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

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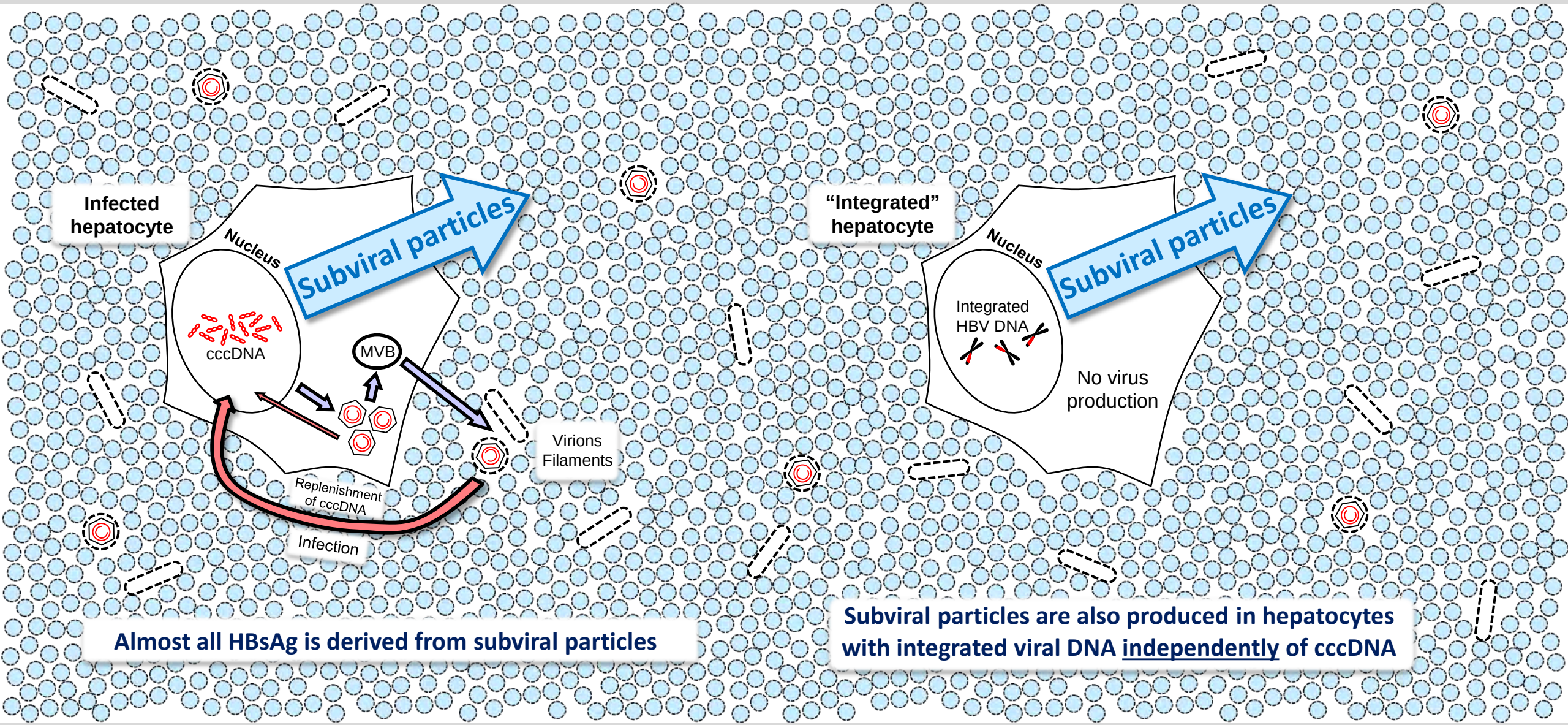
replicor

HBV
INTERNATIONAL MEETING
2018 TAROMINA ITALY

HBsAg production in chronic HBV



Almost all HBsAg is derived from subviral particles

Subviral particles are also produced in hepatocytes with integrated viral DNA independently of cccDNA

HBsAg clearance is essential for functional cure

While circulating HBsAg persists:

- Anti-HBs will be continually neutralized
  Rydell et al., Virology 2017; 509: 67-70
- T-cells will remain in a functionally exhausted state
  Kruse et al., Cytotherapy 2018; 20: 697-705
  Boni et al., J Virol 2007; 81: 4215-4225
  Bertoletti and Gehring, J Gen Virol 2006; 87: 1439-1449
- Innate immunity will be suppressed
  Lebossé et al., J Hepatol 2017; 66: 897-909
- Vaccination / immunotherapy will be ineffective
  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 or re-infection remains!**
  Lai et al. Hepatol 2017; 66: 512A (AASLD 2017)

REP 2139

A nucleic acid polymer

- Phosphorothioate oligonucleotide
- Efficiently targeted to the liver
- No antisense functionality or liver immunoreactivity

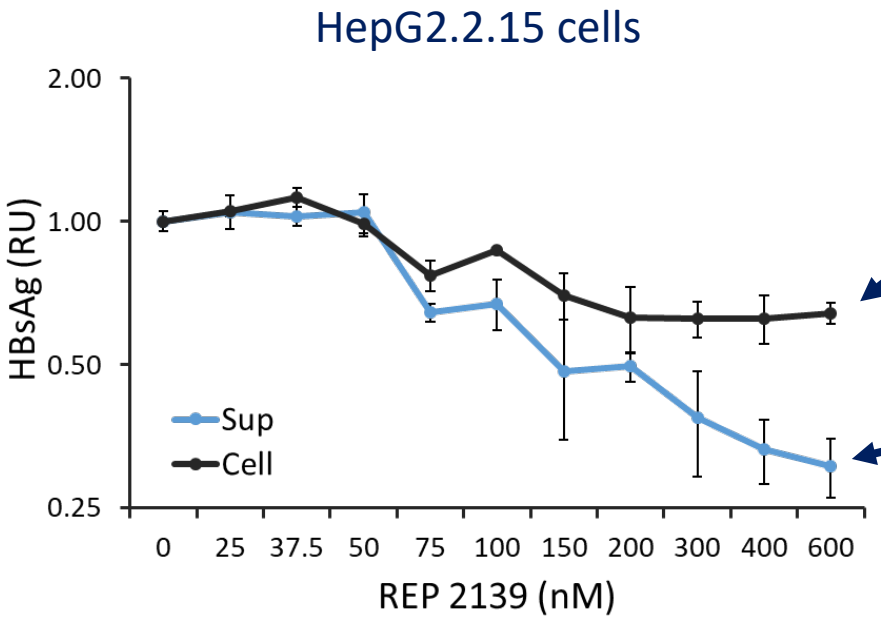
Broad spectrum antiviral activity

- HIV, HSV, CMV, RSV, influenza, ebola, HCV and HBV (+ others)

REP 2139 therapy in chronic HBV and HDV infection

- **Achieves HBsAg and HDV RNA loss**
- **Associated with functional cure of HBV and HDV**

Antiviral effects of REP 2139 in HBV *in vitro*

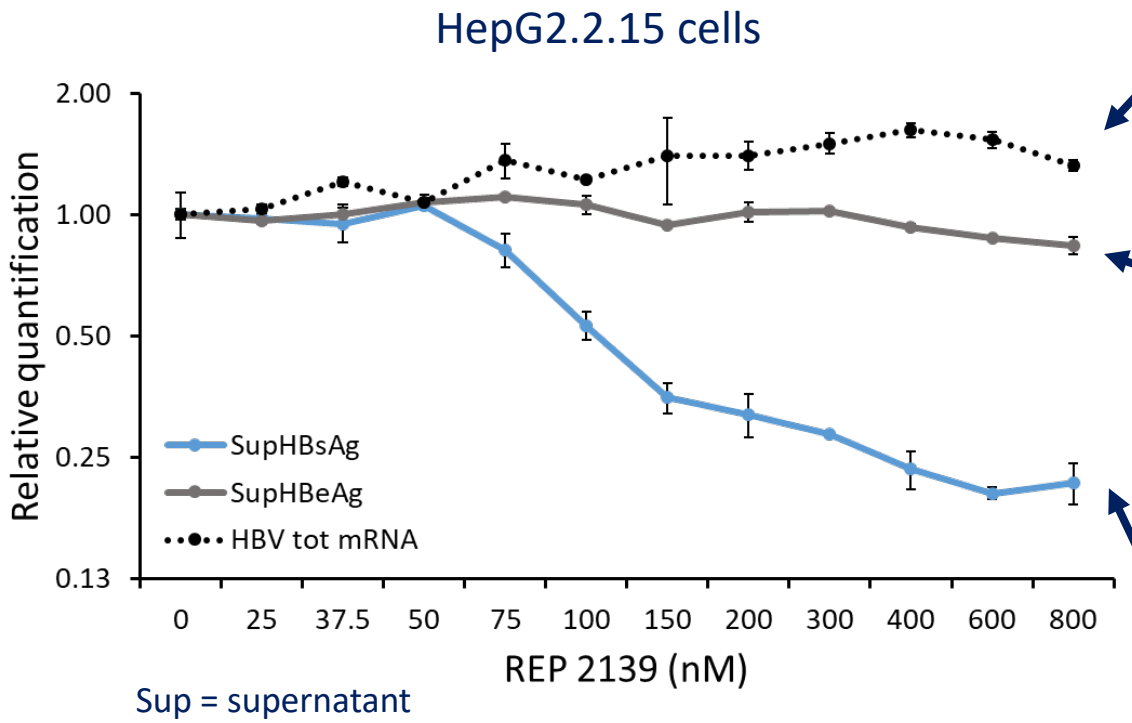


Inhibition of HBsAg release is not accompanied by intracellular HBsAg accumulation
(intracellular HBsAg appears to decrease)

REP 2139 inhibits HBsAg secretion

Blanchet et al., HBV International Meeting 2018, Poster session III

Selectivity of the REP 2139 effect



Sup = supernatant

HBV mRNA not affected
Post-translational effect

HBeAg secretion not affected
Selective for HBsAg

Inhibition of HBsAg secretion likely the primary antiviral effect
inhibition of SVP assembly / release
(effects on virion release not yet excluded)

Blanchet et al., HBV International Meeting 2018, Poster session III

The REP 2139 target…..

REP 2139 does not block entry of HBV or HDV

Guillot et al., PLoS ONE 2017; 12: e0179697
Beilstein et al., J Virol 2018; 92: e01416-17

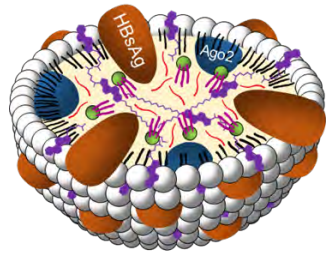
REP 2139 does not interact with HBsAg, HBeAg, HBcAg, HBV or HDV

Beilstein et al., J Virol 2018; 92: 001416-17
Shamur et al., Hepatol 2017; 66: 504A
Bazinet et al., Lancet Gastro Hepatol 2018; 3: e1

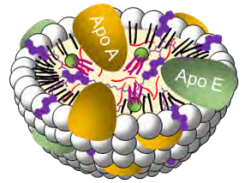
REP 2139 target is a host protein

May be involved in HDL metabolism

- SVP are biochemically similar to HDL
- REP 2139 is inactive in rodent models of HBV (HDL metabolism is different from humans)
  Schöneweis et al., Antiviral Res 2018; 149: 26-33
- REP 2139 is active in DHBV-infected ducks (HDL metabolism mirrors that in humans)
  Quinet et al., Hepatol. 2081; 67: 2127-2140



SVP



HDL

SVP in humans is very similar to HDL

Gavilanes et al., J Biol Chem 1982: 257: 7770-7777
Novellino et al., PLoS One 2012; 7: e31952
Grenier et al., Biochemie. 2010; 92: 994-1002

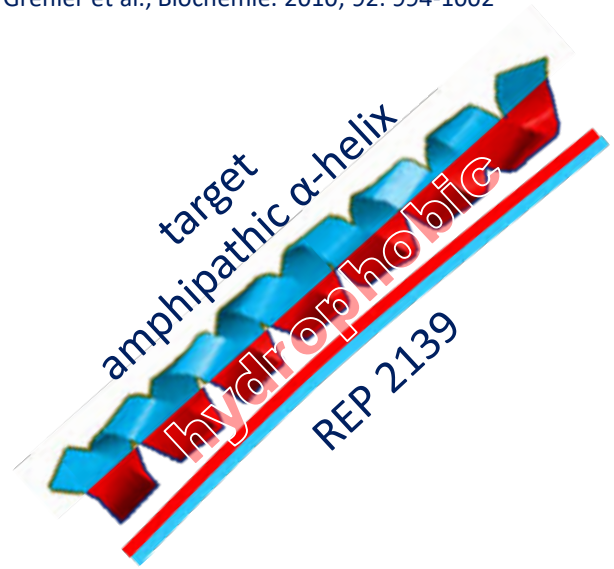
REP 2139 target interface in HBV is an exposed hydrophobic protein domain

Validated *in vitro* in primary duck hepatocytes and in HepG2.2.15 cells

Noordeen et al., Antimicrob Agents Chemother 2013; 57: 5291-5298
Blanchet et al. HBV 2018 International HBV meeting Poster session III

Similar to the NAP target interface found in all other NAP-responsive infectious diseases

Vaillant ACS Inf Dis 2018; epub Sept 10

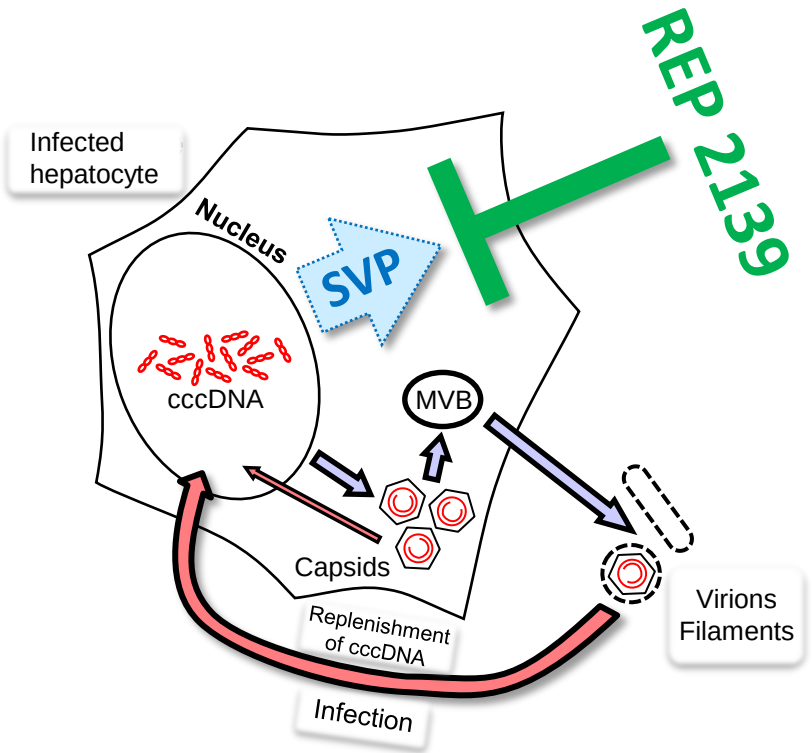


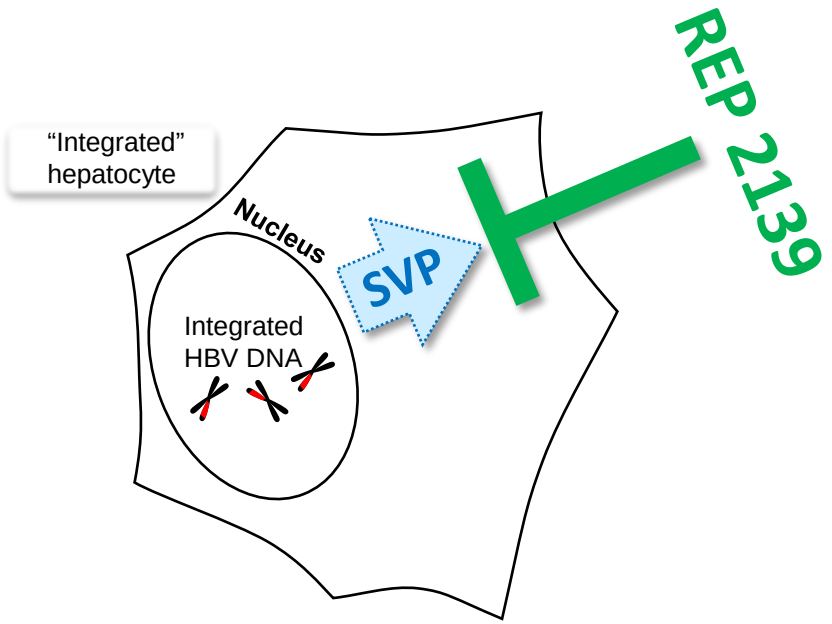
Chronic engagement of the REP 2139 target is safe

No alteration of liver function or lipid metabolism with chronic exposure in pre-clinical and clinical studies

Antiviral mechanism of NAPs

NAPs block the 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

REP 2139 effects *in vivo* and in previous clinical trials

Antiviral response	In vivo (DHBV infected Pekin ducks)	HBeAg positive chronic HBV infection (REP 101 study)	HBeAg positive chronic HBV infection with immunotherapy (REP 102 study)	HBeAg negative chronic HBV/HDV co-infection with immunotherapy (REP 301 study)
Blood	**HBsAg reduction to < LLOQ** HBV DNA reduction to < LLOQ (decoupled from HBsAg clearance)	**HBsAg reduction to < 1 IU/mL** HBsAg seroconversion HBeAg seroconversion HBV DNA and RNA reduction (decoupled from HBsAg clearance)		**HBsAg reduction to < 1 IU/mL** HBsAg seroconversion **HDV RNA clearance** **(target not detected)**
Liver	Clearance of HBsAg and HBcAg Transcriptional inactivation of cccDNA 2-3 log_{10} reduction in cccDNA	Strong, self resolving, asymptomatic transaminase flares (when HBsAg becomes < 1 IU/mL)		Weak transaminase flares (strong following pegIFN add-on when HBsAg < 1 IU/mL)
Functional control after removal of therapy **Clinical benefit without further need for therapy**	**55-66%** blood and liver (functional cure)*	**25%** 5 years of follow-up (inactive HBV)**	**44%** 2 years of follow-up (inactive HBV)**	**36%** (HBsAg)* **55%** (HBV DNA)* **64%** (HDV RNA)* (functional cure) 2 years of follow-up

*HBsAg and HBV DNA or HDV RNA target not detected
**HBV DNA < 2000 IU/mL with normal ALT

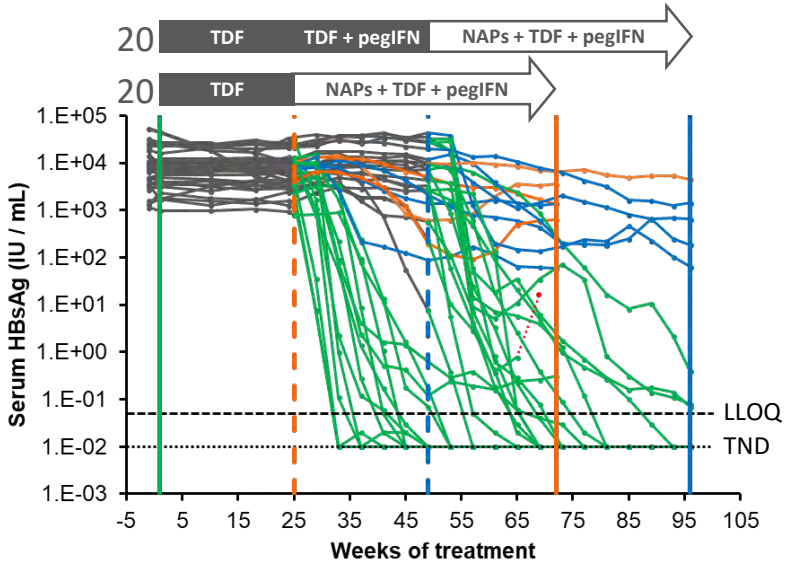
Decoupling of HBsAg and HBV DNA declines a result of selective targeting of SVP assembly / release
HBsAg clearance is accompanied multiple positive effects on immune response to HBV infection
Potent and distinct antiviral mechanism is active against HDV – direct interaction with HDAg

Noordeen et al., PloS One 2015
Roehl et al., Mol. Ther. Nuc. Acids 2017; 8: 1-12
Quinet et al., Hepatol. 2018; 67: 2127-2140
Janssen et al., J. Hepatol. 2015;62: S250
Al-Mahtab et al., PLOS One 2016; 11: e0156667
Bazinet et al., Lancet Gastro. Hep. 2017; 2: 877-889

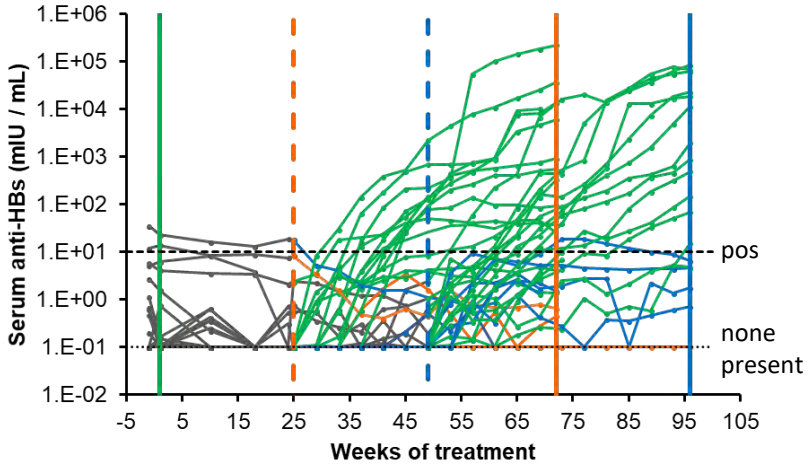
Building a combination regimen with HBsAg loss

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

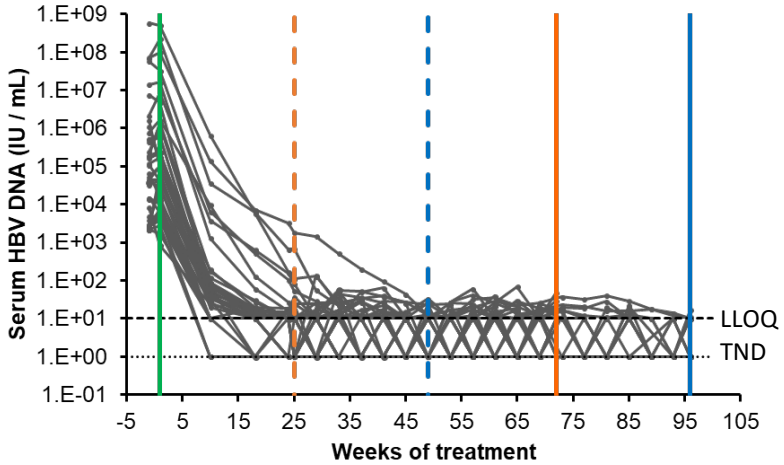
REP 401 study - HBeAg negative chronic HBV mono-infection
40 patients received 48 weeks of REP 2139-Mg or REP 2165-Mg, TDF and pegIFN
Interim analysis from July 7, 2018



REP 2139-Mg = REP 2165-Mg
4/40 non-responders
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)



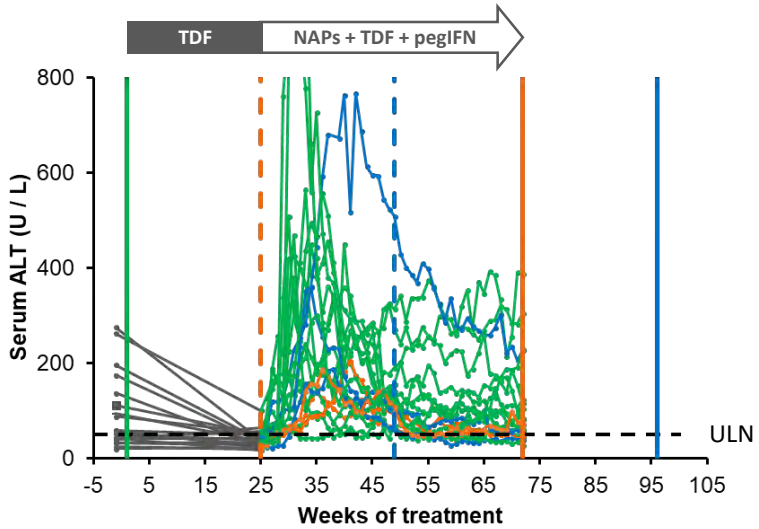
TDF-induced HBV DNA declines unaffected during therapy

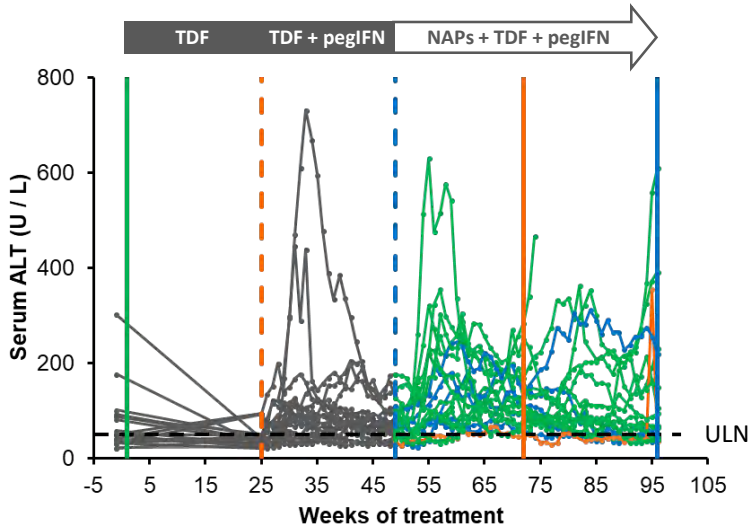
Standard of care only | < 1 log reduction in HBsAg | HBsAg > 1 log reduction but > 1 IU/mL | HBsAg < 1 IU/mL

Building a combination regimen with HBsAg loss

Combination effect with TDF and pegIFN

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 June 1, 2018





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

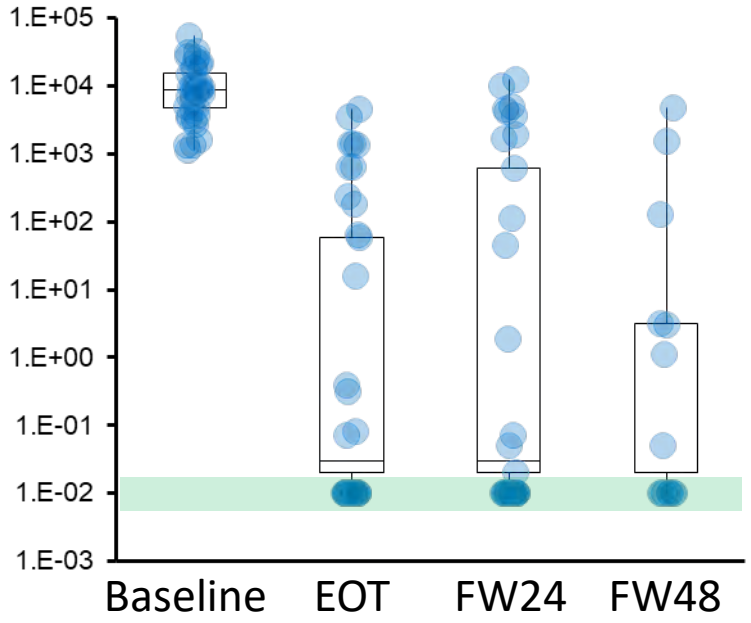
Flares attenuated when NAPs introduced following 24 weeks of pegIFN
Loss of T-cell function with pegIFN(?)

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 as of July 7, 2018

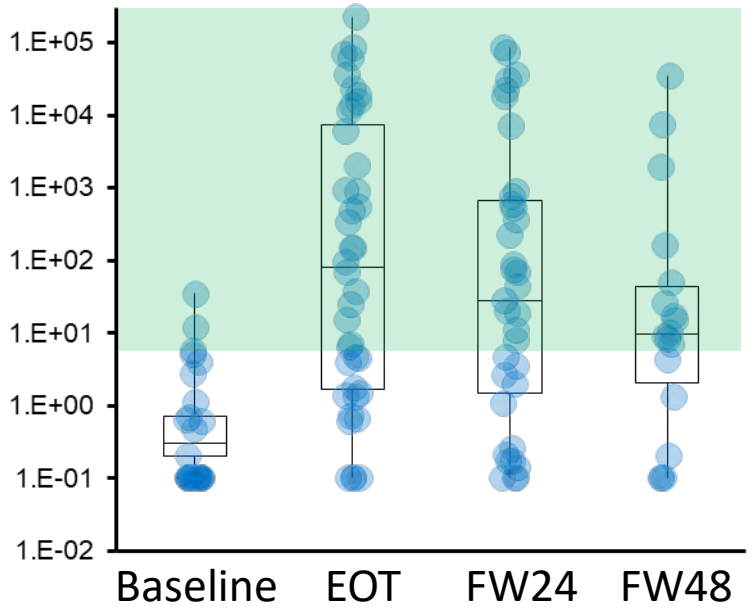
HBsAg (IU/mL)



0% (0/40) | **60%** (24/40*) | **53%** (18/34) | **50%** (8/16)

HBsAg loss
(≤ 0.05 IU/mL)

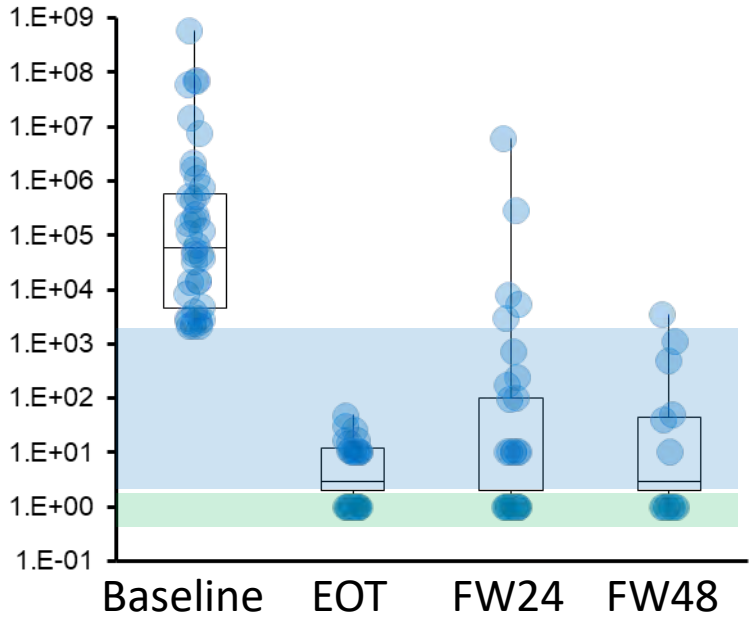
Anti-HBs (mIU/mL)



5% (2/40) | **60%** (24/40*) | **59%** (20/34) | **56%** (9/16)

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

HBV DNA (IU/mL)



0% (0/40) | **55%** (22/40*) | **50%** (17/34) | **62%** (10/16)

HBV DNA target not detected

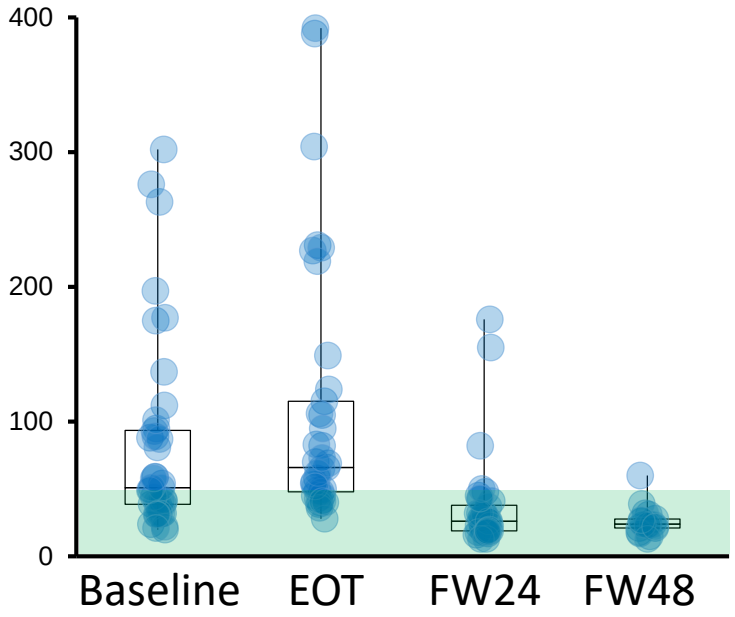
0% (0/40) | **45%** (18/40*) | **38%** (13/34) | **31%** (5/16)

HBV DNA LLOQ to 2000 IU/mL

* 3 patients withdrew from therapy early for personal reasons

REP 401
Liver status during treatment and follow-up

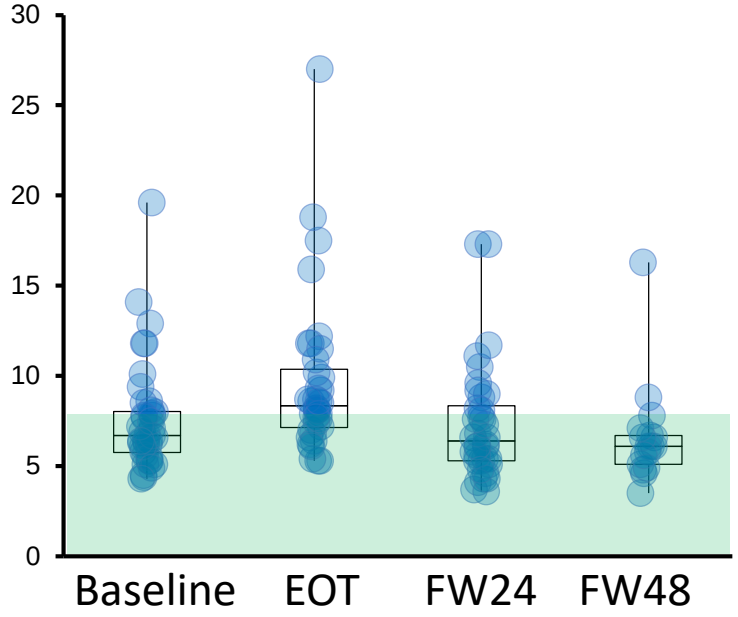
ALT (U/L)



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 (as of July 7, 2018)

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 HBV (HBV DNA ≤ 2000 IU/mL, normal ALT)		44%
Functional cure (HBsAg and HBV DNA target not detected)		41%
Clinical benefit (Low risk of progression, reduced risk of HCC)		**85%**

Summary

REP 2139 blocks release of HBsAg

- Likely by targeted SVP assembly and release
- Accompanied by early decline/clearance of HBsAg and control of HBV replication in the liver

REP 2139 interacts with the large and small forms of HDAg

- Drives clearance of HDV RNA to target not detected which persists during 2 years of follow-up
- Accompanied by normal ALT and declining median hepatic stiffness
- REP 2139 is unique in its combined effects on HBsAg and HDV RNA

REP 2139-Mg is well tolerated when combined with TDF and pegIFN

- High rates of HBsAg loss and seroconversion during therapy
- Asymptomatic (likely therapeutic) transaminase flares suggest clearance of HBV from the liver
- Improved rates of functional control of HBV infection observed after removal of all therapy

Currently 85% of patients have control of infection not requiring treatment in the REP 401 study

Next steps

Transition to subcutaneous dosing

- REP 2139-Mg used in the REP 401 trial is already optimized for SC administration
- POC trial planned in HBV/HDV infection (TDF + pegIFN + SC REP 2139-Mg)

Initiation of phase IIA combination trial in the US

- In collaboration with the ACTG (DAIDS / NIH)
- Will use same triple combination regimen as in the REP 401 trial (NUCs + pegIFN + REP 2139-Mg)
- Will facilitate early initiation of phase IIB trial (with transition to SC)

Assessing other immunotherapies

- PegIFN is much better tolerated in HBV (versus HCV) but results in loss of T-cells during therapy
  Marcellin et al., Liv Int 2008; 28: 477-485
  Micco et al., J Hepatol 2013; 58: 225-233
- Potential for improvement of functional cure rates with interferon-free regimens using other immunotherapies

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

- Affects ~ 10% of patients
- REP 2165 has a faster clearance rate and can be safely dosed at higher frequency to recover HBsAg response
- Predictive markers for patients having poor HBsAg response to REP 2139 under investigation

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A collaborative effort!

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