Establishing functional control of HBV and HDV infection with REP 2139-based combination therapy

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replicor

International HBVCure 2018

HBsAg clearance is essential for functional cure

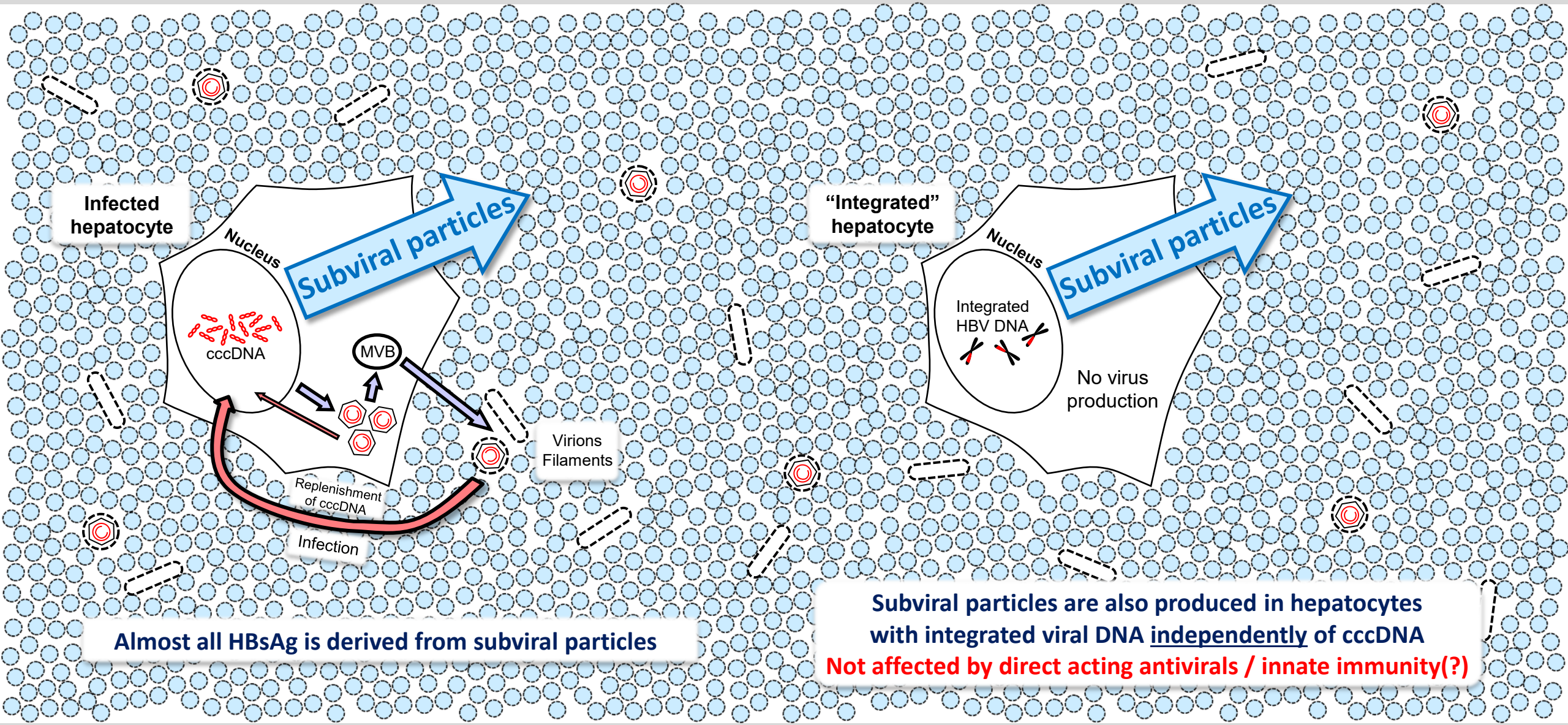
Almost all of the antigen load in HBV infection is HBsAg

Persistent HBsAg is likely to maintain immunosuppression:

- Neutralization of anti-HBs
  - Rydell et al., Virology 2017; 509: 67-70
- Functional exhaustion of HBsAg reactive T-cells and B-cells
  - Kruse et al., Cytotherapy 2018; 20: 697-705
  - Tout et al., J. Immunol. 2018; 201: 2331-2344
  - Boni et al., J Virol 2007; 81: 4215-4225
  - Bertoletti and Gehring, J Gen Virol 2006; 87: 1439-1449
- Suppression of innate immunity
  - Aillot et al., Antimicrob. Agents Chemother. 2018; 62: e01741-17
  - Lebossé et al., J Hepatol 2017; 66: 897-909
  - Yang et al., Int. Immnuopharmacol. 2016; 38: 291-297
  - Kondo et al., ISRN Gastroenterol. 2013; 2013: 935295
- Suppression of the antiviral potential of vaccination / immunotherapy
  - Maini and Pallett, Lancet Gastro Hepatol 2018; 3: 192-202
  - Dembeck et al., Virology 2018; 30: 58-67
  - Al-Mahtab et al., PLoS ONE 2016; 11: e0156667
  - Bazinet et al., Lancet Gastro Hepatol. 2017; 2: 877-889

- **Risk for reactivation of infection if HBsAg persists, even with control of cccDNA!**
  - Lai et al. Hepatol 2017; 66: 512A (AASLD 2017)

HBsAg production in chronic HBV



Almost all HBsAg is derived from subviral particles

Subviral particles are also produced in hepatocytes with integrated viral DNA <u>independently</u> of cccDNA

Not affected by direct acting antivirals / innate immunity(?)

A nucleic acid polymer (NAP)

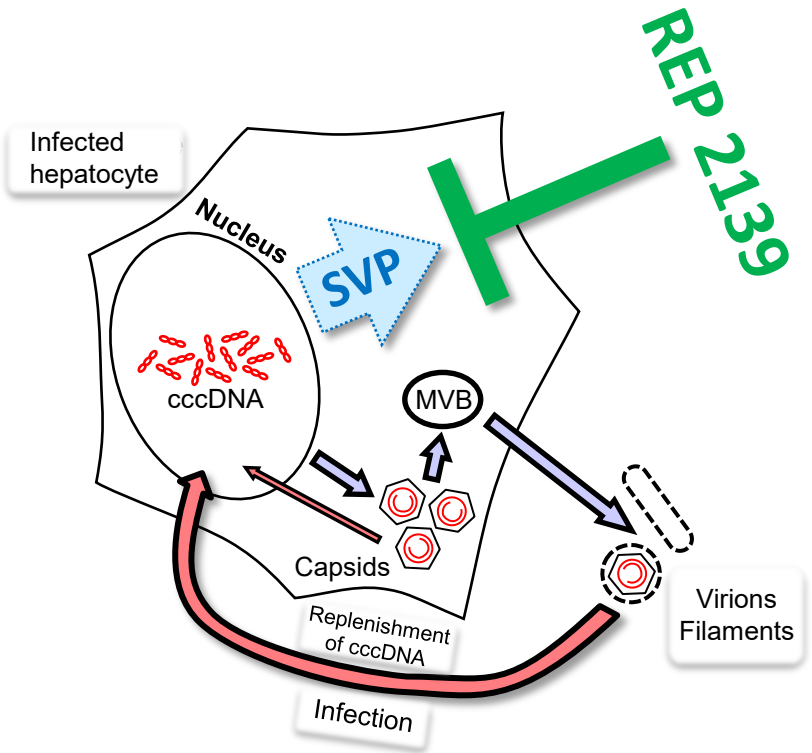
- **Synthesized using well characterized phosphorothioate oligonucleotide (PS-ON) chemistry**
  - **Efficient pharmacologic activity with IV or SC administration in human studies**
  - Long term safety proven in > 15,000 patients in human studies to date in a variety of disease states

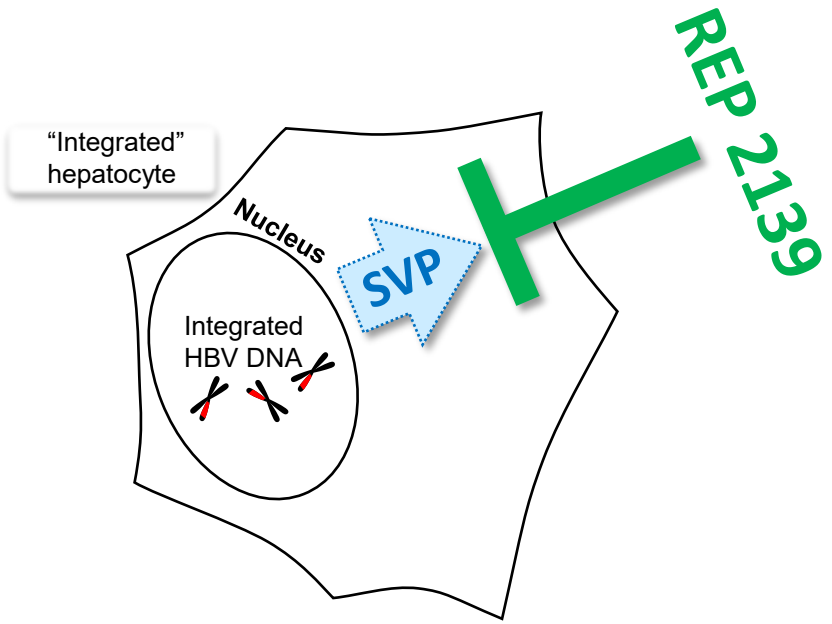
- **REP 2139 – the lead NAP compound**
  - **Confirmed liver uptake with SC administration in monkey studies**
  - Elimination of immunoreactivity drives excellent tolerability in preclinical chronic exposure studies
  - No interaction with HBV or its component proteins
  - Inhibition of SVP assembly drives inhibition of HBsAg secretion and exposes HBsAg to intracellular turnover
    - Host target may be involved in HDL metabolism (SVP are biochemically similar to HDL)
    - NAPs are inactive in rodent models where HDL metabolism does not mirror that in humans
  - **Intrahepatic HBsAg clearance accompanies REP 2139 therapy**

Vaillant, ACS Inf. Dis. 2018; epub Oct 5

Antiviral mechanism of REP 2139 (HBV)

NAPs block the assembly / release of subviral particles from infected or "integrated" hepatocytes





Circulating HBsAg can now be cleared by existing immune function
Critical elimination of HBsAg mediated immunosuppression
Functional cure can be established

Vaillant, ACS Inf. Dis. 2018; epub Oct 5

REP 2139 history in previous clinical studies

Monotherapy:

Active in HBeAg+, HBeAg- and HBV/HDV co-infection
Active in genotypes A, C and D (likely active against all GT)

Rapid 3-7 log reduction in HBsAg (many to < 1 IU/mL)
HBeAg and HBsAg seroconversion (unmasking to < 50 IU/mL)
HBV RNA and HBV DNA clearance
Asymptomatic ALT flares in HBeAg+ when HBsAg < 1 IU/mL (absent in HBeAg-)

With immunotherapy:

Synergy with reduced REP 2139 dose

Increased rate of HBsAg clearance (to < 0.05 IU/mL in most patients)
Clearance of HBcrAg
Increases in circulating anti-HBs
- Timed with start of immunotherapy
- Rapid elevation to > 10,000 IU/mL in most patients

Rapid onset of asymptomatic ALT flares in HBeAg-
- Stronger when HBsAg < 1 IU/mL

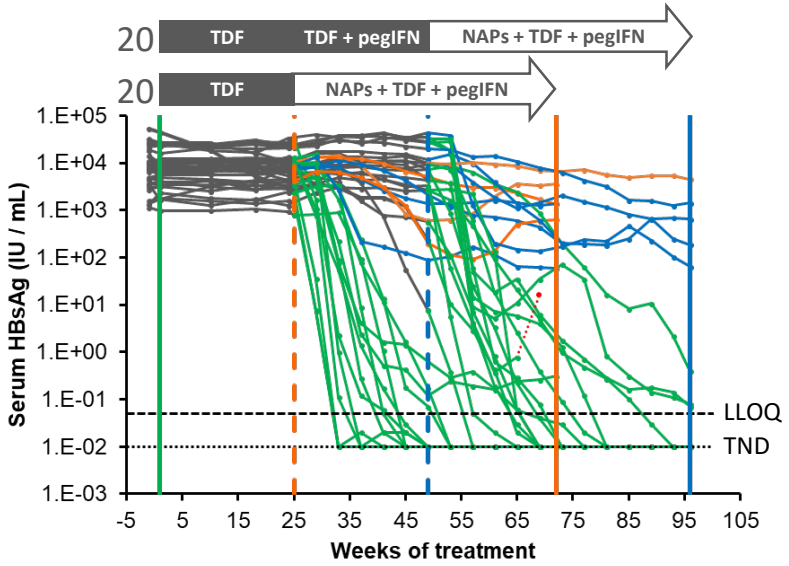
Increased rates of functional cure and inactive HBV

Vaillant, ACS Inf. Dis. 2018; epub Oct 5

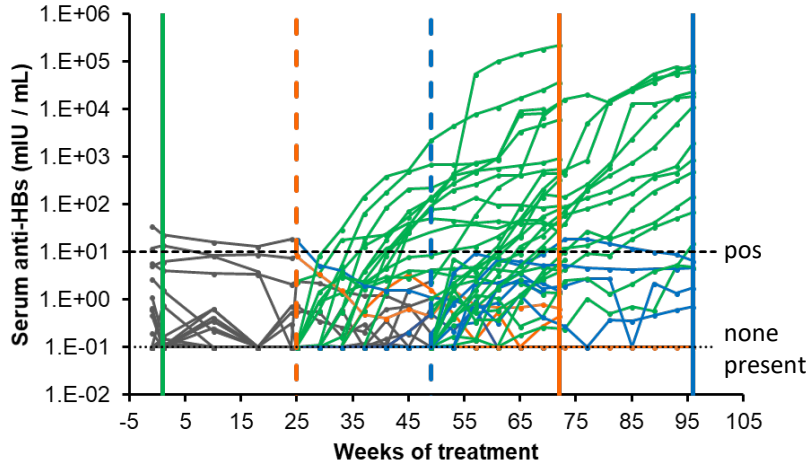
REP 401 study

Combination effect with REP 2139-Mg / REP 2165-Mg, TDF and pegIFN

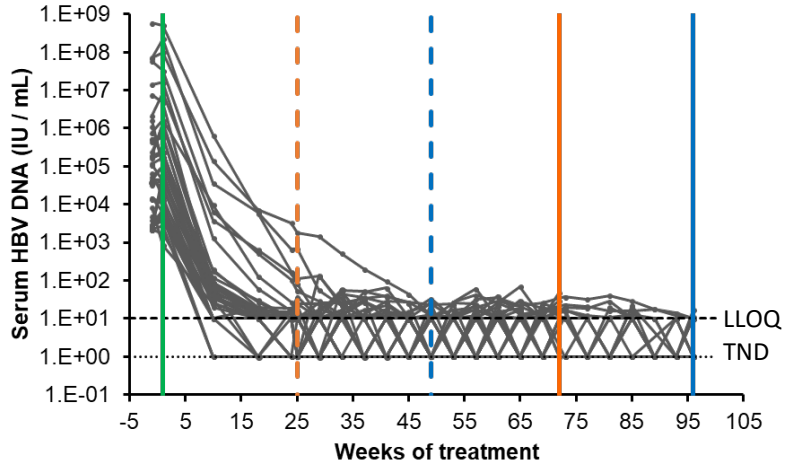
REP 401 study - HBeAg negative chronic HBV mono-infection
40 patients received 48 weeks of REP 2139-Mg or REP 2165-Mg, TDF and pegIFN
Interim analysis from July 7, 2018



REP 2139-Mg = REP 2165-Mg
4/40 non-responders (HBsAg < 1 log reduction)
8/40 HBsAg > 1 log reduction but > 1 IU/mL
28/40 HBsAg < 1 IU/mL
24/40 HBsAg loss (≤ 0.05 IU/mL)



Anti-HBs dramatically increased with the introduction of pegIFN
(but only in patients with HBsAg declines to < 1 IU/mL)



TDF-induced HBV DNA declines unaffected during therapy

Standard of care only | < 1 log reduction in HBsAg | HBsAg > 1 log reduction but > 1 IU/mL | HBsAg < 1 IU/mL

Building a combination regimen with HBsAg loss

Combination effect with TDF and pegIFN

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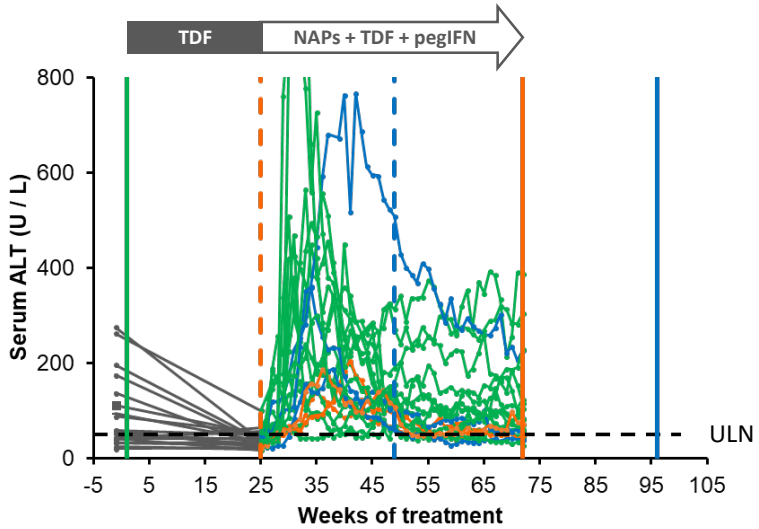
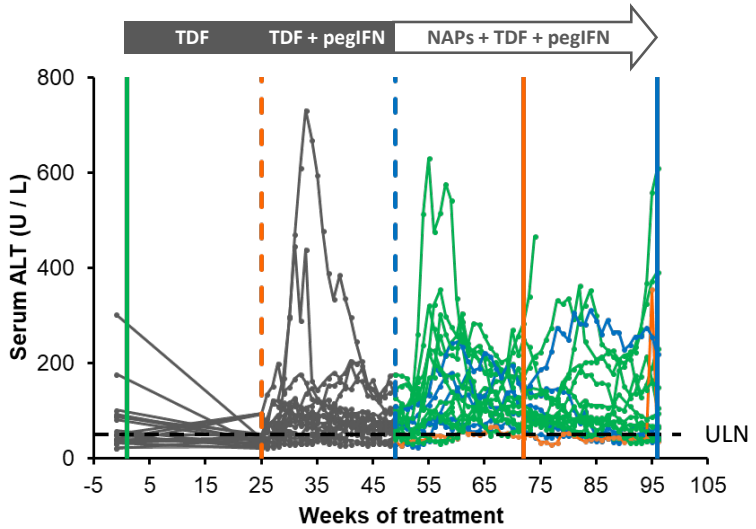




ALT flares observed during immunotherapy
(all otherwise asymptomatic)
(increased intensity in patients with HBsAg declines to < 1 IU/mL)

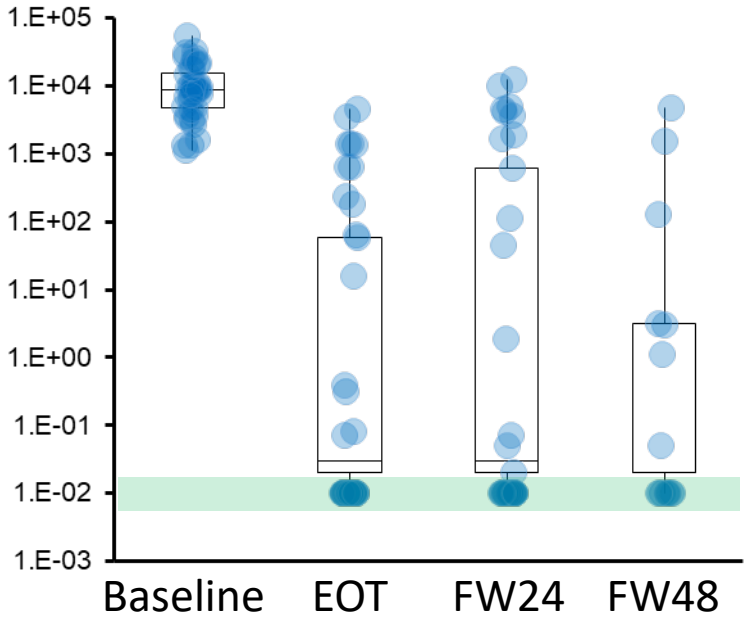
Flares attenuated when NAPs introduced following 24 weeks of pegIFN
Loss of T-cell function with pegIFN(?)

Standard of care only | < 1 log reduction in HBsAg | HBsAg > 1 log reduction but > 1 IU/mL | HBsAg < 1 IU/mL

REP 401
Antiviral performance during therapy and follow-up

34/40 patients have completed treatment and ≥ 24 weeks of treatment-free follow-up

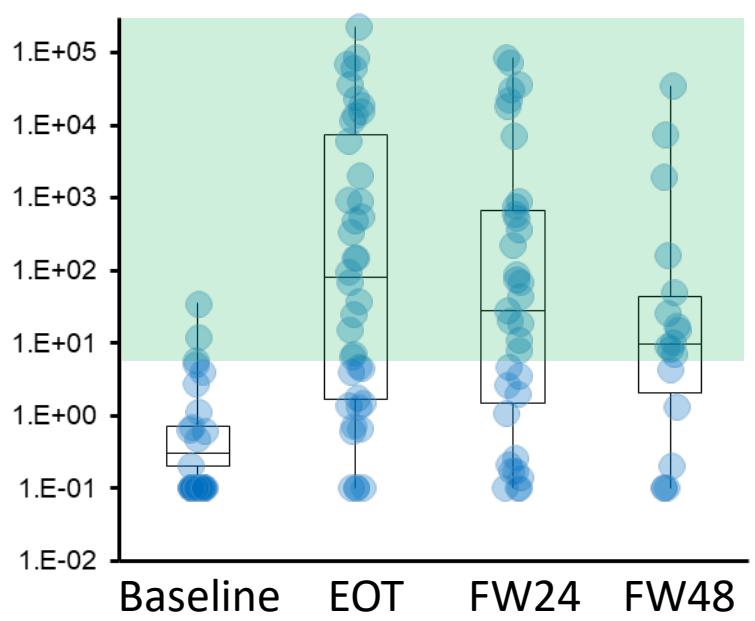
HBsAg (IU/mL)



Baseline	EOT	FW24	FW48
0% (0/40)	60% (24/40*)	53% (18/34)	50% (8/16)

HBsAg loss (≤ 0.05 IU/mL)

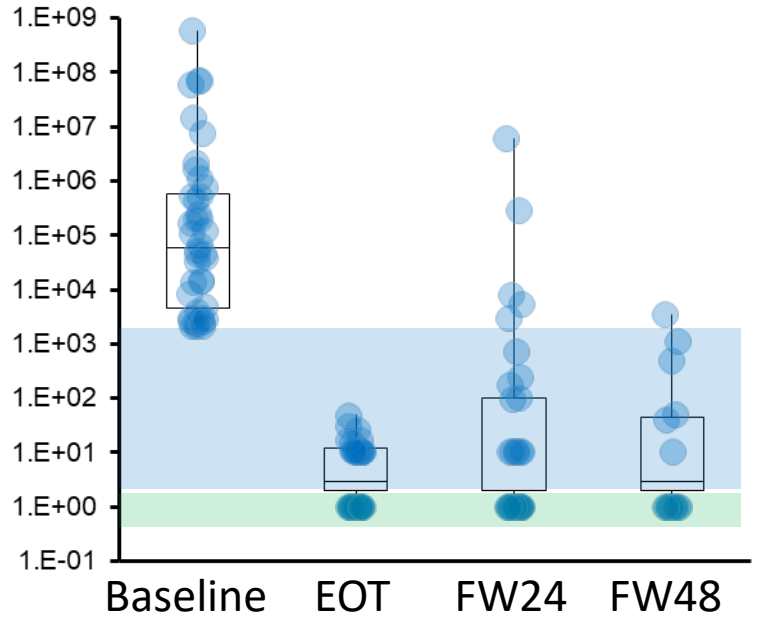
Anti-HBs (mIU/mL)



Baseline	EOT	FW24	FW48
5% (2/40)	60% (24/40*)	59% (20/34)	56% (9/16)

HBsAg seroconversion (Anti-HBs ≥ 10 mIU/mL)

HBV DNA (IU/mL)



Baseline	EOT	FW24	FW48
0% (0/40)	55% (22/40*)	50% (17/34)	62% (10/16)

HBV DNA target not detected

Baseline	EOT	FW24	FW48
0% (0/40)	45% (18/40*)	38% (13/34)	31% (5/16)

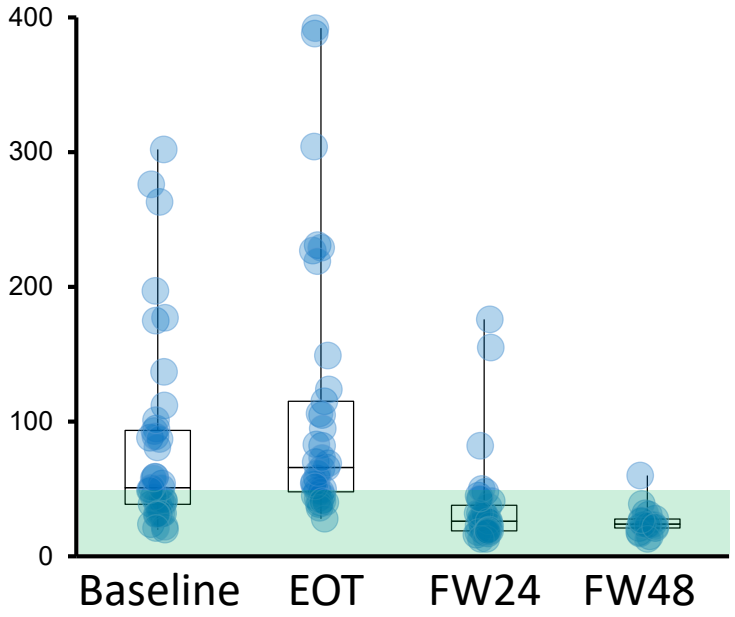
HBV DNA BLOQ to 2000 IU/mL

- 3 patients withdrew from therapy early for personal reasons

BLOQ; below the lower limit of quantification

REP 401
Liver status during treatment and follow-up

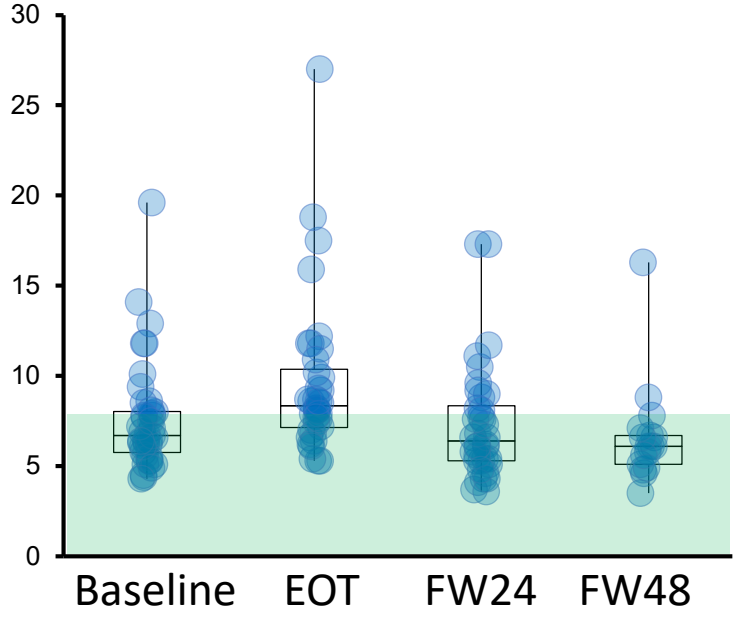
ALT (U/L)



47% (19/40) **32%** (13/40*) **91%** (31/34) **94%** (15/16)

Normal ALT
(≤ 50 U/L)

Median hepatic stiffness (kPa)



52% (21/40) **22%** (9/40*) **62%** (21/34) **81%** (13/16**)

Median hepatic stiffness consistent with F0
(≤ 7 kPa)

Improvement in liver function during follow-up

Improvement compared to baseline

* 3 patients withdrew from therapy early for personal reasons
** 2 FW48 fibroscan results still pending

REP 401 response summary

Patients entered into trial		**40**
End of treatment HBsAg response	> 1 log from baseline	36
	< 1 IU/mL	**27**
	≤ 0.05 IU/mL	**24**
Patients currently completed treatment and ≥ 24 weeks of follow-up		**34**
Inactive CHB (HBV DNA ≤ 2000 IU/mL, normal ALT)		44%
HBV functional cure (HBsAg and HBV DNA target not detected)		41%
Clinical benefit (Low risk of progression, reduced risk of HCC)		**85%**

Summary

REP 2139-based combination therapy uniquely achieves high rates of serum HBsAg loss during therapy

- Accompanied by : Clearance of liver HBsAg, HBcAg, HBV DNA and cccDNA (in animal studies)
  HBeAg and HBsAg seroconversion
  Clearance of serum HBV DNA and HBV RNA and HBcrAg

  High rates of asymptomatic transaminase flares (likely therapeutic in nature)

- **Achieves high rates of functional cure of HBV (HBV RNA and HBcrAg also remain controlled)**
  Effects appear correlated with HBsAg reduction to < 1 IU/mL during therapy

- **REP 401 study: 85% of patients have control of infection not requiring treatment (AASLD EASL guidelines)**

- **Long term safety of REP 2139 well established with 2 years of follow-up (REP 102 and 301 studies)**

REP 2139-Mg Next steps

Please come see us at poster 393 at AASLD (Nov 9) and at the HDIN meeting (Nov 10)

Transition to subcutaneous dosing

- Delivery to liver with SC administration confirmed in monkey studies
- *Excellent IV tolerability predicts excellent SC tolerability of REP 2139-Mg*
- POC trial planned in HBV/HDV infection

Initiation of phase IIA trial in the US (collaboration with ACTG)

- Verify efficacy and safety of REP 401 regimen in multicenter, multi country trial.
- Will facilitate early initiation of phase IIB trial (with transition to SC)

Assessing other immunotherapies

- Potential for improvement of functional cure rates with other immunotherapies
- Can only be assessed with HBsAg reduction to < 1 IU/mL

Development of REP 2165-Mg for the treatment of patients with poor HBsAg response to REP 2139

- Predictive host markers for patients having poor HBsAg response to REP 2139-Mg are under investigation

Acknowledgments

A collaborative effort!

Clinical evaluations:

Montreal, Canada
Michel Bazinet

Dhaka, Bangladesh
Mamun Al-Mahtab

Chișinău, Moldova
Victor Pântea
Valentin Cebotarescu
Lilia Cojuhari
Pavlina Jimbei
Gheorghe Placinta
Liviu Iarovoi
Valentina Smesnoi
Tatiana Musteata
Iurie Moscalu
Alina Jucov

US
Marion Peters
Mark Sulkowski

Clinical virology and assay validation:

Essen, Germany
Adalbert Krawczyk

Munich, Germany
Michael Roggendorf
Hadi Karimzadeh
Hrvoje Mijočević
Zainab Usman

Los Angeles, USA
Peter Schmid
Jeffrey Albrecht

Bobigny, France
Emmanuel Gordien
Frédéric Le Gal

US
Gavin Cloherty

Pre-clinical evaluations:

Adelaide, Australia
Allison Jilbert
Faseeha Noordeen
Catherine Scougall

Lyon, France
Lucyna Cova
Celia Brikh
Jonathan Quinet
Catherine Jamard

Essen, Germany
Michael Roggendorf
Katrin Schöneweis
Mengji Lu
Pia Roppert
Dieter Glebe

Logan, Utah, USA
John Morrey
Neil Motter

Reno, Nevada, USA
Doug Kornbrust

Mechanistic studies:

Montreal, Canada
Matthieu Blanchet
Patrick Labonté

Paris, France
Camille Sureau
Frauke Beilstein
Matthieu Lemasson

Essen, Germany
Ruth Broering
Catherine Real
Joerg Schlaak

Ness Ziona, Israel
Raphael Mayer
Merav Merom Shamur
Ronny Peri-Naor