Update on safety and efficacy in the REP 401 protocol:

REP 2139-Mg or REP 2165-Mg used in combination with tenofovir disoproxil fumarate and pegylated interferon alpha 2a in treatment naïve Caucasian patients with chronic HBeAg negative HBV infection

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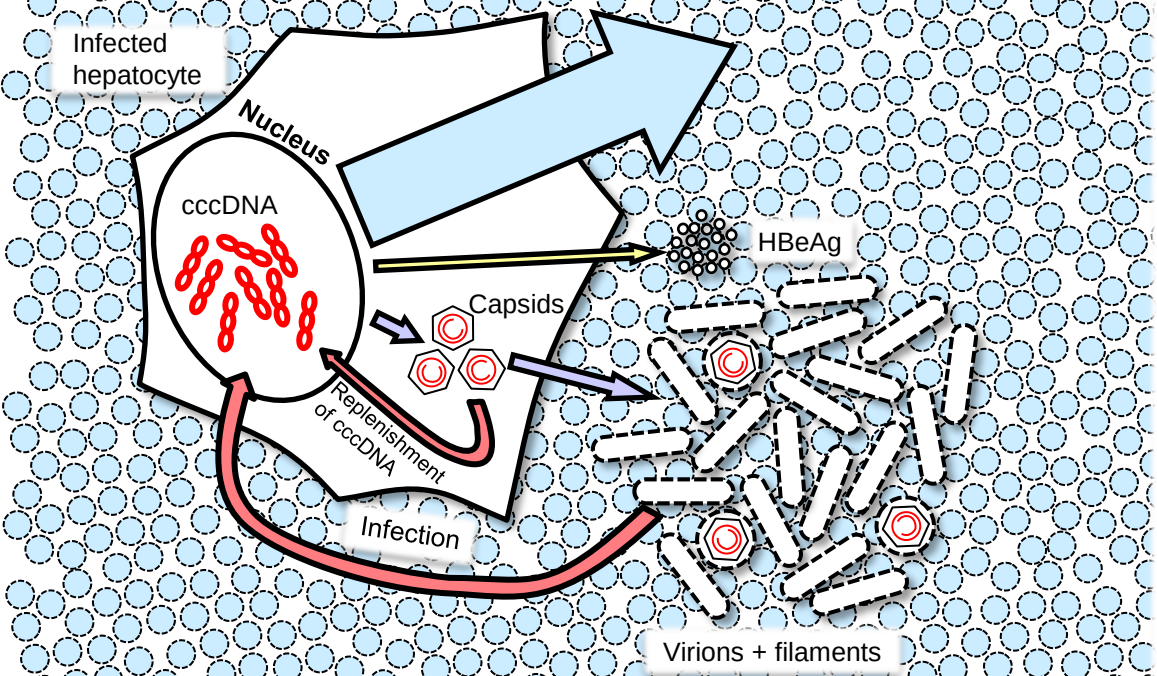
Disclosures

M. Bazinet, A. Vaillant: employees and shareholders in Replicor Inc.

All other authors: no conflicts of interest to declare.

Particle production in HBV

SUBVIRAL PARTICLES: The bulk of circulating HBsAg



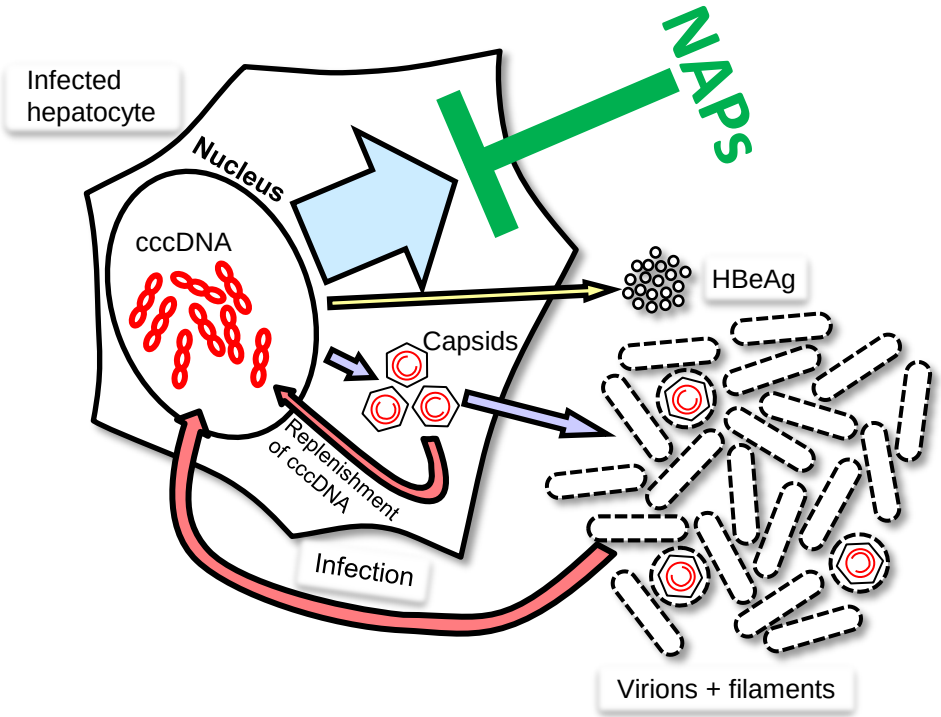
HBsAg is an immunosupressor:

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

M. Bazinet et al., 2016 Hepatology 64: S912A
Al-Mahtab et al., 2016 PLOS One 11: e0156667
Shi et al. 2012 PLOS One 7: e44900
Woltman et al. 2011 PLOS One 6: e15324
Op den Brouw et al., 2009. Immunology, 126: 280-289
Wu et al., 2009. Hepatology, 49: 1132-11
Xu et al., 2009. Molecular immunology, 46: 2640-2646
Cheng et al., 2005. Journal of Hepatology, 43:4 65-471
Vanlandschoot et al., 2002. J. Gen. Virol., 83: 1281-1289

Nucleic Acid Polymers (NAPs)

NAPs block subviral particle release → Efficient HBsAg clearance from the blood



Critical effects of HBsAg clearance:

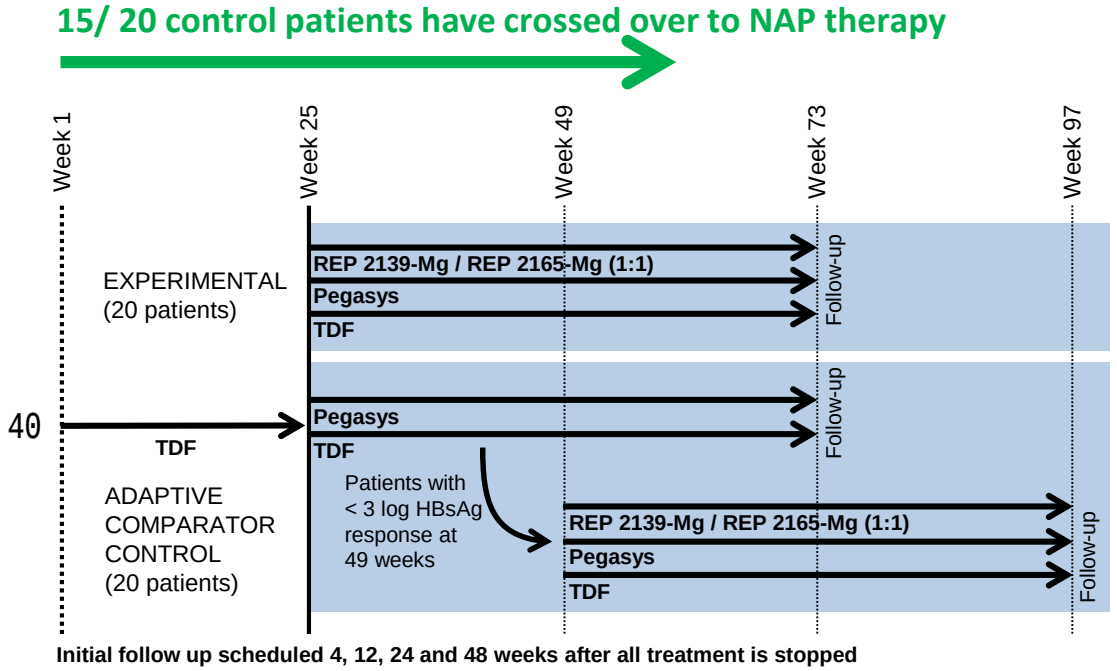
- Unmasking anti-HBs response
- Elimination of HBsAg mediated immunosupression
- Improved response to immunotherapy
- **Functional control can be established in most patients**

Vaillant, 2016. Antiviral Res. 133: 32-40
Al-Mahtab et al., 2016 PLOS One 11: e0156667
M. Bazinet et al., 2016 AASLD Abstract 1848.
Reesink et al., 2016 Hepatol. Int. 10: S2
Noordeen et al., 2015 PLOS One 10: e0140909

REP 401 Design

Clinicaltrials.org # NCT02565719
Randomized, open label, active comparator controlled
3 trial sites (Chisinau, Moldova)

Patient population:
- Treatment naive
- HBeAg negative
- Fibrotic (not cirrhotic)



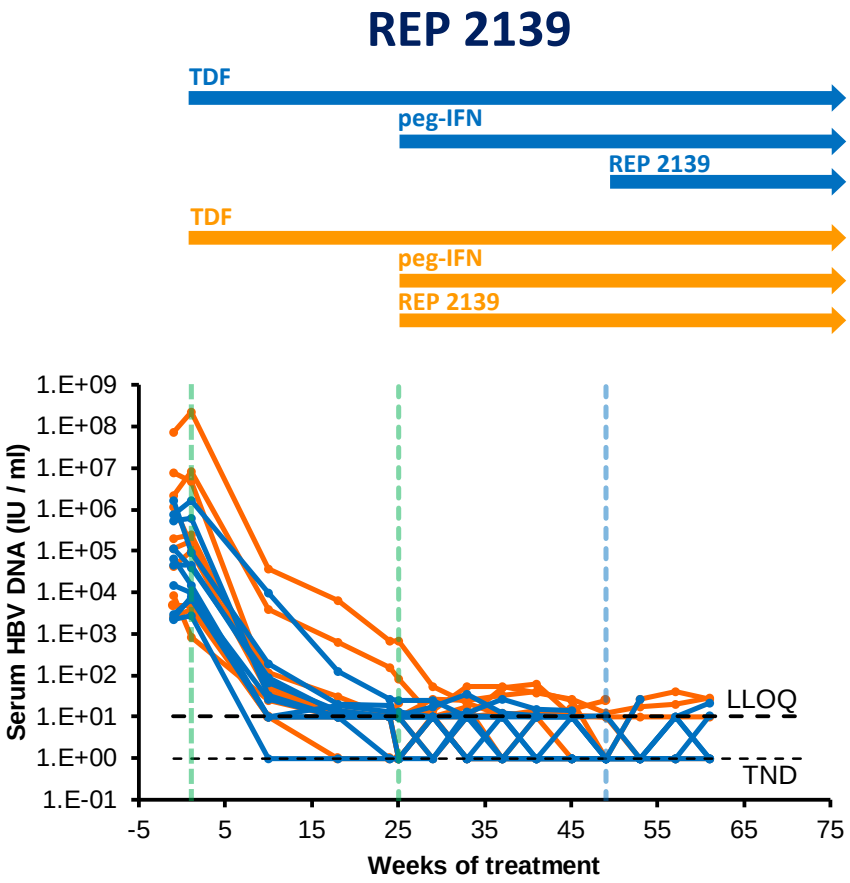
Dosing:
- TDF 300mg PO qD
- Pegasys 180ug SC qW
- NAPs: REP 2139-Mg or REP 2165-Mg 250mg IV qW
- REP 2165 = REP 2139 variant with improved tissue clearance

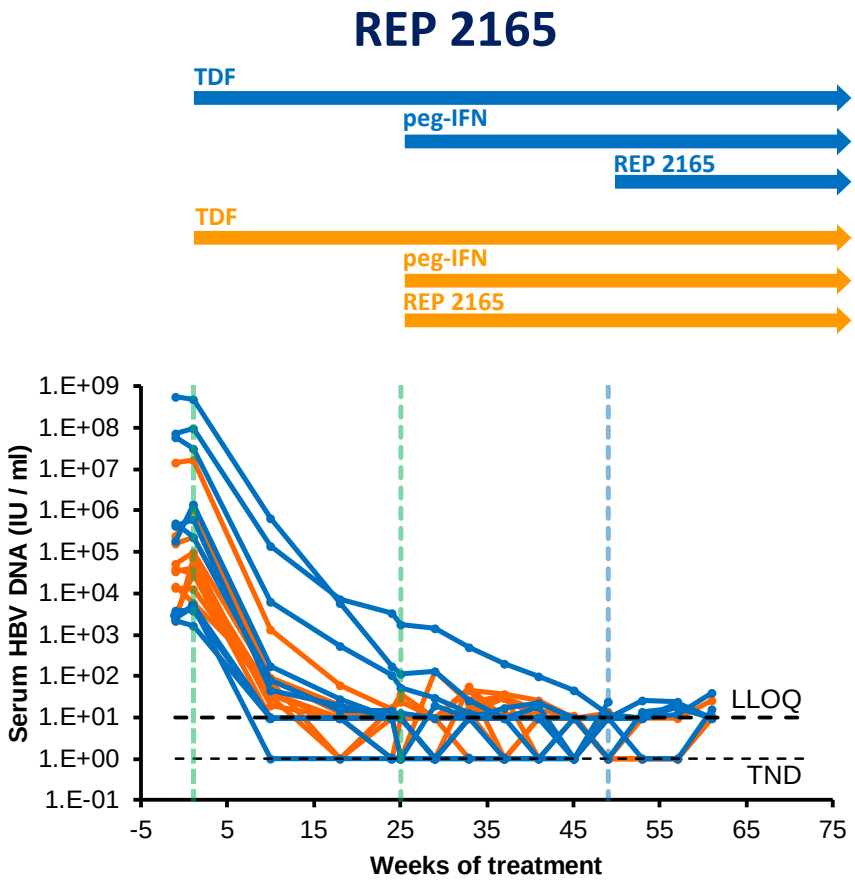
Primary efficacy endpoints:
- Serum HBsAg reduction
- Appearance of anti-HBs
- Functional control maintained after treatment withdrawal
  (≥ 6 months HBsAg < 1 IU/ml, HBV DNA < 1000 copies / ml)

REP 401 patient demographics

Parameter		Adaptive comparator control (TDF + peg-IFN)	Experimental (TDF + peg-IFN + NAPs)
Age (average / median)	Average	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	3	6
	F2-F3	0	3
	F3-F4	3	1
Virologic baseline (average / median)	HBV DNA (IU/mL)	$3.6x10^7$ / $8.7x10^4$	$4.8x10^6$ / $4.8x10^4$
	HBsAg (IU/mL	14775.7 / 9302.5	9018.1 / 8743
	Anti-HBs (mIU/mL)	0.78 / 0.1	2.778 / 0.1

Interim Efficacy data (serum HBV DNA)

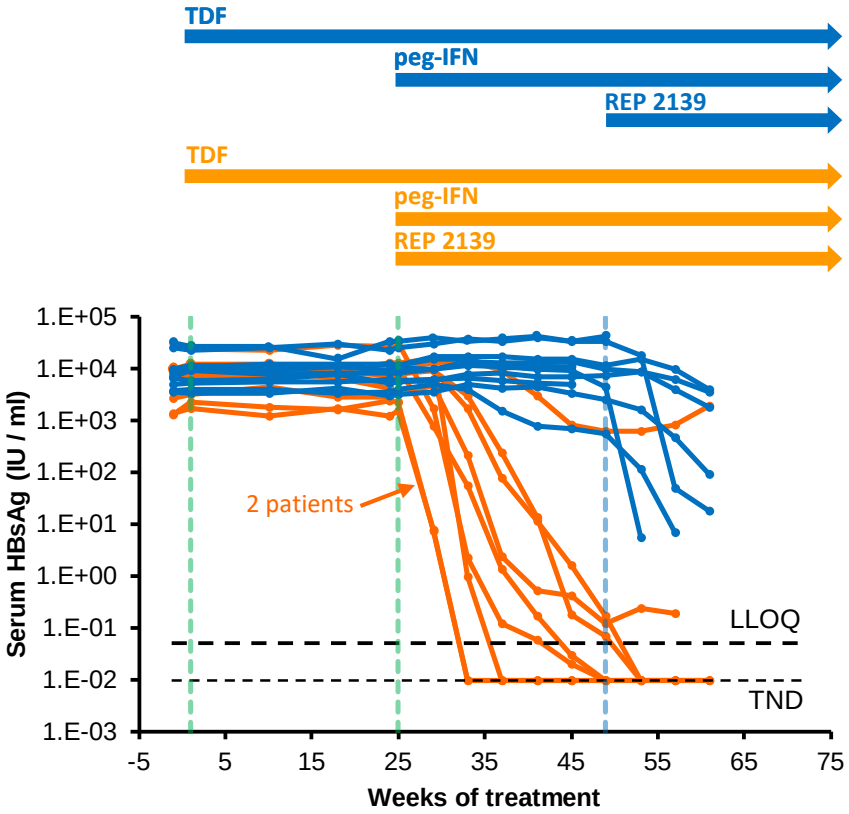




LLOQ = lower limit of quantification (10 IU / ml)
TND = HBV DNA target not detected

Interim Efficacy data (serum HBsAg)

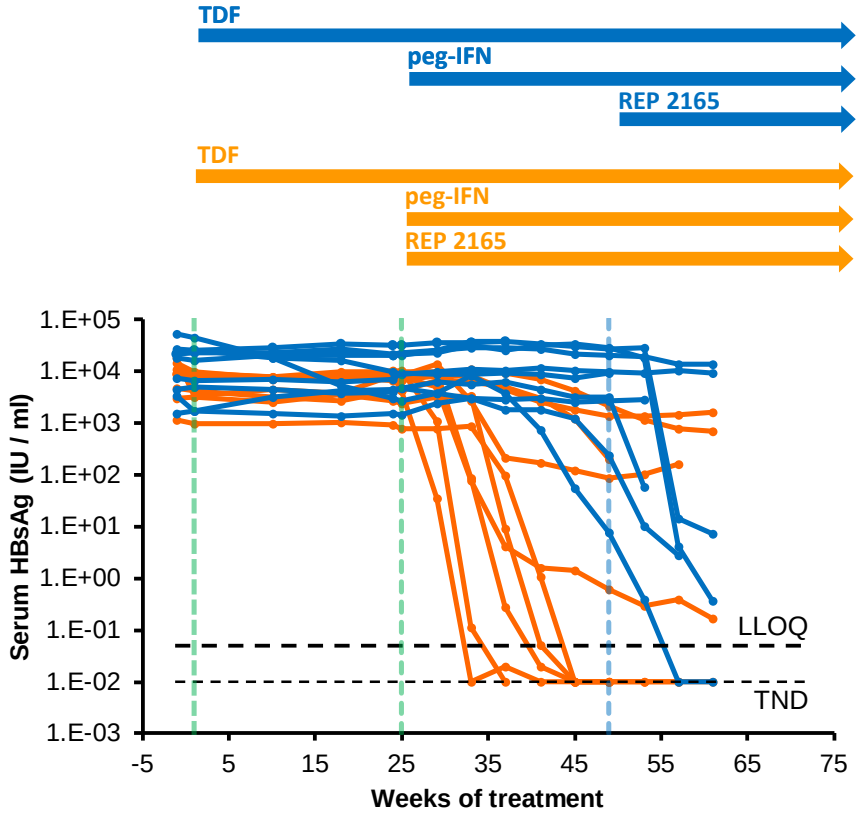
REP 2139



HBsAg response > 4 log: 8/9 0/7

HBsAg loss (≤0.01 IU/mL): 7/9 0/7

REP 2165

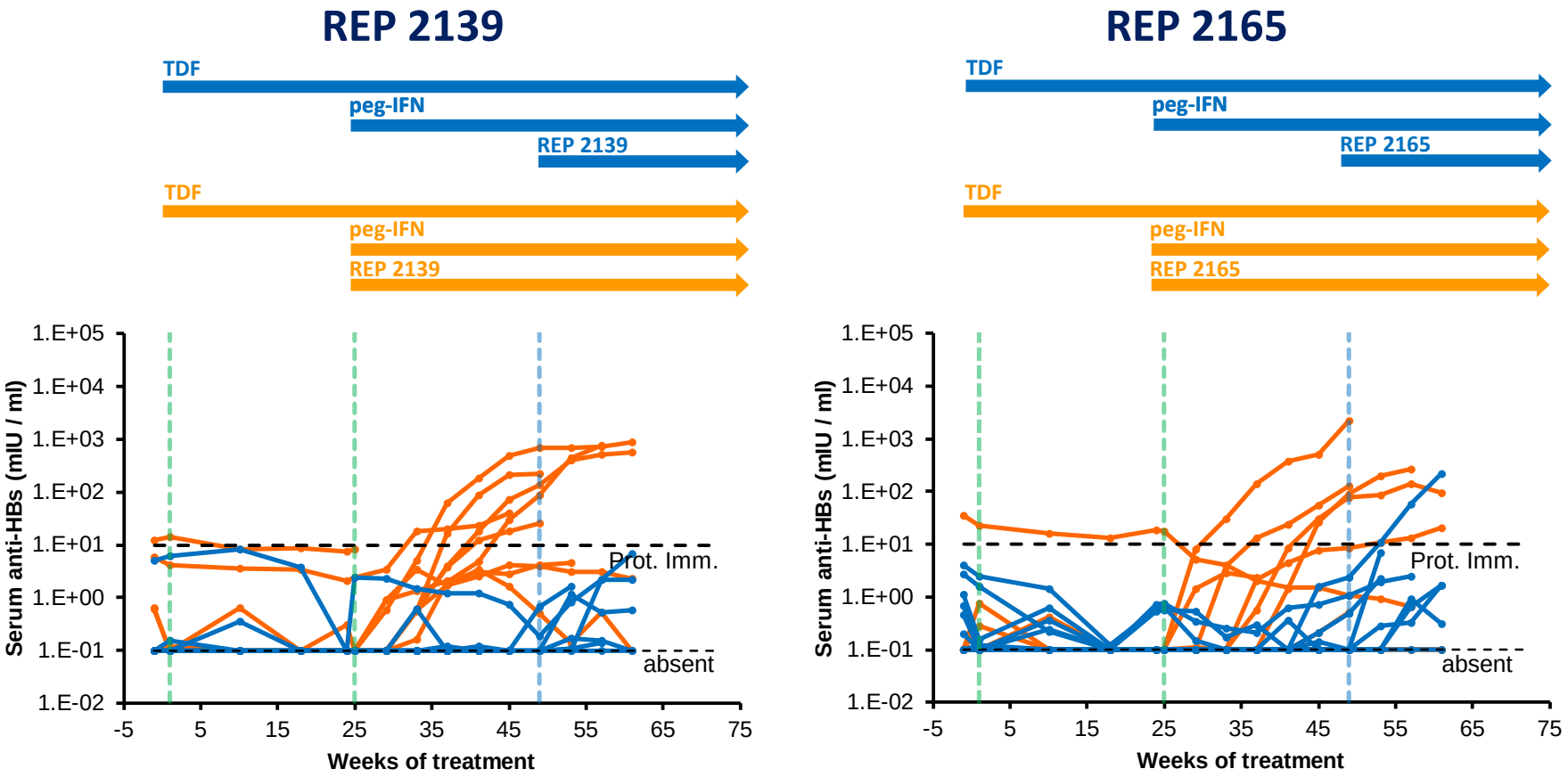


HBsAg response > 4 log: 6/10 2/8

HBsAg loss (≤0.01 IU/mL): 5/10 1/8

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

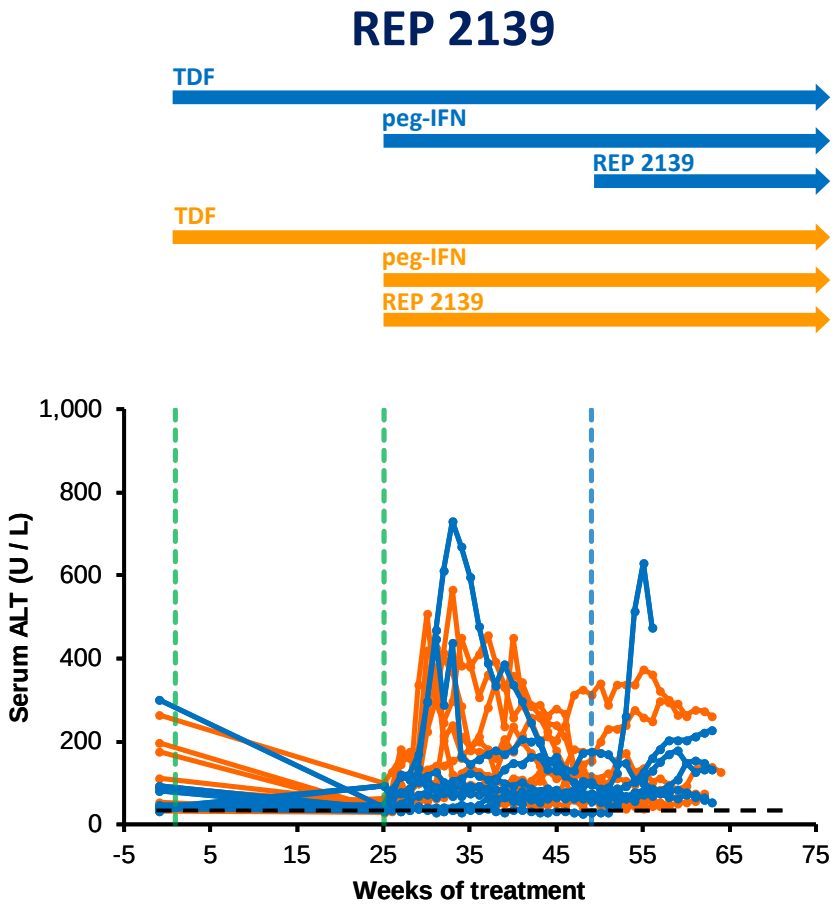
Interim Efficacy data (serum anti-HBs)

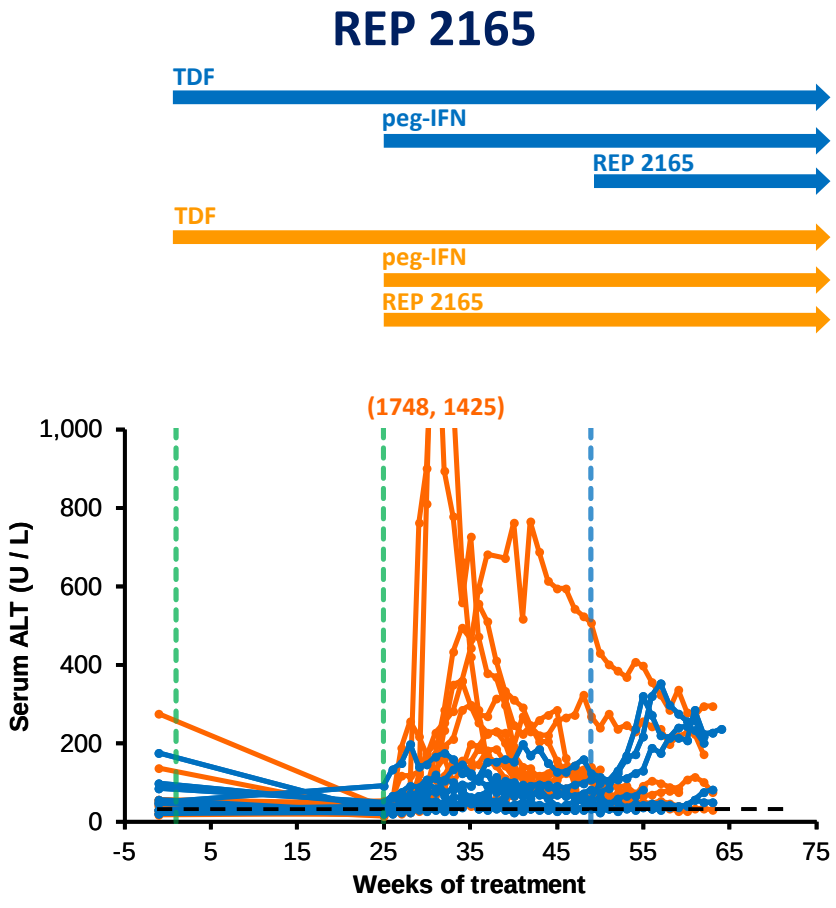


Elevation in serum anti-HBs correlated with extent of HBsAg reduction

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

Interim Efficacy Data (serum ALT)

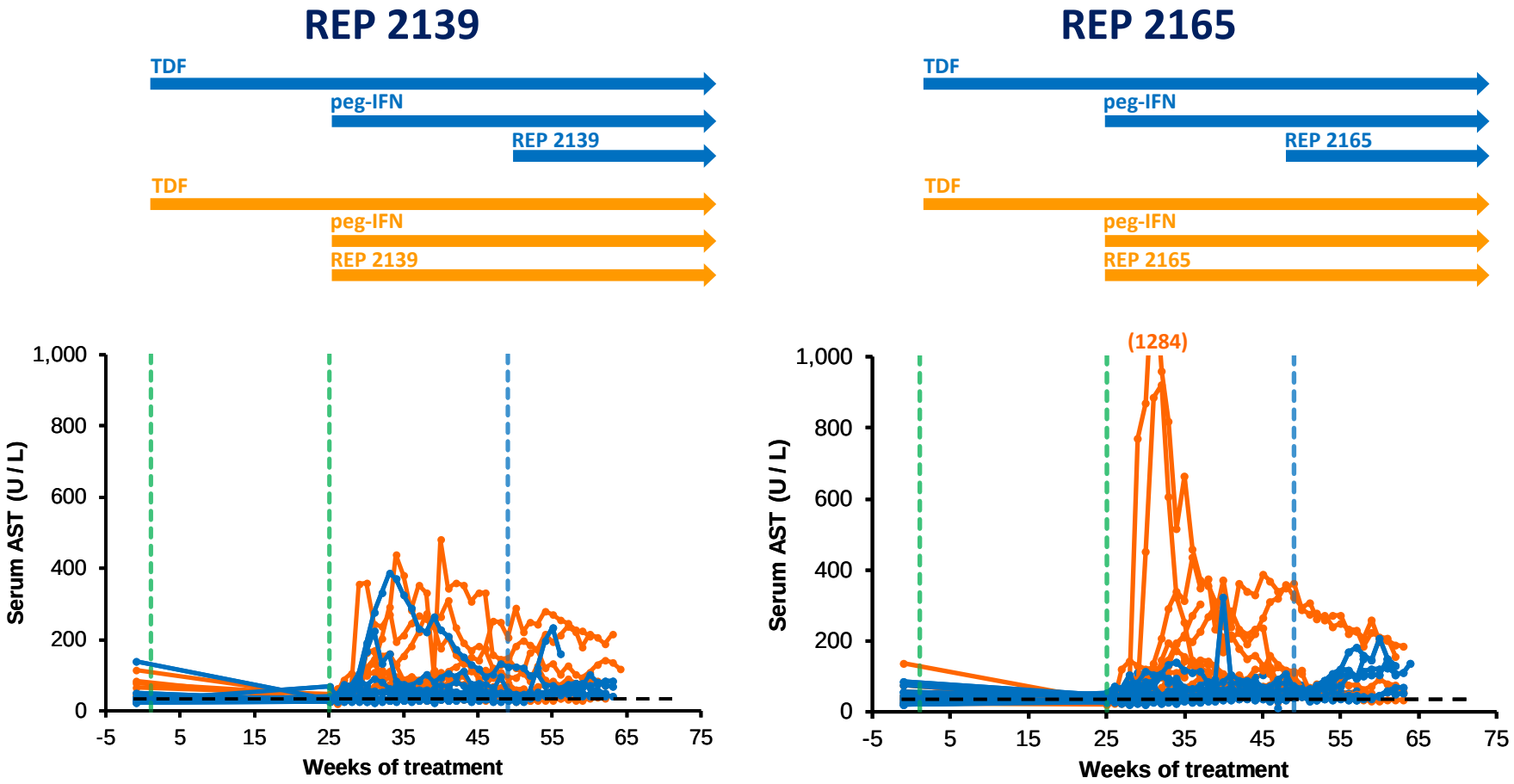




Elevation in serum ALT correlated with HBsAg reduction (self-resolving with continued therapy)

- - - - - - - - upper limit of normal

Interim Efficacy Data (serum AST)



Elevation in serum AST correlated with HBsAg reduction (self-resolving with continued therapy)

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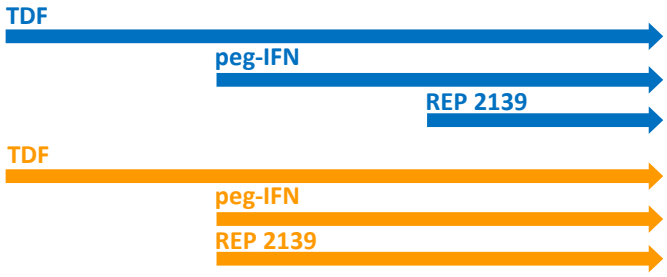
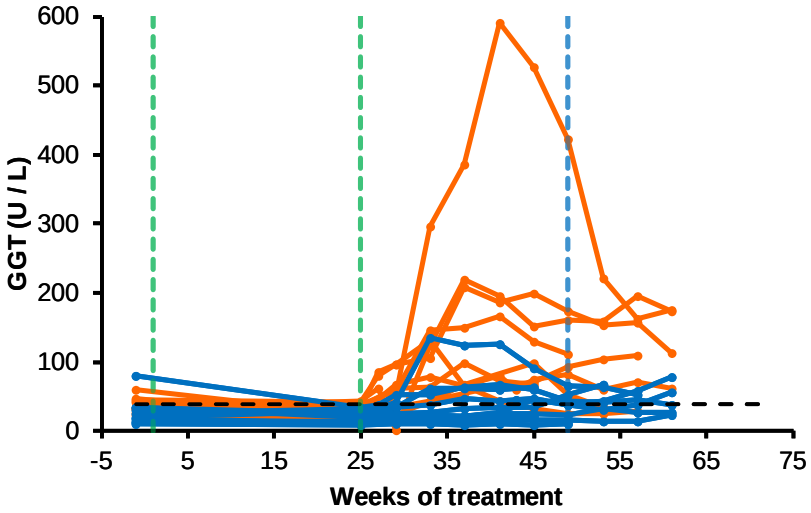
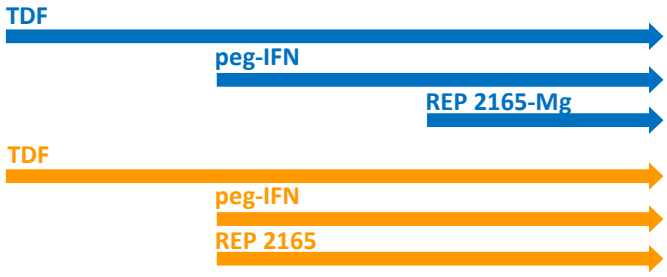
Interim Efficacy Data (serum GGT)

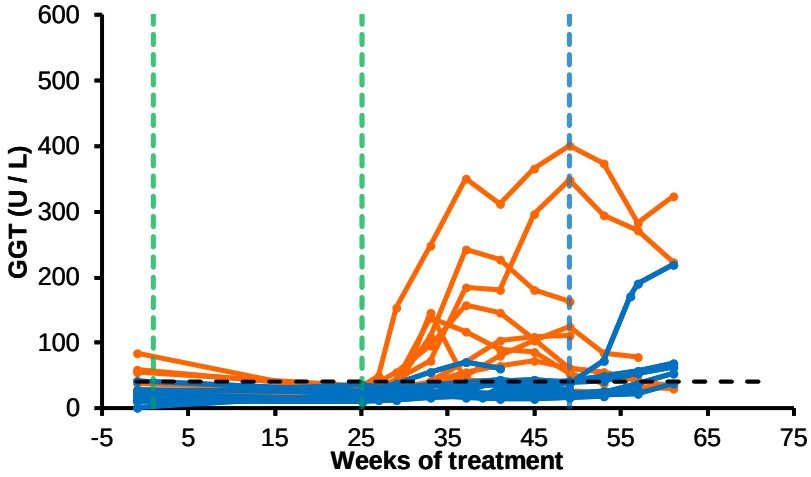
REP 2139





REP 2165

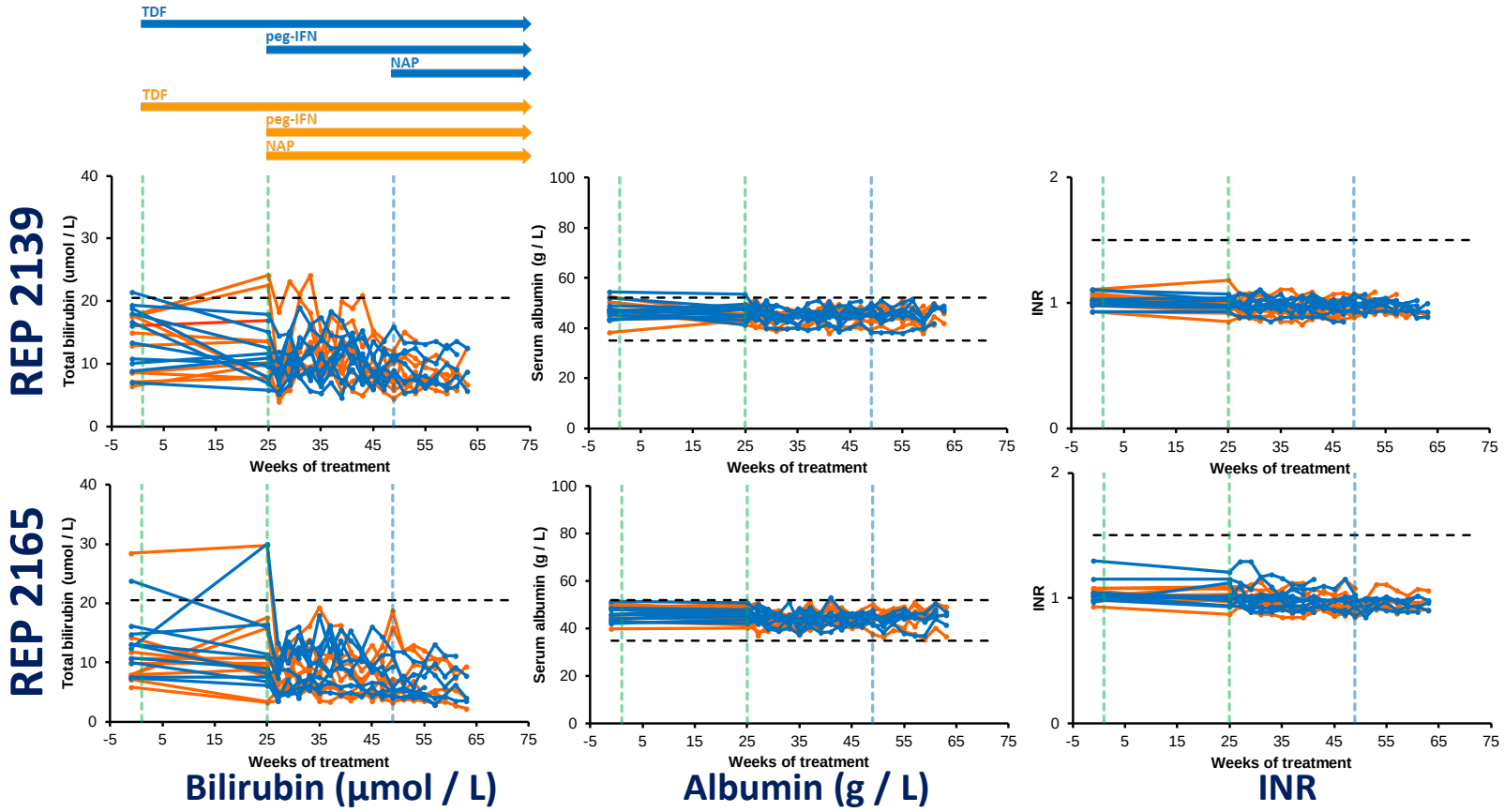




Elevation in serum GGT correlated with HBsAg reduction

- - - - - - - - upper limit of normal

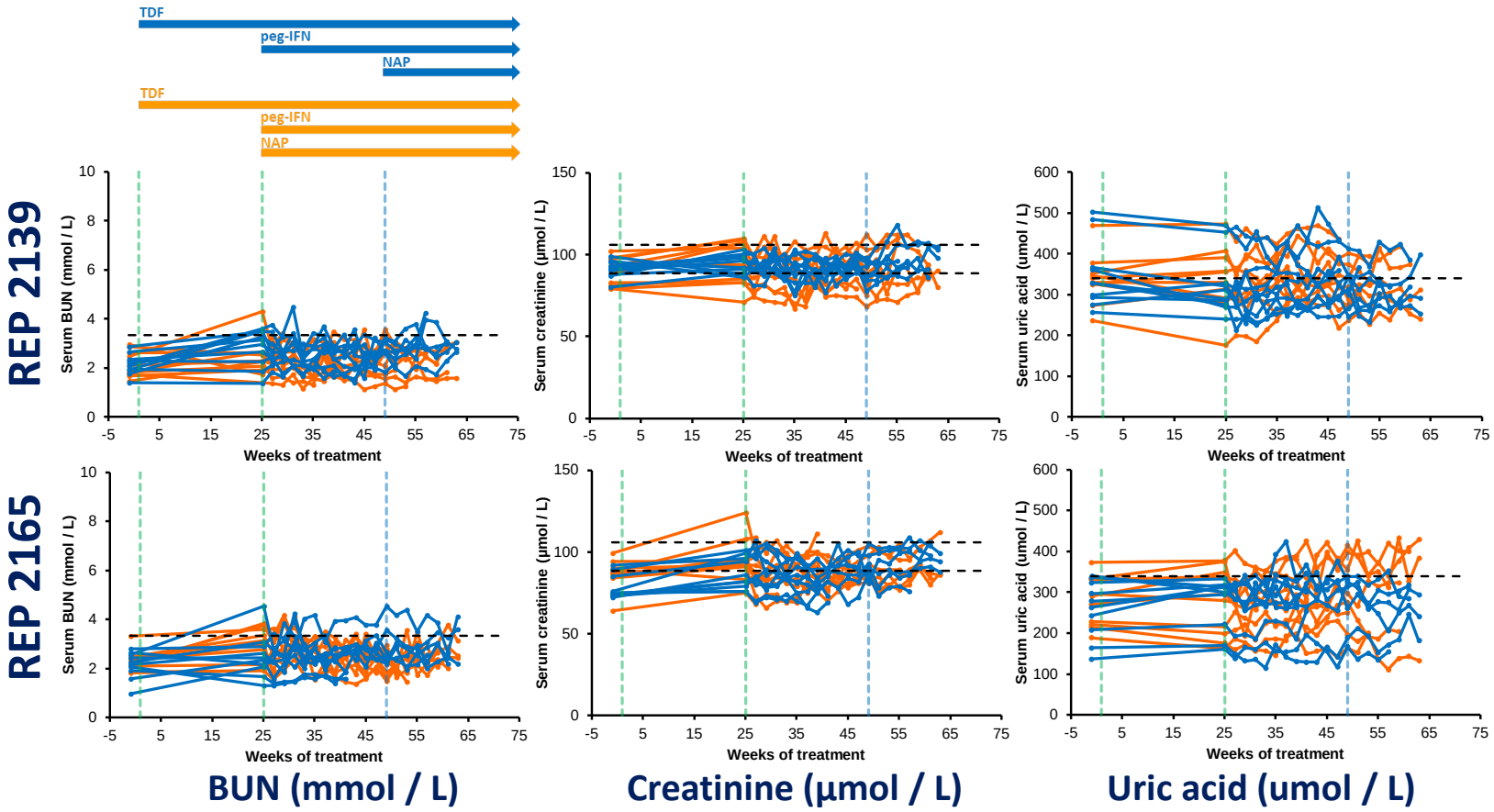
Interim REP 401 Safety Data (liver function)



Liver function normal during transaminase flares

- - - - - - - - upper limit of normal / normal range

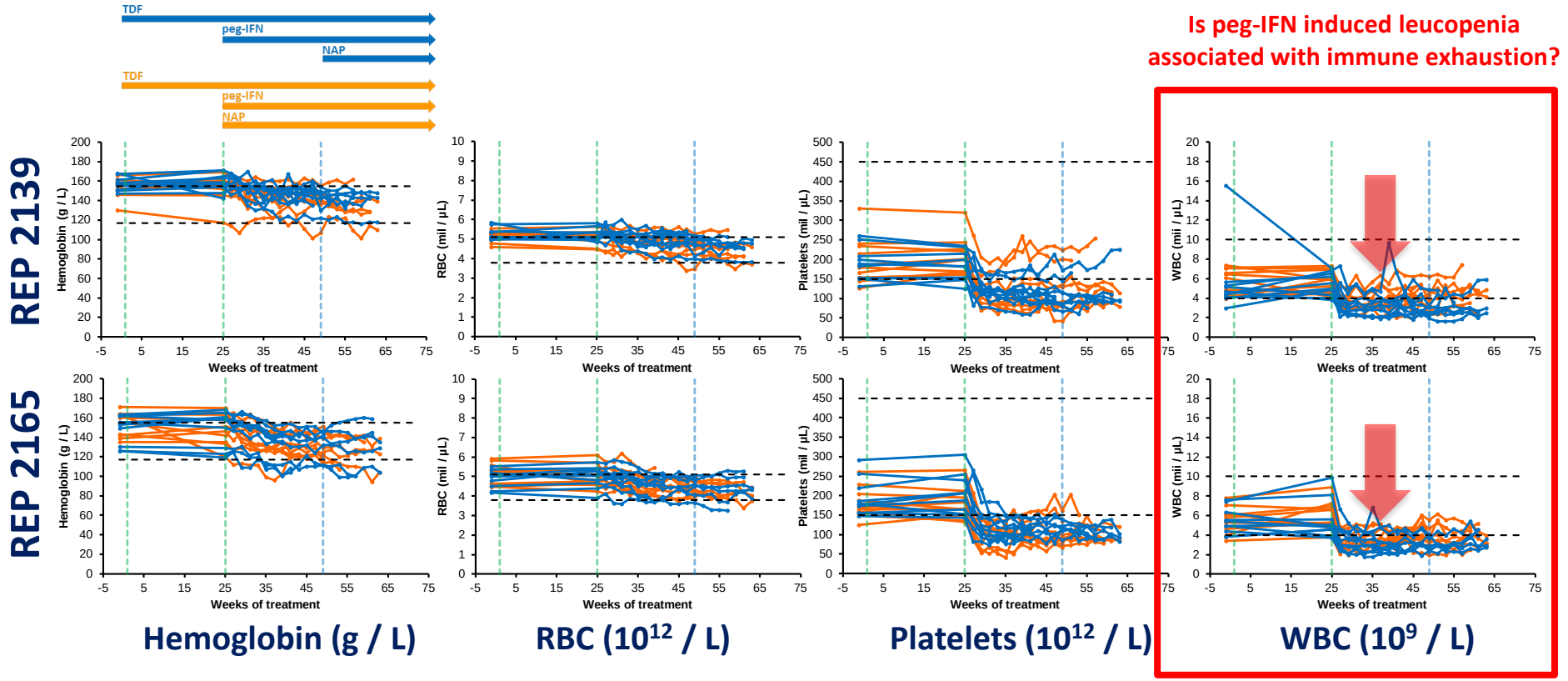
Interim REP 401 Safety Data (kidney function)



Kidney function not altered by the presence of NAPs

- - - - - - - - upper limit of normal / normal range

Interim REP 401 Safety Data (hematology)

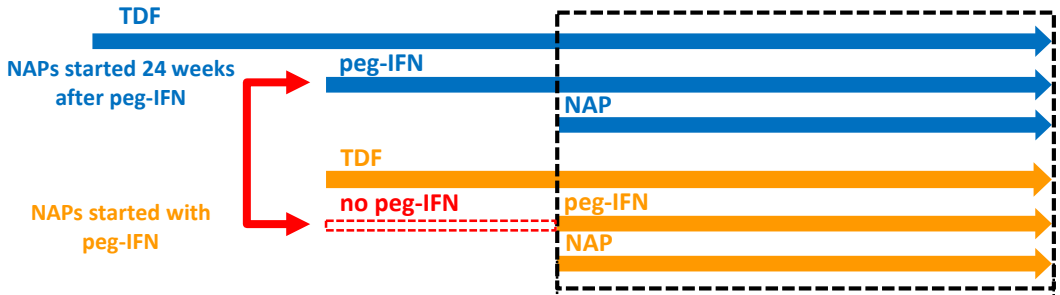


Thrombocytopenia and leucopenia consistent with the introduction of peg-IFN (not altered by presence of NAPs)

- - - - - - - - normal range

NAP-induced HBsAg reduction as a tool for examining response to immunotherapy?

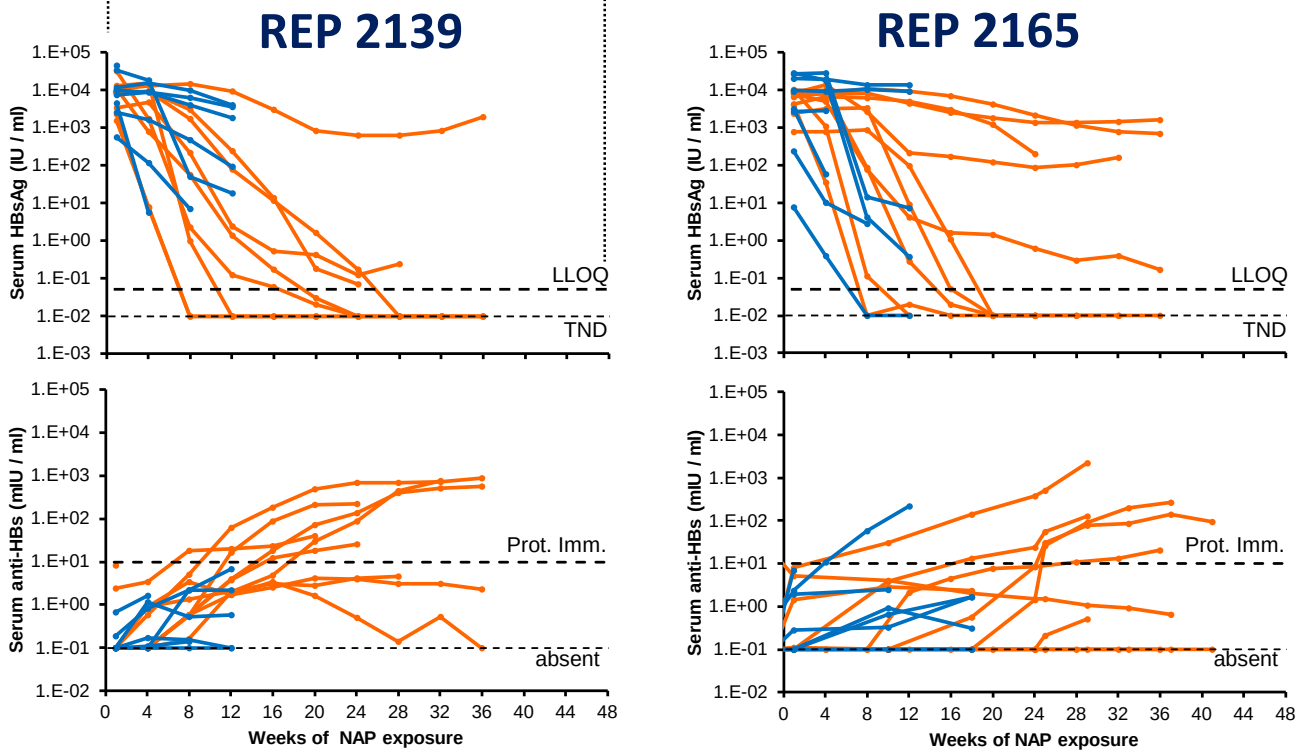
(Synchronization of virologic response to start of NAP therapy)



Comparable HBsAg and anti-HBs response

HBsAg

Anti-HBs



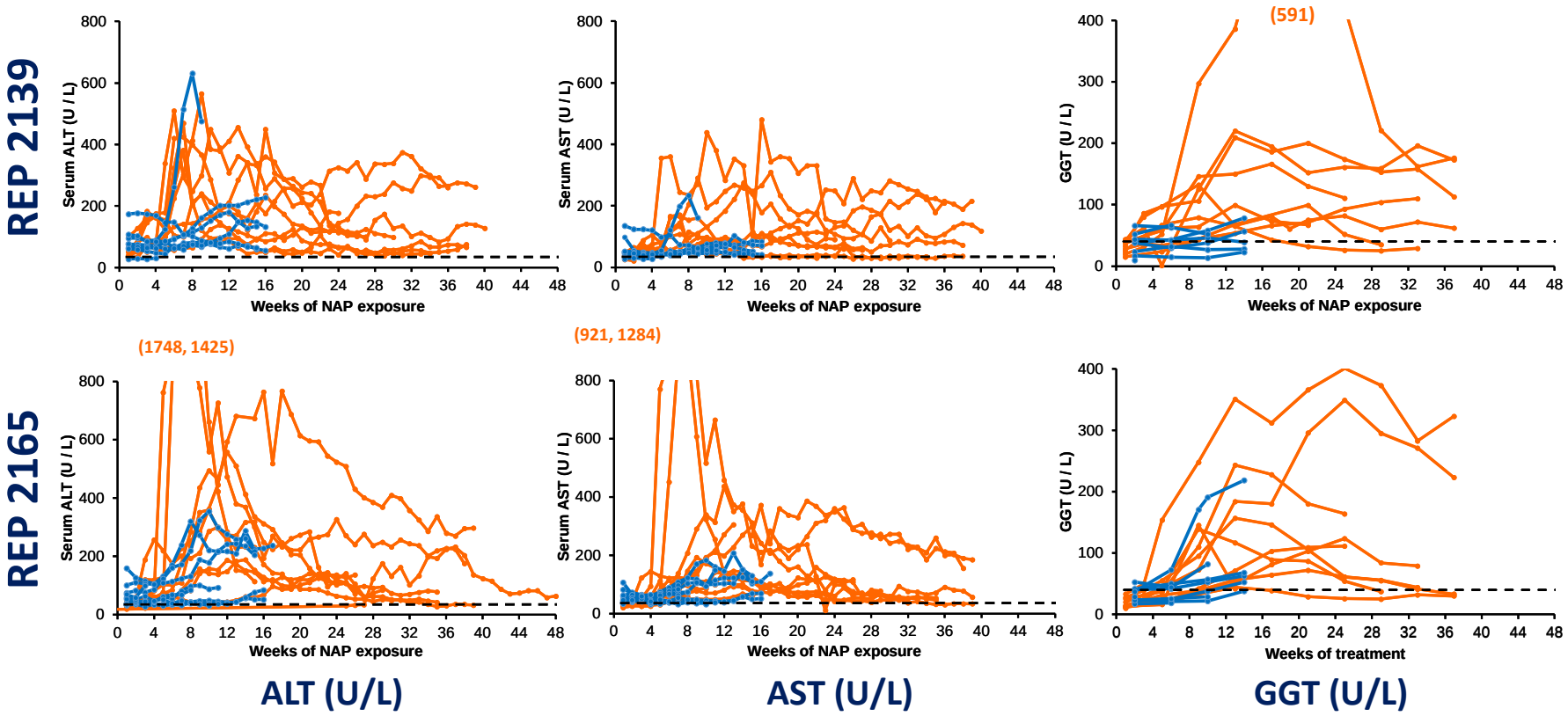
LLOQ: lower limit of quantification (0.05 IU / mL)
TND: HBsAg not detected (0.00 IU / mL)
Prot. Imm.: Architect defined threshold for protective immunity (10 mIU / mL)
Absent: no significant anti-HBs present (≤ 0.1 mIU / mL)

Liver flares are attenuated with initial NAP exposure after 24 weeks of peg-IFN

NAPs started with peg-IFN

NAPs started 24 weeks after peg-IFN

(Synchronization of serum transaminases to start of NAP therapy)



Continued peg-IFN exposure may impede immune response to HBsAg clearance

- - - - - - - - upper limit of normal

Adverse events

NAP administration has been well tolerated to date

- Infusion reactions which spontaneously developed in 2 patients were self resolving after 3-4 weeks with supportive therapy during infusion – may be related to the onset and resolution of concomitant seasonal infections

Peg-IFN therapy is associated with weakness, thrombocytopenia and neutropenia

- not altered by combination therapy with REP 2139 or REP 2165
- otherwise asymptomatic
- managed with supportive therapy and peg-IFN dose reduction

Serious adverse events to date:

- transient profound weakness (1 patient, peg-IFN related)
- appendicitis (1 patient, not treatment related)
- community acquired bronchopneumonia (1 patient, not treatment related)

Summary

REP 2139 and REP 2165 are well tolerated in triple combination with TDF and peg-IFN

Antiviral effect of REP 2139 is conserved with the more rapidly cleared REP 2165

NAP therapy is associated with:

- multilog reduction or clearance of serum HBsAg
- increases in serum anti-HBs
- increased incidence and magnitude of serum transaminase flares
  (otherwise asymptomatic and self resolving)

NAP therapy started after 24 weeks peg-IFN results in attenuated transaminase flares with HBsAg clearance.

- immune exhaustion may be occurring with continued exposure to peg-IFN

Upcoming analyses to be presented:

- HBcrAg and HBV RNA analysis (EASL 2017)