

Preliminary safety and efficacy of 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

(REP 401 protocol)

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



Infectious Disease
Clinic
Toma Ciorbă
Hospital

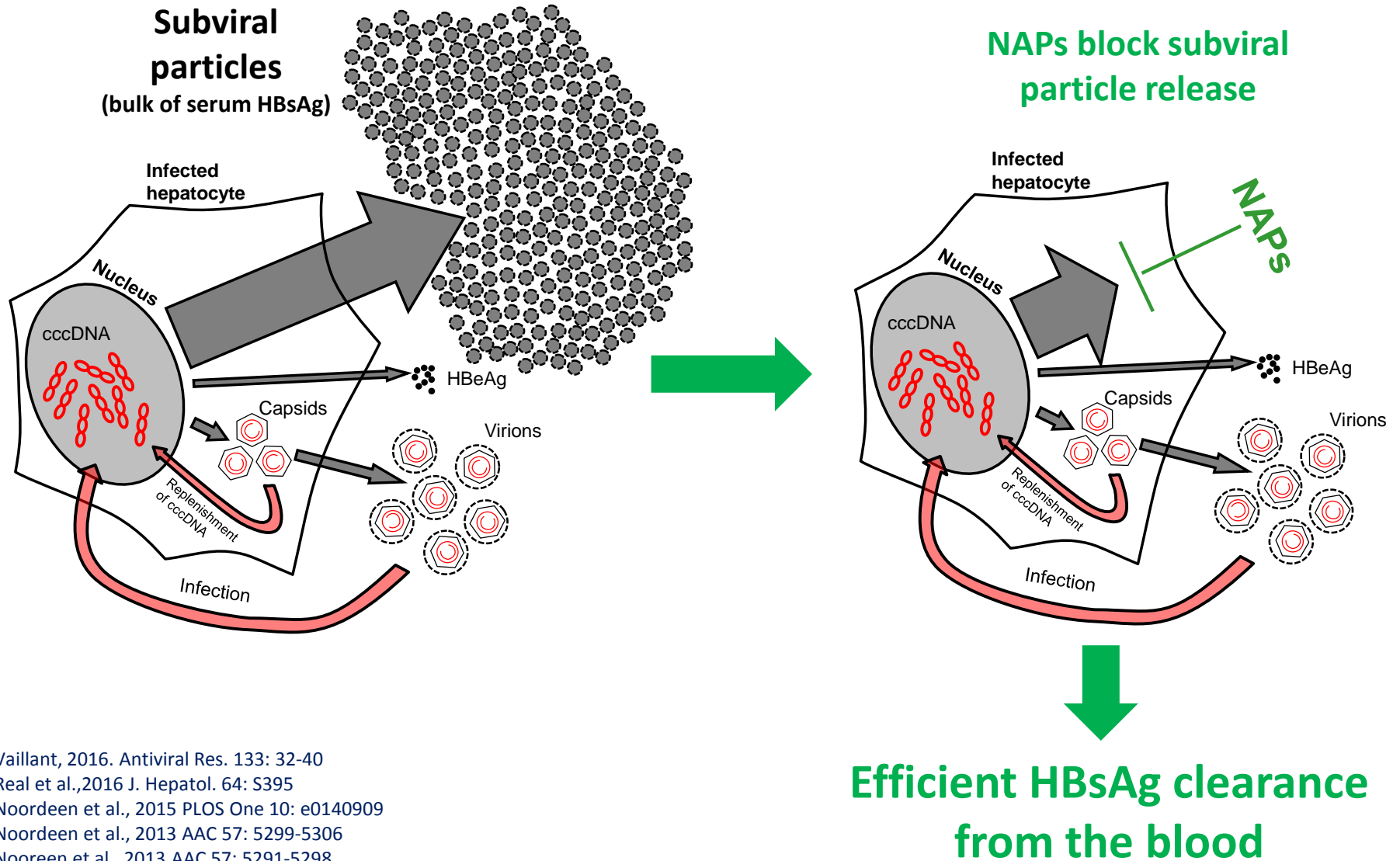


Disclosures

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

All other authors: no conflicts of interest to declare.

Nucleic Acid Polymers (NAPs)



Vaillant, 2016. Antiviral Res. 133: 32-40
Real et al., 2016 J. Hepatol. 64: S395
Noordeen et al., 2015 PLOS One 10: e0140909
Noordeen et al., 2013 AAC 57: 5299-5306
Nooreen et al., 2013 AAC 57: 5291-5298

Critical effects of HBsAg clearance

NAP mediated HBsAg clearance leads to:

Unmasking pre-existing anti-HBs response

➔ clearance of virions (HBV DNA and HBV RNA)

Removal of HBsAg mediated immunosuppression

➔ HBeAg seroconversion (in HBeAg+ patients)

➔ enhanced immune response in the liver (transaminase flares)

➔ establishment of functional control off treatment (in some patients)

Improved effect of immunotherapy

➔ can establish functional control 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
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 401 Protocol

Clinicaltrials.org # NCT02565719

Randomized, open label, active comparator controlled

3 trial sites (Chisinau, Moldova)

40 patients

- treatment naïve HBeAg- chronic HBV infection
- HDV, HCV, HIV negative
- serum HBsAg > 1000 IU / ml
- HBV DNA > 7500 copies / ml
- mild to moderate fibrosis, non cirrhotic.

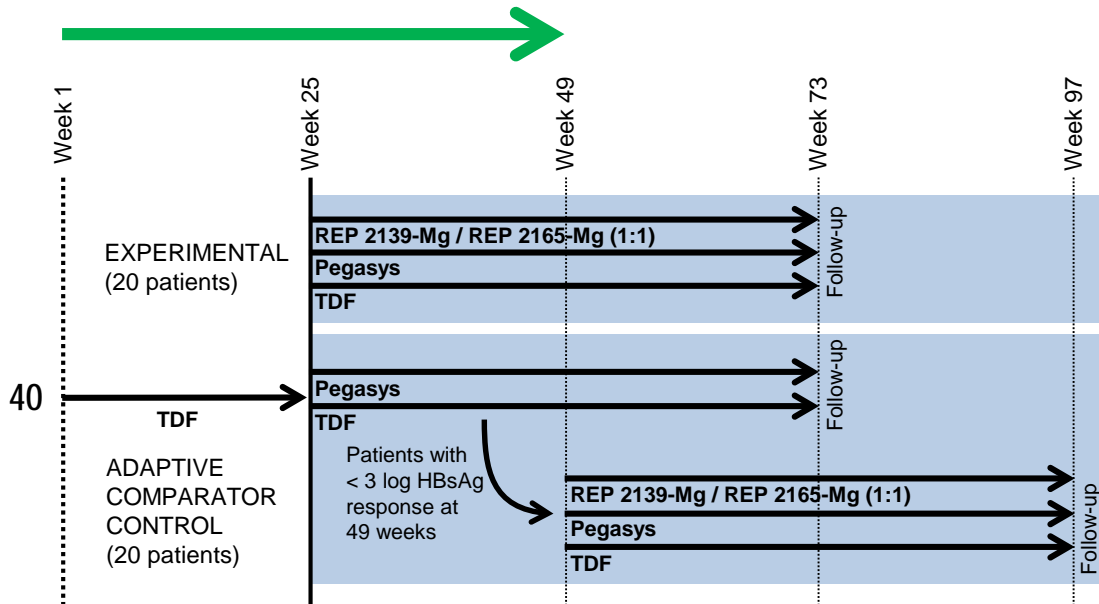
Viremia monitored at University of Duisburg-Essen, Germany:

- Abbott PCR (HBV DNA)
- Abbott Architect Quantitative (q-HBsAg, q-anti-HBs, HBeAg, anti-HBe)

Pre-treatment demographics

Parameter		Adaptive comparator control (TDF + peg-IFN)	Experimental (TDF + peg-IFN + NAPs)
Age	Average	36.9	38.65
	Median	36	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

REP 401 Design



29 patients are > 12 weeks post-randomization (week 25)

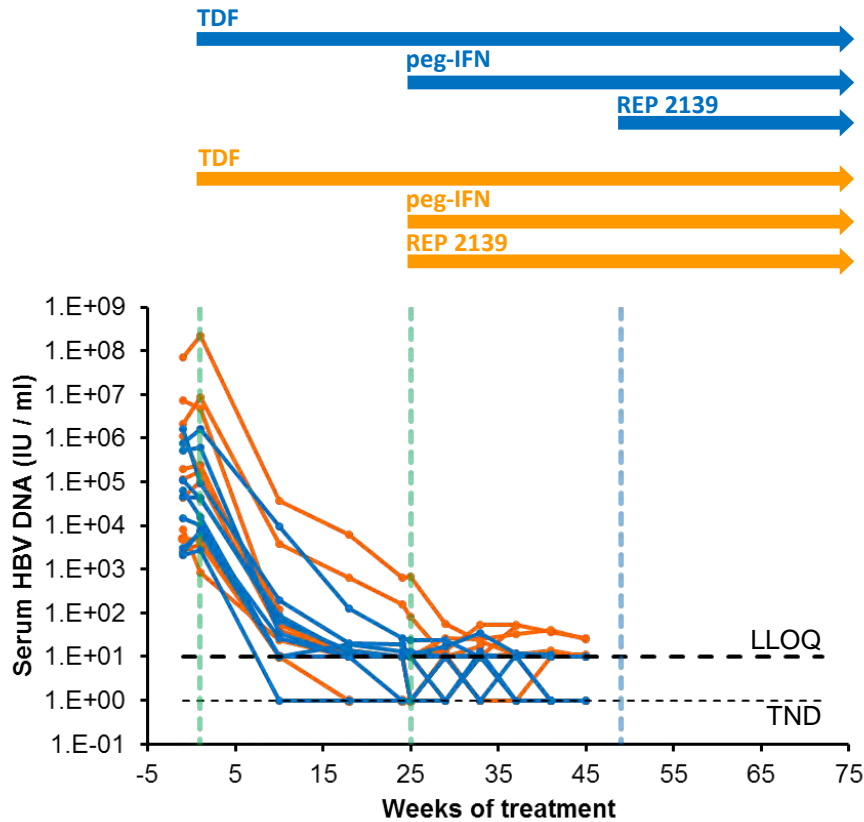
Initial follow up scheduled 4, 12, 24 and 48 weeks after all treatment is stopped

- 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

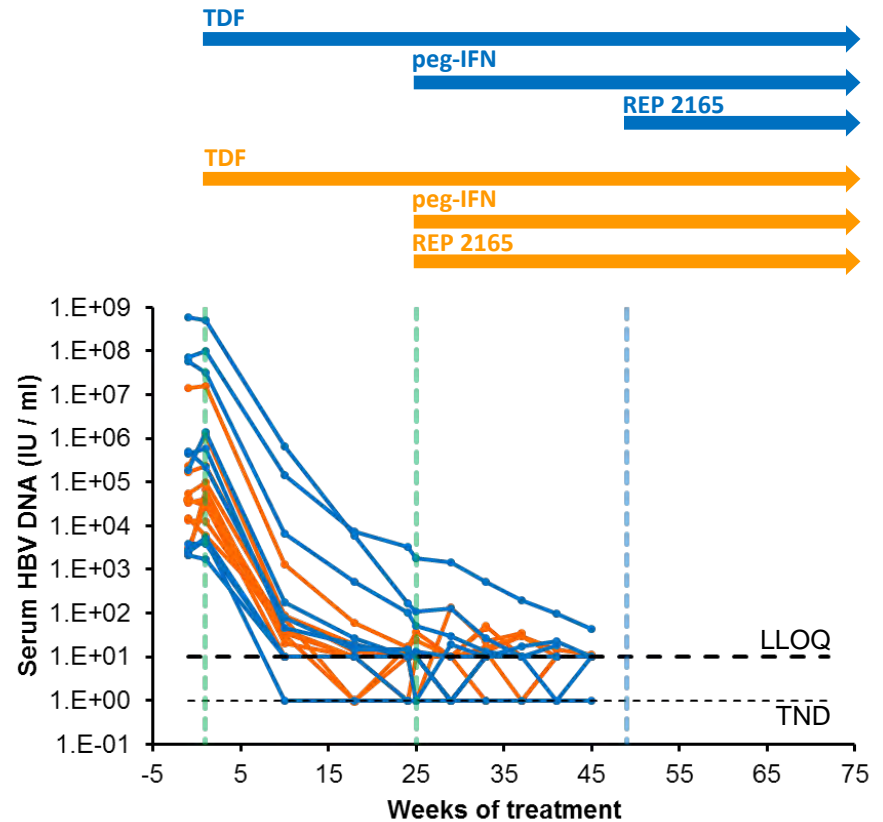
- Primary efficacy endpoints:
- Serum HBsAg reduction
 - Appearance of anti-HBs
 - Functional control maintained after treatment withdrawal (≥ 6 months HBsAg < 1 IU/ml, HBV DNA < 1000 copies / ml)

Interim Efficacy data (serum HBV DNA)

REP 2139



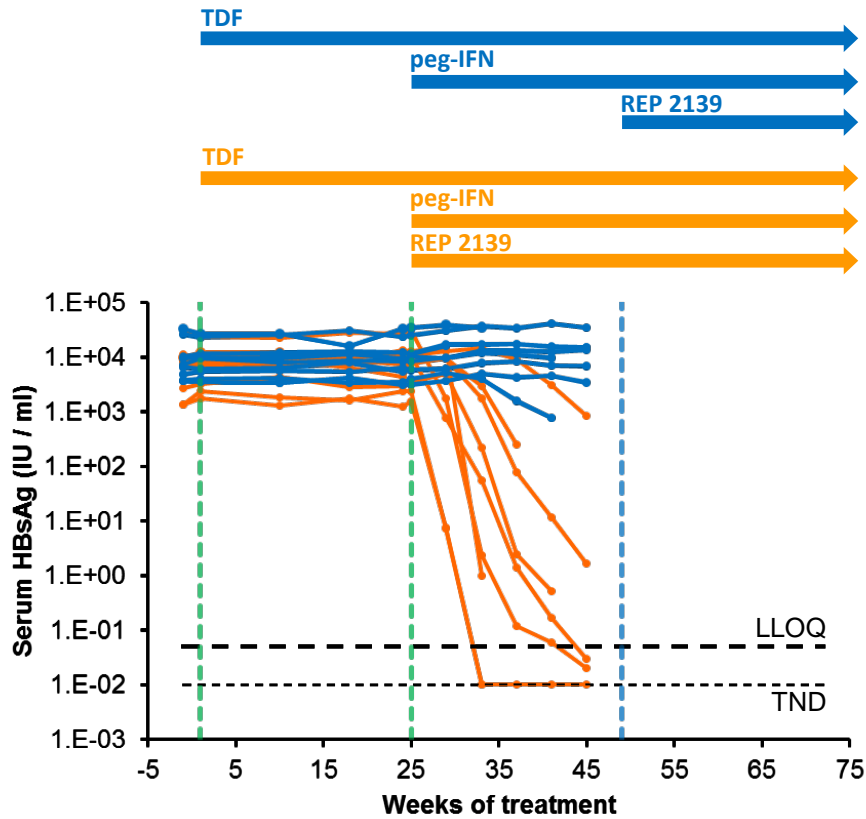
REP 2165



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

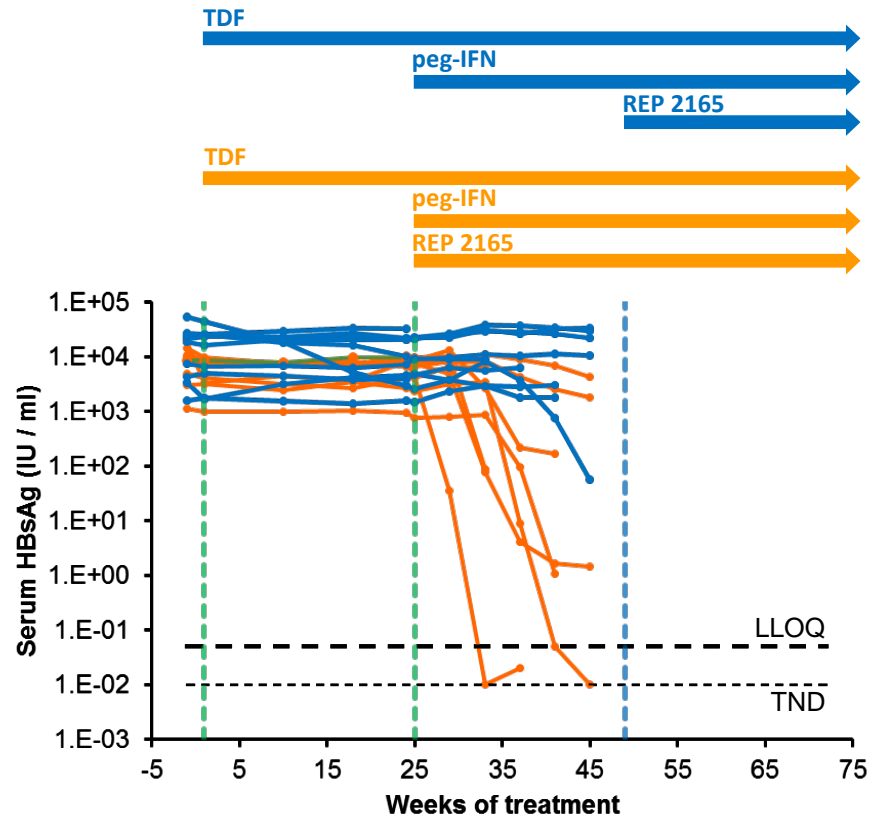
Interim Efficacy data (serum HBsAg)

REP 2139



9/9 HBsAg response > 1 log

REP 2165

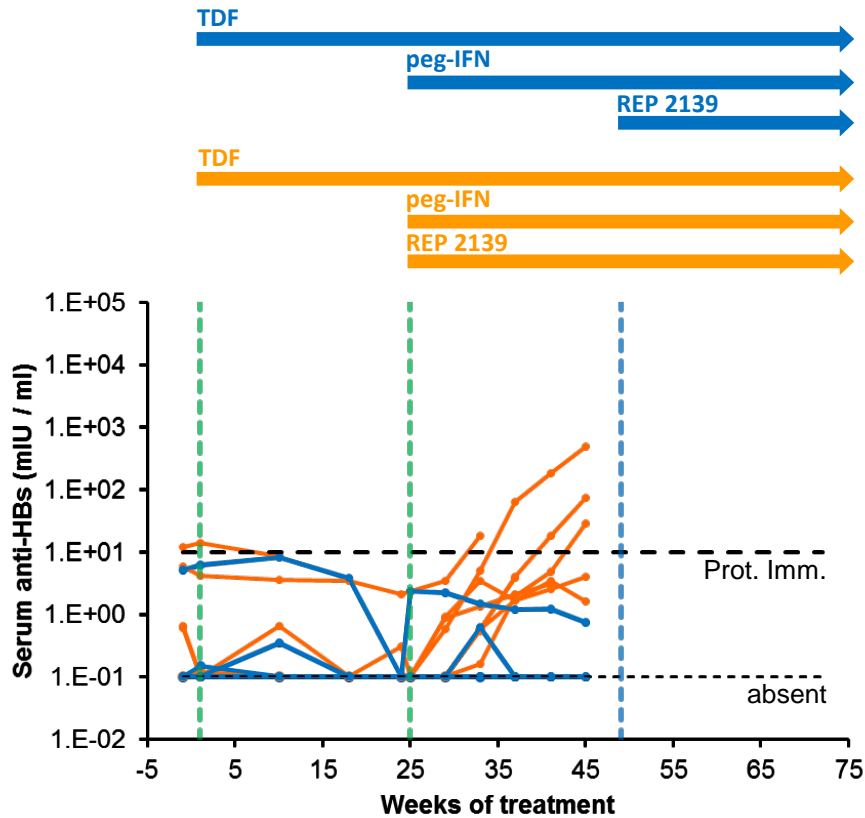


6/9 HBsAg response > 1 log

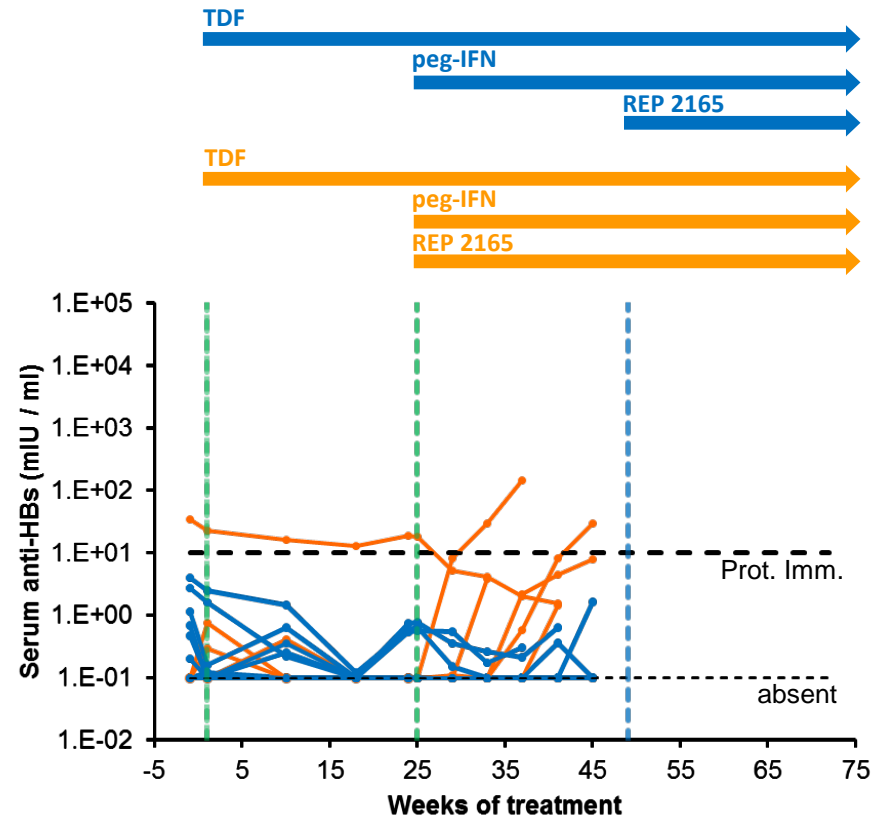
LLOQ = lower limit of quantification (0.05 IU / mL)
TND = HBsAg not detected (0.00 IU / mL)

Interim Efficacy data (serum anti-HBs)

REP 2139



REP 2165

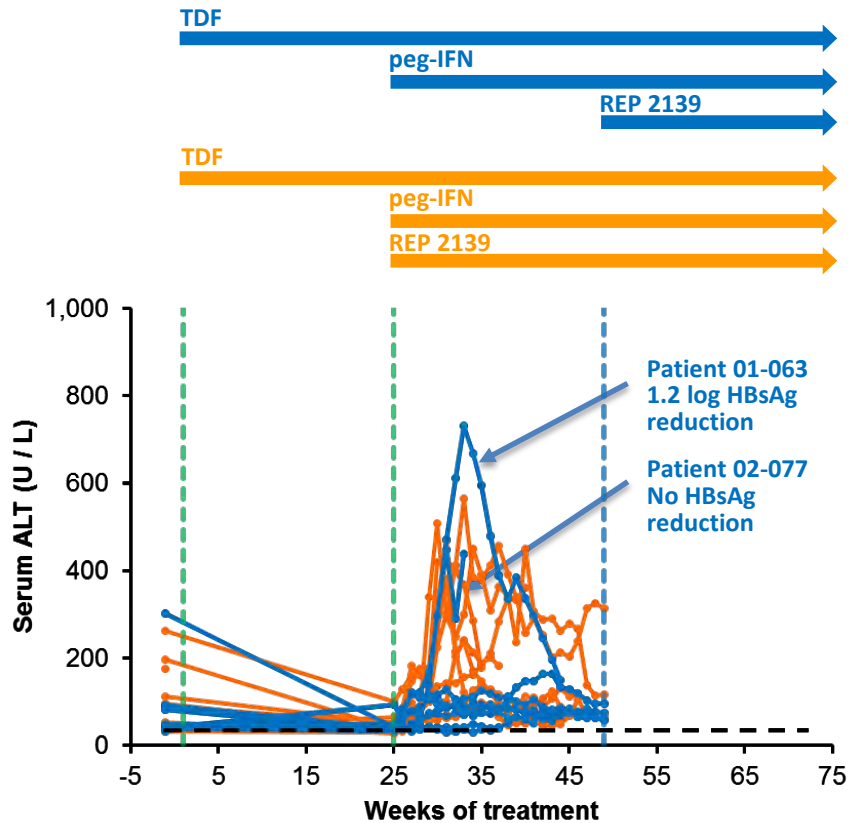


Elevation in serum anti-HBs correlated with extent of HBsAg reduction

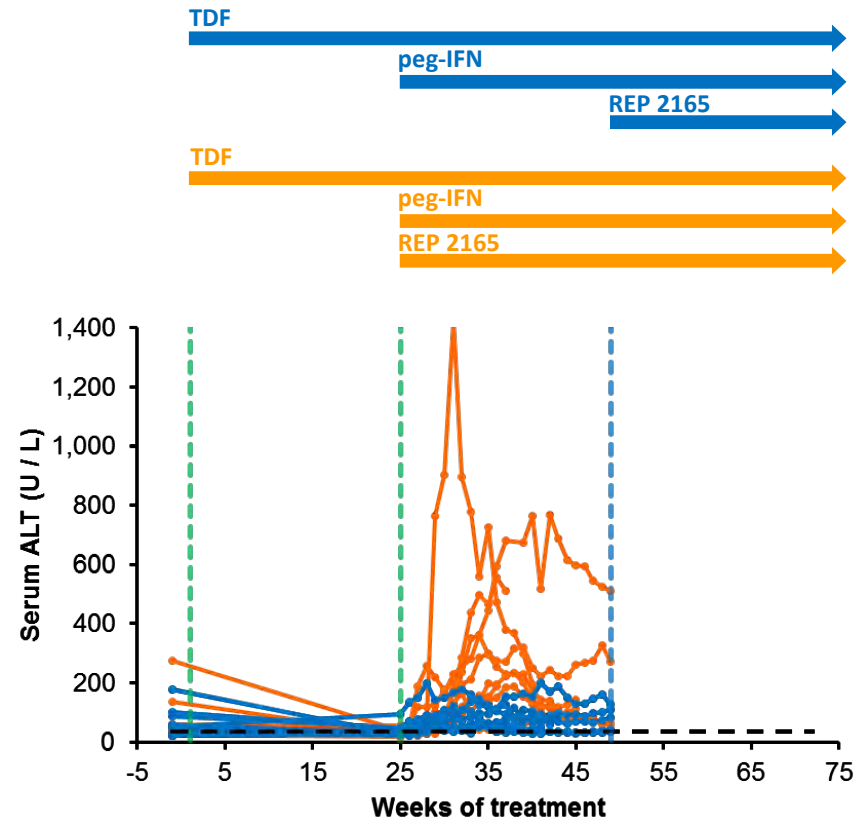
Prot. Imm. = Architect defined threshold for protective immunity (10 mIU / mL)
absent = no significant anti-HBs present (≤ 0.1 mIU / mL)

Interim Efficacy Data (serum ALT)

REP 2139



REP 2165

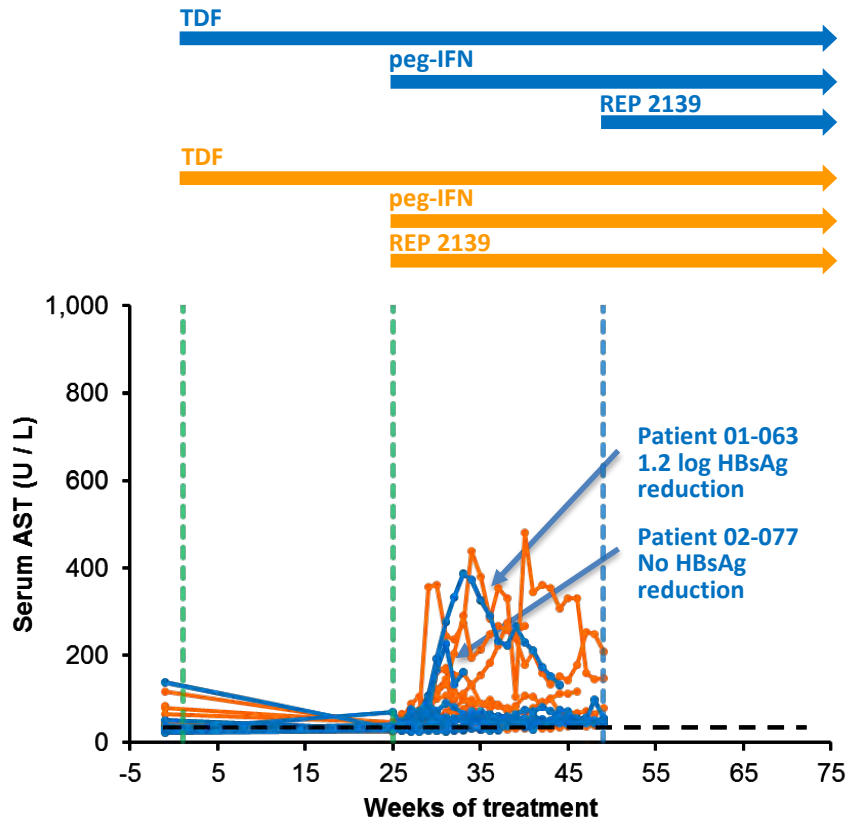


Elevation in serum ALT correlated with HBsAg reduction
(self-resolving with continued therapy)

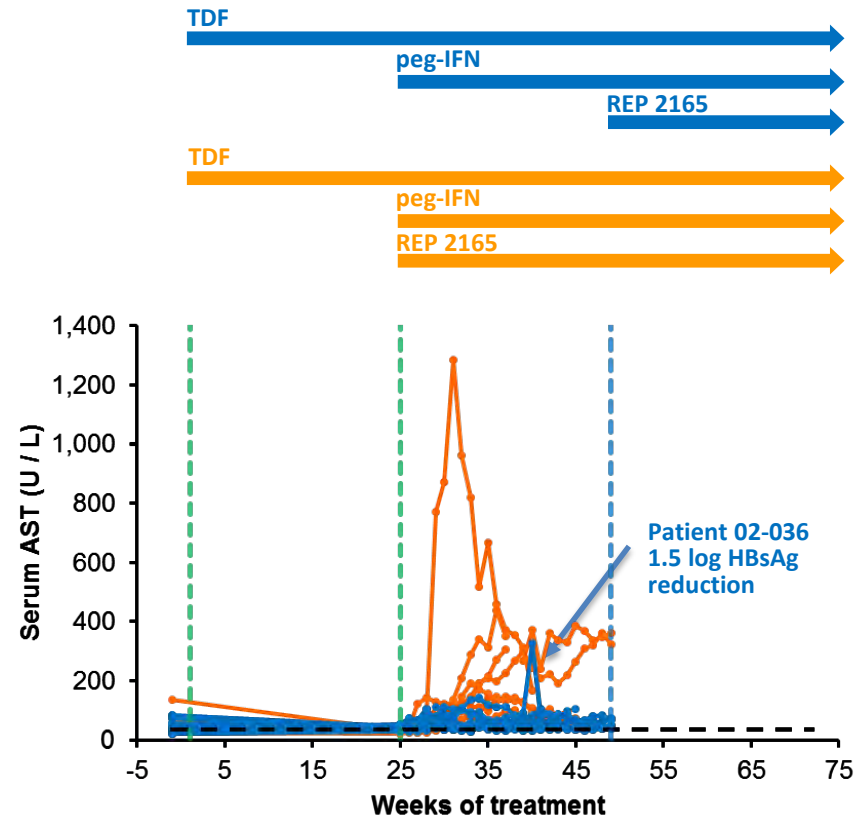
-----upper limit of normal

Interim Efficacy Data (serum AST)

REP 2139



REP 2165

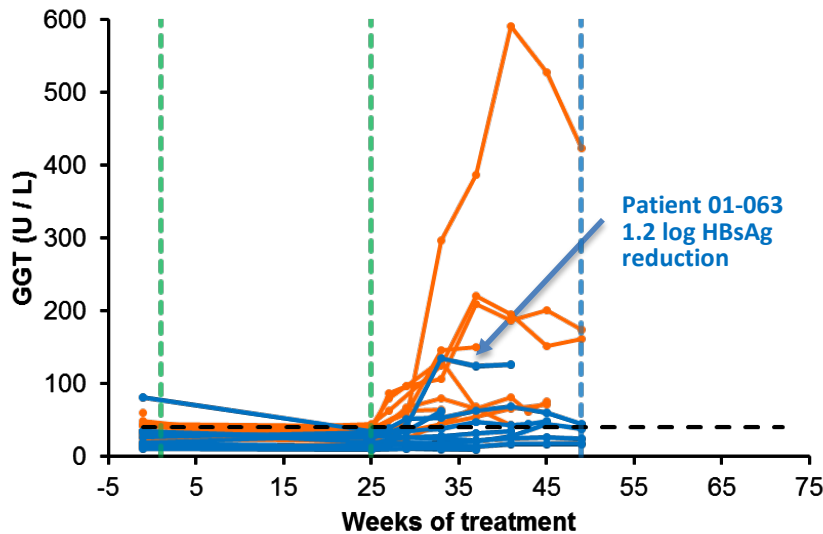
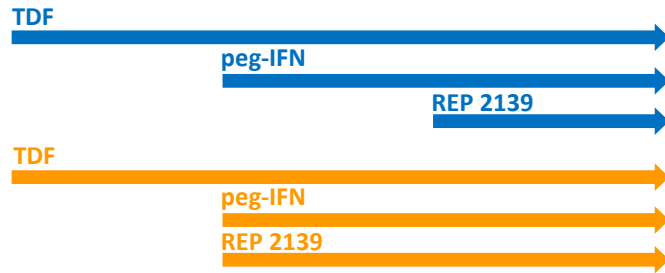


**Elevation in serum AST correlated with HBsAg reduction
(self-resolving with continued therapy)**

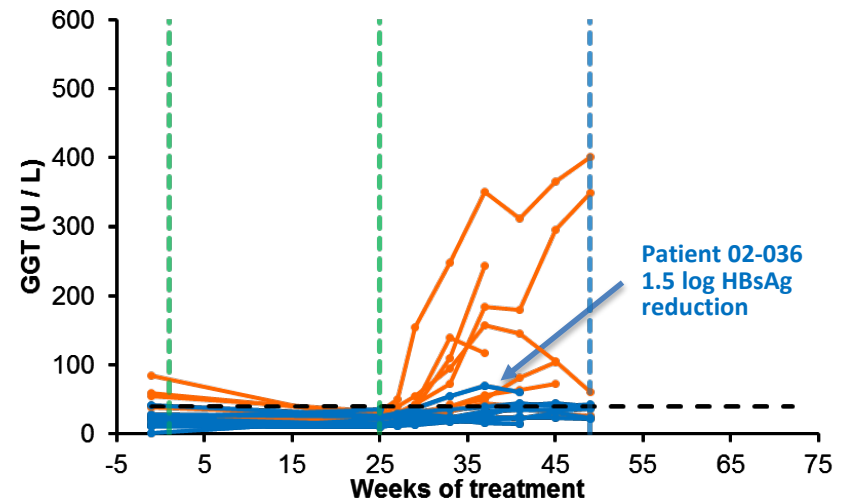
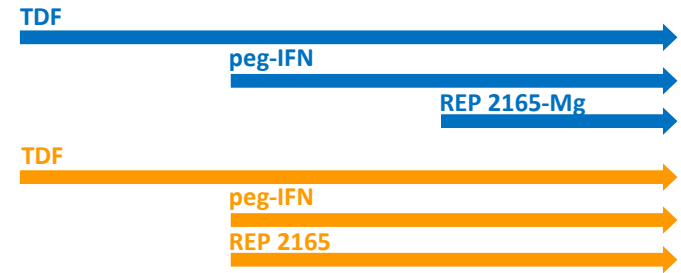
-----upper limit of normal

Interim Efficacy Data (serum GGT)

REP 2139



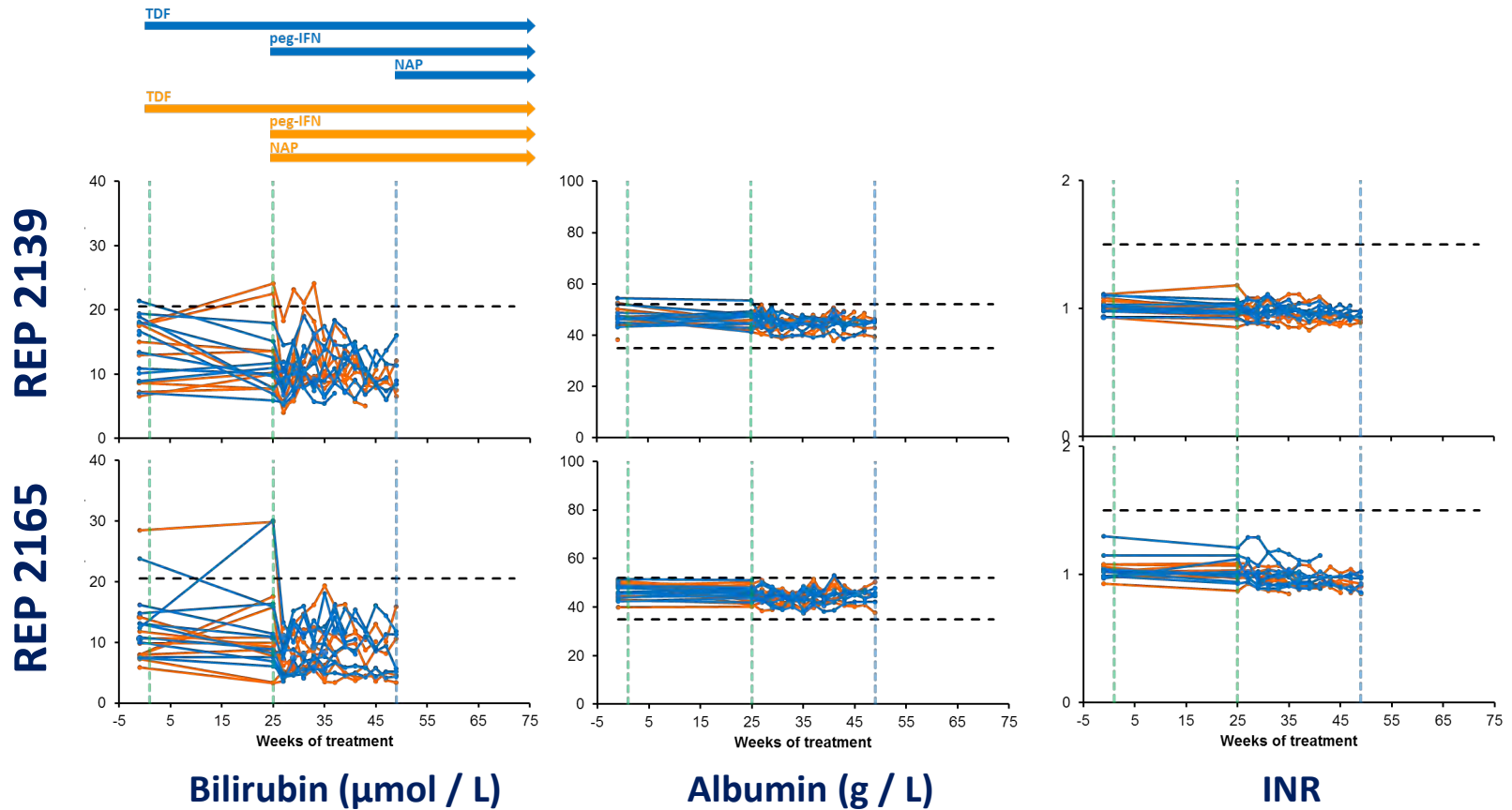
REP 2165



Elevation in serum GGT correlated with HBsAg reduction

-----upper limit of normal

Interim REP 401 Safety Data (liver function)

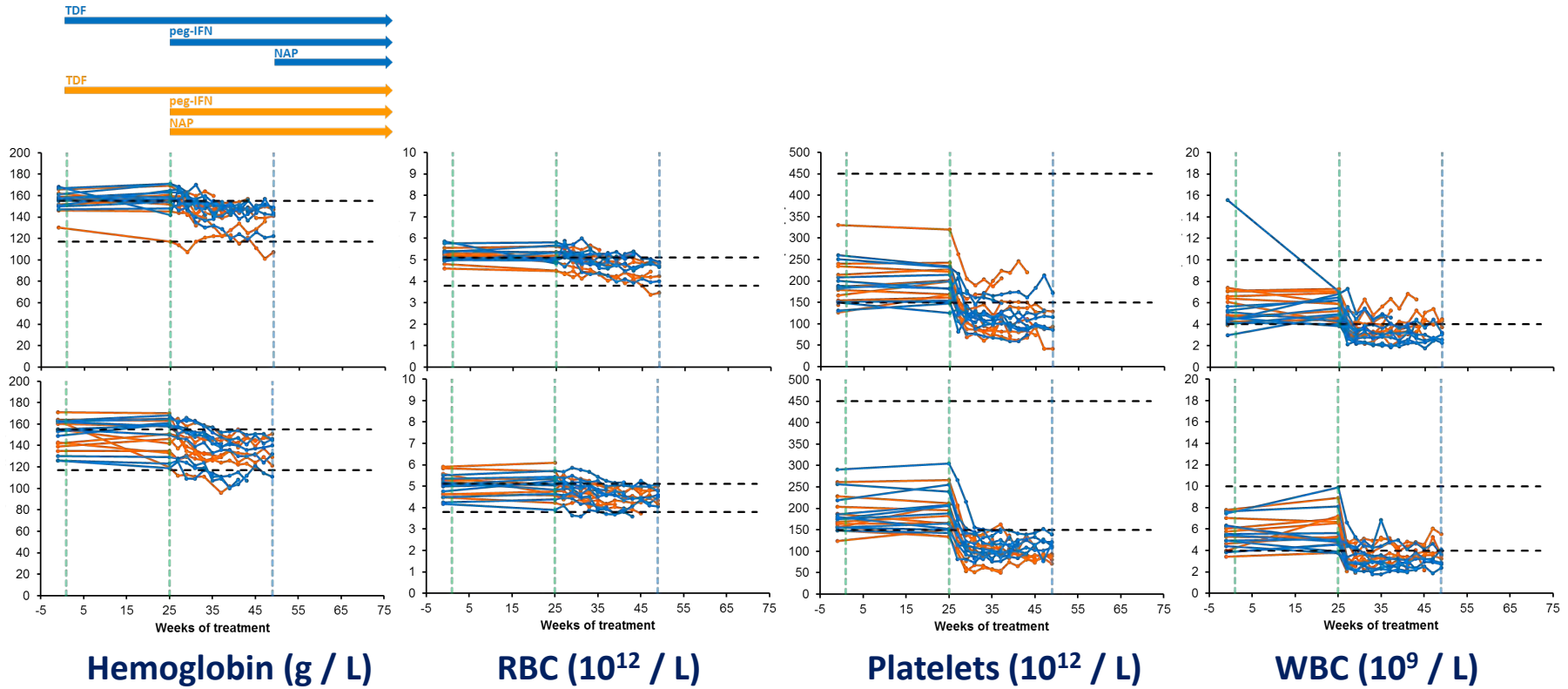


Liver function normal during transaminase flares

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

Interim REP 401 Safety Data (hematology)

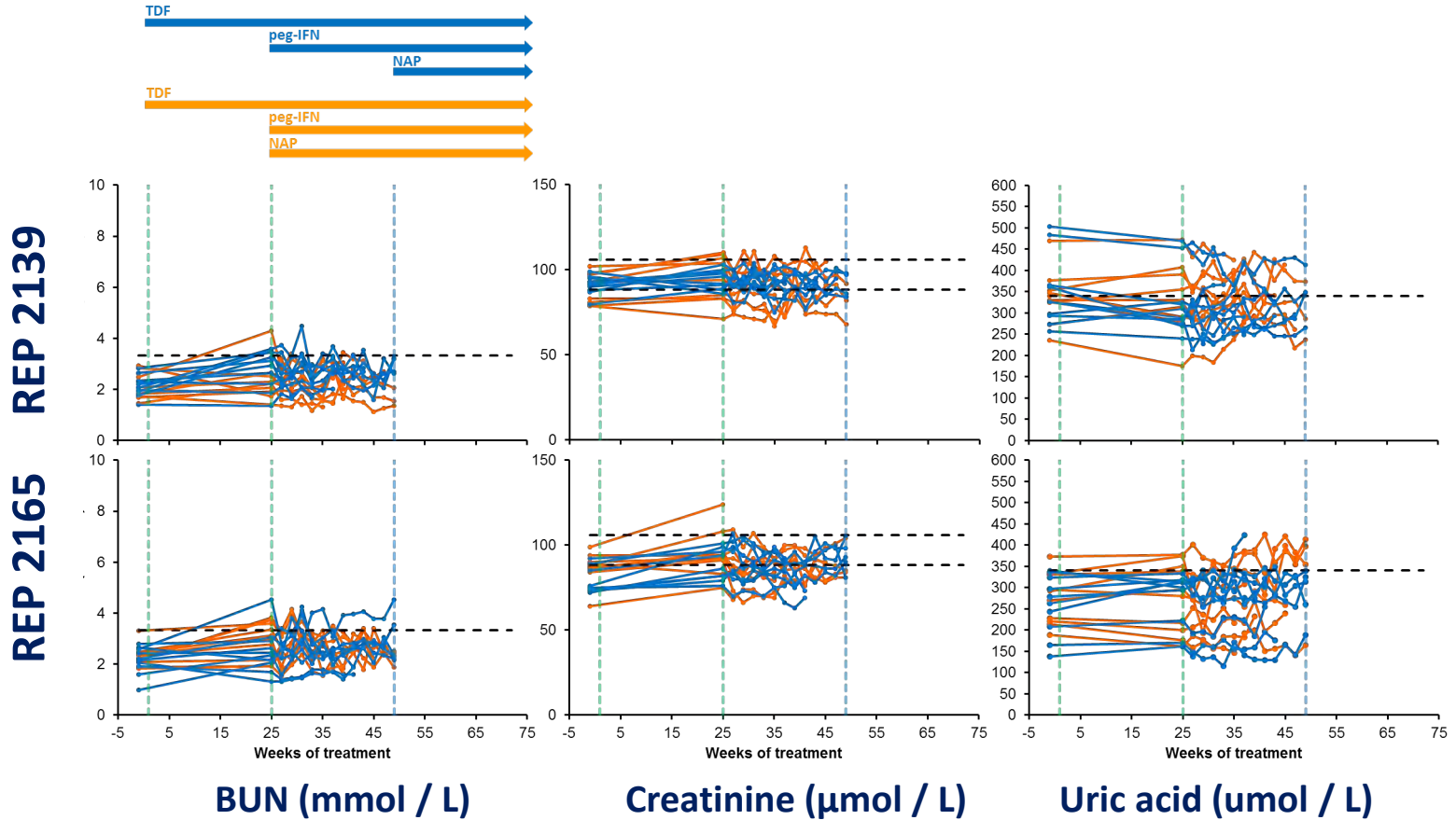
REP 2139
REP 2165



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

----- normal range

Interim REP 401 Safety Data (kidney function)



Kidney function not altered by the presence of NAPs

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

Adverse events

NAP administration has been asymptomatic to date

- Except 1 patient developed infusion reactions after the 20th dose of REP 2165-Mg

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

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)

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

Reproduces effects of NAPs in previous proof of concept trials leading to functional control

- HBeAg+ chronic HBV infection (REP 101, REP 102, REP 201 protocols)
- chronic HBV / HDV co-infection (REP 301 protocol)

Upcoming analyses to be presented:

- Pre-crossover update in all patients (APASL 2017)
- Crossover update in control group (EASL 2017)
- HBcrAg and HBV RNA analysis (EASL 2017)

Vaillant, 2016. Antiviral Res. 133: 32-40
Al-Mahtab et al., 2016 PLOS One 11: e0156667
M. Bazinet et al., 2016 AASLD Abstract 1848