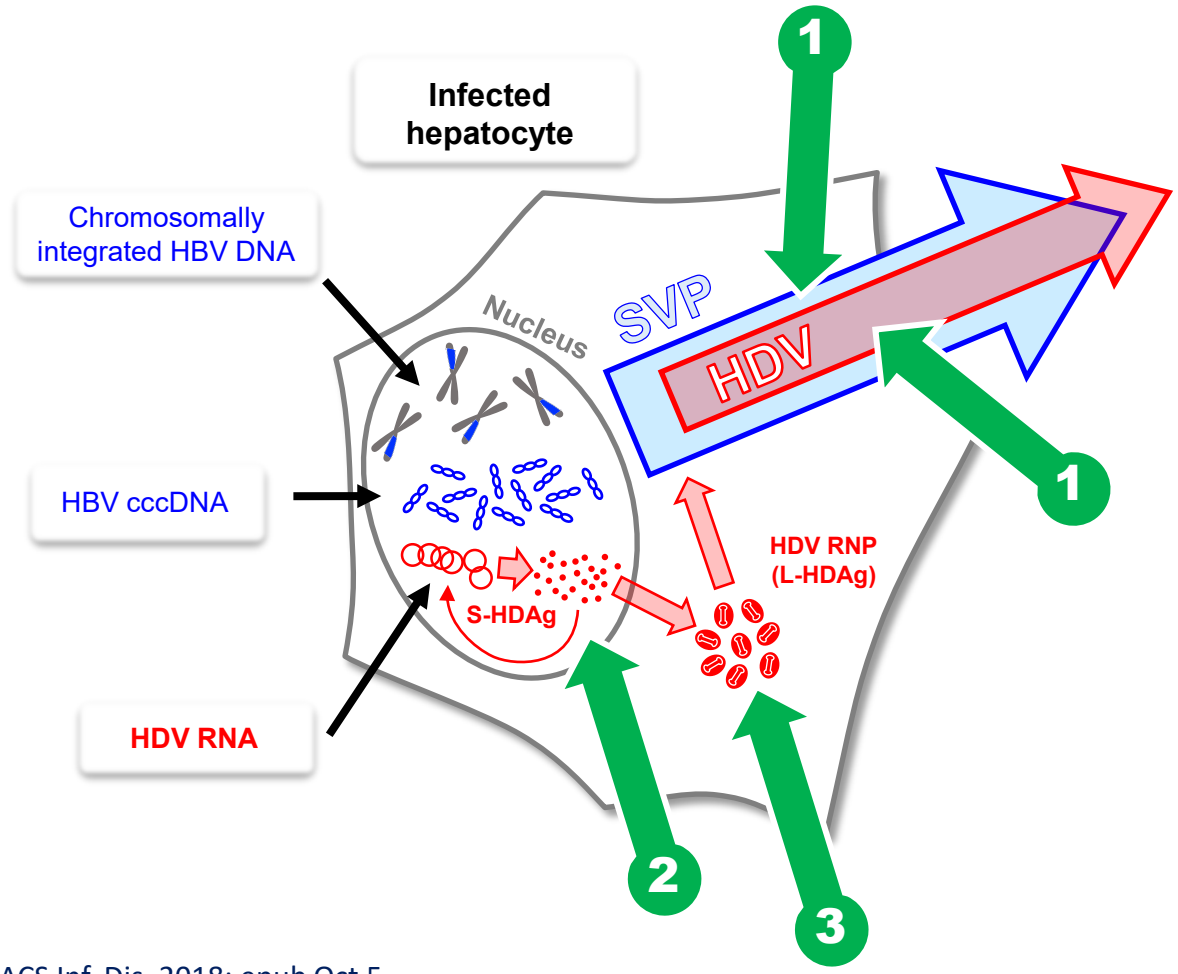
Update on the development of REP 2139-Mg for HBV / HDV infection

Andrew Vaillant, Ph.D.
Chief Scientific Officer
replicor

16th HDIN Meeting in San Francisco (AASLD) November 10th, 2018

Antiviral mechanisms of REP 2139 (HBV / HDV)

HDV is assembled and secreted like HBV SVP



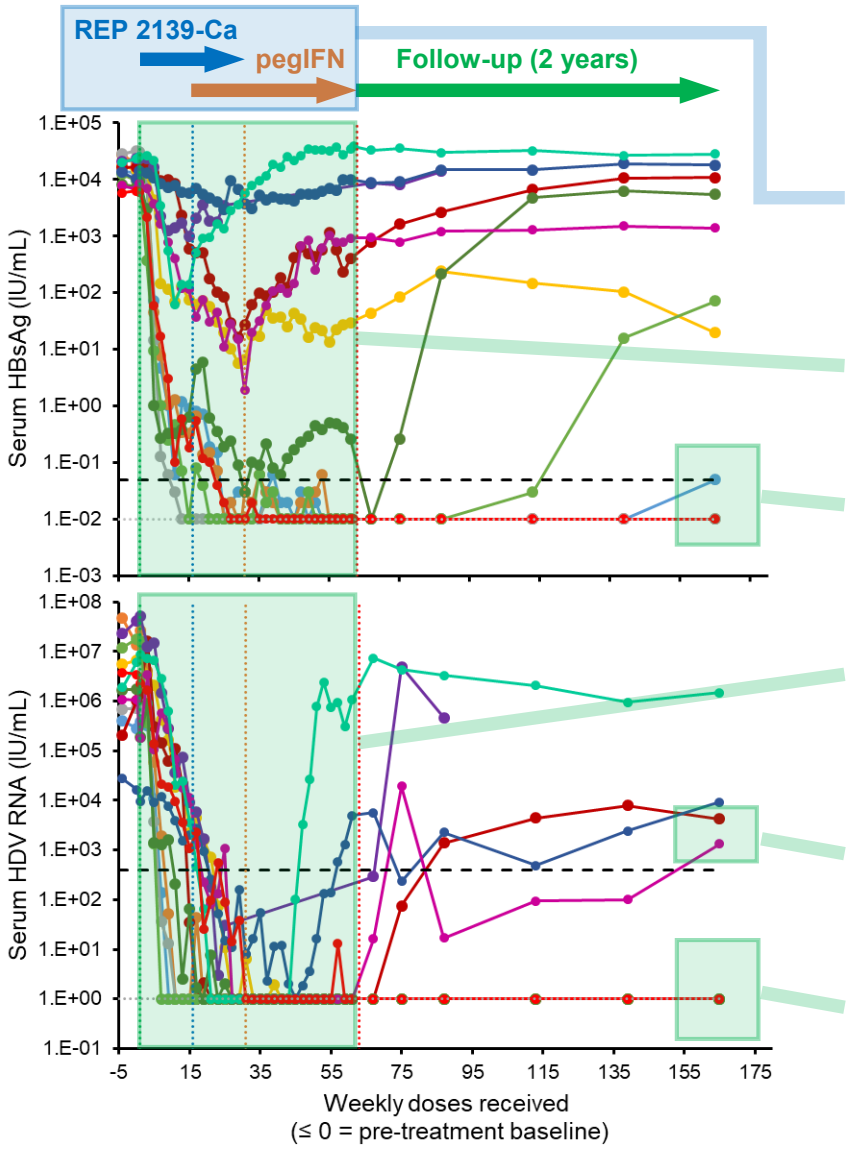
1. **Inhibition of HDV envelopment / secretion**
   Via REP 2139 blockade of SVP assembly / release.

2. **Inhibition of HDV RNA replication**
   Via REP 2139 interaction with the nucleic acid binding domain in S-HDAg.

3. **Inhibition of HDV RNP assembly**
   Via REP 2139 interaction with amphipathic alpha helical domains in HDAg involved in RNP assembly

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

REP 301:
REP 2139-Ca + pegIFN in HBV/HDV



12 patients, HBeAg- chronic HBV / HDV co-infection
(verified 1.5 – 18 years pre-treatment)

Suboptimal regimen to explore safety and efficacy of REP 2139-Ca + pegIFN

On-treatment: HBsAg response in **75%** of patients (HBsAg loss in **42%**)

Follow-up: HBsAg control maintained in **45%** of patients*

On treatment: HDV RNA decline > 5 $\log_{10}$ in all patients
No rebound during REP 2139-Ca
92% achieve HDV RNA TND

Follow-up: 1 patient maintains control of HDV RNA*(> 2 $\log_{10}$ reduction from baseline)
also with inactive HBV

Follow-up: 7/11* maintain HDV RNA target not detected
all with inactive HBV or functional cure of HBV

* In 11/12 patients completing therapy

Bazinet et al., Lancet Hepatol Gastroenterol 2017; 2: 877-889

REP 301 response summary

Patients currently completed treatment and 2-2.5 years of follow-up	11
Inactive CHB (HBV DNA < 2000 IU/mL, normal ALT) *and* **HDV functional control** (> 2 $\log_{10}$ HDV RNA reduction from baseline)	**9%** (1/11)
HDV functional cure (HDV RNA target not detected, normal ALT)	**64%** (7/11) all with inactive CHB (3/11) or functional cure of HBV (4/11) ***all with strong HBsAg response during therapy***
Clinical benefit (Low risk of progression, reduced risk of HCC)	**73%** (8/11)

Suboptimal combination regimen!

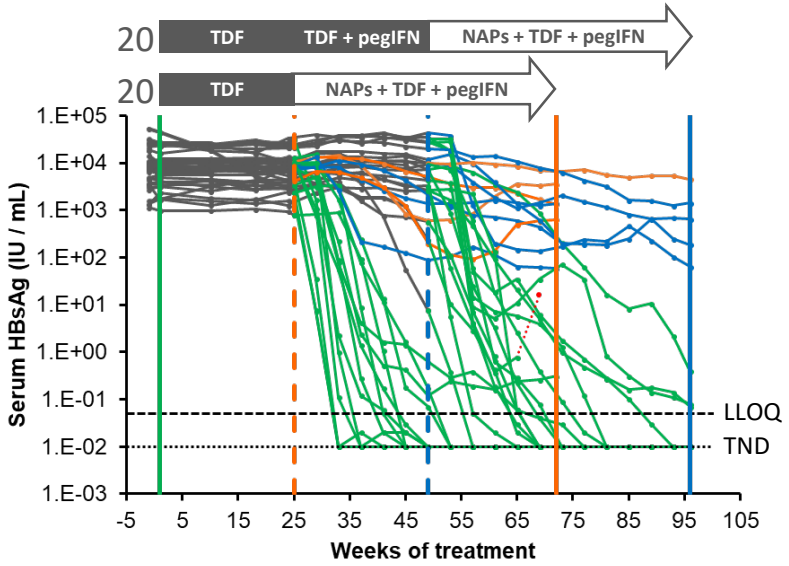
Only 30 weeks of REP 2139-Ca

Only 15 weeks of overlapping combination therapy with pegIFN

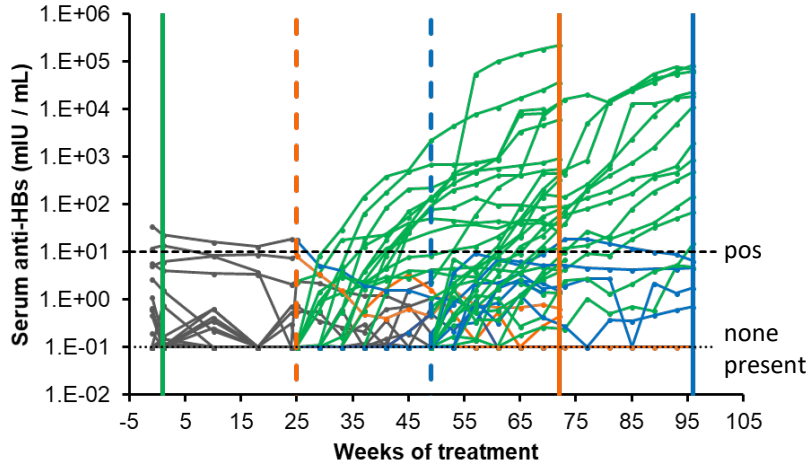
Response rates will improve with a full course of combination therapy

REP 401:
Potentiation of REP 2139-Mg in triple combination regimen

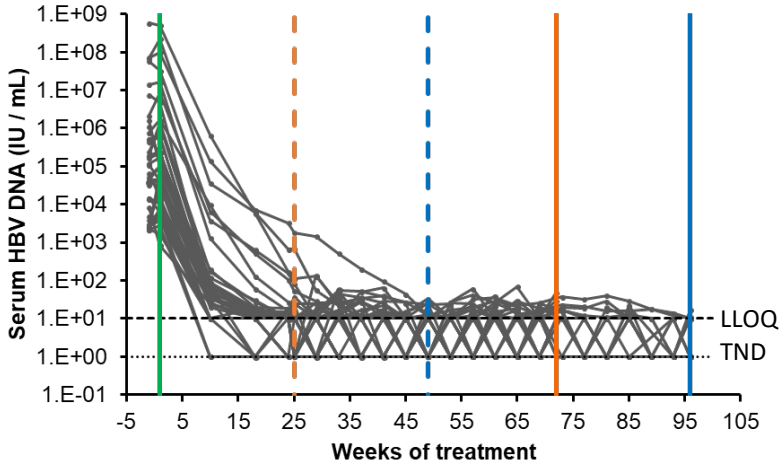
REP 401 study - HBeAg negative chronic HBV mono-infection
40 patients received 48 weeks of REP 2139-Mg or REP 2165-Mg, TDF and pegIFN
Interim analysis from July 7, 2018



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

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%**

HBV / HDV response will improve with the REP 401 regimen

Transitioning REP 2139-Mg to SC administration

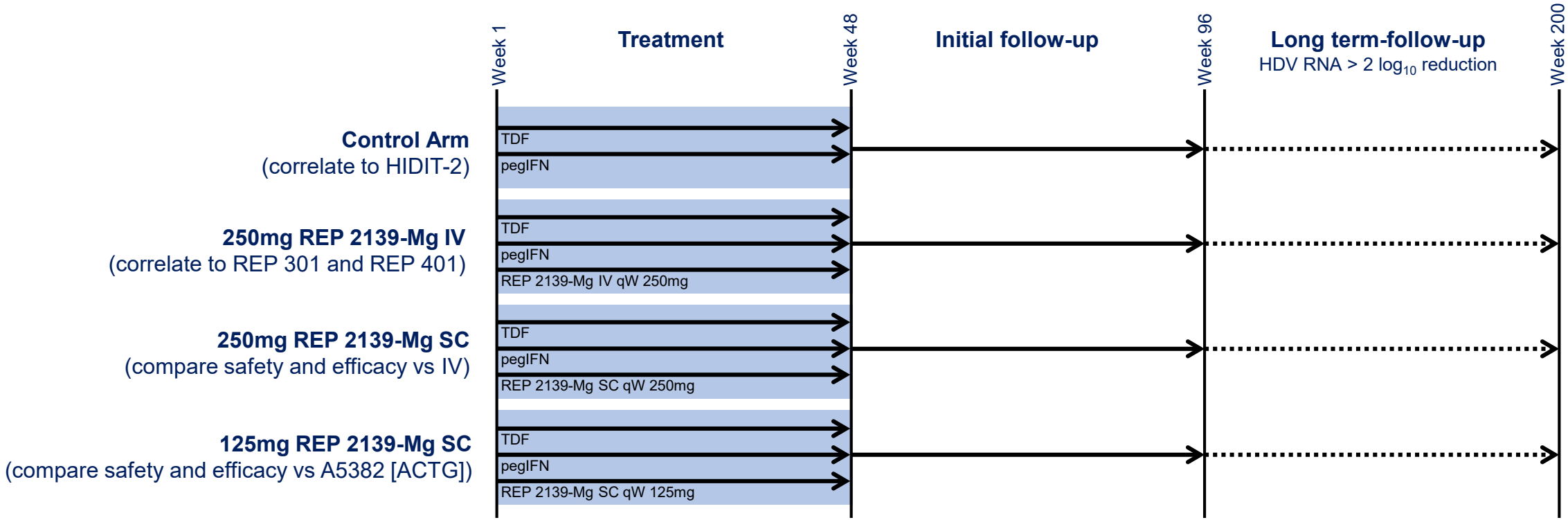
A nucleic acid polymer (NAP)

- **Synthesized using well characterized phosphorothioate oligonucleotide (PS-ON) chemistry**
  - **Efficient pharmacologic activity in the liver with IV or SC administration in human studies**
  - Validated with several liver targets in clinical studies

- **REP 2139-Mg**
  - Confirmed REP 2139 liver uptake with SC administration in monkey studies
  - **Excellent IV tolerability in REP 401 predicts excellent SC tolerability of REP 2139-Mg**

Transitioning REP 2139-Mg to SC administration

The REP 501 protocol:
Comparing safety and efficacy of REP 2139-Mg IV vs SC in combination with TDF and pegIFN



Summary

REP 2139-based combination therapy in chronic HBV/HDV infection

- **Uniquely achieves high rates of serum HBsAg and HDV RNA 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 and HDV (HBV RNA and HBcrAg also remain controlled)**
  Effects are 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)**
  Similar response rates possible in HBV / HDV co-infection with REP 401 regimen

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

REP 2139-Mg Next steps

Transition to subcutaneous dosing

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

- 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

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