GSK HBV Biomarkers

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Disclaimer and Acknowledgments

Background and Aims

Bepirovirsen (BPV; GSK3228836) is an unconjugated antisense oligonucleotide that targets all HBV RNAs, including pregenomic RNA, via RNase H-mediated degradation resulting in a reduction of viral proteins such as HBsAg[1–3]

BPV also exhibits immunomodulatory effects via TLR8[3,4]

BPV has recently completed a Phase 2b (B-Clear) trial designed to investigate the efficacy and safety of 12- or 24-week treatment with BPV in patients with chronic HBV infection on stable NA or not on NA therapy[5]

B Clear Clinical Efficacy Study

Other ongoing BPV studies include:

B Together Sequential Interferon Study

B Fine Mechanism Study

B ThHBV Aso-001 (Bepirovirsen/CHB-targeted immunotherapy)

1. Yuen M-F, et al. *Nat Med*. 2021;27:1725–34; 2. Kole R, et al. *Nat Rev Drug Discov*. 2012;3(11):125–40; 3. You Y, et al. *J Hepatol*. 2022;77(Suppl. 1):S873-S874; 4. Delahaye J, et al. Oral presentation at International HBV meeting 2022; 5. Clinicaltrials.gov (NCT04449029) [accessed April 29, 2022]
HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NA, nucleos(t)ide analog; RNA, ribonucleic acid; RNase H, ribonuclease H; TLR, toll-like receptor.
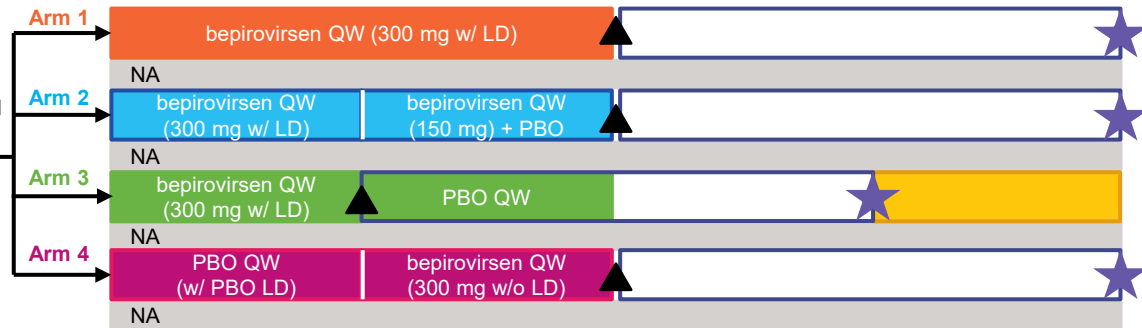
Phase 2b: B-Clear Study Design

Inclusion criteria

- Chronic HBV infection ≥6 months

- ALT ≤2 X ULN
- HBV DNA <90 IU/mL
- HBsAg >100 IU/mL

On-stable NA therapy n=227

Randomized 3:3:3:1

Arm 1 bepirovirsen QW (300 mg w/ LD)
NA

Arm 2 bepirovirsen QW (300 mg w/ LD) | bepirovirsen QW (150 mg) + PBO
NA

Arm 3 bepirovirsen QW (300 mg w/ LD) | PBO QW
NA

Arm 4 PBO QW (w/ PBO LD) | bepirovirsen QW (300 mg w/o LD)
NA
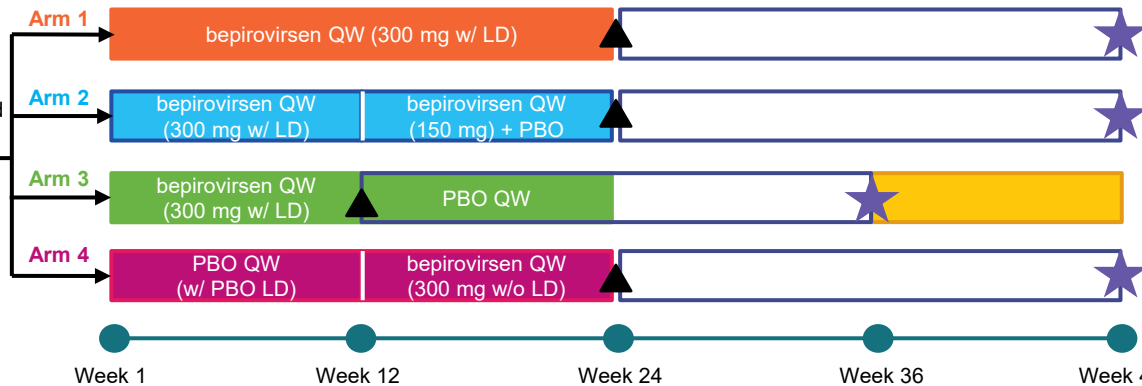
★ Primary endpoint analysis

▮ Additional follow-up period

- ALT <3 X ULN
- HBV DNA >2000 IU/mL
- HBsAg >100 IU/mL

Not currently on NA therapy n=230

Randomized 3:3:3:1

Arm 1 bepirovirsen QW (300 mg w/ LD)

Arm 2 bepirovirsen QW (300 mg w/ LD) | bepirovirsen QW (150 mg) + PBO

Arm 3 bepirovirsen QW (300 mg w/ LD) | PBO QW

Arm 4 PBO QW (w/ PBO LD) | bepirovirsen QW (300 mg w/o LD)

Stratification
- HBeAg positive/negative
- HBsAg ≤3 $\log_{10}$ IU/mL or >3 $\log_{10}$ IU/mL

Week 1   Week 12   Week 24   Week 36   Week 48

Primary endpoint (★): virologic response (HBsAg <LLOD [0.05 IU/mL] and HBV DNA <LLOQ [20 IU/mL]) sustained for 24 weeks from planned end of bepirovirsen treatment in the absence of rescue medication

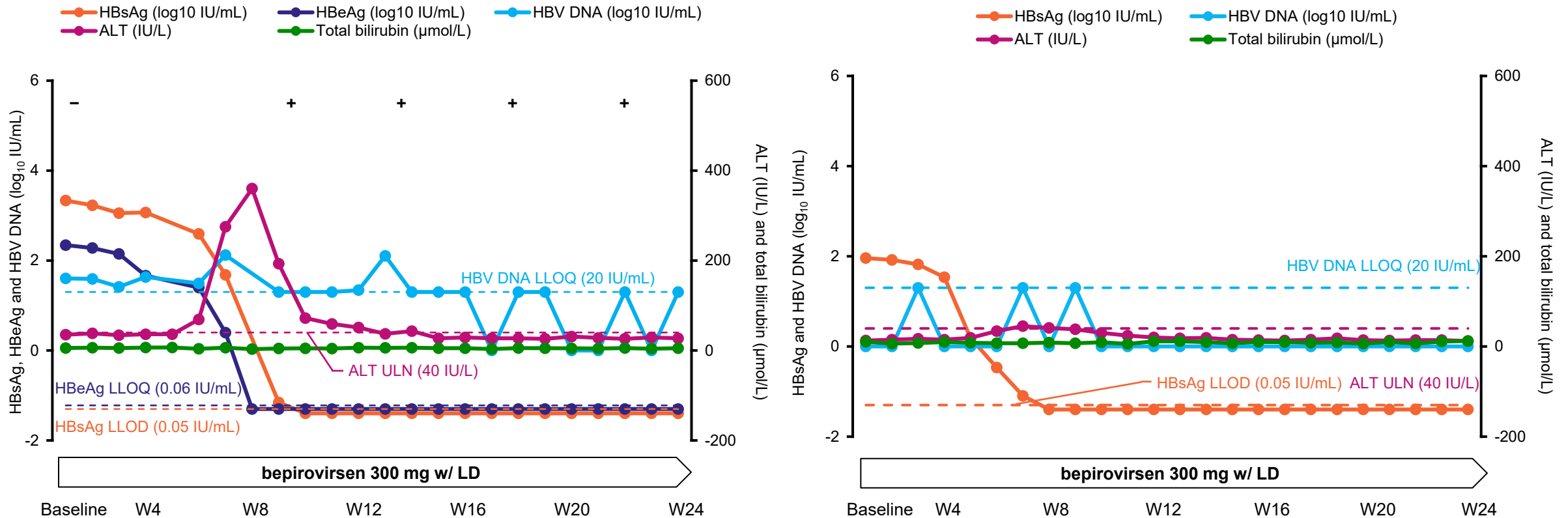# Observed Response to Bepirovirsen in B-Clear

On-NA: 300 mg 24 week

Figure to left reproduced with permission from Yuen M-F, et al. Poster presented at EASL 2022 (Poster No. SAT453). Figure to right independently created by GSK.

+ and − symbols indicate positive and negative anti-HBeAg status, respectively, at the relevant time point.

ALT, alanine aminotransferase; DNA, deoxyribonucleic acid; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LD, loading dose (Days 4 and 11); LLOD, lower limit of detection; LLOQ, lower limit of quantification; NA, nucleos(t)ide analog; ULN, upper limit of normal; W, week; w/, with.

Biomarkers Hold the Key to Differentiation of Response

ROADMAP

A roadmap for serum biomarkers for hepatitis B virus: current status and future outlook

Anna Kramvis[1] ✉, Kyong-Mi Chang[2], Maura Dandri[3,4], Patrizia Farci[5], Dieter Glebe[6,7], Jianming Hu[8], Harry L. A. Janssen[9], Daryl T. Y. Lau[10], Capucine Penicaud[11], Teresa Pollicino[12], Barbara Testoni[13,14], Florian Van Bömmel[15], Ourania Andrisani[16],

Immunological biomarker discovery in cure regimens for chronic hepatitis B virus infection †

Adam J. Gehring[1,2,*], Patricia Mendez[3], Kirsten Richter[4], Hildegund Ertl[5], Eric F. Donaldson[6], Poonam Mishra[6], Mala Maini[7], Andre Boonstra[8], Georg Lauer[9], An de Creus[10], Kathleen Whitaker[11], Sara Ferrando Martinez[12,13], Jessica Weber[14], Emily Gainor[14], Veronica Miller[14]

Virology	Immunology
Standard assays ✓ HBV DNA ✓ HBsAg ✓ HBeAg ✓ anti-HBsAg ✓ anti-HBeAg **Exploratory assays** ✓ HBcrAg ✓ HBV RNA ✓ HBV genotype ✓ HBV mutation profiling	✓ Cytokine profiles ✓ B and T cell immune profiling – Flow ✓ Measures of exhaustion/activation ✓ Functional HBV specific T cell assay ✓ HBV specific B cells ✓ NK cell phenotyping

Kramvis A, et al. *Nat Rev Gastroenterol Hepatol.* 2022;19(11):727–45; Gehring AJ, et al. *J Hepatol.* 2022;77(2): 525−38.

Anti-HBsAg, hepatitis B surface antibody; anti-HBeAg, hepatitis B e antibody; DNA, deoxyribonucleic acid; HBcrAg, hepatitis B core-related antigen; HBeAg; hepatitis B e-antigen HBsAg; hepatitis B surface antigen; HBV, hepatitis B virus; NK, natural killer; RNA, ribonucleic acid.

HBV Biomarker Data Will Provide a Better Understanding to Inform:

PS

Patient Stratification

Understanding patient populations with unique drug or clinical response status allows for selection of the right subjects for bepirovirsen

NR

Path forward in non-responders

Understanding what biology is missing in non-responders informs combinations that might be more effective in certain populations

MD

Mechanistic Differentiation

Understanding mechanistic differences between investigational agents can highlight potential synergistic or differential opportunities

SA

Scientific Advancement

Understanding underlying mechanisms of bepirovirsen to enhance scientific understanding

MD, mechanistic differentiation; NR, non-responder; PS; patient stratification; SA, scientific advancement.
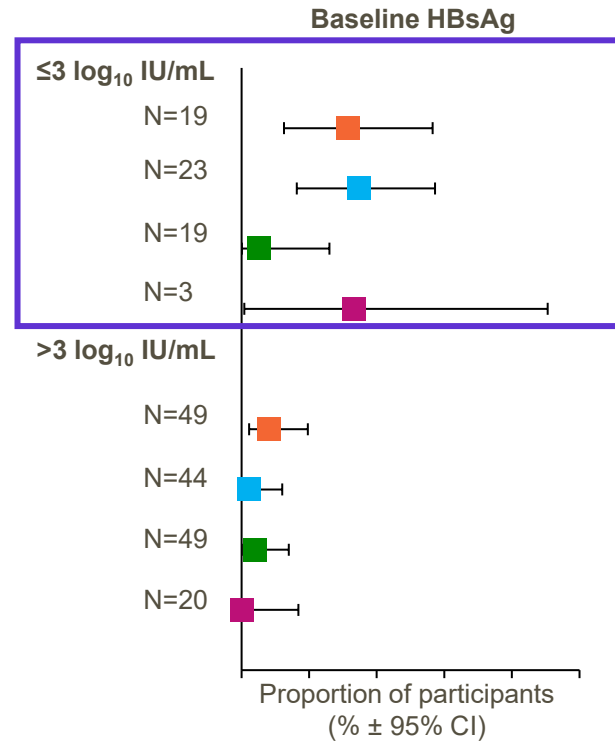
Patient Stratification: Signal to Selection

1. Find signal that differentiates between responders and non-responders in initial study

Phase 2a: Best HBsAg log IU/mL reduction in low HBsAg patients

GSK3228836 300 mg (NA-naïve) (N=12)

HBsAg (Log_{10} IU/ml) vs Day

— HBeAg negative   — HBeAg positive
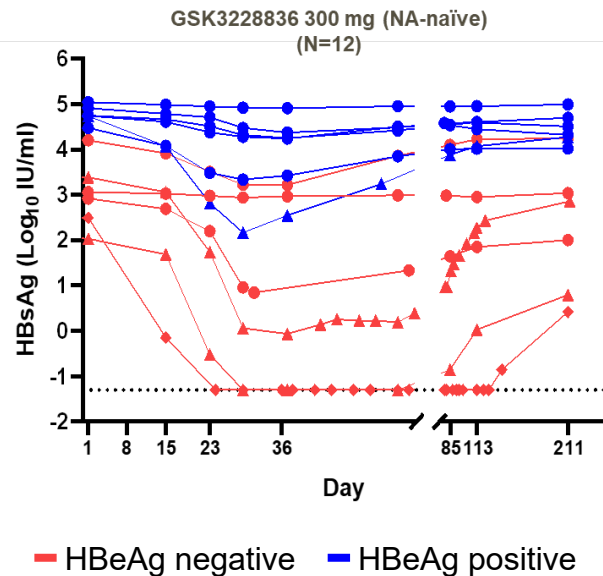
2. Verify observation in independent study

Phase 2b: Baseline HBsAg predicts log IU/mL response

Baseline HBsAg

≤3 log_{10} IU/mL
- N=19
- N=23
- N=19
- N=3

>3 log_{10} IU/mL
- N=49
- N=44
- N=49
- N=20

Proportion of participants (% ± 95% CI)

3. Implement assay fit for patient selection in next study

Phase 3: Use of HBsAg for patient selection

Will a More Sensitive HBsAg Assay Be Needed?

Simulated HBsAg profiles following 300 mg QW dosing for 24 weeks

Response status
- Non-responder
- Relapse
- Sustained response
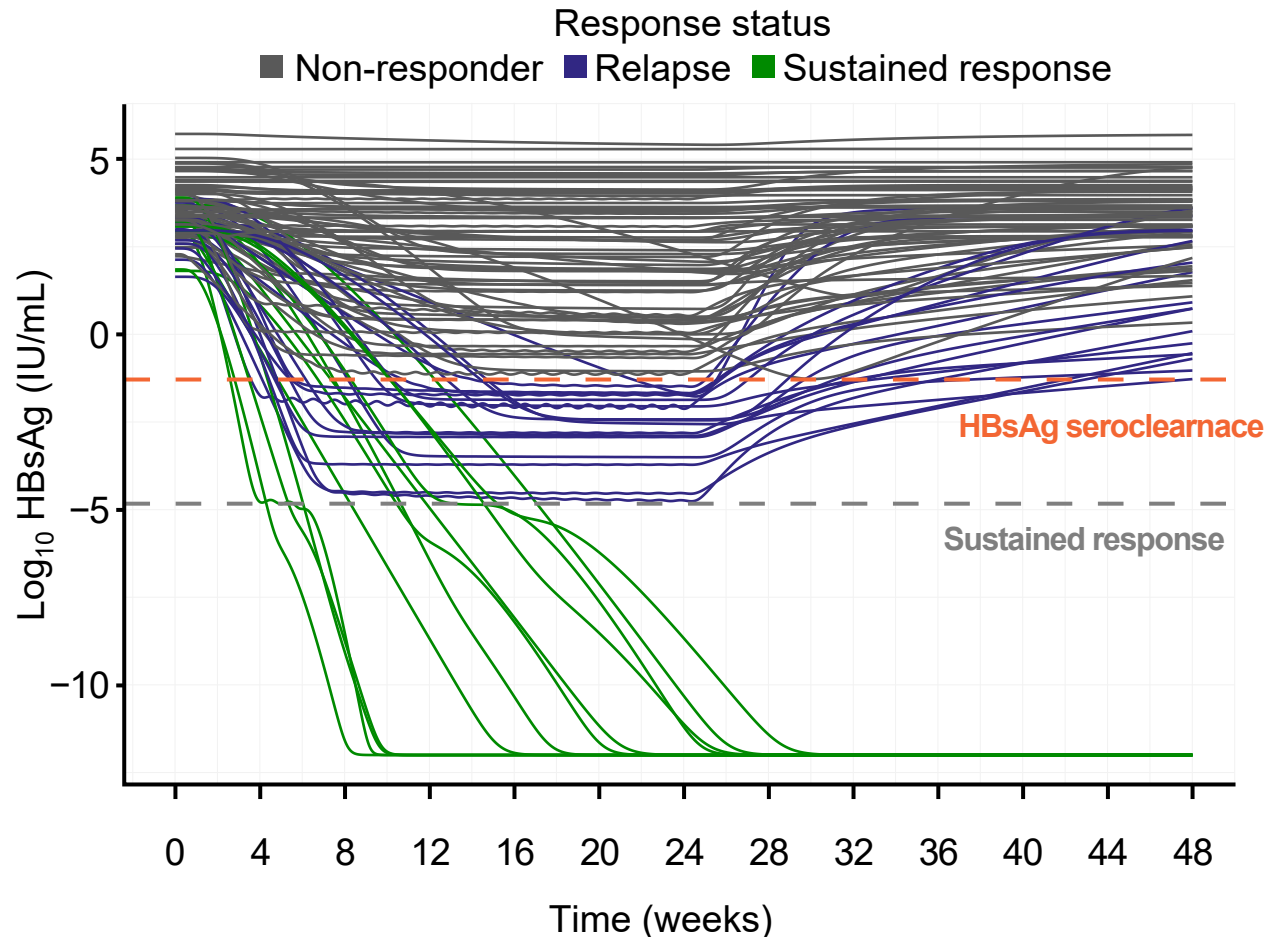
- FDA guidelines defines **HBsAg loss <0.05 IU/mL**

- A likelihood-based method was implemented to predict HBsAg values below the lower limit of detection (<0.05 IU/mL) to provide a complete HBsAg profile during on- and off-treatment periods

- Subjects who achieve HBsAg seroclearance but do not hit a lower threshold are predicted to eventually **relapse**.

- More sensitive assays may be needed:
  - → To help **validate** model predictions
  - → **Monitor** patients with precision

Some Challenges

- Monitoring peripheral biomarkers versus site of action in the liver
- Diversity of response (responders, partial responders, non-responders)
- Operational considerations:
  - Timing of sample collection
  - Blood volumes
  - Isolation of quality PBMCs
  - "Big Data" integration
- Sensitivity of assays – for example, HBcrAg, HBV RNA
- Lack of commercial assays – HBV RNA
- Assessing genotype in patients on NA

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HBcrAg, hepatitis B core-related antigen; HBV, hepatitis B virus; NA, nucleos(t)ide analog; PBMC, peripheral blood mononuclear cell; RNA, ribonucleic acid.