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Analysis of HBsAg isoforms during and after NAP-based combination therapy in the REP 301, REP 301-LTF and REP 401 studies.

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INTRODUCTION

Nucleic acid polymers (NAPs) inhibit the assembly / secretion of HBV spherical subviral particles (SVP) without affecting the secretion of HBeAg or Dane particles[1,2]. This effect is driven by selective targeting of the host HSP40 chaperone DNAJB12 (LBP 42). In HBeAg negative HBV mono-infection, NAP combination therapy achieved 78% virologic control (HBV DNA ≤ 2000 IU/mL, normal ALT) with 39% further achieving functional cure (HBsAg < 0.05 IU/mL, HBV DNA target not detected, normal ALT) (REP 401 study, NCT02565719)[1].

Retrospective analysis of participants with HBeAg negative HBV / HDV co-infection receiving suboptimal NAP-based combination therapy (REP 301 study[2], NCT02233075 and REP 301-LTF study[3], NCT02876419) and HBV mono-infection receiving TDF + pegIFN + NAPs in the REP 401 study yielded combined HBV outcomes of 18/52 (35%) functional cure, 19/52 (36%) virologic control and 15/52 (29%) rebound. The goal of this study was to analyze the dynamics of S-HBsAg, M-HBsAg and L-HBsAg during and after NAP therapy in the REP 301 / 301-LTF and 401 studies.

MATERIAL & METHODS

Frozen serum samples (n=1153) from all 52 participants in the REP 301 / REP 301-LTF and REP 401 studies were analyzed using the Abbott research use only (RUO) assays for HBsAg isoforms (large [L], medium [M] and total [T]). T-HBsAg was used to assess total HBsAg present. From this population of HBsAg, the presence of M-HBsAg and L-HBsAg was determined. The relative change over time in S-HBsAg relative to the other isoforms was inferred by the change in the ratio over time of T-HBsAg to M-HBsAg. Measurements with S/Co < 1 were excluded from the ratio / trend analysis. HBsAg isoform response was compared to previously published quantitative HBsAg (qHBsAg) responses[1-3].

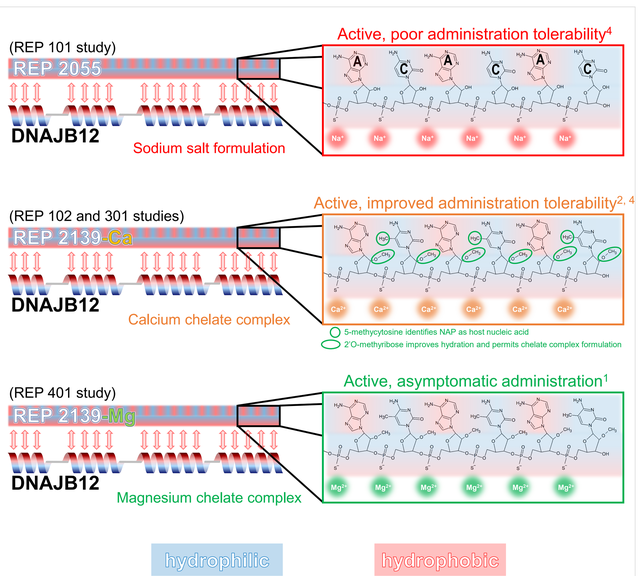

Figure 1. Clinical optimization of NAP therapy from early NAP studies through the REP 301 and REP 401 studies.
Chemical structure of NAPs and interaction with the host chaperone DNAJB12 driving selective inhibition of SVP assembly in clinical studies describing optimizations in chemistry from REP 2055 to REP 2139 and from calcium chelate complexes to magnesium chelate complexes. Charge distributions involved in DNAJB12 are indicated in red and blue.

RESULTS

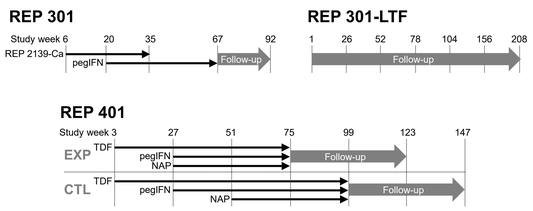

Figure 2. Design of REP 301, 301-LTF and 401 studies. The REP 301 study examined the safety and efficacy of an overlapping regimen of REP 2139-Ca (see Fig 1) and pegIFN in participants with HBeAg negative chronic HBV / HDV co-infection. The REP 301 study induced 24 weeks of follow-up which was extended to 3.5 years in the REP 301-LTF study. The REP 401 study examined the safety and efficacy of 48 weeks of TDF + pegIFN + REP 2139-Mg (see Fig 1) or REP 2165-Mg. Follow-up in the REP 401 study was 48 weeks.

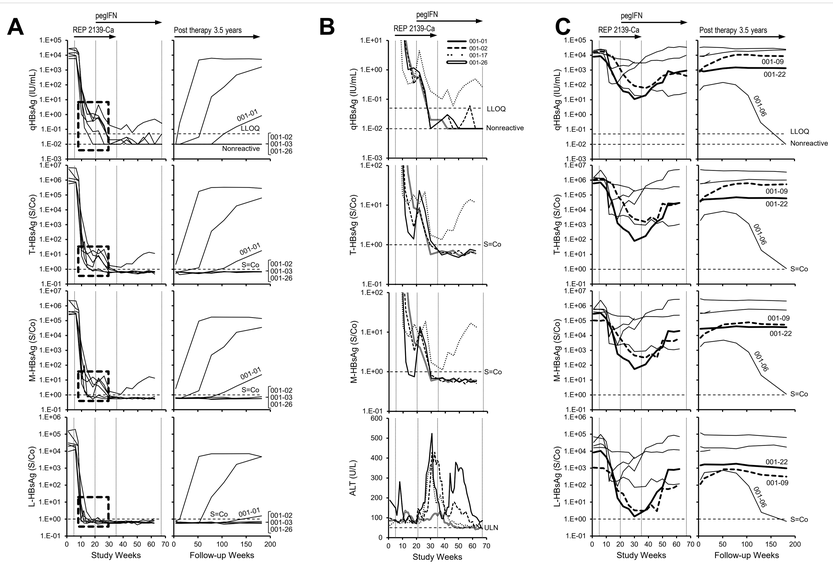

Figure 3. HBsAg isoform response in the REP 301 / 301-LTF studies
Dynamics of qHBsAg (top), T-HBsAg (middle top), M-HBsAg (middle bottom) and L-HBsAg (bottom) are presented for the following:

A) The 6 participants with strong qHBsAg response.
B) The 4 participants with delayed q, T and M-HBsAg clearance at the end of REP 2139-Ca monotherapy (see boxes in (A)) correlated with peg-IFN induced ALT flares (bottom).
C) The 6 participants with moderate qHBsAg response.

Minor HBsAg rebound in participant 001-01 was comprised mostly of S-HBsAg and M-HBsAg (A). Participants where moderate qHBsAg decline included better overall clearance of L-HBsAg are highlighted in (C). Treatment paradigms are shown at the top. LLOQ = 0.05 IU/mL.

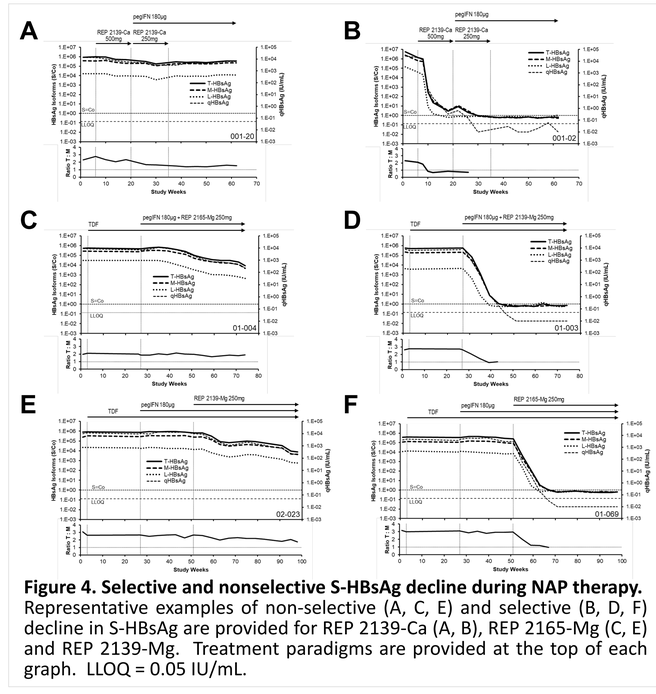

Figure 4. Selective and nonselective S-HBsAg decline during NAP therapy.
Representative examples of non-selective (A, C, E) and selective (B, D, F) decline in S-HBsAg are provided for REP 2139-Ca (A, B), REP 2165-Mg (C, E) and REP 2139-Mg. Treatment paradigms are provided at the top of each graph. LLOQ = 0.05 IU/mL.

Table 2. Correlation between selective S-HBsAg decline and qHBsAg response

qHBsAg response (decline from baseline)	Number of participants	Selective S-HBsAg decline	P-value (X2 analysis)
< 2 $\log_{10}$ IU/mL	10	1	< 0.01
> 2 $\log_{10}$ IU/mL	42	39	

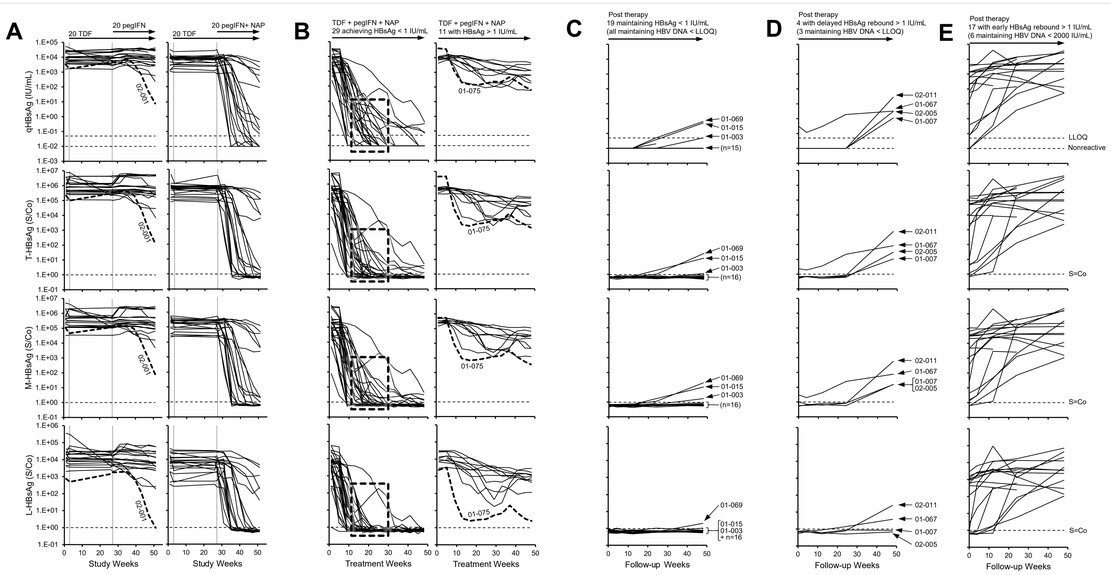

Figure 4. HBsAg isoform response in the REP 401 study.
Dynamics of qHBsAg (top), T-HBsAg (middle top), M-HBsAg (middle bottom) and L-HBsAg (bottom) are presented as follows:

A) Control (left) and experimental (right) groups during the first 48 weeks of the study.
B) Participants with strong (left) and moderate (right) qHBsAg response during 48 weeks of TDF + pegIFN + NAPs
C) Participants maintaining qHBsAg < 1 IU/mL during follow-up
D) Participants with delayed qHBsAg rebound > 1 IU/mL
E) Participants with early qHBsAg rebound > 1 IU/mL

More efficient clearance of L-HBsAg when qHBsAg becomes < 10 IU/mL or in selected participants with moderate qHBsAg response are highlighted (A and B, dashed boxes/lines). Selective rebound of q, T and M-HBsAg in occurs in participants in (C) and (D). Treatment paradigms are shown at the top. LLOQ = 0.05 IU/mL.

CONCLUSIONS

1. **Selective effects on S-HBsAg clearance during NAP therapy are consistent with selective inhibition of SVP assembly and secretion in human HBV infection during NAP therapy.**
2. **Suppression of all HBsAg isoforms during follow-up in participants establishing functional cure indicate the control established is profound.**
3. **Delayed clearance of S-HBsAg and M-HBsAg may indicate clearance of integrated HBV DNA correlated with host mediated transaminase flares.**
4. **Minor HBsAg rebound during follow-up may reflect HBsAg production from integrated HBV DNA and not cccDNA.**

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DISCLOSURES

Employment (Replicor, MB, AV) shareholder (Replicor, MB, AV)

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