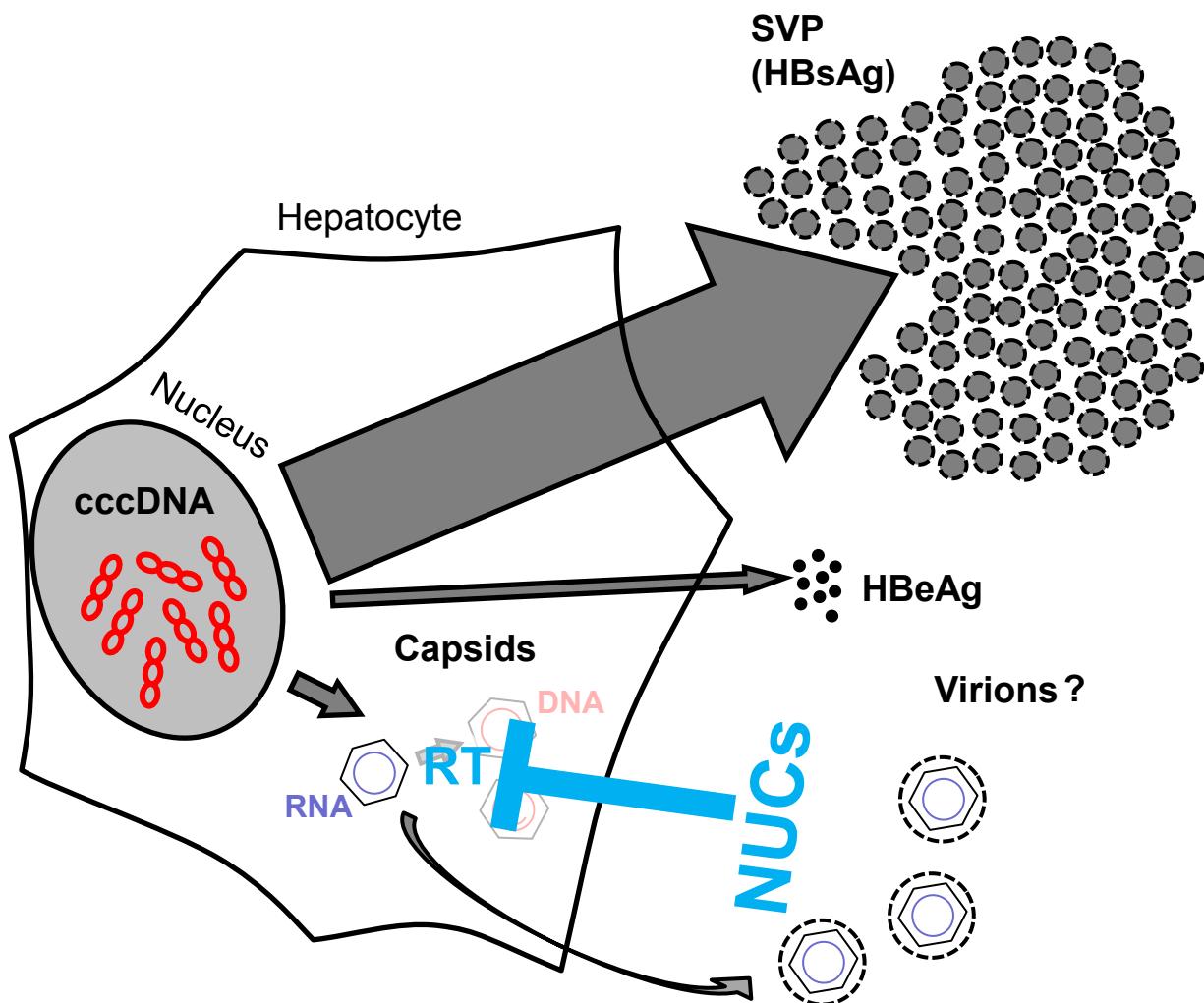
- Peginterferon-α
 - + Potential immune-mediated control of HBV
 - Significant side-effects
- Nucleos(t)ide analogues
 - + Potent viral suppression
 - Limited off-therapy response

Need for new therapeutic approaches:

→ Enhance loss of HBeAg and HBsAg

Hypothesis

Serum Hepatitis B RNA levels in NUC treatment?



Serum HBV RNA^{1,2,3}

1. Zhang et al. *J Med Virol.* 2003
2. Bommel van et al. *Hepatology.* 2014
3. Jansen et al. *AASLD 2013; EASL 2014*

Introduction

Nucleic Acid Polymers (NAPs) in Hepatitis B

- NAPs have entry and post entry antiviral effects in HBV infection in vitro¹
- The post-entry NAP effect appears to be linked to clearance of serum HBsAg²

Hypothesis:

- NAPs prevent subviral particle (SVP) formation

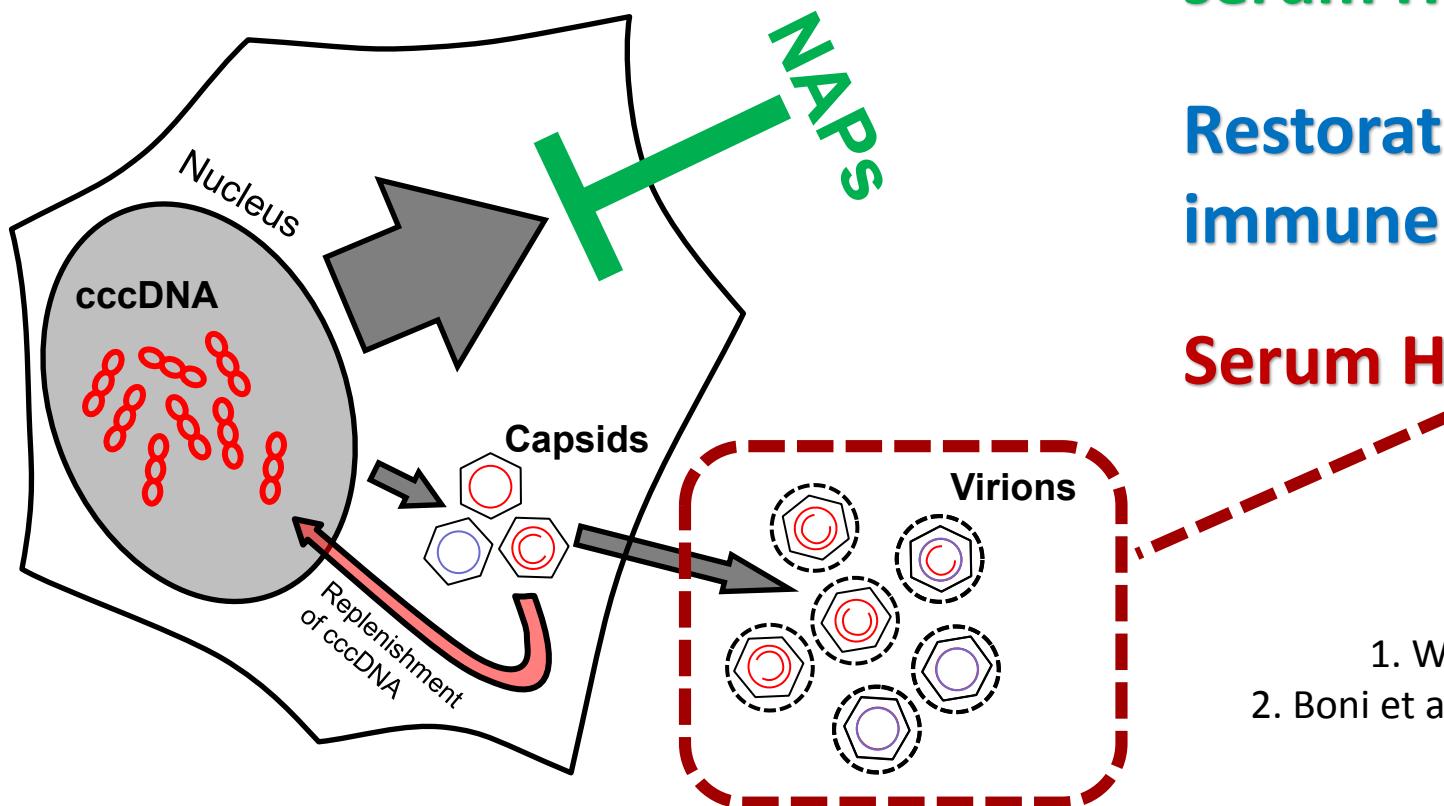
REP 2139 = (A,5'MeC)20 PS-ON, fully 2'O-methylated

REP 2139-Ca = Calcium chelate complex of REP 2139
(improves administration tolerability)

1. Noordeen et al. *Antimicrob Agents Chemother.* 2013; 5291-5298
2. Noordeen et al. *Antimicrob Agents Chemother.* 2013; 5299-5306

Hypothesis

Serum Hepatitis B RNA levels in NAP treatment?



**Elimination of
serum HBsAg**

**Restoration of
immune response?^{1,2}**

Serum HBV RNA?

1. Wu et al. *Hepatology*. 2009

2. Boni et al. *Gastroenterology*. 2012

Research Question

- Kinetics of serum HBV-RNA in patients dosed with nucleic acid polymer (NAP) REP 2139-Ca?

REP 102 protocol: Phase II proof of concept trial

Dr. Mamun Al-Mahtab, (Dhaka, Bangladesh)

Dosing: 2011 – 2012, Follow-up *ongoing*

Patient Cohort

Inclusion criteria REP 102 protocol

- 12 Chronic Hepatitis B patients
- HBeAg-positive
- HBV DNA $10^5 – 10^8$ copies / mL
- Treatment naive
- Metavir \leq F3 (fibroscan)
- ALT $< 3 \times$ ULN

Patient Cohort

Study dosing REP 102 protocol

n = 12

REP 2139-Ca

20-24 Weeks

REP 2139-Ca – 500mg qW 2 hour IV

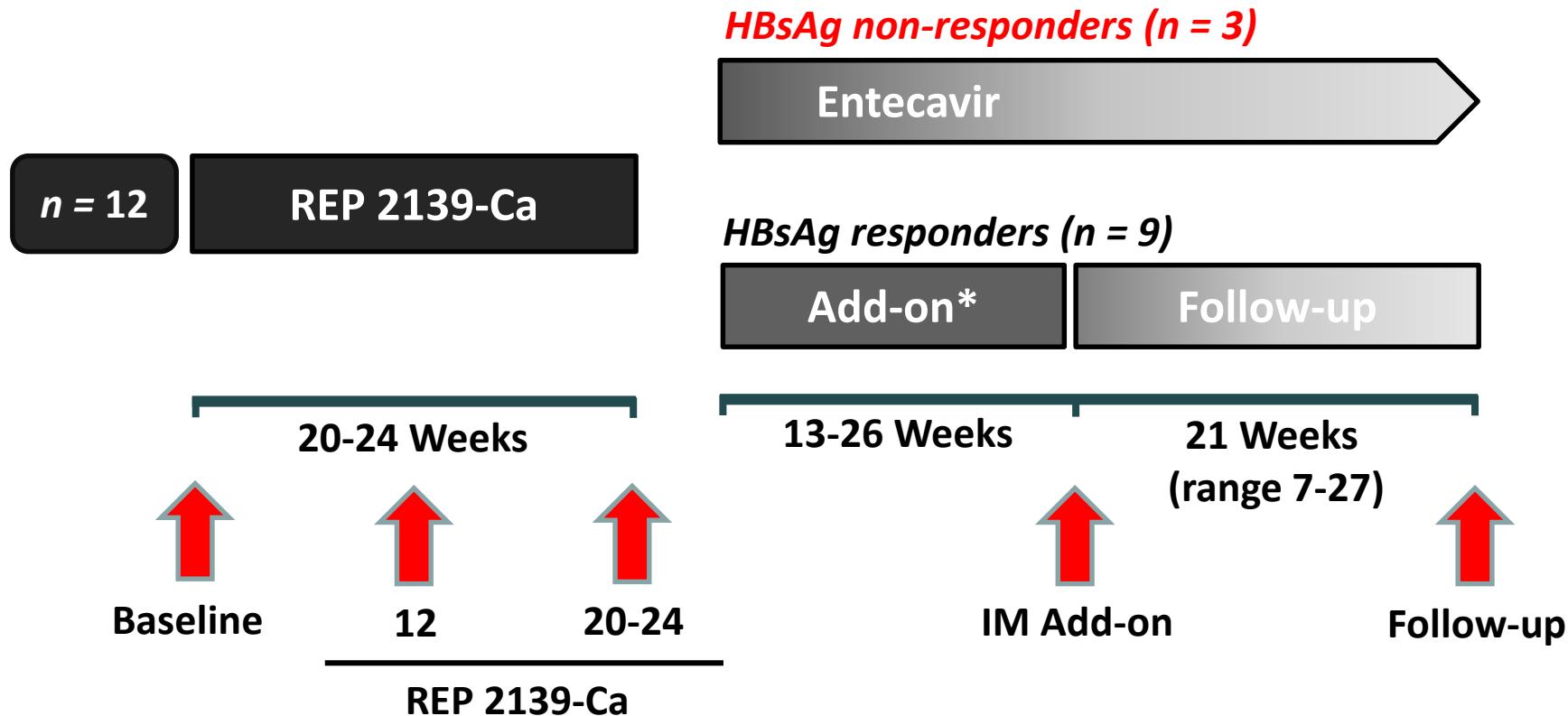
*Add-on: Pegasys™ 180 ug SC qW

and/or

Zadaxin™ (thymosin alpha-1) 1.6mg SC 2qW

Patient Cohort

Time points of HBV RNA measurement

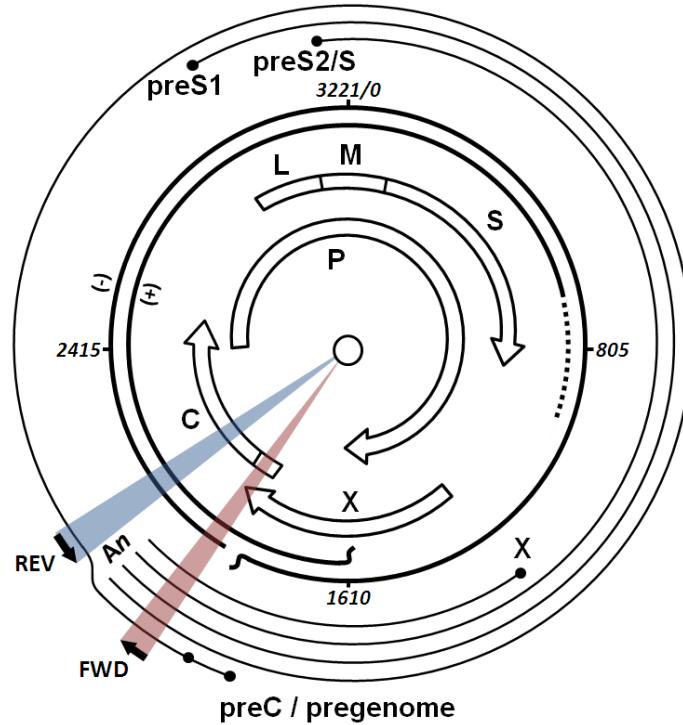


- Serum (-20°C) sent to AMC for HBV RNA measurement
- Compared to HBV DNA (Cobas), and HBsAg (Architect)

Methods

Serum HBV RNA Quantification^{1,2}

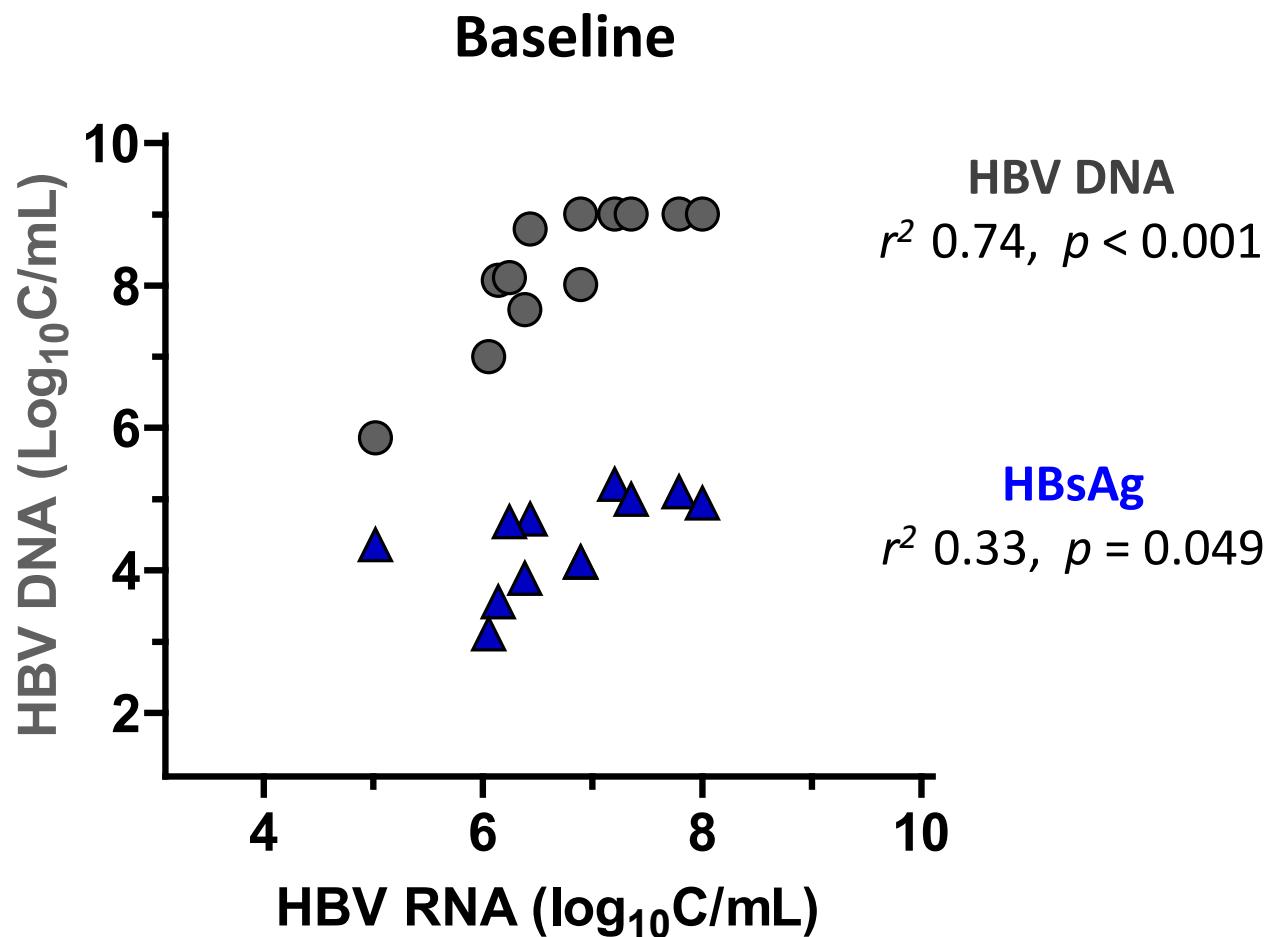
- RNA isolation in plasma
- DNase treatment
- Quantitative RT-PCR specific for HBV-RNA



1. Laras et al. *Virology* 2002.
2. Jansen et al. *AASLD 2013; EASL 2014*.

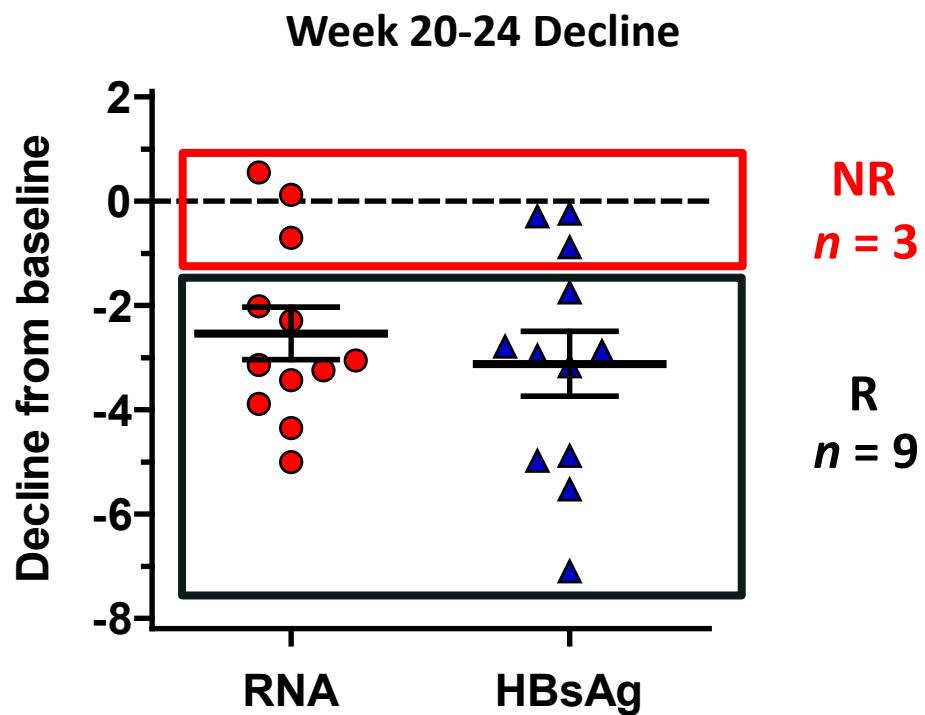
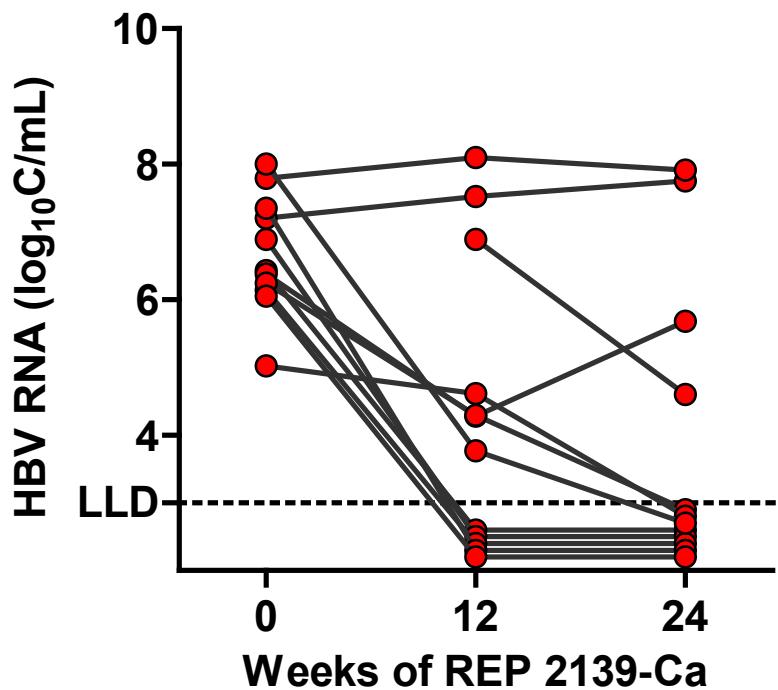
Results

Baseline Serum HBV RNA Levels



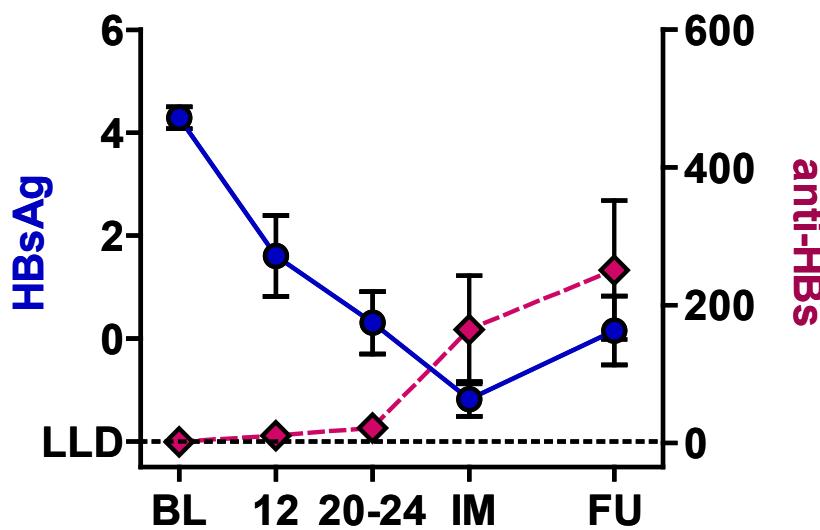
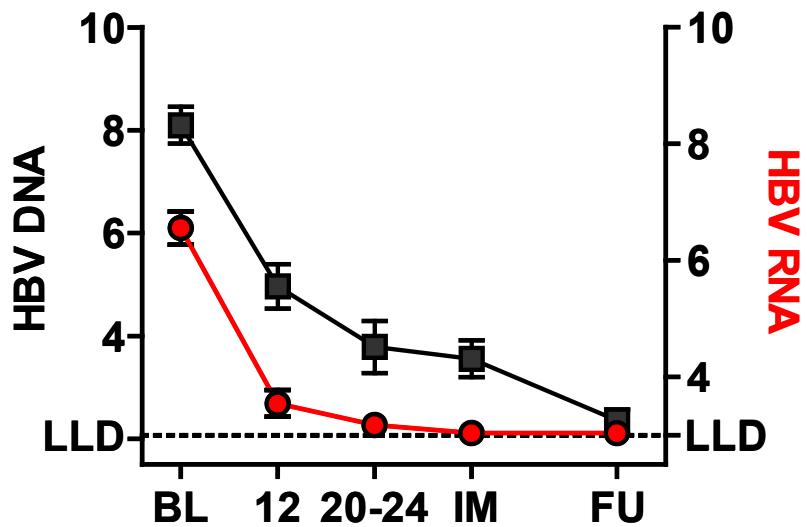
Results

Serum HBV-RNA Decline During REP 2139-Ca Treatment



Results

Serum HBV-RNA in REP 2139-Ca Responders (n = 9)



Mean \pm SEM

HBV DNA, HBV RNA; \log_{10} C/mL

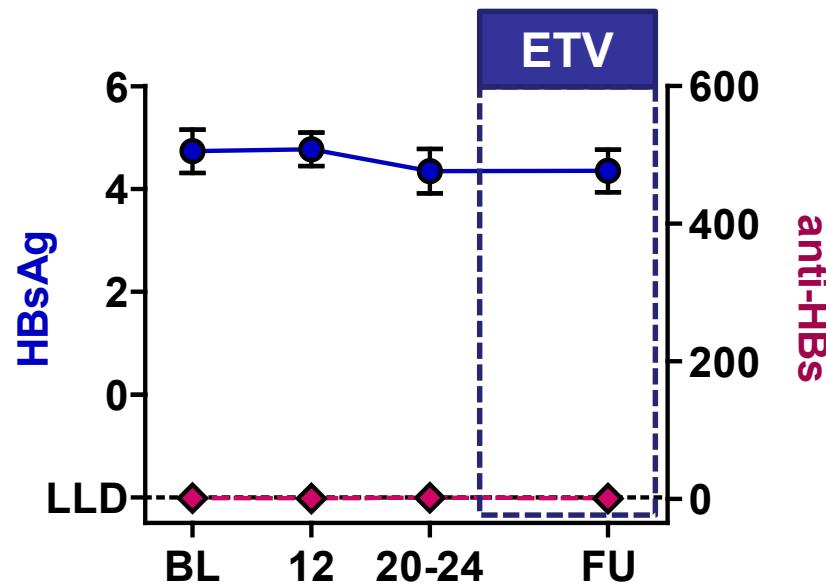
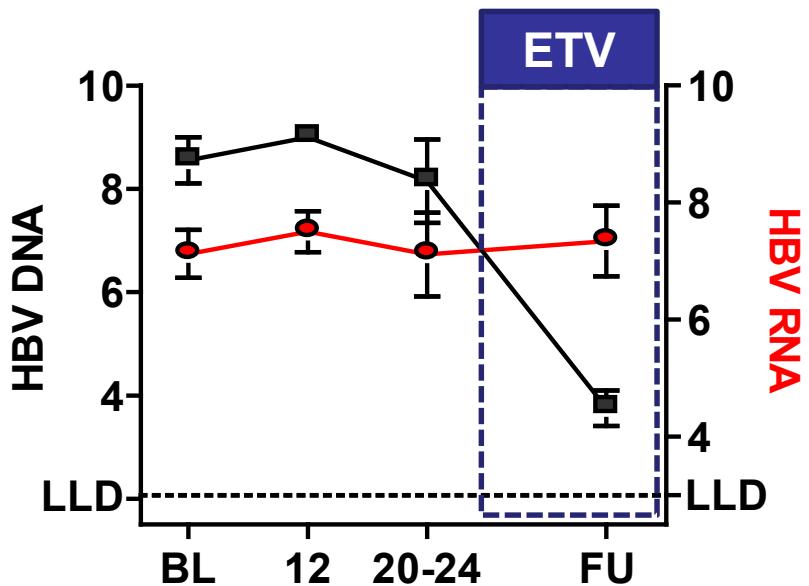
HBsAg; \log_{10} IU/mL

anti-HBs; U/L

At FU: 4/9 patients
HBsAg <0.05 IU/mL
+ anti-HBs positive

Results

Serum HBV-RNA in REP 2139-Ca Non-Responders ($n = 3$)



Mean \pm SEM

HBV DNA, HBV RNA; \log_{10} C/mL

HBsAg; \log_{10} IU/mL

anti-HBs; U/L

Conclusions

- Treatment of CHB patients with REP 2139-Ca resulted in a pronounced decline of serum HBV-RNA in 9/12 of patients
- In 3/12 patients (non-responders) HBV-RNA levels were unaffected, both before and after treatment with entecavir.
- Related abstracts:

Topic	Abstract Number
Preclinical evaluation of NAPs <i>in vivo</i>	P0542
HBV <i>in vitro</i> activity of NAPs	P0556
Clinical cytokine analysis (REP 102)	P0659
HDV <i>in vitro</i> activity of NAPs	LP26
HBV / HDV clinical data (REP 301)	LO2