Establishment of High Rates of Functional cure of HBeAg negative chronic HBV with REP 2139-Mg Based Combination Therapy

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Breaking the chronicity of chronic HBV infection

HBV infection has occurred in ~ 2 billion people:

- Typically resolved and well controlled by host immunity.

Chronic HBV infection still persists in up to 350 million people. **WHY?**

HBsAg likely prevents the establishment of immune control:

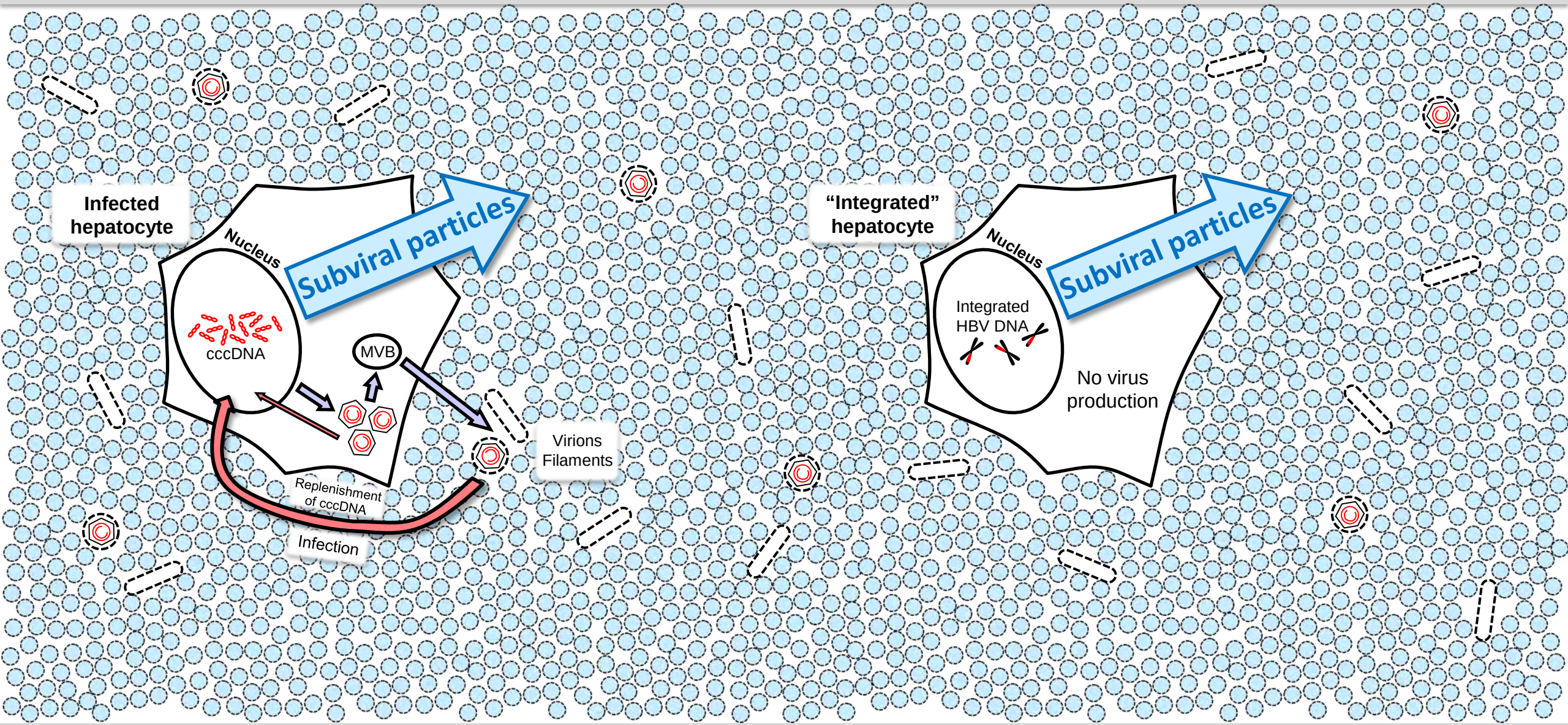
HBsAg is the most abundant circulating viral antigen

- Produced independently from virions (as subviral particles)
- Largely derived from integrated HBV DNA
- **Cannot be targeted by direct acting antivirals**

HBsAg is an important immune checkpoint inhibitor in chronic HBV infection

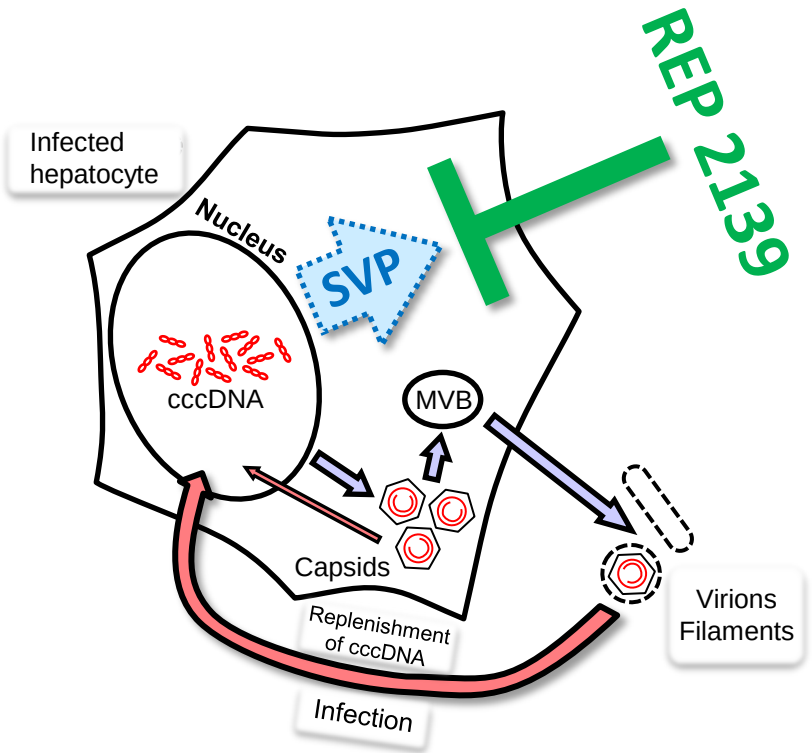
- Inhibits innate and adaptive immunity
- Exhausts the B- and T-cell response

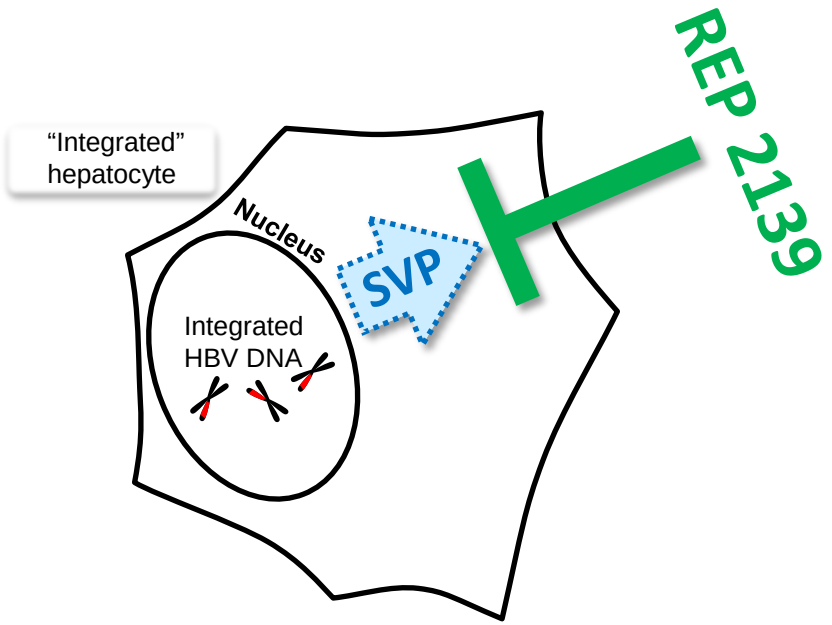
HBsAg production in chronic HBV



Antiviral effect of REP 2139

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





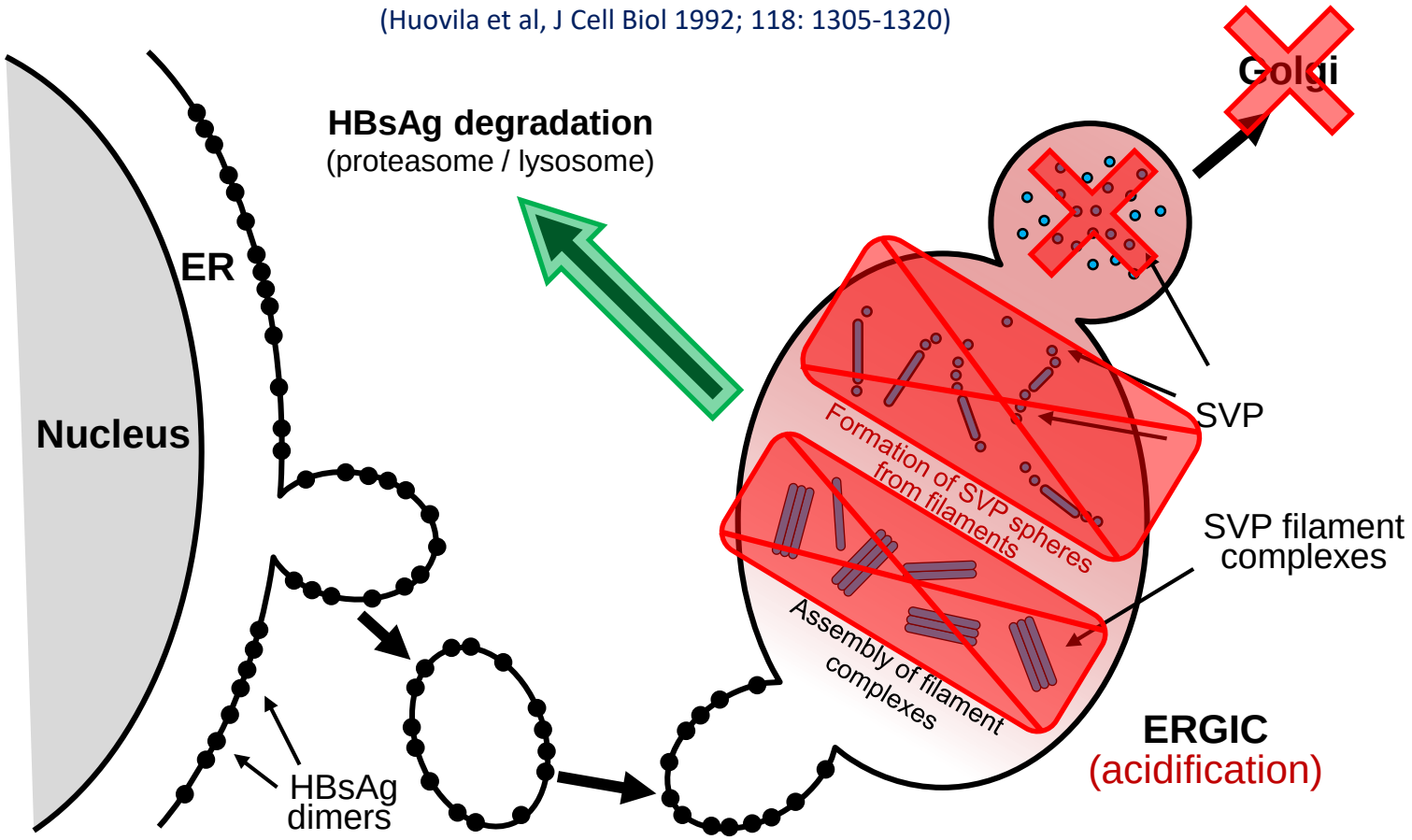
Circulating HBsAg can now be cleared by existing immune function
Critical elimination of HBsAg mediated immunosuppression
Functional cure can be established

Mechanism of action of REP 2139 in HBV

HBV subviral particle assembly pathway

(from cccDNA or integrated HBV DNA)

(Huovila et al, J Cell Biol 1992; 118: 1305-1320)



REP 2139 enters the ERGIC and inhibits SVP morphogenesis (host target currently unknown)

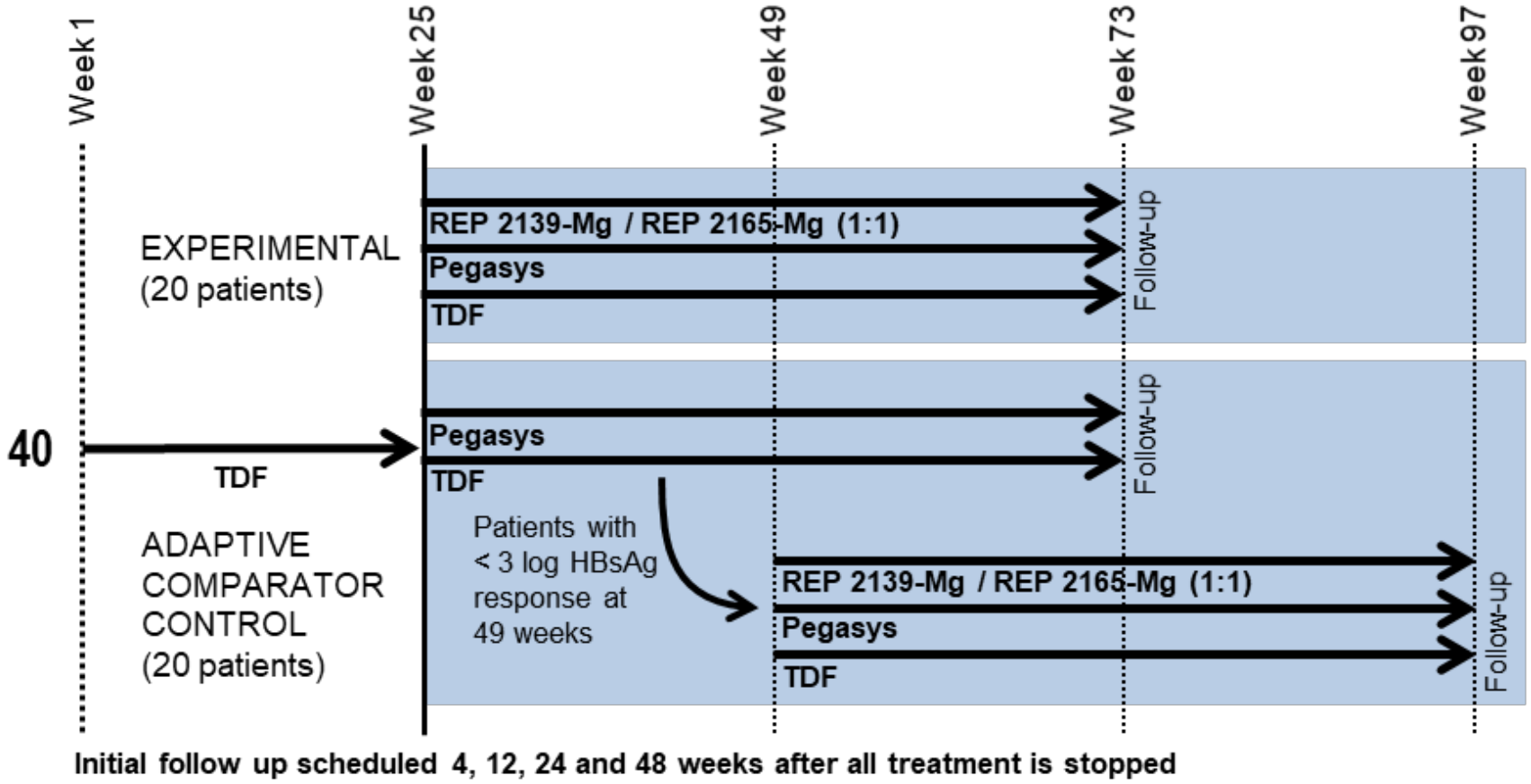
Intracellular degradation of HBsAg is enhanced

Inhibition of HBsAg secretion (from cccDNA or integrated HBV DNA) is accompanied by declines in intracellular HBsAg

Blanchet et al., Antiviral Res 2019; 164: 87-105

REP 401 Study

Clearing HBsAg to improve immunological recovery



TDF 300mg PO qD

Pegasys 180ug SC qW

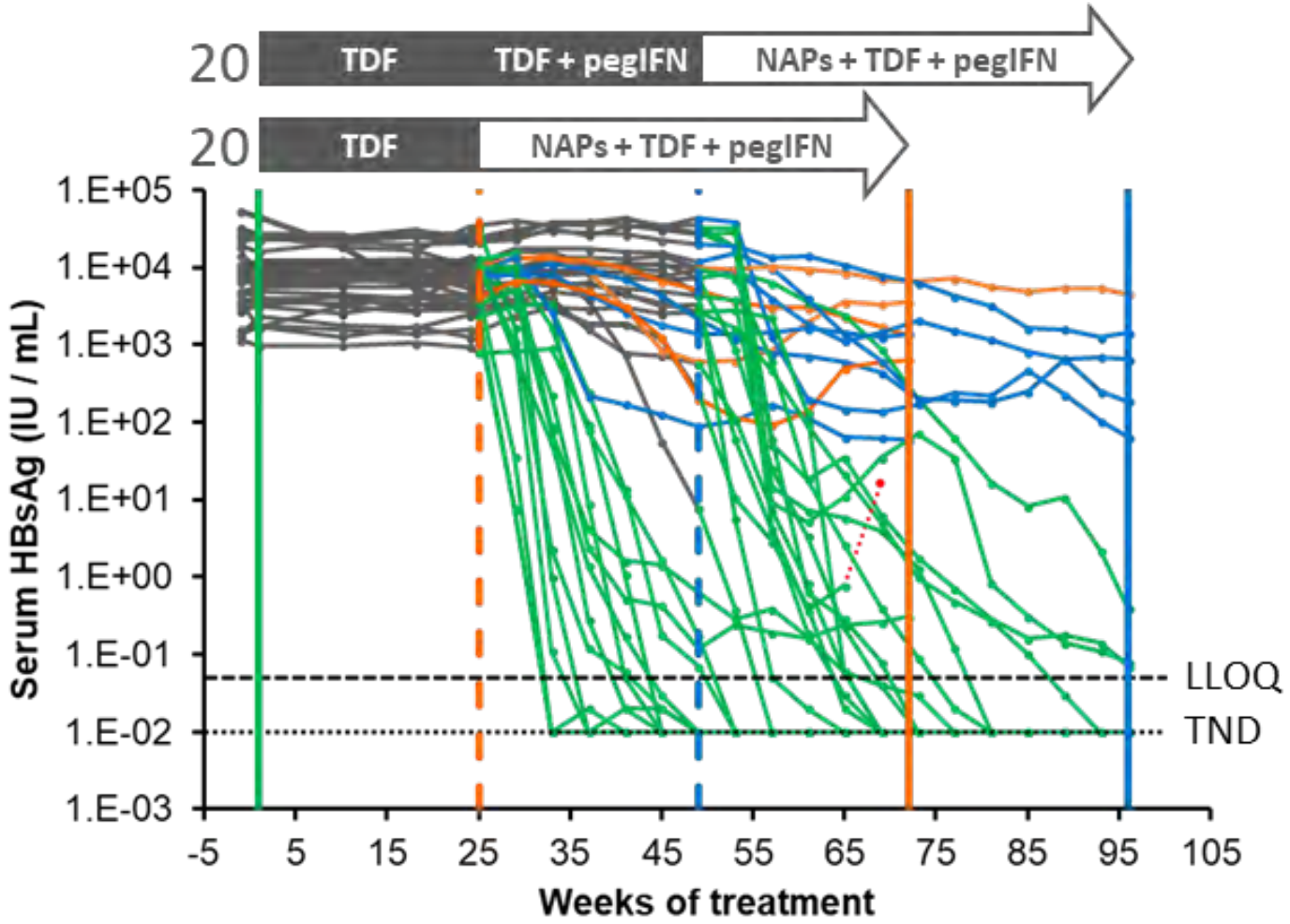
NAPs: REP 2139-Mg or REP 2165-Mg 250mg IV qW

REP 2165 = REP 2139 variant with improved tissue clearance

Roehl et al., Mol Ther Nuc Acids 2017; 8: 1-12

REP 401 on-treatment HBsAg response

LLOQ = lower limit of quantification (0.05 IU/mL)
TND = HBsAg not detected (0.00 IU/mL)



REP 2139-Mg = REP 2165-Mg

4/40 non-responders

8/40 HBsAg > 1 log reduction but > 1 IU/mL

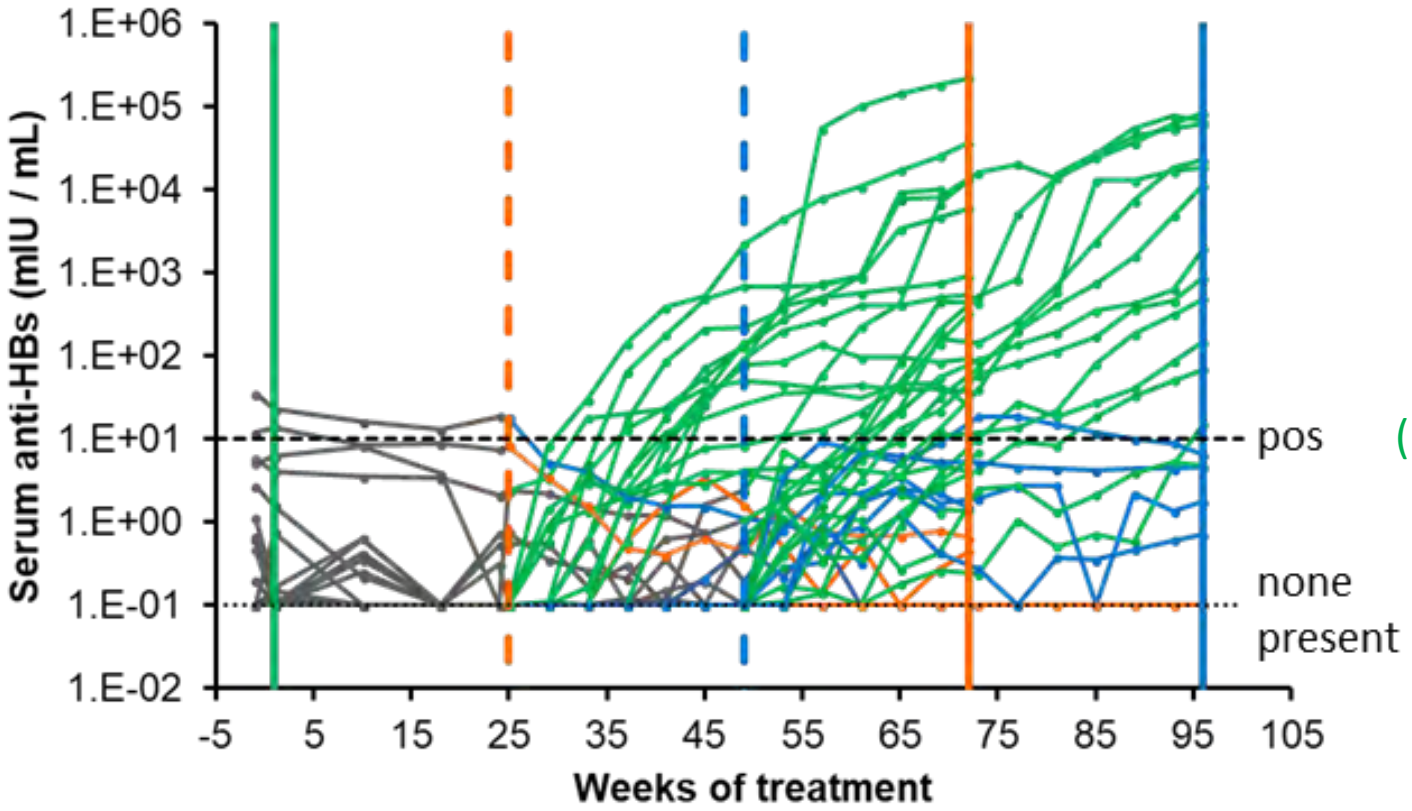
28/40 HBsAg < 1 IU/mL

24/40 HBsAg loss (≤ 0.05 IU/mL)

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

REP 401 on-treatment anti-HBs response

Prot. Imm. = threshold for protective immunity (10 mIU / mL)
absent = no significant anti-HBs present (≤ 0.1 mIU / mL)

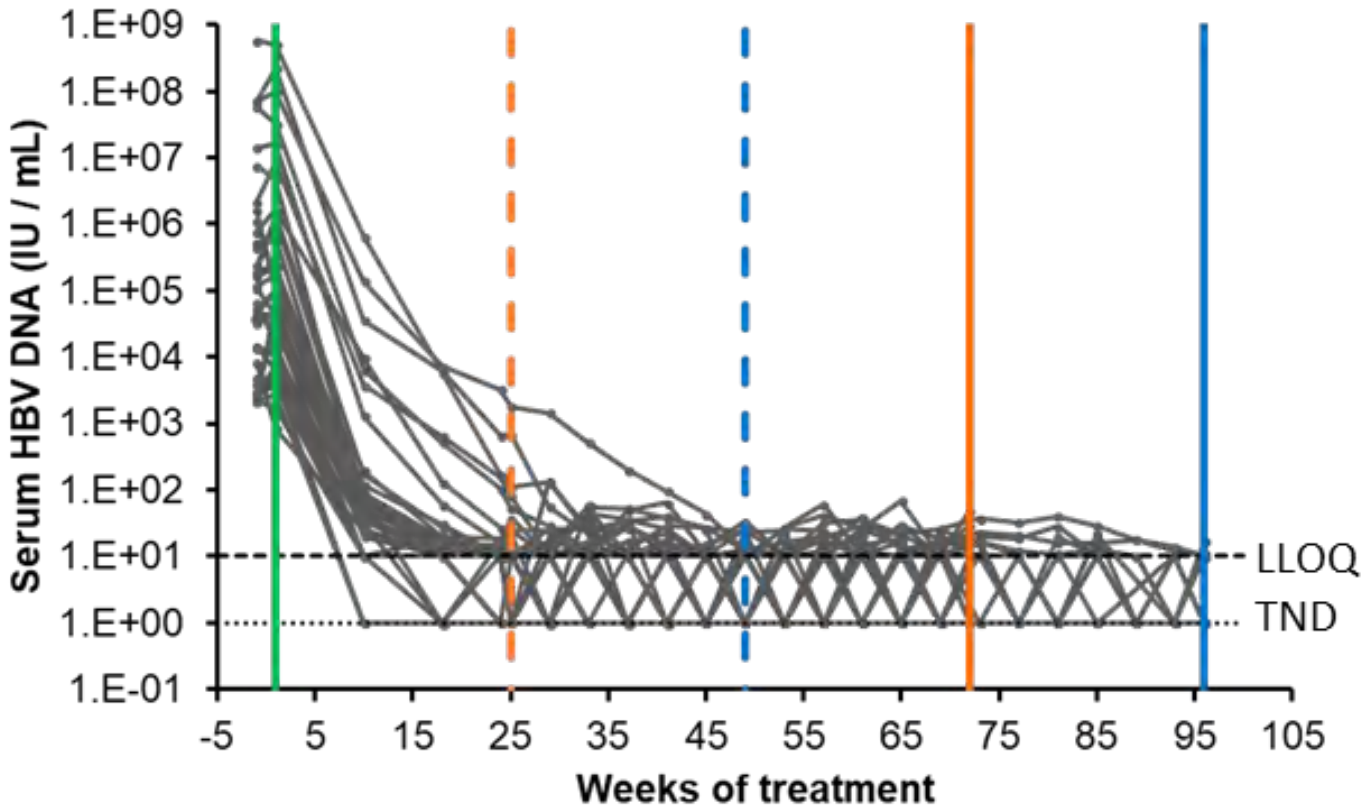


Anti-HBs dramatically increased with the introduction of pegIFN
(but only in patients with HBsAg declines to < 1 IU/mL)

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

REP 401 on-treatment HBV DNA response

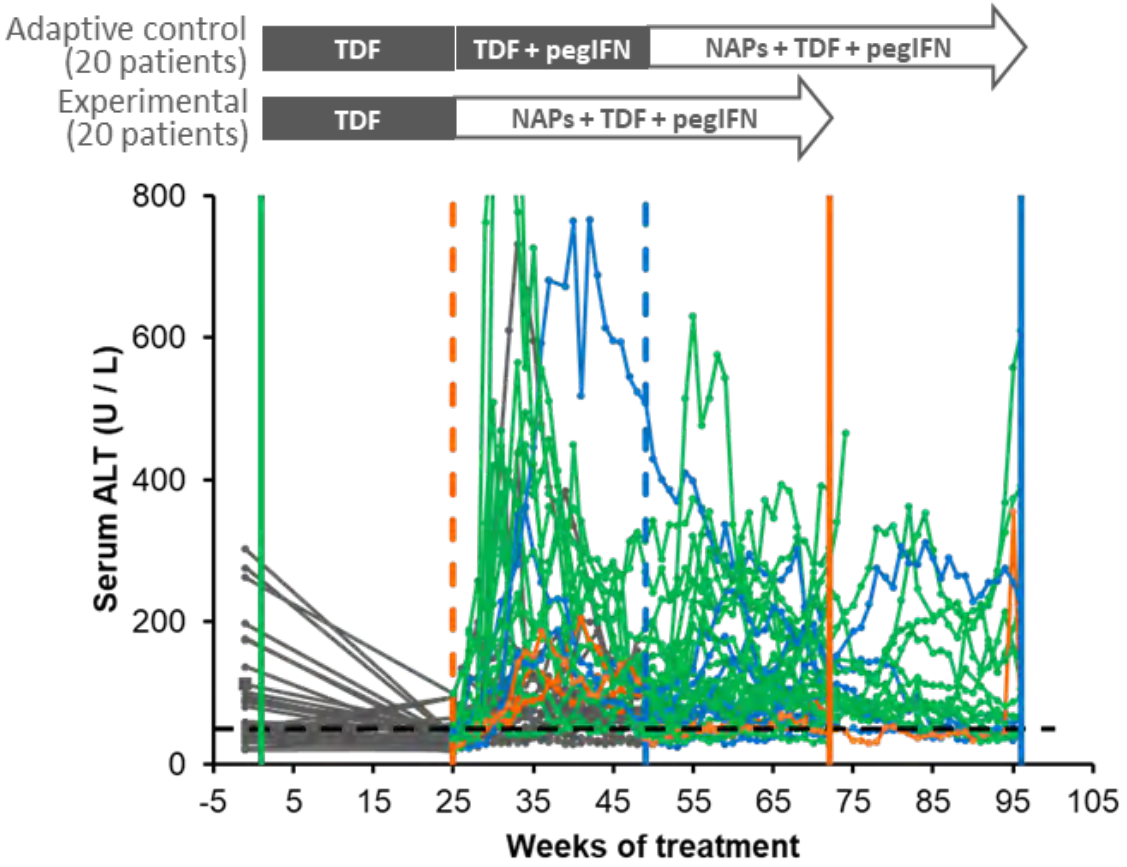
LLOQ = lower limit of quantification (10 IU/mL)
TND = HBV DNA PCR product not detected in assay



TDF-induced HBV DNA declines unaffected during therapy
(no negative drug-drug interactions)

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

Clearance of infected / integrated hepatocytes



Transaminase flares occur in 38/40 patients

Appear to be immune-mediated:

- Timing correlated with antiviral response
- Strength correlated with HBsAg response
- All self-resolving either during therapy or follow-up
- Liver function is continually normal throughout (bilirubin, albumin, INR)
- Otherwise asymptomatic

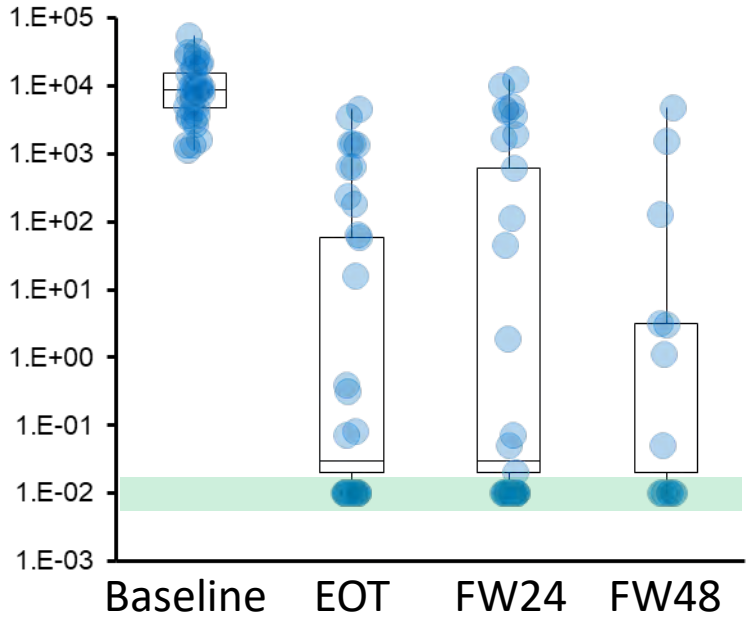
Correlated with the establishment functional control

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

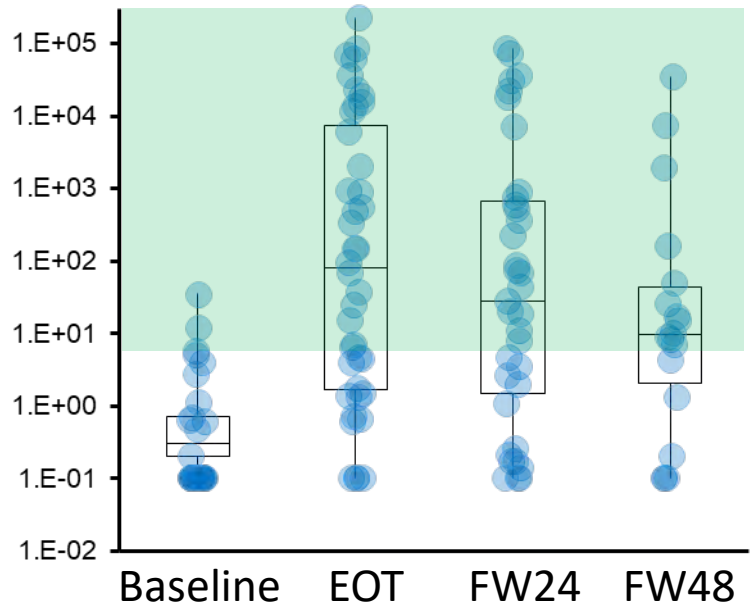
HBsAg (IU/mL)



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

HBsAg loss (≤ 0.05 IU/mL)

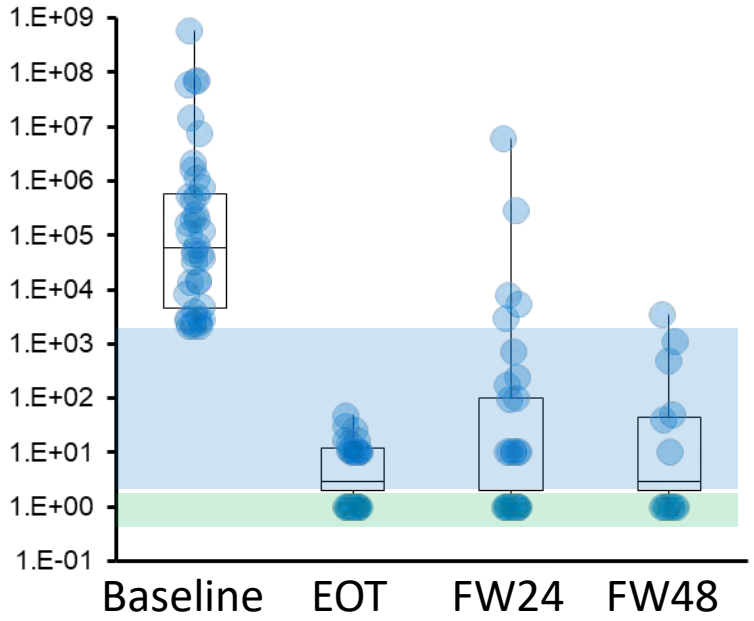
Anti-HBs (mIU/mL)



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

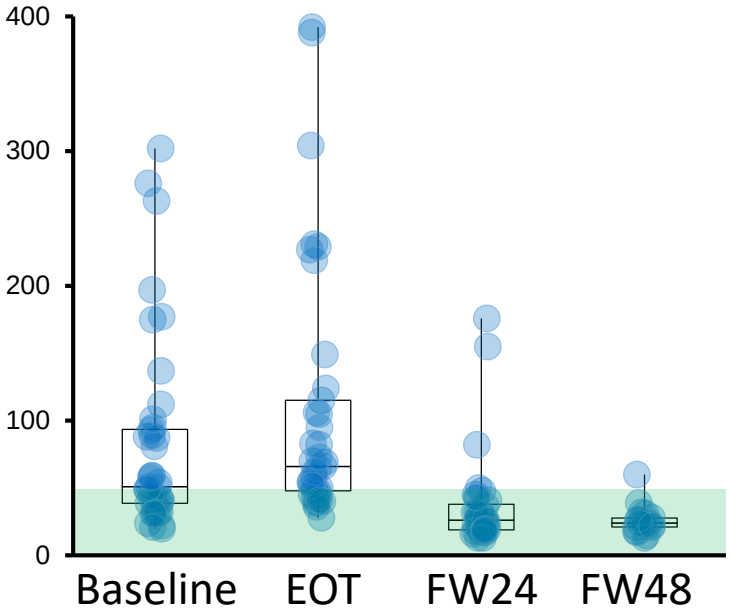
Baseline	EOT	FW24	FW48
0% (0/40)	45% (18/40*)	38% (13/34)	31% (5/16)

HBV DNA LLOQ to 2000 IU/mL

EOT = end of treatment
* 3 patients withdrew from therapy early for personal reasons

REP 401
Liver status during treatment and follow-up

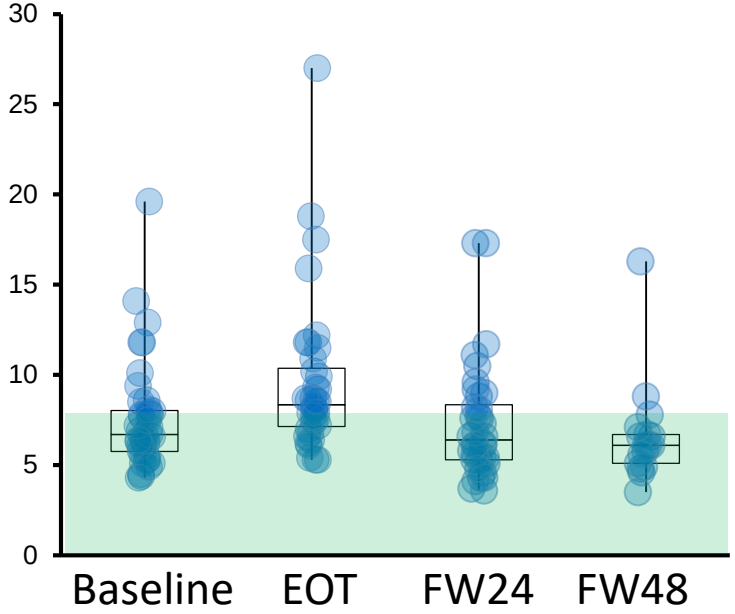
ALT (U/L)



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

Significant improvement compared to baseline

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

Interim 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 HBV (HBV DNA ≤ 2000 IU/mL, normal ALT)		44%
Functional cure (HBsAg and HBV DNA target not detected)		41%
Clinical benefit, no therapy required (Low risk of progression, reduced risk of HCC)		**85%**

REP 2139-Mg next steps

Transition of REP 2139-Mg to subcutaneous dosing

- REP 2139-Mg is already optimized for SC administration
- REP 2139-Mg SC formulation is administered via IV in the REP 401 protocol

Initiation of phase IIA triple combination trial in the US

- In collaboration with the ACTG (DAIDS / NIH)
- Will use same regimen as in the REP 401 trial (NUCs + pegIFN + REP 2139-Mg)

Assessing other immunotherapies

- PegIFN is much better tolerated in HBV than in 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

- Functional cure rates may improve with other immunotherapies
  - Thymosin alpha 1 (T-cell agonist)
  - TLR / RIG-I agonists
  - Therapeutic vaccines

A collaborative effort !

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