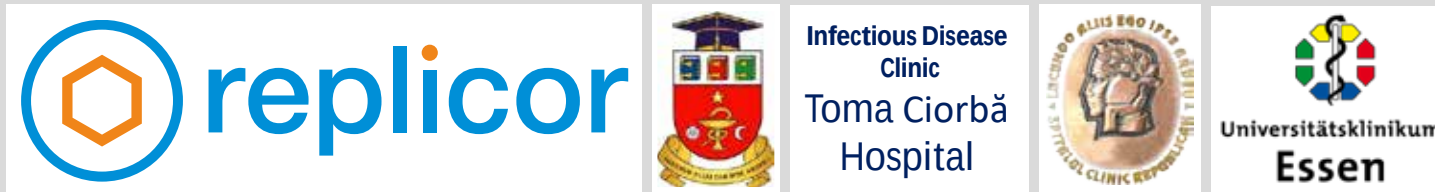
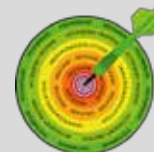


Establishment of functional control and normalization of liver function in HBeAg negative chronic HBV infection following combined therapy with REP 2139, tenofovir disoproxil fumarate and pegylated interferon α -2a.

M. Bazinet, V. Pantea, G. Placinta, I. Moscalu, V. Cebotarescu, L. Cojuhari, P. Jimbei, L. Iarovoi, V. Smesnoi, T. Musteata, A. Jucov, A. Krawczyk, A. Vaillant

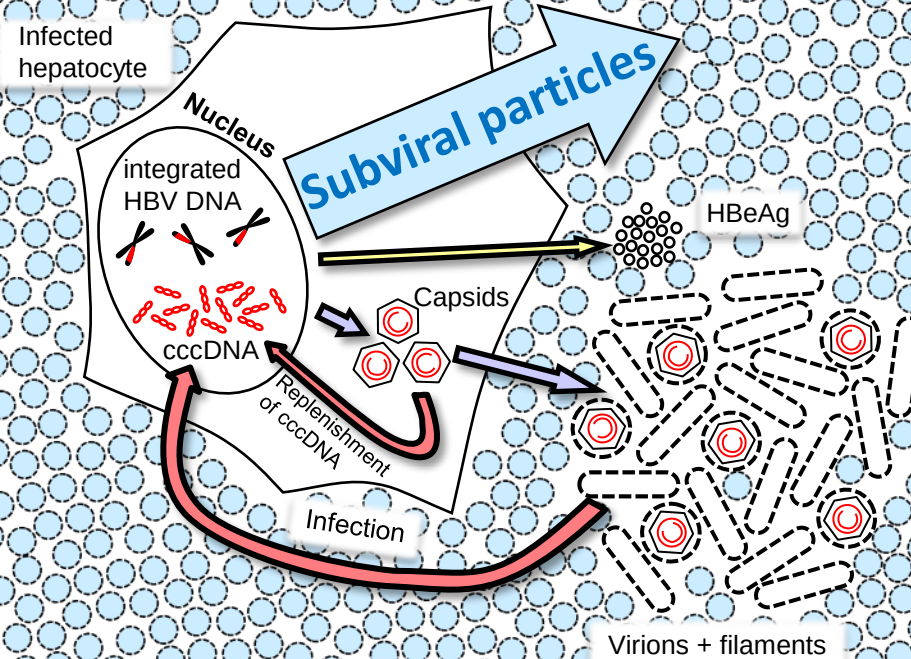


HEP DART 2017 Kona, HI, USA
December 7, 2017



Particle production in HBV

THE HBsAg PROBLEM:
almost all HBsAg is derived from subviral particles



HBsAg is an immunosuppressor:

- Masks anti-HBs response
- Blocks signalling mechanisms in innate and adaptive immunity
- Blocks the effect of immunotherapies
- **HBsAg clearance is crucial to achieving functional control and remission of HBV infection**

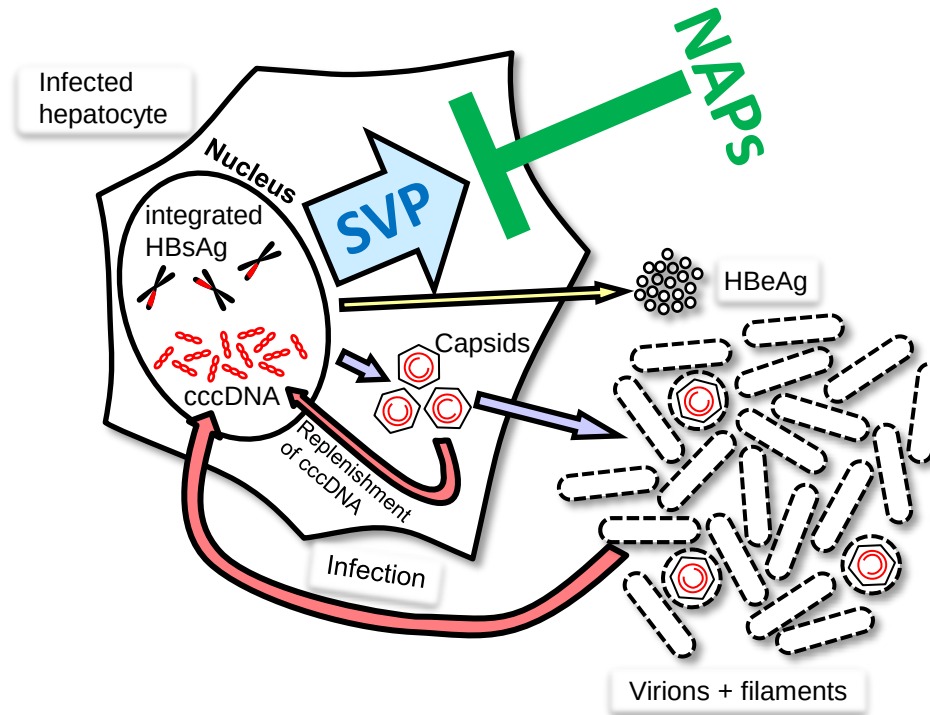
Bazinet et al., 2017 Lancet Gastro&Hep 2: 877-889
Al-Mahtab et al., 2016 PLOS One 11: e0156667
Cheng et al., 2005. Journal of Hepatology, 43:4 65-471
Op den Brouw et al., 2009. Immunology, 126: 280-289
Shi et al. 2012 PLOS One 7: e44900
Vanlandschoot et al., 2002. J. Gen. Virol., 83: 1281-1289
Woltman et al. 2011 PLOS One 6: e15324
Wu et al., 2009. Hepatology, 49: 1132-11
Xu et al., 2009. Molecular immunology, 46: 2640-2646

REP 2139 mechanism of action in HBV

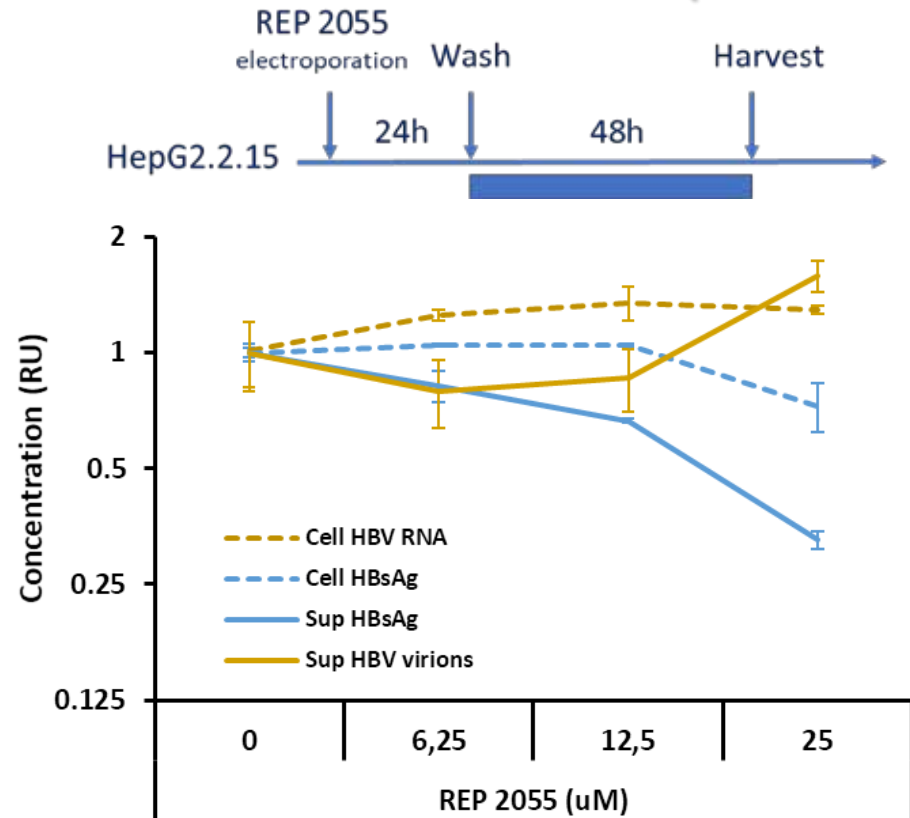
NAPs block subviral particle release
from cccDNA and integrated HBV DNA



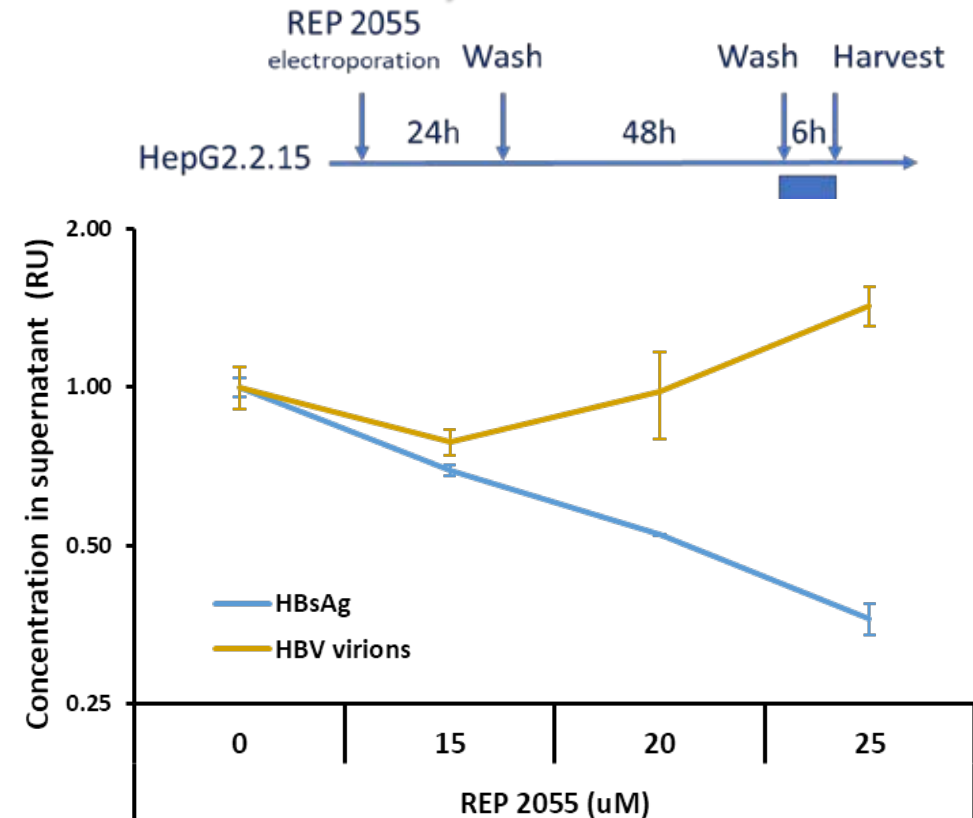
Efficient HBsAg clearance
from the blood



Mechanism of action of NAPs (*In vitro* in HepG2.2.15 cells)



NAPs selectively inhibit SVP secretion
Post-translational mechanism
No increase in intracellular HBsAg

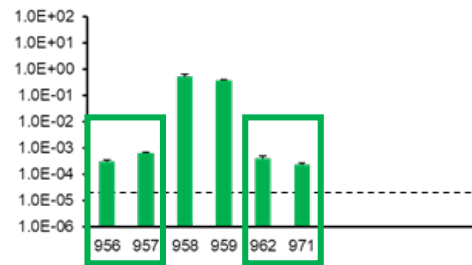
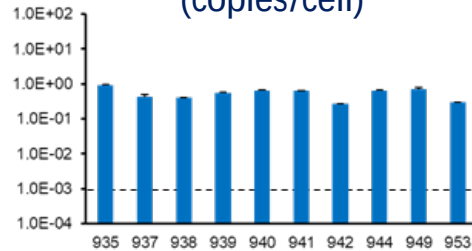


Host target yet to be confirmed
(Apo B, E and H are current candidates)

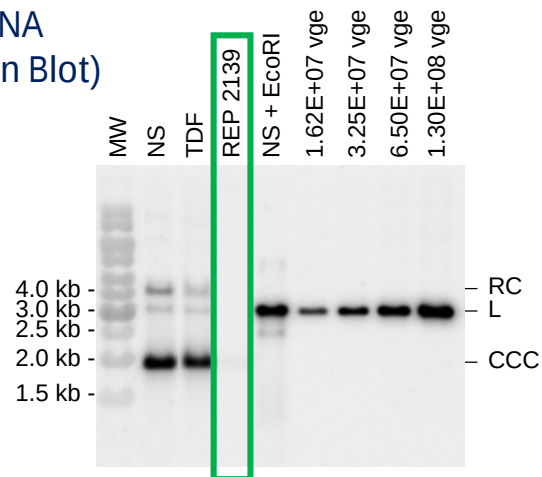
Clearance of surface antigen by REP 2139 establishes control of cccDNA *in vivo*

DHBV infected ducks – Liver analysis 8 weeks after removal of therapy

cccDNA
(copies/cell)

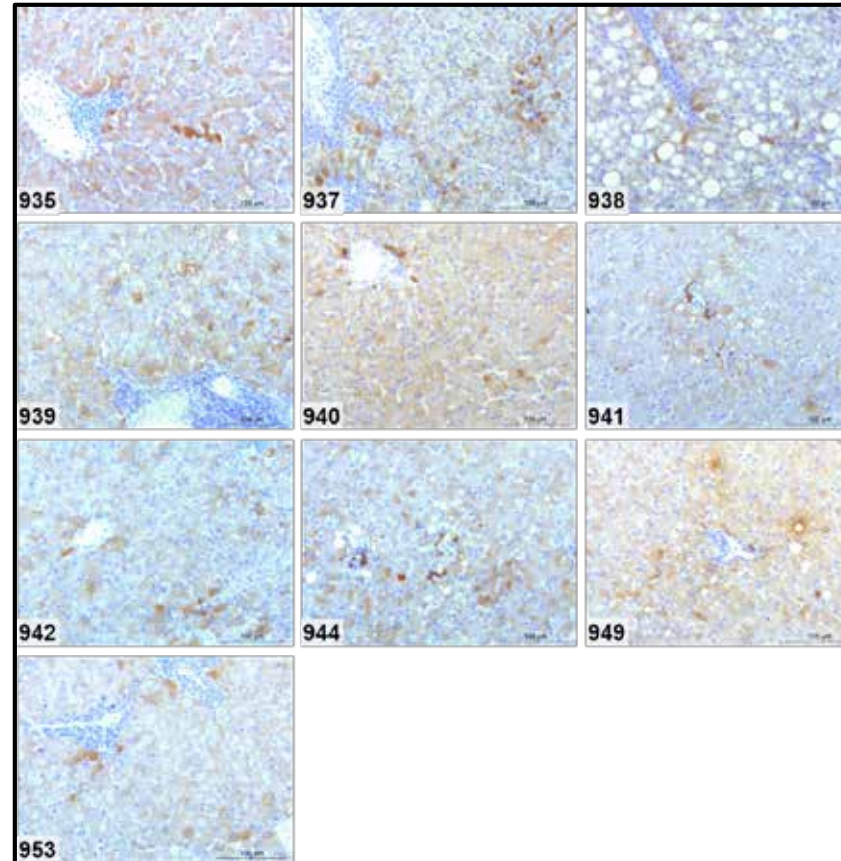


cccDNA
(Southern Blot)

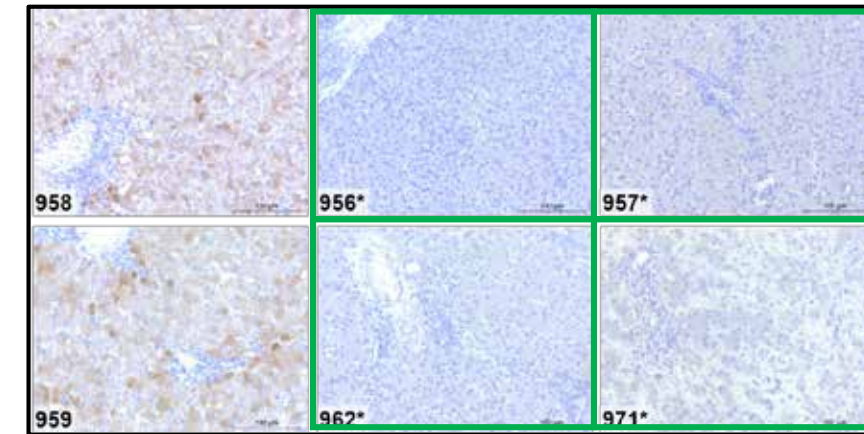


Surface antigen IHC

TDF



REP 2139



Multilog reduction in cccDNA and DHBsAg clearance in the liver persists after removal of therapy

Quinet et al., 2017 (submitted)

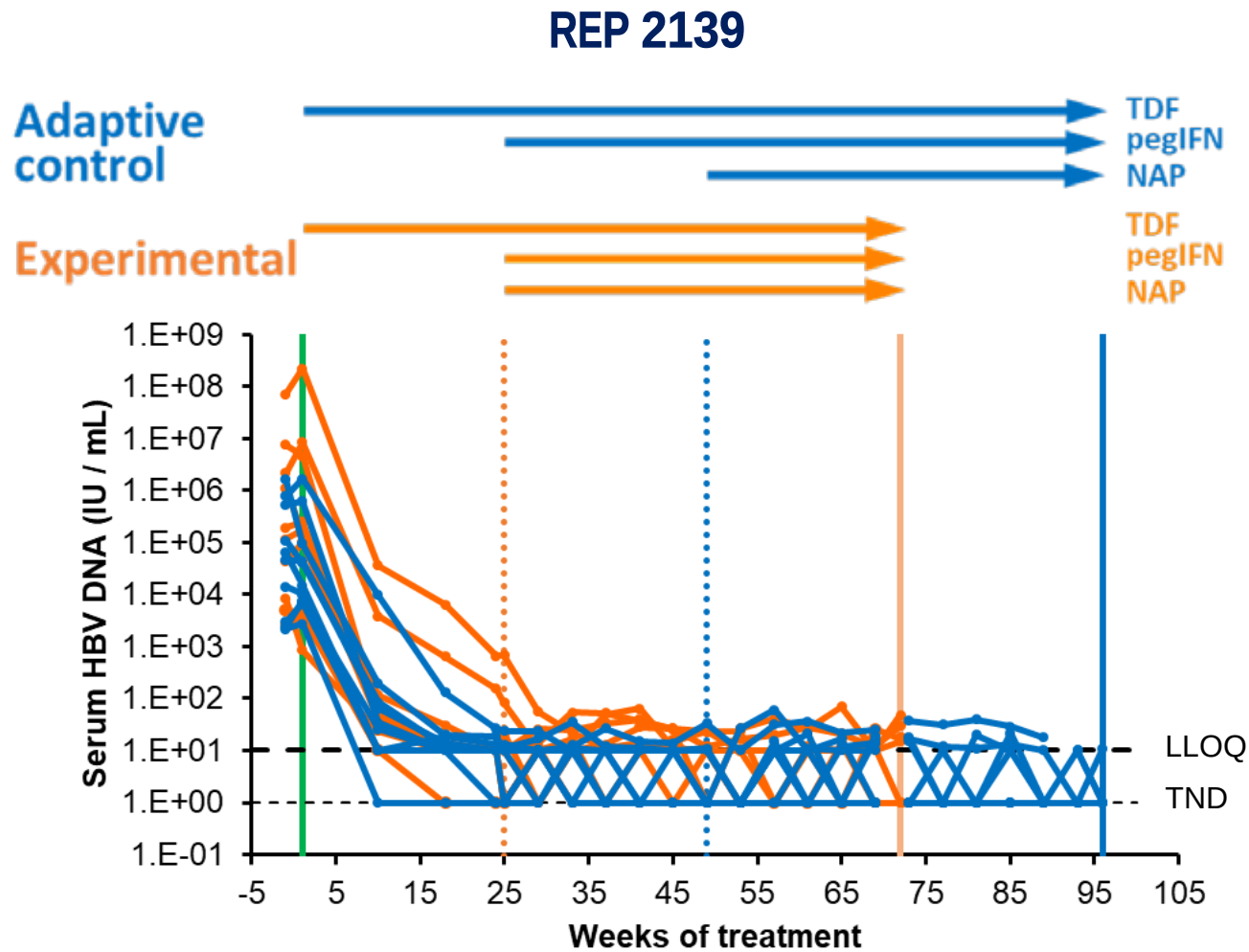
REP 401 trial update

REP 2139 + TDF + pegIFN
in HBeAg- chronic HBV infection

REP 401 patient demographics

Parameter		Adaptive comparator control (TDF + peg-IFN)	Experimental (TDF + peg-IFN + NAPs)
Age (average / median)		36.9 / 36	38.6 / 39.5
Sex		27M / 3F	26M / 4F
HBV genotype	A	1	2
	D	19	18
Metavir score (based on Fibroscan)	F0-F1	12	10
	F2	4	6
	F2-F3	0	3
	F3-F4	4	1
Virologic baseline (average / median)	HBV DNA (IU/mL)	3.6×10^7 / 8.7×10^4	4.8×10^6 / 4.8×10^4
	HBsAg (IU/mL)	14775.7 / 9302.5	9018.1 / 8743
	Anti-HBs (mIU/mL)	0.78 / 0.1	2.778 / 0.1
ALT (average / median)		71.65 / 49	91.95 / 56.5

On-treatment HBV DNA response



TDF effect is unaltered in triple combination with pegIFN and REP 2139

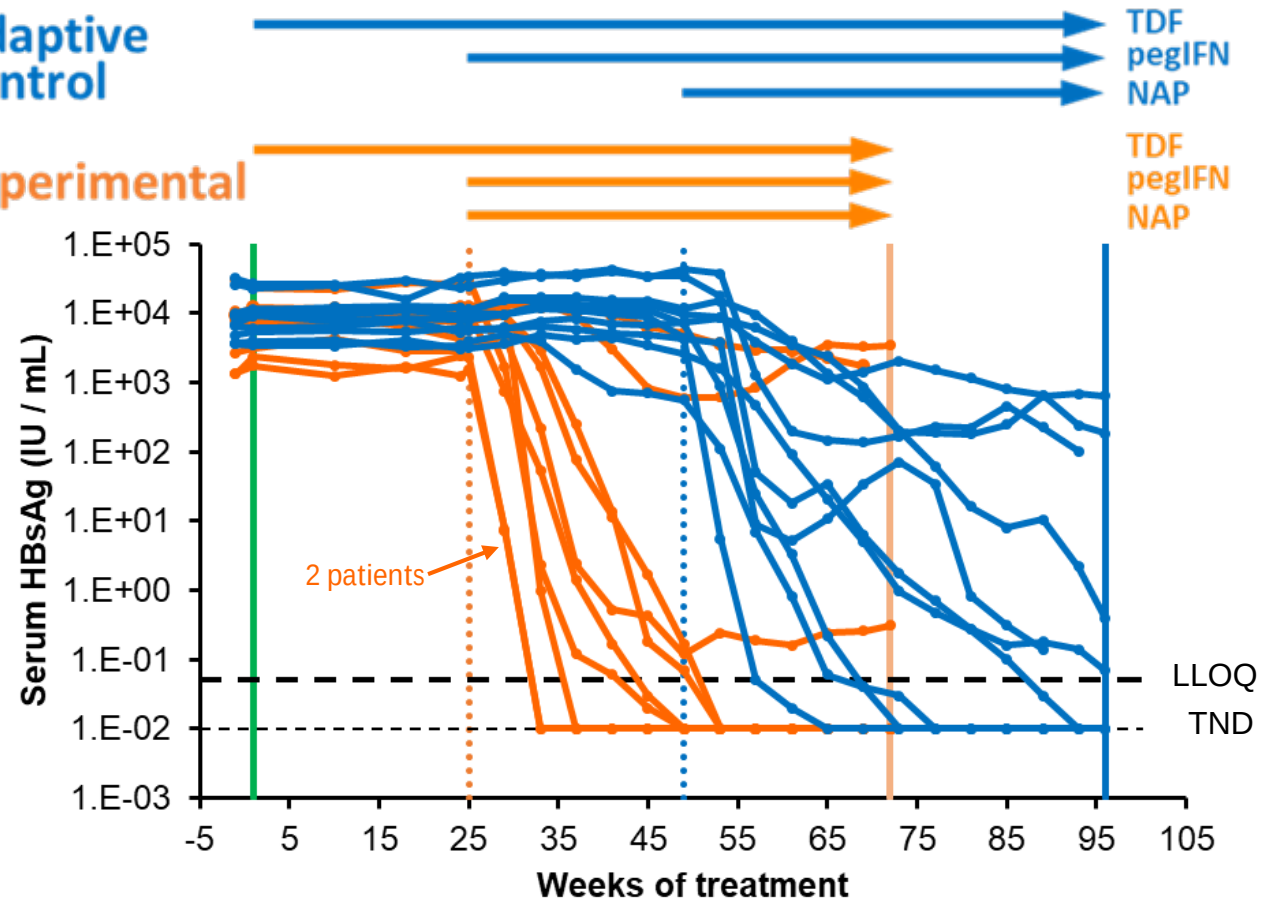
LLOQ = lower limit of quantification (10 IU / ml)
TND = HBV DNA target not detected

On-treatment HBsAg response

REP 2139

Adaptive
control

Experimental



HBsAg < 1IU/mL: 8/10 7/10
HBsAg loss (≤ 0.01 IU/mL): 7/10 4/10

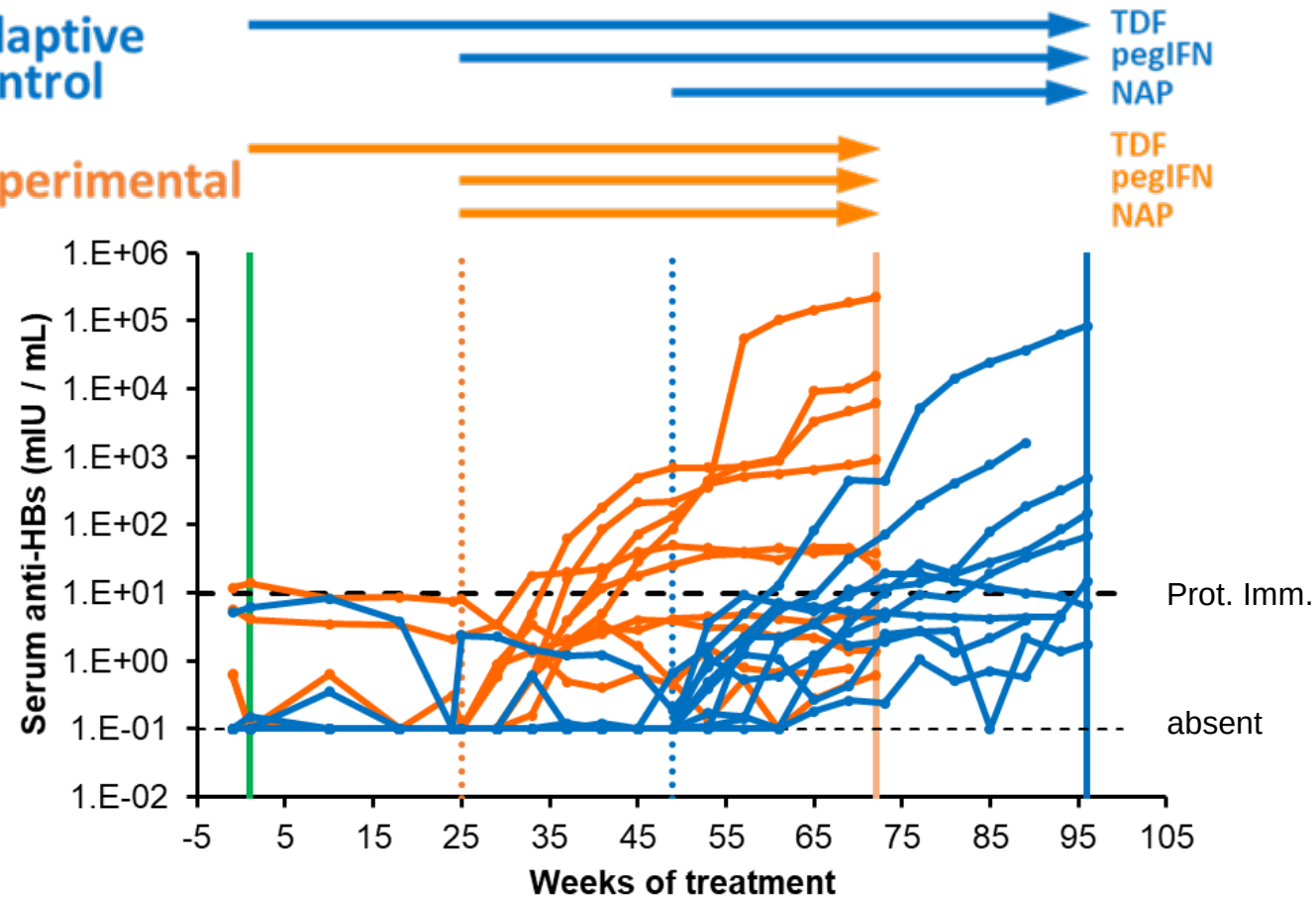
LLOQ = lower limit of quantification (0.05 IU/mL)
TND = HBsAg not detected (0.00 IU/mL)

On-treatment anti-HBs response

REP 2139

Adaptive
control

Experimental

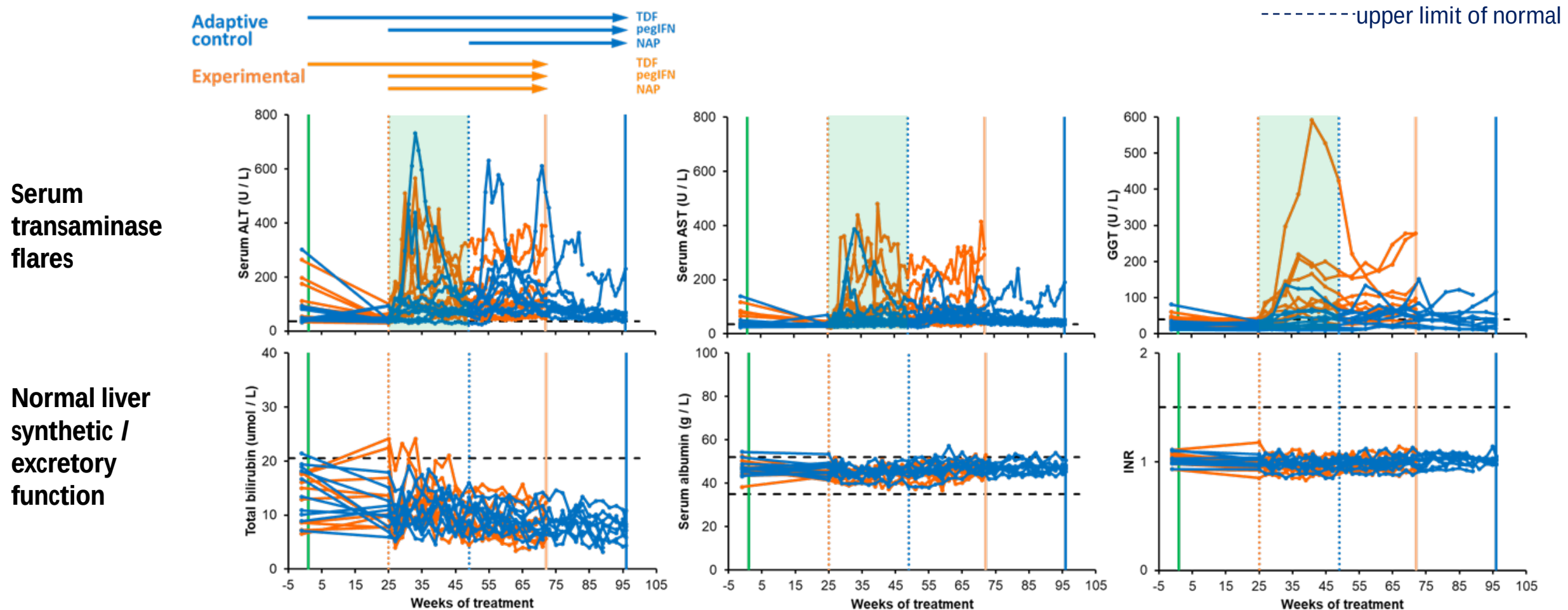


Elevation in serum anti-HBs
correlated with introduction of
pegIFN

Restricted to patients with
HBsAg < 1IU/mL

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

Therapeutic transaminase flares



Magnitude and incidence of transaminase flares is increased when HBsAg < 1IU/mL
Patients are asymptomatic throughout the course of these flares

Interim REP 401 follow-up data (no antiviral therapy present)

REP 2139 experimental group

Patient	Genotype	Parameter	Baseline	EOT	FW4	FW12	FW24
01-003	D1	HBsAg (IU/mL)	7809	TND	TND	TND	TND
		anti-HBs (mIU/mL)	0.61	6147	6287	2631	520
		HBV DNA (IU/ mL)	116900	48	10	TND	TND
		ALT (U/L)	32	115	47	33	26
		AST (U/L)	28	130	53	35	30
02-005	A2	HBsAg (IU/mL)	31184	TND	TND	TND	TND
		anti-HBs (mIU/mL)	<0.1	920	25419	6551	590
		HBV DNA (IU/ mL)	2641	30	<LLOQ	<LLOQ	<LLOQ
		ALT (U/L)	39	304	247	80	45
		AST (U/L)	29	292	179	79	45
02-015	D1	HBsAg (IU/mL)	10921	3510	4256	4807	4520
		anti-HBs (mIU/mL)	<0.1	0.62	0.14	2.84	4.72
		HBV DNA (IU/ mL)	43650	15	74	521900	175
		ALT (U/L)	54	50	19	125	19
		AST (U/L)	30	68	27	79	27
02-024	D1	HBsAg (IU/mL)	1368	TND	TND	TND	TND
		anti-HBs (mIU/mL)	0.64	1.4	1.12	9.14	11
		HBV DNA (IU/ mL)	8312	TND	TND	<LLOQ	<LLOQ
		ALT (U/L)	88	58	25	34	23
		AST (U/L)	38	39	32	28	28
01-046	D2	HBsAg (IU/mL)	8514	TND	TND	TND	<LLOQ
		anti-HBs (mIU/mL)	<0.1	15529	14037	3404	358
		HBV DNA (IU/ mL)	70600000	TND	TND	TND	TND
		ALT (U/L)	112	388	244	37	27
		AST (U/L)	66	315	154	48	37
01-067	D1	HBsAg (IU/mL)	2716	0.31	0.12	0.3	1.91
		anti-HBs (mIU/mL)	<0.1	4.04	1.58	0.54	0.17
		HBV DNA (IU/ mL)	194000	TND	TND	14	93
		ALT (U/L)	95	45	39	34	26
		AST (U/L)	44	37	29	26	24
01-026	D1	HBsAg (IU/mL)	8766	TND	TND	TND	TND
		anti-HBs (mIU/mL)	<0.1	25	26	16	8.01
		HBV DNA (IU/ mL)	7533000	TND	TND	TND	TND
		ALT (U/L)	197	124	25	24	21
		AST (U/L)	117	103	30	31	27
02-019	D1	HBsAg (IU/mL)	9721	TND	TND	TND	
		anti-HBs (mIU/mL)	<0.1	223055	286756	177925	
		HBV DNA (IU/ mL)	4916	17	12	TND	
		ALT (U/L)	41	105	55	36	
		AST (U/L)	31	63	37	30	
01-077	D2	HBsAg (IU/mL)	1334	TND	TND	TND	
		anti-HBs (mIU/mL)	5.81	38	30	31	
		HBV DNA (IU/ mL)	2183000	TND	TND	TND	
		ALT (U/L)	263	70	34	24	
		AST (U/L)	78	61	33	25	
03-023	D1	HBsAg (IU/mL)	9595	1737*			
		anti-HBs (mIU/mL)	12	0.78*			
		HBV DNA (IU/ mL)	1132000	TND*			
		ALT (U/L)	175	50*			
		AST (U/L)	85	35*			

- Functional control achieved on treatment (HBsAg < 1IU/mL, HBV DNA < LLOQ).
 - Functional control persistent during follow-up (functional remission).
 - Clinical benefit persists during follow-up despite rebound in infection.
- *latest on treatment available

**Functional remission of HBV infection present in 8/10 patients
after all antiviral therapy is removed**

**All with normal liver function
(ALT/AST/bilirubin/albumin/INR)**

TND = 0.00 IU/mL (HBsAg) or no PCR product detected (HBV DNA)
LLOQ = < 0.05 IU/mL (HBsAg) or < 10 IU/mL (HBV DNA)

Interim REP 401 follow-up data

(detail of two patients in the REP 2139 experimental group)

Patient	Genotype	Parameter	Baseline	EOT	FW4	FW12	FW24
01-003	D1	HBsAg (IU/mL)	7809	TND	TND	TND	TND
		anti-HBs (mIU/mL)	0.61	6147	6287	2631	520
		HBV DNA (IU/ mL)	116900	48	10	TND	TND
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		HBV DNA (IU/ mL)	2641	30	<LLOQ	<LLOQ	<LLOQ
		ALT (U/L)	39	304	247	80	45
		AST (U/L)	29	292	179	79	45

	Functional control achieved on treatment (HBsAg < 1IU/mL, HBV DNA < LLOQ).
	Functional control persistent during follow-up (functional remission).

TND = 0.00 IU/mL (HBsAg) or no PCR product detected (HBV DNA)
LLOQ = < 10IU/mL

ULN (ALT / AST) = 50 U/mL

Summary

NAPs block assembly and secretion of SVPs

- Host target currently under investigation (apolipoprotein?)

HBsAg levels <1IU/mL are required for efficient response to immunotherapy

- **HBsAg <1IU/mL is reliably achieved with REP 2139**

Response to immunotherapy with HBsAg <1IU/mL is universally potentiated

- Increased anti-HBs production, magnitude and incidence of therapeutic transaminase flares
- **High rate of functional control (80%) on-treatment which persists after all therapy is removed (functional remission).**

Acknowledgments

A collaborative effort!

Clinical evaluations:

Montreal, Canada
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Dhaka, Bangladesh
Mamun Al-Mahtab

Chişinău, Moldova
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Frauke Beilstein
Matthieu Lemasson

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