Assessment of the effect of HBV viral genotype on bepirovirsen efficacy using a population PKPD modeling approach

Digital poster

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Background

- Bepirovirsen (BPV) is an antisense oligonucleotide that reduces the level of RNA in patients with chronic hepatitis B virus (HBV) infection[1]
- A mechanistic pharmacokinetic-pharmacodynamic (PK/PD) model was developed to capture the time course of PK and HBV surface antigen (HBsAg) changes observed in Phase 2 studies[2]
- Baseline HBsAg level is a significant predictor of BPV response[2]
- The effect of HBV virus genotype could not be accurately assessed previously due to a high percentage of missing data in participants on nucleos(t)ide (NA) therapy

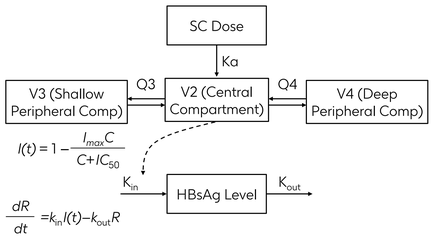
Aims

Assess the effect of different HBV genotypes as an independent predictor of BPV efficacy that is separate from the baseline HBsAg level using the PK/PD model. Assess if there is a correlation between HBV genotype and baseline HBsAg level in a post-hoc analysis

Methods

- A serological assay was added post hoc to determine HBV genotype in Phase 2 studies[1,3]

Figure 1: **Diagram for the PK/PD structural model**



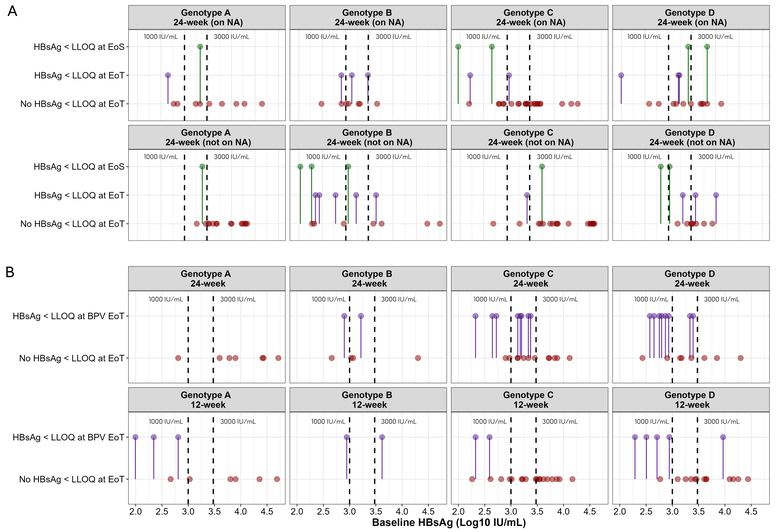
Phase 2 studies:

- B-Clear (study 209668): BPV 24 week-treatment, 1 arm on stable NA therapy and 1 arm not on NA therapy[1]
- B-Together (study 209348): BPV for 12 or 24 weeks, followed by up to 24 weeks of pegylated interferon (Peg-IFN) sequential therapy[3]

- Effect of genotype on BPV response was assessed as covariates on model parameters and shown using ETA-covariate plots

Results

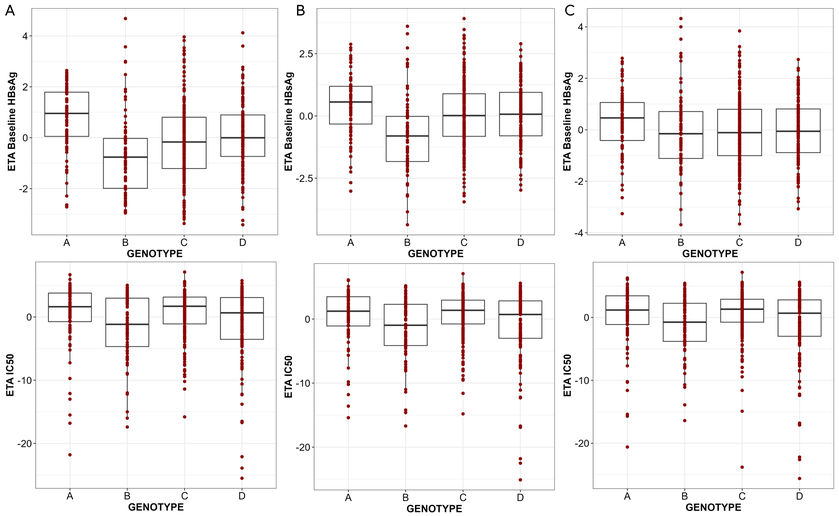
Figure 2: **Response (HBsAg < LLOQ) at end of treatment and end of study* by cohort and genotype for (A) B-Clear and (B) B-Together studies**



*End-of-study results not shown for B-Together due to possible confounding with Peg-IFN treatment
EoT: end of BPV treatment; EoS: end of study; LLOQ: lower limit of quantification

- Although numbers are very small, HBV genotypes A and D may maintain response better than genotypes B and C

Figure 3: **Effect of genotype on the between-subject variability of baseline HBsAg and IC_{50}. (A) Base model (B) final model with baseline HBsAg as covariate on IC_{50} (C) genotype B as covariate on baseline HBsAg in the final model**



ETA: between-subject variability; IC50: concentration to reach half of the response

- HBV genotype A seems to have higher values for baseline HBsAg, while genotype B seems to have lower values for baseline HBsAg and for IC_{50}
- Inclusion of genotype B on baseline HBsAg reduced the objective function value (OFV) by 38 points, and the correlation with lower IC_{50} seems to be less evident
- Inclusion of genotype B on IC_{50} did not improve the model (increased OFV by 6 points)

Conclusions

HBV genotype B appears to be correlated with lower baseline HBsAg level in HBV patients

HBV genotype does not provide additional predictive power or explanation of the variability in response to BPV once the effects of baseline HBsAg are accounted for

BPV is not expected to have a different efficacy profile across HBV genotypes

References

1. Yuen MF et al. *N Engl J Med* 2022;387(21):1957–68
2. Youssef A et al. AASLD 2022 (Poster No. 5057)
3. Buti M et al. Presented at AASLD 2023 (Abstract #42723, Oral #49)

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Disclosures

AY, JB, RE, MP and AN are GSK employees and hold GSK shares.
ACCC is a student worker at GSK

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