REP 2139 monotherapy and combination therapy with pegylated interferon: Safety and potent reduction of HBsAg and HDV RNA in Caucasian Patients with chronic HBV / HDV co-infection

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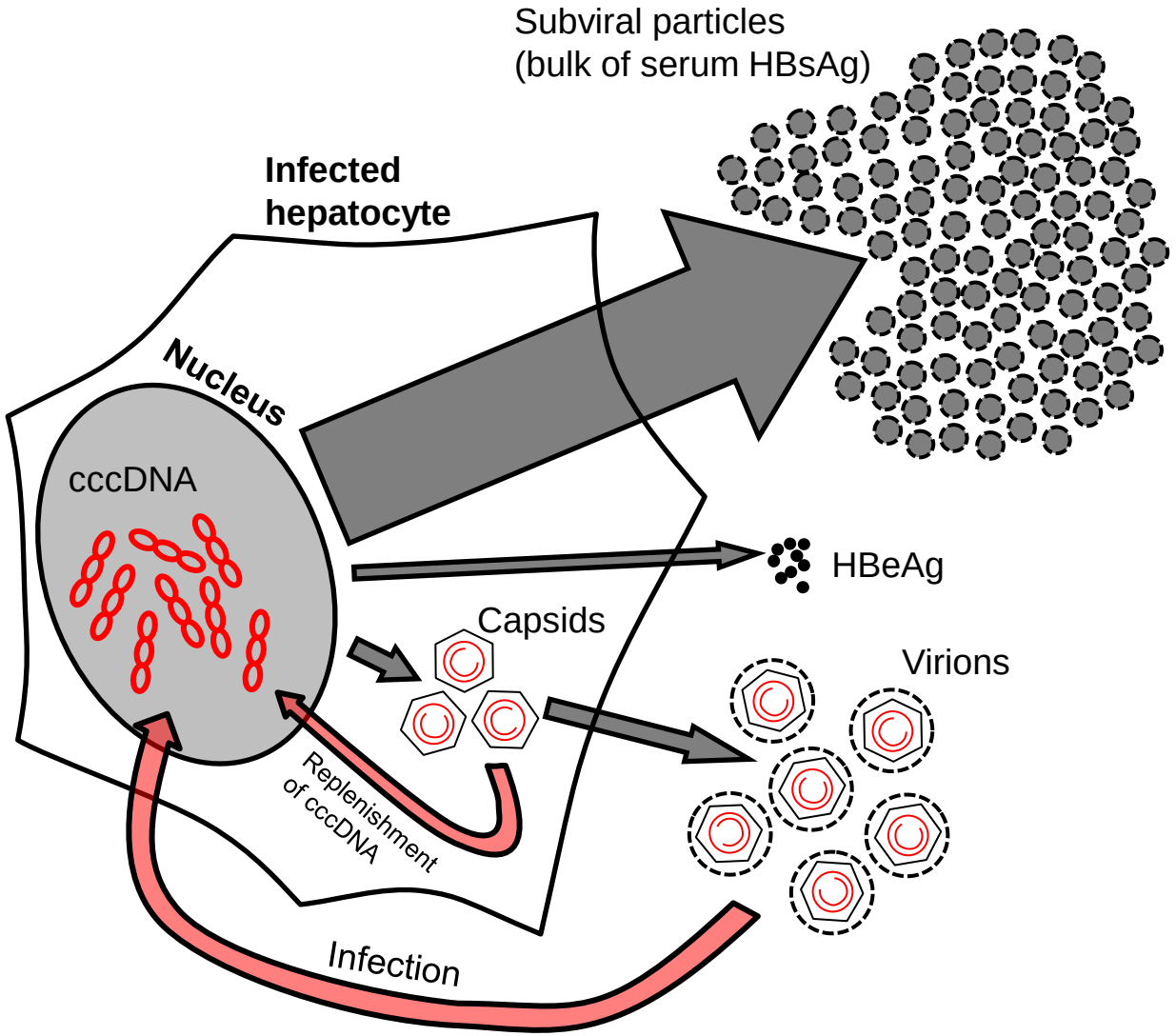
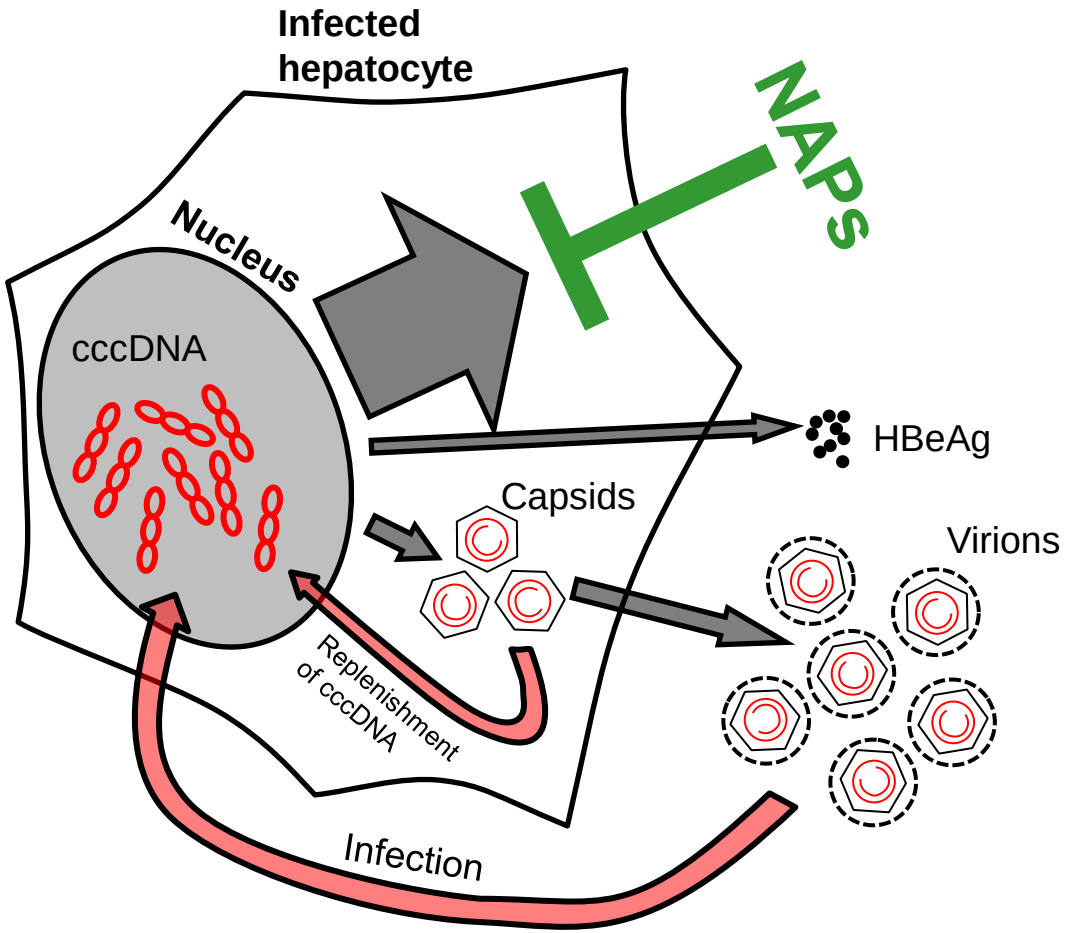
Nucleic Acid Polymers (NAPs)

- Synthetic, amphipathic polymers (oligonucleotides)
  NOT antisense (think heparin sulfate….) -> block viral entry
- Post-entry effects appear critical for antiviral effect in vivo
- Naturally taken up by hepatocytes with parenteral administration
- Interfere with apolipoprotein / HBsAg interactions required for HBV subviral particle (SVP) assembly
- Target the host apolipoprotein H (no resistance)
- Effect is selective for SVPs (virions not directly targeted)

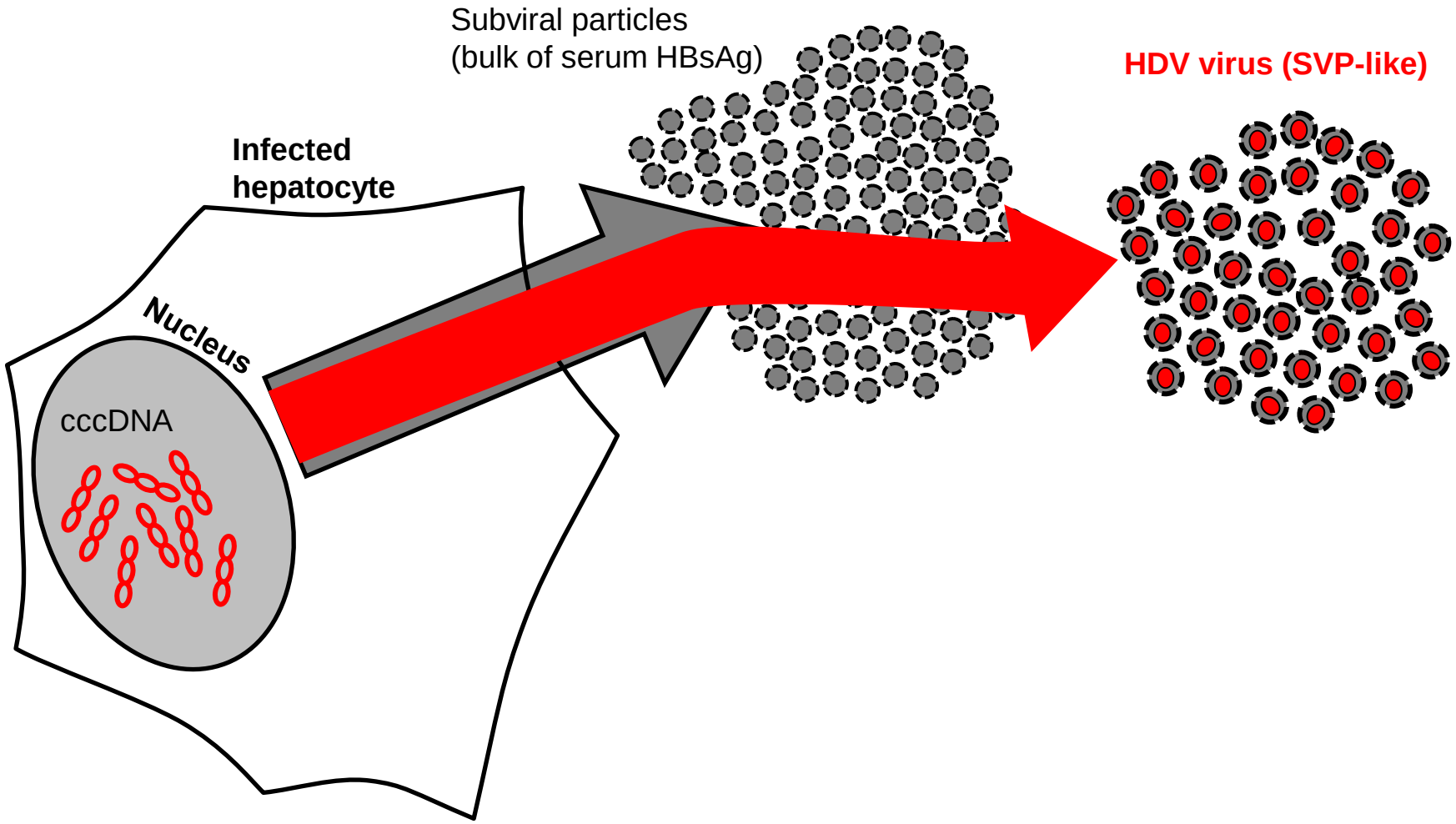
Particle production in HBV infection



The NAP effect in HBV infection



Potential NAP effect in HDV



Bonino et al., 1986 J. Virol. 58: 945-950

REP 2139-Ca + Pegasys® in HBV / HDV co-infection (REP 301)

Caucasian patients treated in Chisinau, Moldova
CRO monitored trial compliant with EU GCP
Clinicaltrials # NCT02233075

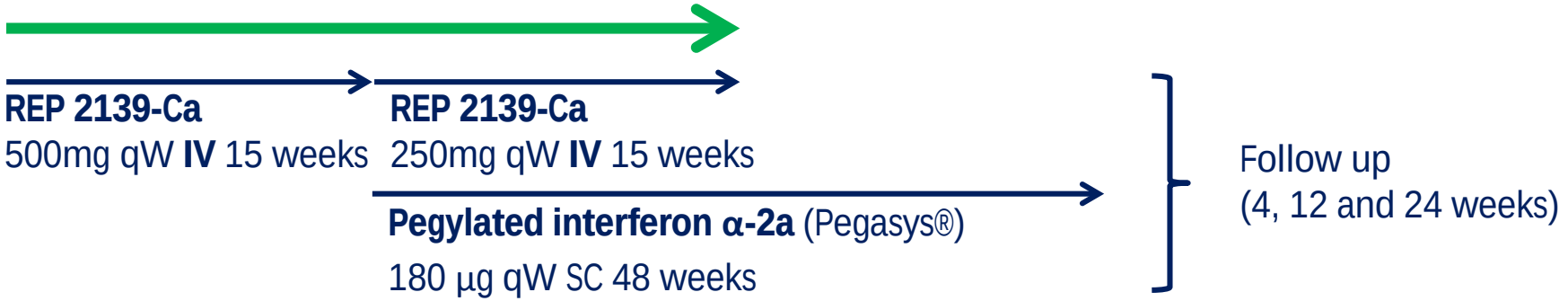
12 patients enrolled with HBV / HDV co-infection at the start of treatment:

- Anti-HDAg+
- Serum HBsAg > 1000 U / ml
- HBeAg-
- compensated liver disease
- mild to moderate fibrosis, non cirrhotic.

Viremia monitored at University of Duisburg-Essen, Germany:

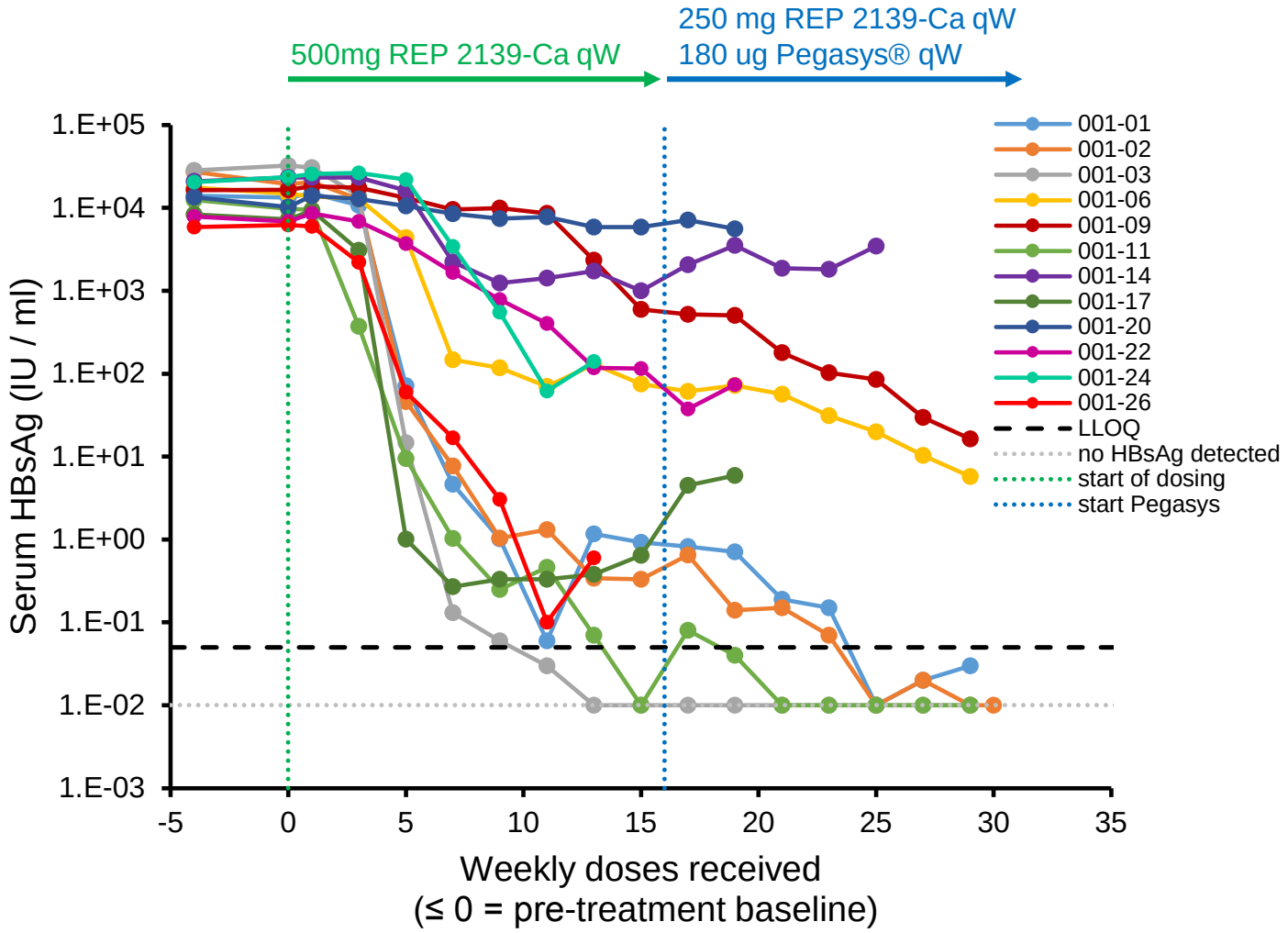
- Abbott PCR (HBV DNA)
- Abbott Architect (HBsAg and anti-HBs)
- Robogene RT-PCR (HDV RNA)
- Diasorin (anti-HDAg)

REP 301 Trial Design

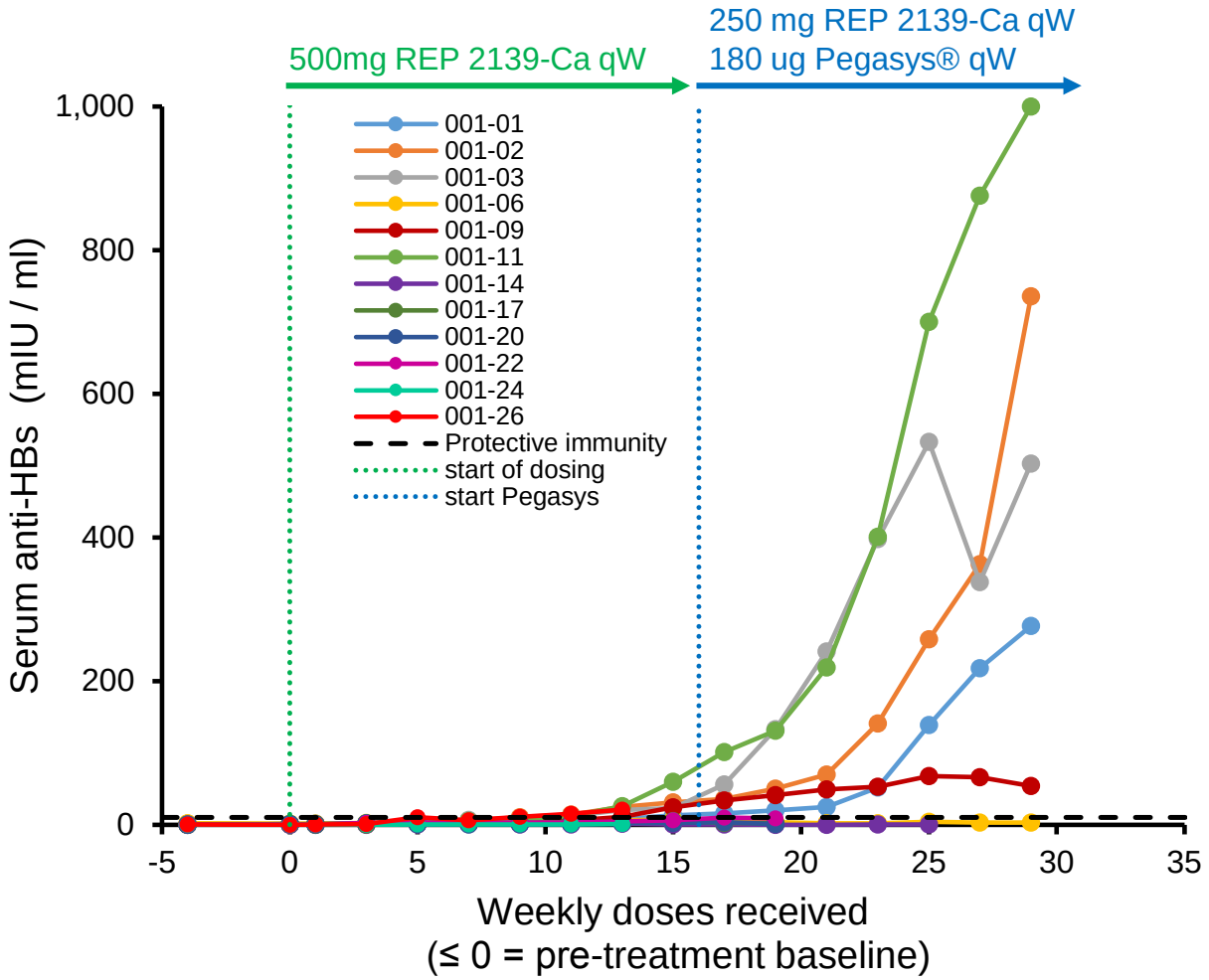


REP 2139-Ca qW regimen is well established for this drug class (PS-ONs)

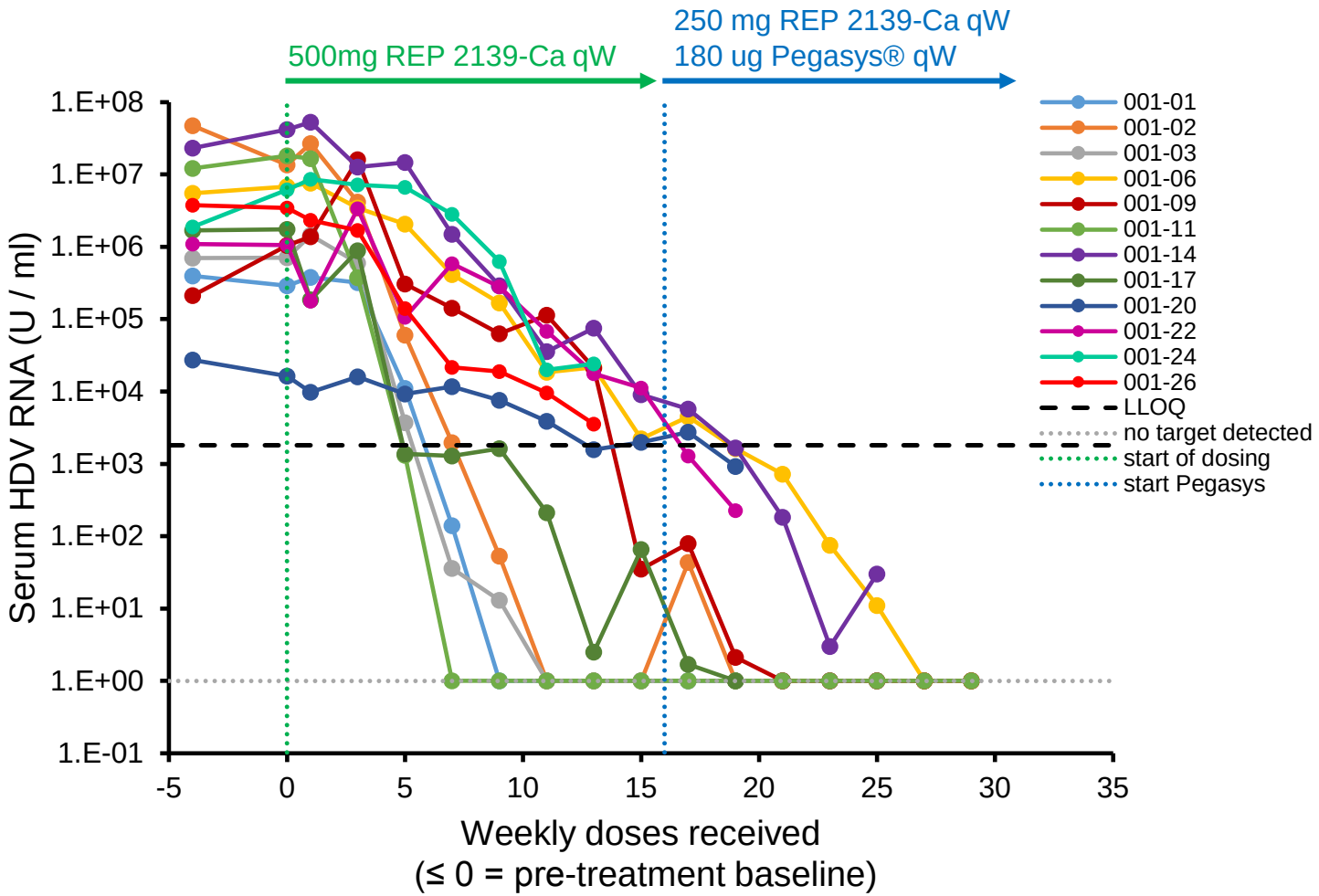
Interim REP 301 Efficacy Data (serum HBsAg)



Interim REP 301 Efficacy Data (serum anti-HBs)

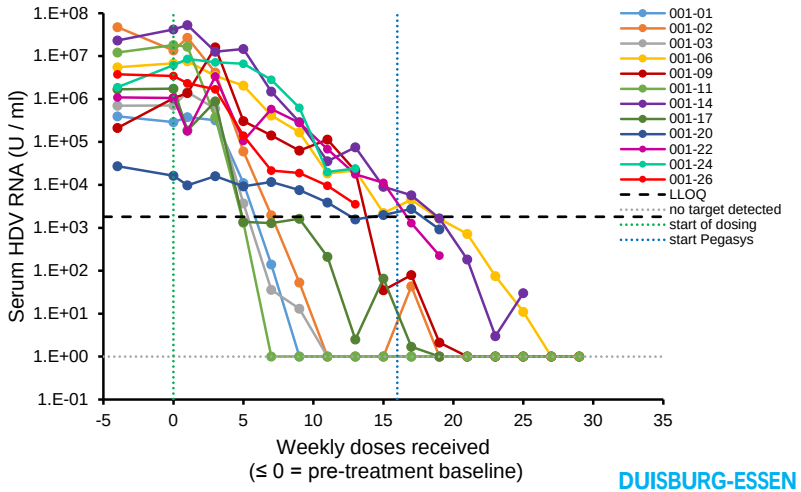


Interim REP 301 Efficacy Data (serum HDV RNA)



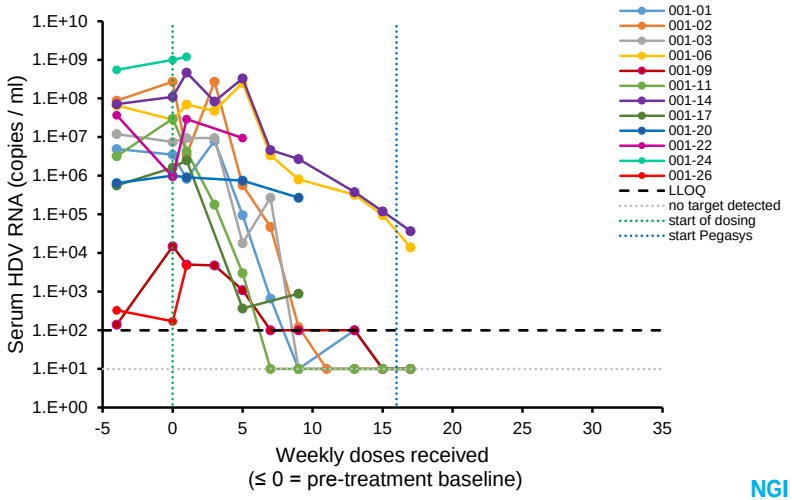
Validation of REP 301 HDV RNA

Study site



DUISBURG-ESSEN

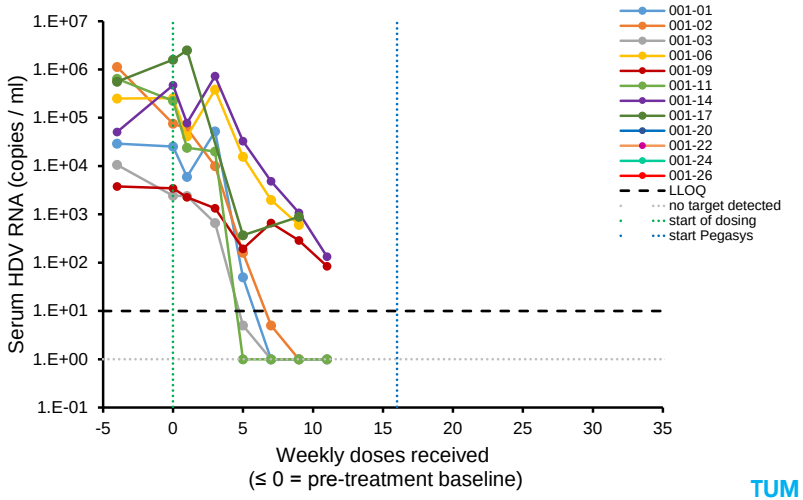
Validation site #1



NGI

GT1 primer set on
separate serum samples

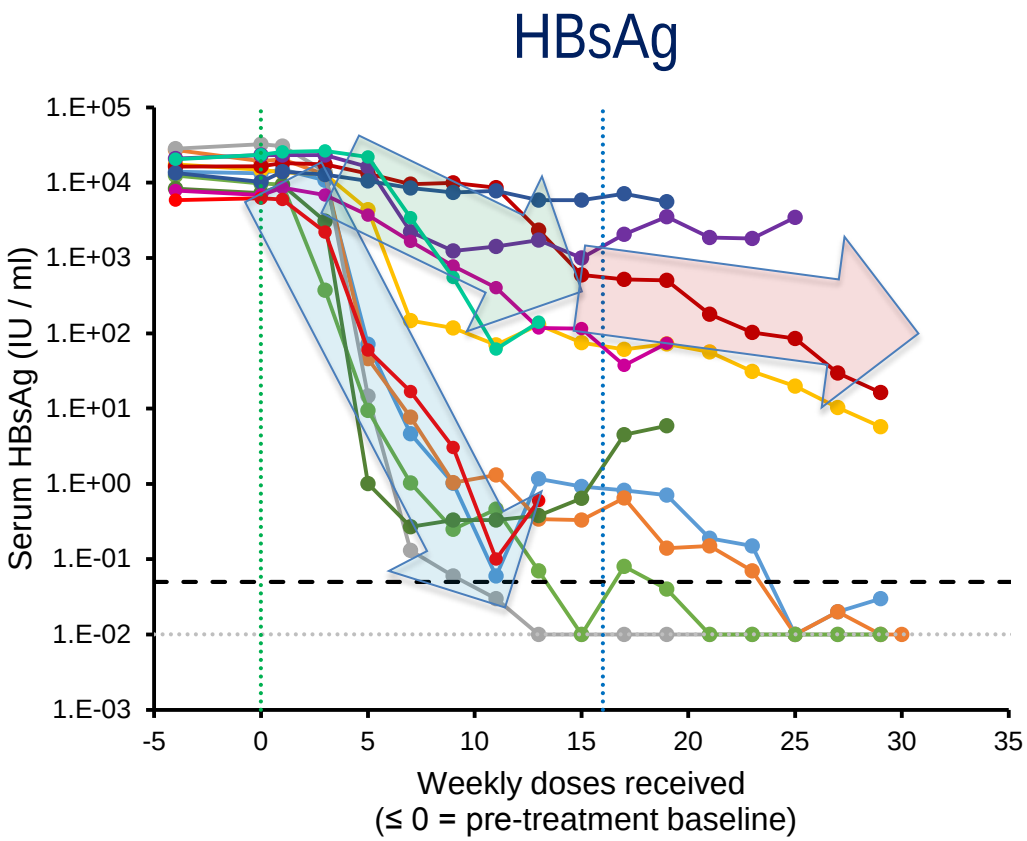
Validation site #2

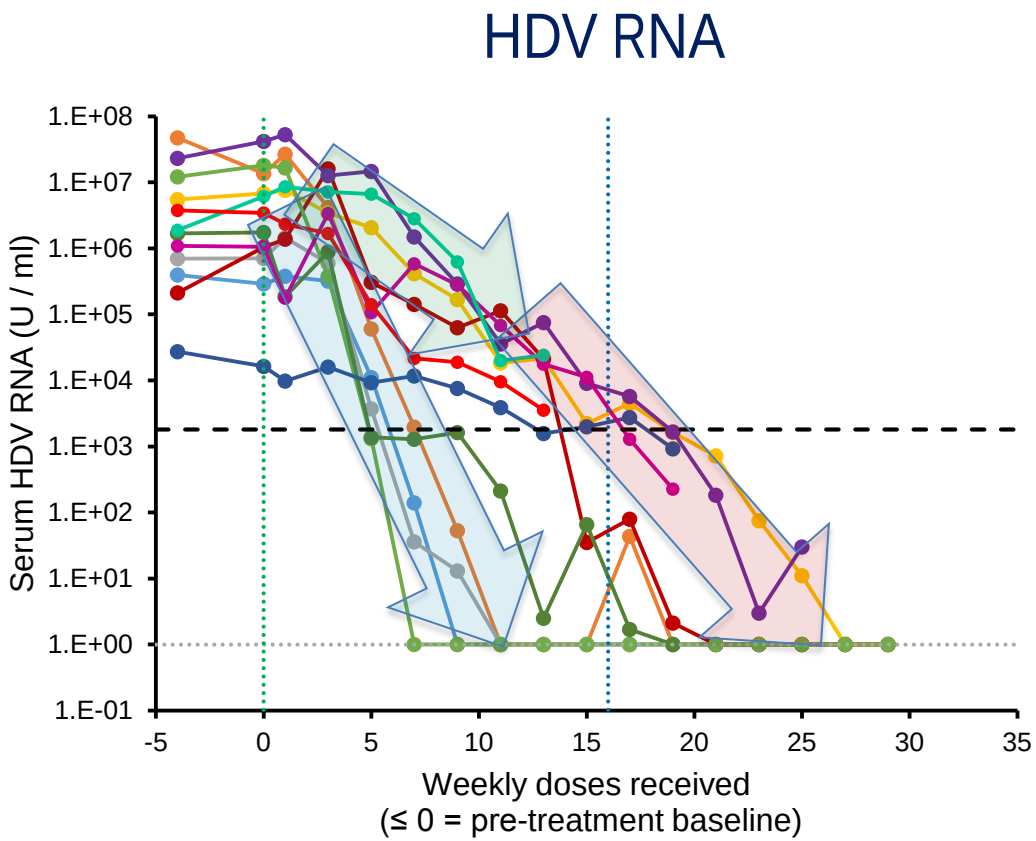


TUM

Independent primer set on RNA
from study site

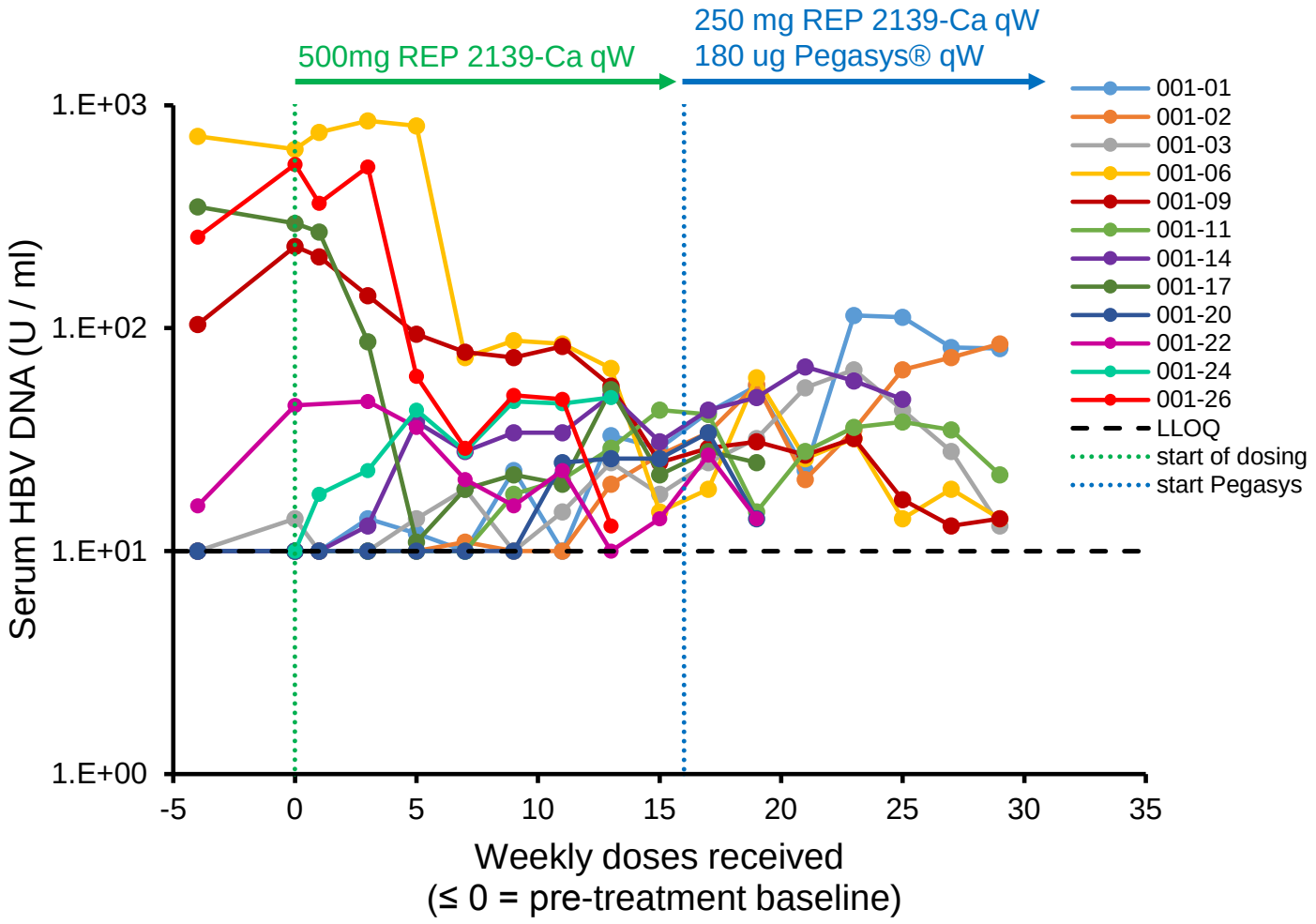
HBsAg versus HDV RNA response





Multiple antiviral effects may be present

Interim REP 301 Efficacy Data (serum HBV DNA)



REP 2139-Ca safety profile in the REP 301 protocol (interim analysis)

- All AEs are grade 1-2 (fever, redness or headache) and are associated with IV infusion:
  - typically become less frequent as dosing regimen progresses
  - self-resolve after completion of IV infusion (infrequenty requiring supportive treatment)
  - attributed to the presence of phthalate plasticisers in IV tubing

- Clinical serology monitored weekly with no clinically significant findings

- One patient removed from dosing after 10 weeks of Pegasys® exposure due to Pegasys®-related DILI.

Summary

Serum HBsAg clearance previously observed with NAPs in Asian patients is replicated in Caucasian patients.

REP 2139-Ca can simultaneously reduce HBsAg and HDV RNA

- multiple antiviral mechanisms
- de-repression of serum HBV DNA – NUC therapy may be required

REP 2139-Ca is well tolerated and does not alter tolerability of Pegasys®.

- may provide an additional productive antiviral response.

NAP-based antiviral therapy may become an important new treatment option for patients with HBV / HDV co-infection.

Acknowledgements

Validation of HDV RNA test results were performed at:

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Dr. Peter Schmid

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